UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Context and neuroinflammation in the posterior dorsomedial striatum impair different aspects of goal-directed decision-making

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under the supervision of Dr. Laura A. Bradfield

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Certificate of original authorship

I, *Arvie Rodriguez Abiero* declare that this thesis, is submitted in fulfilment of the requirement for the award of the *Doctor of Philosophy*, in the School of Life Sciences, Faculty of Science at the *University of Technology Sydney*.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualification at any other academic institution.

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A JOURNEY DOWN UNDER: Arvie's #RoadToPhD in Australia

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
APA	American Psychological Association
ASD	Autism spectrum disorder
BBB	Blood brain barrier
BLA	Basolateral amygdala
BSA	Bovine Serum Albumin
CEA	Central nucleus of the amygdala
CNS	Central nervous system
CR	Conditioned response
CS	Conditioned stimulus
CSTC	Cortico-striato-thalamo-cortical
DH	Dorsal hippocampus
DLS	Dorsolateral striatum
DREADDs	Designer receptor exclusively activated by designer drugs
FR	Fixed-ratio
$GABA_A$	γ-Aminobutyric acid type A

GFAP	Glial fibrillary acidic protein
IBA1	Ionized calcium binding adaptor molecule 1
IL	Infralimbic cortex
LiCl	Lithium chloride
lOFC	Lateral orbitofrontal cortex
LPS	Lipopolysaccharide
MD	Mediodorsal thalamus
MDD	Major depressive disorder
mOFC	Medial orbitofrontal cortex
MS	Multiple sclerosis
NAc	Nucleus accumbens
NeuN	Neuronal nuclei
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
O-R	Outcome-response
PD	Parkinson's disease
pDMS	Posterior dorsomedial striatum
PET	Positron emission tomography
PIT	Pavlovian instrumental transfer

PL	Prelimbic area
RI	Random interval
R-O	Response-outcome
RR	Random ratio
SEM	Standard error of the mean
S-O	Stimulus-outcome
S-R	Stimulus-response
SUD	Substance use disorder
TLRs	Toll-like receptors
UNODC	United Nations Office on Drugs and Crime
UR	Unconditioned response
US	Unconditioned stimulus
VTA	Ventral tegmental area
WHO	World Health Organization

ABSTRACT

Compulsive disorders such as substance use disorder and obsessive compulsive disorder are a pervasive problem characterized by the loss of control over one's actions, resulting in the persistent performance of repetitive behaviours. Preclinical animal models have afforded many important insights into the behavioural mechanisms of compulsive disorders, but these have been limited in scope. For instance, compulsive disorders are known to be chronically relapsing and both human and animal-based studies have suggested that relapse is particularly common following exposure to certain contexts. However, the vast majority of these data have been derived from situations involving a single (active) lever response, whereas in the real world individuals have an array of choices available that lead to multiple outcomes. Therefore, it was the first aim of the current study to use a preclinical rat model to measure how various contexts might affect the propensity to relapse in a two action, two outcome paradigm for the first time. Preclinical studies have also been limited in scope in investigating the brain mechanisms of compulsive disorders. Although multiple studies have identified the neural circuitry of various types of action control and reward-seeking, they have failed to identify the endogenous mechanisms that drives dysfunction in these circuits. Neuroinflammation is a primary candidate, as it has been identified in the striatum of individuals with compulsive disorders; individuals who also display deficits in action selection. Therefore, it was the second aim of this thesis to determine whether neuroinflammation in the posterior dorsomedial striatum (pDMS) causes alterations in cue-guided and goal-directed action selection. Together, the two aims of this thesis combined to comprise the overall aim of my doctoral thesis, which was to investigate the behavioural and brain

mechanisms of compulsive disorders in a more ecologically valid manner than current preclinical studies.

The experiments tested under Aim 1 are presented in Chapter 3. For these experiments I used an outcome-selective reinstatement design – a procedure involving choice between two actions and outcomes – and explored how this was affected by altering the physical context in rats. In Experiment 1, when tested immediately after extinction, selective reinstatement was intact (i.e. Reinstated > Nonreinstated) for animals that were tested in the extinction context (groups AAA and ABB) but was impaired for groups in which extinction and testing occurred in different contexts (groups ABA and AAB). Experiment 2 was conducted identically, except that rats received two extinction sessions over two days and tested one day later. This time, all groups demonstrated intact outcome-selective reinstatement regardless of context. Analysis of c-Fos expression in several brain regions revealed that only c-Fos expression in the posterior dorsomedial striatum (pDMS) was related to intact reinstatement performance.

The experiments conducted under Aim 2 are presented in Chapter 4. In the first experiment (Experiment 3) I injected the endotoxin lipopolysaccharide (LPS) into the pDMS of rats to induce neuroinflammation, then tested whether this altered control over action selection. On a test of specific Pavlovian instrumental transfer (sPIT), LPS animals did, but Sham controls did not, selectively respond on the lever that earned the same outcome as the stimulus currently presented (i.e. Same > Different). When given a subsequent outcome devaluation test, both groups responded more on the valued than the devalued lever (i.e. Valued > Devalued), but the difference was larger for group LPS. Outcome-selective reinstatement did not differ between groups. The results of Experiment 3 suggested that pDMS neuroinflammation might increase motivation generally, or facilitate goal-directed

action specifically, and this was tested by in a novel rat cohort in Experiment 4. Results were consistent with it doing both; group LPS had higher breakpoint than Shams on a progressive ratio test, whereas group LPS remained goal-directed after Sham controls were shown to be habitual. Immunohistochemistry analyses showed that the increased number of astrocytes but not microglia in pDMS was related to the behavioural effects, as was c-Fos-NeuN intensity, suggesting that the activation of astrocytes had caused neuronal excitability and the changes in behaviour. Experiment 5 confirmed this directly by selectively altering astrocytic signalling in the pDMS using chemogenetics to activate a Gi pathway in astrocytes, which abolished performance on sPIT and devaluation (but not reinstatement), suggesting that intact astrocytic signalling is necessary for each effect.

Taken together, the results of the experiments presented in this thesis demonstrate, for the first time, that the reinstatement of responding in multiple action-outcome paradigm is primarily context-independent, and that neuroinflammation in the pDMS does alter action control, specifically through the activation of astrocytes, by facilitating it in an aberrant manner. I argue that this process could contribute to compulsivity by causing an excess reliance on goal-directed processes.

Keywords: posterior dorsomedial striatum, compulsive behaviours, contextual modulation, goal-directed action, neuroinflammation, astrocytes

Manuscript associated with this thesis

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Poster Presentation: Outcome-selective reinstatement involving choice is partially context-dependent, and is associated with activation of the dorsomedial striatum

CHAPTER 1

CONTEXT AND CHOICE:

DOES WHERE WE ARE INFLUENCE WHAT WE CHOOSE TO DO?

1.1 General Introduction

The ability to cognitively control actions in pursuit of a goal is critical to adaptive behaviour, whether that goal be something as distinguished as an Olympic medal, as labour-intensive as writing a PhD thesis, or as simple as buying a snack. The ability to perform actions automatically, outside of cognitive control, is also central to adaptive functioning. For instance, the ability of my fingers to habitually find each key as I type this sentence frees up a certain amount of cognitive capacity that allows me to think about the content of what I type. The balance between goal-directed and habitual action control can become disrupted, however, as can the brain mechanisms that underlie them, in neuropsychiatric disorders such as disorders of compulsion (e.g. substance use disorder (SUD) and obsessive compulsive disorder (OCD)).

Over the last two decades, laboratory studies of goal-directed and habitual action control have provided several fundamental insights into the behavioural and brain mechanisms of each, as well as how these mechanisms might become dysfunctional in various compulsive disorders. Causal studies conducted in animals have revealed the neural circuitry that underlies the ability to behave in a goal-directed or habitual manner (see Bradfield & Balleine, 2017, for review), and correlational neuroimaging evidence indicates that this circuit is highly homologous to the action selection circuit in people (Balleine & O'Doherty, 2010; de Wit et al., 2012; Liljeholm et al., 2011; Valentin et al., 2007). A number of animal studies have shown that the balance between habitual and goal-directed action control becomes disrupted after exposure to certain drugs such as methamphetamine (Furlong et al., 2018; Furlong et al., 2017), or alcohol (Corbit et al., 2012), causing an overreliance on habitual control. This is in line with evidence from human studies, in which individuals with SUD have been shown to be

unable to select actions adaptively, and this shift appears to coincide with alterations in the neural circuitry from the goal-directed to the habit circuit (Corbit & Janak, 2016; Sjoerds et al., 2013).

Despite these fundamental advances, however, several gaps in knowledge remain. For instance, despite the increasing recognition that the world inhabited by humans is highly complex, this complexity into the experiments has often failed to be translated to animal studies in the laboratory. For example, the phenomenon of 'reinstatement' refers to the increased performance of an action (or response to a stimulus) that had previously been reduced when surprisingly paired with a reward after a period of being unrewarded. Similarly, 'renewal', otherwise known as 'context-induced reinstatement', occurs when an action (or stimulus) that was unrewarded in one context resurfaces in a novel context, or in a context in which that action was previously paired with reward. Both renewal and reinstatement have been suggested to be models of relapse to drug-seeking or other compulsive-like actions following treatment (Bouton & Bolles, 1979; Bouton et al., 2021; Bouton et al., 2011; Delamater, 1997) and are therefore useful for understanding the behavioural and brain mechanisms underlying relapse. In contrast to the real-world, however, in which individuals are faced with an array of options as to which action to perform, reinstatement and renewal in the laboratory have typically only ever involved a single action (or stimulus) being paired with a single outcome. Therefore, it was the first aim of the current thesis to investigate the behavioural and potential brain mechanisms of renewal and reinstatement in an animal model involving a choice between two actions that earn two distinct outcomes. The experiments conducted under this aim are reported in Chapter 3.

The second aim of this thesis was to directly investigate how the brain mechanisms of goal-directed action become disrupted in compulsive-like disorders. As mentioned, the neural circuit underlying goal-directed actions and habits has been successfully delineated over the last two decades as a result of extensive studies conducted in both humans and animals. What is not clear from these studies, however, is how this circuit becomes dysfunctional in individuals with compulsive-like disorders. That is, although it is clear from animal studies that lesioning or inactivating neurons within each brain region of interest will disrupt the balance between goal-directed actions and habits – just as occurs in compulsive individuals – the extent of neuronal death or silencing induced in these studies is not reflective of what is observed in these individuals. Indeed, post-mortem studies often fail to find any differences at all in the number of neurons between compulsive individuals and healthy controls(Harper et al., 2003), despite alterations in behaviour.

Therefore, the question remains as to what the endogenous mechanism might be that is causing the alteration in behaviour. Neuroinflammation is an excellent candidate, because post-mortem studies of autopsied individuals with compulsive disorders have revealed increased levels of inflammatory markers (Crews & Vetreno, 2014; He & Crews, 2008), and microglial and astrocytic activation that is reflective of a neuroinflammatory response have also been observed in rodents exposed to various drugs of abuse (Narita et al., 2005; Wang et al., 2019; Zhao et al., 2013). Therefore, it was the second aim of the current thesis to test whether neuroinflammation in the posterior dorsomedial striatum (pDMS) was sufficient to disrupt the balance between goal-directed and habitual action control. The pDMS was selected because it is a brain region that has been proposed by several studies to be the neuro-anatomical locus of goal-directed action control(Yin, Knowlton, et al., 2005; Yin, Ostlund, et al., 2005). Further experiments under this aim focused on the specific role of

pDMS astrocytes in goal-directed action using chemogenetics. These experiments are reported in Chapter 4.

To briefly recap, it was the first aim (Aim 1) of the current thesis to investigate whether reinstatement – a model of relapse – is specific to a particular outcome, and whether this specificity depends on the current physical environment, or context. The second aim (Aim 2), was to examine whether inducing neuroinflammation in the pDMS, the neuroanatomical locus of goal-directed action control, impairs various aspects of decision-making, and to further explore the neuron-glia interactions that underlie such impairments. Each of these aims contributed to the overall aim of the current thesis, which was to investigate the behavioural and brain mechanisms of dysfunction in goal-directed decision-making as observed in compulsive disorders in a more ecologically valid manner, to improve our understanding of how and why these disorders develop, with a long-term hope that this will inspire better treatment outcomes.

All experiments were conducted in rats, as they provide an anatomically and functionally homologous model that affords a high degree of experimental control. Moreover, the current experiments were conducted with food outcomes rather than addictive drugs, due to the fact that administering a drug can and does, in and of itself, alter the properties of the very underlying neural (and glial) circuits I am attempting to study, as well as the mental state of the animal. Alcohol, for instance, has broad pharmacological effects such as altering levels of various neurotransmitter systems which include dopamine, serotonin, endogenous opiates, glutamate, and GABA (Gamma-aminobutyric acid) (Valenzuela, 1997). Alcohol is itself a γ-Aminobutyric acid type A ($GABA_A$) agonist, and agonising GABA throughout the brain might

affect processes such as locomotion and general cognitive function which then could indirectly affect decision-making performance. Using food outcomes instead avoids this issue.

1.2 Burden and clinical characteristics of compulsive disorder

Disorders of compulsion, such as SUD and OCD, are chronic debilitating illnesses, and pose significant public health concern. Indeed, these two disorders have been recognized as two of the 10 most common neuropsychiatric disorders worldwide (Dattani et al., 2021; National Collaborating Centre for Mental Health (UK), 2011; American Psychiatric Association (APA), 2013; World Health Organization (WHO), 2019). It should be noted that although individuals with either SUD or OCD could be considered 'compulsive' in the sense that they repetitively elicit the same – largely unwanted – actions, SUD and OCD are categorized as clinically distinct as they each feature several unique characteristics (Blom et al., 2011; Figee et al., 2011; Meunier et al., 2012). Such disorders are characterized by persistent susceptibility to perform unwanted repetitive behaviours, resistance to relapse, and the loss of flexible, goal-directed control over drug use and maladaptive behaviour (Cazares et al., 2021; Charlton et al., 2019; Johnson et al., 2020; Namba et al., 2021; Vaghi et al., 2019). In each condition, the disruption of cognitive control occurs as a person seeks to prevent undesirable emotional and/or physical distress by engaging in behaviours that, over time, become unwanted and time consuming. For example, people who suffer from SUD might repeatedly pursue the use of a substance whilst neglecting their relationships and responsibilities, and for OCD patients, this involves obsessional thoughts and compulsive rituals that take up several hours of each day, causing adverse health, financial, and social outcomes.

These disorders are also highly problematic from both societal and economic standpoints. In the United States the economic burden of SUD/OCD is substantial, amounting to more than

$740 billion annually for SUD and estimated to be $8.4 billion for OCD (National Institute on Drug Abuse, 2017; DuPont, et al., 1995). Globally, approximately 35 million people have been diagnosed with SUD, and substance use is indirectly and directly responsible for 11.8 million deaths each year (Roth et al., 2018; Ritchie et al., 2022; United Nations Office on Drugs and Crime (UNODC), 2019). On the other hand, approximately 2 - 3% of the general population has OCD, which is about 1 in 40 adults in the U.S or 1 in 50 people in Australia(Carmi et al., 2022; Flaum et al., 2020; Dyason et al., 2022). Studies have reported that the lifetime prevalence for co-occurring SUD and OCD are consistently in the range of 25 percent (Blom et al., 2011; Mancebo et al., 2009).

These issues are compounded by the fact that current FDA-approved pharmacotherapies and cognitive-behavioural treatments have been met with limited clinical success for a significant number of patients (Pierce et al., 2012; Swierkosz-Lenart et al., 2023). One potential reason for this is because our understanding of these disorders have been developed based on preclinical models of habitual drug taking and seeking, or simple responses to cues, and have ignored the loss in goal-directed action control that is not directly captured by either process. For instance, individuals with SUD often continue to compulsively perform an action, despite wishing they could stop themselves but finding they cannot. In healthy individuals, cognitive goal-directed control is usually sufficient to inhibit a tendency towards a habit (Balleine et al., 2015; Corbit, 2018), but in compulsive individuals this is clearly not the case. Thus, it is essential that neurobiological and neurobehavioural research provide a better understanding of the systemic, cellular, and molecular changes that are impacted by the loss in cognitive control and aberrant action selection associated with compulsion.

1.3 Defining Compulsion

Defining compulsivity as a trait (i.e. outside of the diagnostic criteria for specific compulsive disorders) is not necessarily straightforward, as there are multiple definitions throughout the literature, and they aren't always consistent. The APA dictionary of psychology defines compulsivity as, '*a type of behaviour (e.g., hand washing, checking) or a mental act (e.g., counting, praying) engaged in to reduce anxiety or distress*'. This may well apply to many or even most compulsive actions, but doesn't really capture the repetitive nature of the compulsive act nor the reportedly irresistible need to perform it. Indeed, it is possible to think of many 'normal' or healthy behaviours that would fit within this definition, such as washing your hands to alleviate anxiety after being sneezed on whilst riding the bus, particularly during the COVID pandemic. Another definition was offered by Robbins et al. (2012), who suggested that compulsivity is '*a hypothetical trait in which actions are persistently repeated, despite adverse consequences*'. However, this definition could be considered a bit too narrow as not all actions performed compulsively will necessarily have adverse consequences, and not every time they are performed. Most recently, Luigjes et al. (2019), searched PubMed for articles in human psychiatric research with 'compulsive behaviour' or 'compulsivity' in the title and reviewed 28 articles in the literature that define compulsivity. Based on this, they offered the following definition: '*Compulsive behaviour consists of repetitive acts that are characterized by the feeling that one 'has to' perform them while one is aware that these acts are not in line with one's overall goal*' (Luigjes et al., 2019, p.10). Once again, however, this definition could be seen as not entirely satisfactory because there are situations in which compulsive acts *are* performed in line with one's overall goal - if that goal is to alleviate anxiety for example.

Therefore, finding a unitary and satisfactory definition of compulsivity may be elusive, which provides a challenge for studying it in the laboratory – particularly in animals whose thoughts and mental states cannot be directly measured. Nevertheless, each definition does clearly share the fact that the compulsive individual has suffered from a loss of cognitive control over their ability to select actions, which is something I can study in animals in the laboratory with carefully controlled tasks. Of course, it is also possible that an individual or animal has lost their capacity for action control in a manner that is not compulsive. Thus, although I am investigating the conditions (both behavioural and brain conditions) that lead to a loss of action control in the current thesis with a view to drawing implications for compulsivity, the findings here might also apply more generally to situations in which these conditions might also disrupt action control in a manner that is not necessarily compulsive, as will be discussed.

1.4 Pavlovian and instrumental learning

Although there is evidence of a genetic component to many compulsive disorders (Volkow et al., 2019), these genes tend to predispose individuals to these disorders rather than predetermine their development, suggesting that learning also forms a large part of developing a compulsive phenotype. As such, in order to understand such disorders, it is important to understand how learning occurs, first in a fundamental sense and then to consider how such learning might contribute to the development of compulsion.

Learning is the process by which new knowledge and behaviours are acquired from experience. The two types of learning that are central to behavioural psychology are classical (Pavlovian) and instrumental (operant) conditioning (Rescorla and Solomon, 1967). Both classical and instrumental conditioning are forms of associative learning, which refers to the

organism learning to associate stimuli in the environment or their behaviours with significant events, such as punishments and/or rewards. These two types of learning have been extensively studied.

Like many great scientific advances, Ivan Petrovich Pavlov, a Russian physiologist, discovered classical conditioning by accident. Pavlov observed that the dog he was studying began to salivate in response to the presentation of a stimulus (a noise) after it had repeatedly been paired with food, suggesting that the dog had associated the noise with the food. This phenomenon is now called Pavlovian conditioning and, in accordance with its associated terminology, involves pairing a previously neutral stimulus (the noise in this example) with an *unconditioned stimulus (US)* (e.g. food) to produce an *unconditioned response (UR)* (e.g. salivation). After learning, the stimulus alone will evoke the *conditioned response (CR)*, at which point the noise in this example is known as the *conditioned stimulus (CS)* and salivating in response to the noise is the CR. (Pavlov, 1927).

Pavlovian conditioning provides some insight into the learning that underlies compulsive disorders, including SUD and OCD. For example, Pavlov's work helps explain why some individuals with SUD often have a craving and/or experience relapse when they are in a drug-related environment (a pub) where they spent years performing actions compulsively. Recall that in Pavlov's experiment, the noise served as a stimulus to the dogs. Food was on its way! Likewise, certain stimuli and contexts can powerfully signal the arrival of a certain outcome, such as a bar that is paired with alcohol that will come to elicit an expectation of alcohol when an individual walks past it, compelling the individual to drink. Pavlov's work further demonstrated that once learned, the noise-food association was very difficult for dogs to unlearn even if the noise was repeatedly presented without food, because the salivation

response would reduce, but then spontaneously returned after a few hours. As will be discussed in detail below, the persistence of stimulus-outcome (S-O) associations and the difficulty unlearning them is one reason why exposure to drug-related stimuli can result in a relapse.

Instrumental (or operant) conditioning, on the other hand, is the learning that occurs when an action is rewarded or punished, leading to an increase or decrease (respectively) in the likelihood of that action being repeated. It was first described by Thorndike (1905) and later by Skinner (1938), who defined operant actions as any behaviour that *'operates'* on the environment to create an action or response. Skinner demonstrated how positive reinforcement worked by putting a hungry rat in his Skinner box. The box contained a lever, and as the rat moved about the box it would press the lever by accident, causing a food pellet to drop in. After several pairings of lever pressing with the food pellet, the rat would learn to press the lever immediately next time when placed in the box, which was taken as evidence of instrumental learning. Although Skinner himself believed such conditioning to be evidence of reflexive learning, most researchers have now adopted the nomenclature of instrumental conditioning proposed by Thorndike, which affords the organism voluntary control over an association formed between a response and an outcome (R-O). Such associations must be independent from S-O associations (S-O rather than CS-US under Pavlovian terminology). Moreover, instrumental responses can become responses to stimuli (S-R associations – the type of association envisaged by Skinner) under certain circumstances, and these are thought to promote habitual instrumental responding.

Like Pavlovian conditioning, instrumental conditioning also contributes to compulsion and compulsive-like behaviour. For example, an individual with OCD might experience obsessive

thoughts about germs or any contamination, causing them to feel anxiety. By engaging in ritual behaviour like constantly washing hands, a person with OCD may experience temporary relief from anxiety symptoms. This positive result can reinforce ritual behaviour. However, the behaviour may be repeated so often as to become habitual, meaning that it is completed in response to the surrounding stimuli rather than in pursuit of the goal of relieving anxiety. Compulsions often go another step further again compared to habits, because when punished, habits tend to revert to goal-directed actions (e.g. if crossing the road absent-mindedly as a car comes fast around the corner, you might jump backwards and take extra caution when crossing the road). Compulsions, however, tend to persist even in spite of punishment, such as the individual who washes their hands until they are red and sore, and who misses out on many fun and fulfilling activities due to fear of contamination.

1.5 Measuring relapse in the laboratory

Compulsive disorders tend to be chronically relapsing disorders, with an estimated 40-60% of individuals returning to the performance of their compulsive actions after a period without doing so (Brecht & Herbeck, 2014; Schellekens et al., 2015). Relapse refers to the increase in responding that is observed after a period of abstinence, treatment, or intervention, such as a return to drug seeking in SUD or once again performing compulsive actions after successfully learning not to in OCD. The reasons underlying why individuals might relapse are complex and multifaceted, and it is not possible to entirely replicate all these conditions in animal studies in the laboratory. Nevertheless, there are several popular procedures that attempt to model various aspects of relapse that have led to valuable insights about learning and its propensity to return after reducing.

Two commonly used procedures to model relapse are renewal and reinstatement. These phenomena have been shown to occur in both Pavlovian and instrumental learning and are substantially robust. In each, the animal is typically first trained to administer a drug, food, or other rewarding substance, which is earned by performing a response such as lever pressing (or in conjunction with the presentation of a CS). Treatment is then modelled via a process known as 'extinction' during which responding (or CS presentations) no longer earn the desired outcome, during and after which responding declines. Reinstatement is observed if the animal is later subject to an unsignalled, unearned delivery of the outcome, causing responding to re-emerge (de Wit & Stewart, 1981; Stretch & Gerber, 1973). Renewal (sometimes referred to as context-induced reinstatement), on the other hand, is the increase in responding that is observed if the animal is placed into a context other than that in which extinction took place (Bouton et al., 2011; Delamater, 1997), and is especially robust if that context was previously paired with the reinforcer in question.

Renewal has been argued to model relapse that occurs when an individual is exposed to a context that elicits a return in responding. For example, it is thought that an individual in recovery from SUD is more likely to relapse if they visit various locations that are associated with the consumption of their drug of choice; in Figure 1, the man might be more likely to drink a beer when sitting in the pub but might choose the soft drink when sitting at home. Reinstatement, on the other hand, models a situation in which an individual is exposed to the outcome once again, such as the smoker who relapses after a puff on a cigarette.

Figure 1: Does where we are influence what we do? A man decides between a soft drink and a beer in the pub vs. sitting at home.

Renewal and reinstatement demonstrate that the reduction in responding that occurs during extinction is not a result of the response being erased or unlearned. Rather, animals appear to form a new response-no outcome association (or stimulus-no outcome association) during extinction that is simultaneously retained alongside the original R-O association. It has been argued that because the co-existence of each type of association is somewhat ambiguous, in the sense that the CS/response is no longer a good predictor of whether or not

the outcome will occur, and context cues or the unsignalled appearance of the outcome can reduce this ambiguity somewhat by indicating that outcome is likely to occur. As such, these cues evoke responding that is in line with the excitatory CS/R-O association, causing it to once again increase (Bouton et al., 2021; Bouton et al., 2014).

Although renewal and reinstatement are useful models of relapse, they do not fully capture the richness of the relapse environment. One key way in which they fail to do so in the vast majority of studies, is by evoking a single, active response for a single outcome. In the 'real world', however, an individual performing a single response for a single outcome in a uniform environment is rare. Rather, as noted in a recent review (Vandaele and Ahmed, 2021), people are far more likely to be faced with scenarios in which they can choose between multiple actions that have multiple outcomes, and will therefore learn a multitude of S-O, R-O, and S-R associations. A person who both drinks alcohol and smokes cigarettes, for example, might associate multiple contexts (e.g. at bars, the balcony at home, garden at work etc) with both behaviours.

It is for this reason that it is the aim of the empirical chapter – Chapter 3 – to begin to capture some of this complexity at a preclinical level, by determining how selective reinstatement in a choice-based procedure is influenced by context. Specifically, I ask whether increases in multiple responses for multiple outcomes, rather than selective responding for a single outcome, is more likely after a change in physical context. For example, would a person who has been through treatment, and thus abstinent from both alcohol and cigarettes, but then relapses on one of these drugs in their local bar also be more likely to relapse on the other? And are they more likely to relapse on both in this context than if they were in another, more neutral context?

1.5.1 Renewal (also known as context-induced reinstatement)

The phenomenon of renewal was first demonstrated in Pavlovian conditioning (Bouton & Bolles, 1979), and later replicated in instrumental conditioning (e.g. Bouton et al., 2011). As mentioned above, renewal refers to the return in responding that occurs when an organism is exposed to a context other than the context in which extinction took place. In most laboratory studies, these contexts are distinguishable through the use of visual, olfactory, and tactile stimuli that are unique to each.

There are several ways in which renewal can occur, but ABA renewal is the most common and most robust. In ABA renewal, a stimulus or response is initially paired with an outcome in Context A, then extinguished in a different context, Context B, after which the animal is returned to Context A where responding tends to increase again (i.e., it has been renewed). This increase is apparent when their responding is compared to animals who were trained, extinguished, and tested all in the same context (AAA), or trained in one context, but extinguished and tested in another (ABB). Renewal also occurs when animals are trained and extinguished in one context and then tested in another (AAB renewal) or trained and extinguished in different contexts and then tested in a third context (ABC renewal) (Bouton et al., 2021; Bouton et al., 2011). I will explore several of the seminal studies that describe renewal in Pavlovian and instrumental conditioning below.

The first animal study of renewal (Bouton & Bolles, 1979) was conducted in a Pavlovian fear conditioning paradigm. Specifically, rats were given 15 pairings of a noise and a footshock in one context, Context A, then exposed to multiple noise presentations without the footshock present in Context B. When tested in Context B, conditioned suppression of lever pressing for grain pellets remained low, but when returned to the training context (A) or

exposed to a third context (C) suppression returned, thus demonstrating ABA and ABC renewal, respectively. Together, these experiments demonstrated that the noise-footshock association learned in Context A had not been unlearned, but was instead simply masked by the extinction process in Context B. Once that mask was removed by the alteration in context, rats were once again able to demonstrate evidence of their initial learning.

Since this seminal study, renewal has been demonstrated multiple times in a number of different paradigms and with many different variations (Bouton & Brooks, 1993; Bouton & Peck, 1989; Tamai & Nakajima, 2000; Crombag & Shaham, 2002; Harris et al., 2000; Todd, 2013). Hence renewal, ABA renewal in particular, is a very robust phenomenon (Bouton et al., 2021; Bouton et al., 2011). Bouton and colleagues (1983; 1989) have interpreted observations of renewal to indicate that the extinction context serves to 'gate' the retrieval of the extinction association (e.g. CS-no footshock) so that this association is expressed primarily when the animal is tested in the context in which extinction occurs (ABB), but not elsewhere (Bouton, 2002). Thus, ABC and AAB renewal effects occur because the response is liberated from an inhibitory process that operates in the extinction context.

Renewal has also been demonstrated in instrumental conditioning. Bouton et al. (2011) trained two groups of rats (group AAB and group ABA) to press a lever which was reinforced with a food pellet for 5 days in Context A. Extinction then took place in either Context A (group AAB) or Context B (group ABA) for 4 days, during which the lever was available but presses on it were not reinforced. Finally, rats were tested for single 10-min renewal either in the same context as initial lever press training (group ABA) or a different context (group AAB). When tested, lever pressing returned relative to animals extinguished and tested in the same context (group ABB), thus demonstrating both ABA and AAB renewal (see Figure 2A).

Like Pavlovian conditioning, renewal of instrumental responding has also been observed when the animal is tested in a third context that has not been associated with either conditioning or extinction (ABC renewal). Bouton et al. (2011) again trained rats to press a lever for food pellets in Context A and extinguished them in Context B, but this time tested them in a novel context (Context C) where rats increased their rate of responding relative to testing in context B (Bouton et al., 2011). Despite the observation of ABC renewal, however, it is notable that ABC renewal was also not numerically large (see Figure 2B).

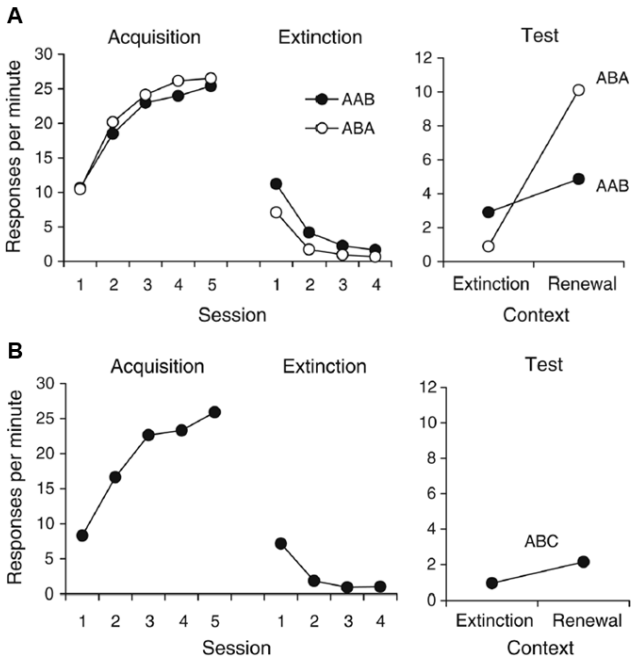

Figure 2. Results of (A) ABA, AAB, and (B) ABC renewal in instrumental conditioning. Reproduced from Bouton et al. (2011) – Figures 1 and 3. ***Reproduced with permission.***

Prior to its demonstration in instrumental conditioning studies involving lever pressing for food in Bouton's studies, renewal has been described within the drug-seeking and relapse literature where it is usually referred to as 'context-induced reinstatement' (Crombag et al., 2008), although these studies were typically not as meticulously controlled. For example,

Crombag and Shaham (2002) first demonstrated the ABA renewal of drug seeking for instrumental responding using a heroin-cocaine mixture (speedball) in rats. First, rats were trained on a fixed-ratio (FR) 1 (each lever press is reinforced) schedule of reinforcement to self-administer speedball for 10 days in Context A. Then, extinguished in a context that was different from the drug-taking context, Context B, for 20 days. Finally, rats were tested for renewal of speedball seeking in Context A, and found that rats drug seeking increased relative to animals tested in Context B. Context-induced reinstatement has also been demonstrated using drug rewards like methamphetamine, nicotine, alcohol (Diergaarde et al., 2008; Hamlin et al., 2007; Rubio et al., 2015; Zironi et al., 2006) as well as other reinforcers, including food pellets and sucrose (Hamlin et al., 2006; Nakajima et al., 2000).

It is worth noting, however, that AAB and ABC renewal are not so readily observed in studies using drug reinforcers. For instance, Crombag and Shaham (2002) did not observe AAB renewal following self-administration of a speedball, and Fuchs and colleagues (2005) demonstrated ABA but not AAB renewal of cocaine self-administration. Other studies that have failed to demonstrate AAB renewal include one by Bossert and colleagues (2004) who investigated it in heroin self-administration, and another by Diergaarde and colleagues (2008) who studied nicotine. A study by Zironi and colleagues (2006) failed to observe ABC renewal in rats trained to self-administer alcohol but did demonstrate ABC renewal effect in rats trained to self-administer sucrose.

Bouton and colleagues (2021; 2011) have built upon their 'contextual-gating' theory of renewal to explain why AAB and ABC renewal may not be as robust as ABA renewal. Specifically, whereas returning the animal to the training context (Context A) can 'gate' the retrieval of the R-O association in favour of the response-no outcome association learned in

Context B, being placed in a different context that does not evoke an expectation of reinforcement or nonreinforcement, as occurs in AAB and ABC renewal, is still somewhat ambiguous. As a result, placement in these contexts will only elicit responding that partially renews, in line with the uncertainty of whether or not to expect reinforcement (Bouton et al., 2021; Bouton et al., 2011).

1.5.2 Reinstatement

Reinstatement, like renewal, is thought to be a contextually-mediated phenomenon (Delamater, 1997). Specifically, when the outcome is delivered on test in a manner that is unsignalled – i.e., unpaired with the response – it is thought to imply that the outcome is once again available within that context, and this increases the propensity to respond. Consistent with this idea, reinstatement is reduced if the outcome is presented in a context different to that of initial training or test (Baker et al., 1991). However, an alternative account has been proposed in which the outcome itself could provide a local 'context' of reinforcement. For instance, when rats learn to press a lever for pellets they will often retrieve and consume a pellet, then shortly afterwards perform their next lever press. This is thought to lead to the formation of pellet-lever press (i.e. outcome-response (O-R)) associations in addition to the more traditionally considered lever press-pellet (i.e. R-O) associations. It has been argued that during reinstatement testing, therefore, when the pellet is later delivered in the absence of a preceding lever press, it could activate these O-R associations in such a way the outcome acts as a stimulus or context that drives the response regardless of the physical context (Bouton et al., 2021).

The context-dependence of reinstatement has been observed in both fear conditioning and appetitive conditioning (Bouton, 1984; Bouton & Bolles, 1979; Bouton & King, 1983;

Bouton & Peck, 1989) and, like renewal, has been argued to depend on the retrieval of the association between the stimulus/response and outcome over and above retrieval of the stimulus/response-no outcome association. That is, if an animal simultaneously retains both associations, the unsignalled presentation of the outcome that usually occurs the day prior to the reinstatement test is thought to signal the availability of reinforcement within that context and will thus preferentially evoke the retrieval of the R-O association. This retrieval is what is thought to underlie the return of conditioned responding on test (Bouton & Swartzentruber, 1991). If the unsignalled presentation occurs in a context other than that in which the CS-outcome association was learned, however, it is not as efficient in restoring its memory and will not evoke as much responding (as reviewed in Bouton et al., 2021).

The reinstatement effect has also been observed in instrumental conditioning following extinction of the instrumental response as early as 1980s using cocaine and heroin (de Wit & Stewart, 1981, 1983). Rats were trained to self-administer cocaine (1 mg/kg/injection) for 2- to 3-h daily sessions, and they were occasionally given noncontingent priming cocaine injection. Then rats were given daily test sessions (1 - 2h) followed by extinction in which the syringe containing cocaine solution was replaced by a syringe containing saline. Rats were given either a second saline injection or an infusion of one of the following drugs: amphetamine, apomorphine, ethanol, heroin, methohexital, morphine, 30 minutes after the extinction. All animals were tested only once with each drug. Amphetamine, apomorphine, and morphine but not ethanol, heroin, or methohexital, reinstated previously cocaine-reinforced responding. A previous paper suggests that drugs other than the previously self-administration drug increase the tendency to respond to the extent that their stimulus properties resemble those of the self-administered drug (Gerber & Stretch, 1975). Given that amphetamine and apomorphine have been shown to have stimulus properties that are highly

similar to cocaine, it was expected that both amphetamine and apomorphine would be effective in the reinstatement of previously cocaine-reinforced responding in the experiment. The authors also suggested that one reason of the reinstatement of responding is that the drug stimulus acquires "discriminative stimulus control" over responding which if a stimulus that has been present when responses are reinforced subsequently "evokes" the response (de Wit & Stewart, 1981). Two years after, they published another paper using heroin instead of cocaine. The procedure was essentially the same as that described above, except that 30 minutes after extinction rats were given a test injection of one of the following drugs: heroin, morphine, AP, amphetamine, cocaine, clonidine or another saline injection. Heroin, morphine and, to a lesser extent, amphetamine and apomorphine also reinstated heroin-reinforced responding whereas cocaine and clonidine did not. Other researchers also replicated the same result (Bossert et al., 2011; Kalivas & McFarland, 2003; McFarland & Kalivas, 2001), and others have shown outcome-specificity of reinstatement using different flavoured food pellets (Calu et al., 2013; McLaughlin & Floresco, 2007).

Figure 3. The design of the outcome-selective reinstatement.

Despite the fact that some of the studies above did demonstrate that reinstatement is an outcome-specific phenomenon, this was exclusively shown between-subjects, on a single outcome after extinction on a single R-O (or S-O) association. However, reinstatement has also been demonstrated in a two action-two outcome paradigm, where the presentation of each outcome selectively reinstates responding on the action that previously earned it. As depicted in Figure 3, Ostlund and Balline (2007) first trained rats to press a left lever for pellets and a right lever for sucrose (or vice versa, counterbalanced) then gave rats an extinction session during which neither lever earned any outcome. Immediately after extinction, rats received two unsignalled presentations of each outcome, separated by several minutes of extinction on both levers. Each unsignalled presentation produced an increase in responding – i.e. reinstatement – that was selective to the lever that had earned the outcome. That is, delivery of the sucrose outcome selectively elicited responding on the sucrose lever, and pellet delivery elicited presses on the pellet lever (Reinstated > Nonreinstated).

In this same paper, Ostlund and Balleine further demonstrated that outcome-selective reinstatement depends on O-R rather than R-O associations. They first did this through an experiment in which they shifted the current incentive value of one of the two the outcomes by feeding it to satiety to devalue it. They found that, although this reduced the overall vigor of responding, it did not alter the selectivity of reinstatement regardless of which outcome was devalued. If the outcomes had been functioning as a goal of lever pressing in this paradigm, as they would if R-O associations were being evoked, the selectivity of reinstatement for the devalued outcome should have been abolished. This is because the animals did not value the outcome and did not want it, as shown in a separate test. The fact that it did not, therefore suggested that the outcomes were not functioning as a goal of lever pressing in this paradigm.

In a final experiment, Ostlund and Balleine trained each outcome to explicitly function as both a stimulus for, and a goal of, lever pressing. To do this, they trained animals such that unsignalled deliveries of each outcome were followed by lever presses that earned an outcome. Specifically, for animals in the congruent group, the contingencies were: pellet: (left lever→pellet), sucrose: (right lever→sucrose), or vice versa, counterbalanced. When tested, therefore, this group should reinstate on the same lever regardless of whether the outcome functioned as a goal or stimulus. For the incongruent group, rats were trained so that pellet: (left lever→sucrose), sucrose: (right lever→pellet) (or vice versa, counterbalanced). In this group, if the outcome functioned as a stimulus during reinstatement, then animals should have reinstated responding on the lever it *preceded* (in the above example this would be pellet→left lever, sucrose→right lever). If it were functioning as a goal, on the other hand, this group should reinstate responding on the lever press that *earned* it during training (i.e. pellet→right lever, sucrose→left lever). When tested, the incongruent group clearly reinstated on the lever that the outcome had preceded, demonstrating that the outcome was functioning as a stimulus not a goal, providing further evidence to suggest that O-R associations rather than R-O associations underpinned the selective reinstatement effect (Ostlund & Balline, 2007).

Although the context-specificity of reinstatement in a single-action, single-outcome paradigm has been demonstrated across several studies, whether reinstatement in a two action/outcome paradigm is also context-specific is unknown. This question will form the basis of the experiments in the first empirical chapter of this thesis, Chapter 3. These experiments will be explained in more detail below, but will determine both a) whether or not responding in such a paradigm is subject to renewal and reinstatement generally (i.e., the elevation in responding that is observed after contexts are shifted and unsignalled outcomes

delivered), and b) whether any observed reinstatement is outcome-specific across changes in context.

1.5.3 Spontaneous recovery

It is worth briefly mentioning another widely known model that is not directly investigated in this thesis but is highly relevant to animal models of relapse - that of spontaneous recovery, as first described by Pavlov (1927). Spontaneous recovery is defined as the recovery of extinguished behaviour that occurs when the CS or instrumental response is tested after time has passed following the conclusion of extinction (Bouton et al., 2021). It is one of the most basic recovery-from-extinction phenomena and is so-called because the extinguished response appears to recover 'spontaneously' over time, without intervention. Like renewal and reinstatement, spontaneous recovery is extremely robust and has been observed in Pavlovian conditioning studies with drug reinforcers (LeCocq et al., 2018; Peters & De Vries, 2014) as well as in instrumental conditioning using drug self-administration (Di Ciano & Everitt, 2002; Peters et al., 2008; Rodd-Henricks et al., 2002; Shaham et al., 1997). Also, like renewal and reinstatement, spontaneous recovery has been argued to occur due to the shift in context that occurs between extinction training and test, although this time the context is a temporal rather than a physical one, or one linked to the features of the US itself (Bouton, 1988; Bouton & Swartzentruber, 1991). Spontaneous recovery therefore provides another layer of evidence that original (e.g. R-O) learning survives the extinction procedure.

1.6 Contextual control of goal-directed actions and habits

Because the experiments in the current thesis primarily involve instrumental rather than Pavlovian conditioning, I will now explore the contextual control of instrumental actions more broadly. As mentioned, instrumental actions are actions that are elicited under either habitual

or goal-directed action control, and which controller is active at a particular time can determine the context-dependency of that action. The features and definitions of goal-directed actions and habits will be explored more thoroughly in the following chapter, but here it is sufficient to note that goal-directed actions are those that are flexibly deployed with the aim of achieving a particular goal and as such rely on R-O associations. Habits are inflexibly deployed in response to stimuli present in the environment such that they rely on S-R associations.

When studying animals in the laboratory, it can be difficult to determine whether they are acting in a goal-directed or habitual manner. A rat that presses a lever and receives a pellet, for example, may have pressed the lever with the goal of getting the pellet in mind, or might have pressed the lever simply because that response has been reinforced many times previously. To operationalize goal-directed actions versus habits, therefore, Balleine and Dickinson (1998) suggested that goal-directed actions are motivated by a) the current value of the outcome and b) the contingency between the response and outcome. In order to determine whether or not an action is goal-directed, a test called outcome devaluation is often employed. Again, this procedure will be explored in detail in the next chapter but briefly, it typically involves training a rat or mouse to press a lever (or pull a chain, or some other action) for a food, which is later reduced in value, either by prefeeding it to satiety or pairing it with illness. Animals that subsequently reduce their performance of the action when tested in extinction are said to be goal-directed, because they are sensitive to both the current value of the food, and the contingency between the response and the food as recalled from training. Animals that do not reduce their responding after devaluation are thought to be habitual.

Much of the behavioural research conducted in rodents has attempted to model relapse and has shown that instrumental responses, and particularly habitual responses governed by S-R associations, paired with food or drug outcomes do indeed tend to be performed more when tested in the training context relative to other contexts. Actions that are goal-directed, on the other hand, appear to be more context-independent. This is because, as implied by the name, actions that are goal-directed are controlled by the desire for a particular goal rather than any surrounding stimuli, including context. For instance, my desire to eat ice cream over other food alternatives might transcend home, work, and other environments. In a sense then, the 'context' for this goal-directed action of ice cream-seeking is the retrieval of the mental representation of the ice cream within an appropriate motivational state (e.g. hunger, stress) rather than the physical location.

Although not involving a choice scenario *per se* Thrailkill and Bouton (2015) did demonstrate the fact that actions under habitual (S-R) control are context-dependent, whereas goal-directed (R-O) actions are not. This is particularly exemplified by their final experiment (Experiment 4) for which they trained two groups of rats to press a single lever for food pellets in Context A. The first 'goal-directed' group received a total of 90 lever press-outcome responses across three training sessions (group 1), and the second 'habitual' group received 360 such pairings over 12 training sessions (group 2). Rats were also exposed to Context B across training that differed from Context A with regards to flooring, odours, and wallpaper. For half of the animals in each group, the pellets were reduced in value using taste aversion learning. That is, over several days the pellets were paired with illness induced by lithium chloride (LiCl). Control animals also received LiCl injections/pellet presentations but in an unpaired fashion, on different days.

As shown in the bottom graph of Figure 4A, when tested in extinction (i.e. lever presses did not earn any pellets on test), undertrained animals were sensitive to devaluation because those that received paired taste aversion (90 – P) reduced their responding relative to animals that received unpaired LiCl/pellet presentations (90 – U). This result confirms that animals in this group were indeed lever-pressing in a goal-directed manner. Notably, however, the size of the devaluation effect (i.e. Unpaired > Paired) did not differ regardless of whether animals were tested in Contexts A or B. This was not the case for animals that received 360 R-O pairings, as shown in the top graph of Figure 4A. These animals were not sensitive to devaluation (Paired = Unpaired), and were thus lever pressing in a habitual manner, because responding in the paired (360 – P) and unpaired (360 – U) animals was identical. However, these animals did demonstrate a significant reduction in responding when tested in Context B relative to Context A. These findings suggest that although habits are context-dependent, goal-directed actions are not.

Several other studies have confirmed the context-dependence of habits. For instance, Thrailkill et al. (2016) demonstrated that instrumentally chained behaviours (which has been argued to be the definition of a habit; Dezfouli & Balleine, 2012), are specific to the context in which they are learned, and that a context-switch can 'renew' the instrumental chain previously learned in that context after animals learn a different chain in a different context. Moreover, Bouton et al. (2020) trained rats to press a lever for either a grain pellet or a sucrose pellet reinforcer. Then, half the rats received a single session in which the sucrose pellet was substituted to grain pellet or usual grain pellet was substituted to sucrose. The other half (control rats) continued to receive the original outcome. After a reinforcer devaluation phase, which was achieved by pairing the pellet with LiCl for half the animals (the other half received unpaired presentations), lever pressing was then tested in extinction. They

found that lever pressing was not affected by conditioning a taste aversion to the reinforcer, confirming that the rats are acting in a habitual manner. However, after an unexpected switch in reinforcer type, the lever-press response was affected by taste aversion conditioning, suggesting that it had returned to a goal-directed action. The authors argued that in this study the outcome itself could provide a local 'context', and as such provided additional evidence of the context-dependency of habits.

In addition, Steinfeld and Bouton (2020) showed that a physical context switch will cause a habitual action that was once goal-directed in another context to 'renew' and again become goal-directed. Rats were trained for lever pressing for three sessions to create a goal-directed action in Context A, then received a more extensive amount of training of the same response to create a habit in Context B. Then once again using a taste aversion conditioning, the reinforcer was devalued in both contexts, and lever pressing tested in both contexts. They observed that the response remained habitual in Context B, but was goal-directed in Context A.

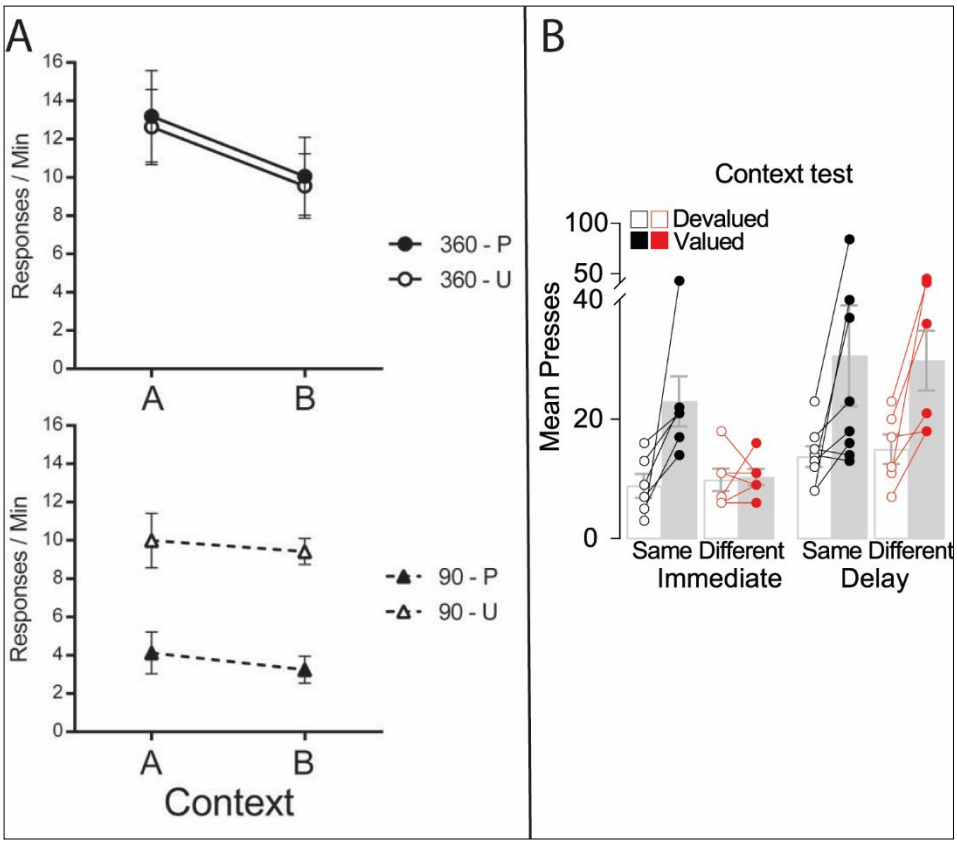

Figure 4: The relationship between goal-directed actions and their surrounding context.

A) Reproduced from Thrailkill and Bouton ([2015] – Figure 7): the top graph demonstrates that an overtrained action was not sensitive to devaluation (Paired = Unpaired) but was sensitive to context (Context A > Context B), the top graph demonstrates the opposite pattern for an undertrained action; i.e. sensitivity to devaluation (Unpaired > Paired) but not context (Context A = Context B).

B) Reproduced from Bradfield et al., ([2020] – Figure 2E). When tested immediately after initial lever press training, animals were sensitive to devaluation (Valued > Devalued) in the 'same' context they were trained in, but not the 'different' context (Valued = Devalued). When tested after a one week delay, animals were sensitive to devaluation (Valued > Devalued) regardless of test context.

Despite the general finding that goal-directed actions are context-independent, Bradfield et al. (2020) recently demonstrated that such actions can sometimes be context-dependent, but only transiently, immediately after initial learning. Like Thrailkill and Bouton (2015) above, they also employed an outcome devaluation procedure, but one that differed from theirs in

several ways. Specifically, rats were trained to press a left lever for one food outcome (sucrose or pellets) and a right lever for the other food outcome in a particular context. After reaching a criterion of 20 outcomes per lever over 1-2 days of lever press training, one of the outcomes was prefed to satiety to reduce its value relative to the other outcome. Animals were then given a choice between the two levers on test during which no food outcomes were delivered. Half of the animals were tested in the same context they had been trained to lever press in, and the other half were tested in a different context. Importantly, the different context was not novel and thus unlikely to evoke neophobia, as animals had received both reinforced and nonreinforced prior exposures to it. As shown in Figure 4B, of the animals tested immediately (i.e. the day after lever press training), those tested in the same context displayed the typical devaluation result (Valued > Devalued, shown in Figure 4B), whereas those tested in the different context were impaired (Valued = Devalued). If animals were tested after a one week delay, however, devaluation was intact (Valued > Devalued) regardless of the test context.

Superficially, the findings of Bradfield et al. (2020) might appear to contradict those of Thrailkill and Bouton (2015) who, after only 3 days of lever press training (relative to 1-2 days) found goal-directed actions to be expressed equally in different contexts. There are, of course, a number of differences in methodologies between these studies including the number of R-O contingencies trained (single lever-outcome vs. two levers-two outcomes), devaluation method (taste aversion vs. specific satiety) and the study designs (between-subjects vs. a mixed between x within-subjects design), any of which could account for the different findings. The devaluation methods used could be of particular importance, however. This is because the specific satiety procedure employed by Bradfield et al., was carried out 1 day after the final day of lever press training, and animals were tested that same day. In contrast, the taste aversion procedure employed by Thrailkill and Bouton took place over 12 days, thus

inserting a 12-day delay between the last day of lever press training and test. This delay, according to the results of Bradfield et al., would be sufficient for the goal-directed actions to become independent of their context, explaining why Thrailkill and Bouton found goal-directed actions would transfer between contexts even after such a short amount of lever press training.

It has been argued that an alteration in motivational state could in and of itself constitute a type of context (Bouton et al., 2021). If this is the case, then the experiments conducted by Bradfield et al., (2020) essentially involved two context changes: a change in the physical context, and a change in motivational state from hunger to satiety. As all animals in all groups underwent sensory specific satiety, however, including controls that demonstrated intact performance, it would appear that a shift in motivational state alone is not sufficient to disrupt goal-directed actions. Nevertheless, it could be argued that control animals tested in the 'same' context experienced only one context change (i.e., motivational state) whereas animals tested in the different context experienced two context changes, in both motivational state and physical context. Perhaps it is simply that changing two contexts produces a more dramatic effect on behaviour than only changing one.

However, the fact that all animals demonstrated intact devaluation performance, regardless of physical context, when tested after a one week delay argues against this idea. This is because it demonstrates that goal-directed actions were intact for animals that experienced a change in 3 types of context: physical context, motivational state, and temporal context, suggesting that a simple summation of context changes is not sufficient to impair such actions. Moreover, Parkes et al. (2016) demonstrated that sensory-specific satiety itself transfers freely across contexts for up to 2 hours post-devaluation. This suggests that any

motivational state that results from satiety should apply equally to the same and different contexts in my study (as testing occurred right away post-specific satiety) and thus should not have contributed to the impairment in goal-directed actions observed in the different context.

These studies suggest that goal-directed actions transfer readily between contexts approximately one week after initial learning. It is notable, however, that the R-O contingencies that goal-directed actions depend on remained stable throughout each of the experiments described so far. In experiments from other studies, where rodents have been trained to learn multiple, competing R-O contingencies, goal-directed actions have been shown to depend on their context even once again after multiple days of training or delays. For example, Trask and Bouton (2014) trained rats over 6 days to press a lever for sucrose pellets and pull a chain for grain pellets in one context (Context A), and to perform the opposite contingencies (i.e. lever press-grain, chain pull-sucrose) in Context B. One of the two outcomes was then devalued using taste aversion (i.e. paired LiCl injections and grain or sucrose pellet presentations) over 8 days. On test, Trask and Bouton found that devaluation selectively reduced the response associated with that outcome according to context. Similar findings have been reported by Killcross and colleagues (2008; 2007), who devised a series of Stroop-style tasks for rodents in which the same responses led to different outcomes in a way that was context (and stimulus)- dependent.

There is one more instance in which goal-directed actions have been rendered context-dependent, even when the underlying R-O contingencies remain stable: when those contexts have been pre-trained to be highly emotionally or motivationally salient through multiple pairings with outcomes such as alcohol (Ostlund et al., 2010), methamphetamine (Furlong et al., 2018), or junk food (Kendig et al., 2016). These studies all employed the same, or very

similar, outcome devaluation procedures to those used by Bradfield et al., (2020), but with context-outcome pairings occurring prior to lever press training. Following this training, animals were tested in either the training context, a neutral context, or in the pre-trained context. Devaluation performance was intact (Valued > Devalued) in all contexts except for that which had been previously paired with the highly salient or motivational outcome (Valued = Devalued). As performance was intact in the neutral context, in which no lever press training took place, this demonstrates once again that goal-directed actions ordinarily transfer readily from the training context to other contexts. The authors noted that there are several potential reasons for the impairment of goal-directed control in the salient context, such as arousal, sensitisation, or conditioned aversion. They argue, however, that the specific pattern of results is most consistent with the highly salient context promoting habitual over goal-directed responding, which once again reinforces the context-dependence of habits and further suggests that habits don't necessarily have to be trained in a particular way (e.g. overtrained, using interval schedules etc) in order to be induced by exposure to certain contexts.

Overall, the experiments described here reveal that the relationships between contexts, stimuli, and action control are complex and varied, even in rodents. This is evident despite the relatively small number of relevant studies, and it is likely that further studies will reveal even more complexity. As discussed above, outcome-selective reinstatement differs from both habits and goal-directed actions in the sense that it is thought to depend on O-R associations (Ostlund & Balline, 2007), and its susceptibility to changes in context is still unknown. Nevertheless, the outcome in an O-R association is thought to function as a stimulus that drives the response. This suggests that outcome-selective reinstatement relies on S-R associations in much the same way as habits do and might thus be expected to be

context-dependent in the same way. This prediction will be tested by the experiments in Chapter 3.

1.7 Neural mechanisms of relapse and reinstatement

A number of studies in both rodents and humans have begun to identify the neural pathway mediating relapse/reinstatement. Using animals, several brain areas involved include the basolateral amygdala (BLA), the orbitofrontal cortex (OFC), the dorsal hippocampus (DH), the prefrontal cortex (PFC), the dorsal striatum, and those of the mesocorticolimbic dopaminergic (DA) system particularly in the mesoaccumbens DA system consisting of cell bodies in the ventral tegmental area (VTA) with projecting axons to the nucleus accumbens (NAc) and its glutamatergic inputs (Fibiger et al., 1992; Fuchs et al., 2007; Fuchs & See, 2002; Ito et al., 2000; Kalivas & Volkow, 2005; Koob, 1992; Wang et al., 2010).

The BLA appears to mediate the context-induced reinstatement (renewal) of many rewarding substances. For instance, reversible BLA inactivation prevented context-induced reinstatement of cocaine seeking in rats (Fuchs et al., 2005) and context-induced reinstatement of alcohol seeking in rats by microinjections of an opioid receptor antagonist (Marinelli et al., 2010), suggesting that an intact BLA is necessary for the context-induced reinstatement of each. Other rat studies have confirmed that this is the case for cocaine (Hamlin et al., 2008) and alcohol (Hamlin et al., 2007; Marinelli et al., 2007), and others still have shown it to also be involved in the reinstatement of sucrose (Hamlin et al., 2006).

Because the hippocampus is known to have a central role in mentally representing and encoding context, the hippocampus has also been investigated for its role in context-induced reinstatement. One study found that reversible inactivation of DH through the infusions of tetrodotoxin were also shown to prevent the context-induced reinstatement of cocaine

seeking in rats (Fuchs et al., 2005). Likewise, (Luo et al., 2011) inactivated the DH targeting the CA3 subregion and prevented context-induced reinstatement of cocaine seeking in rats. Moreover, it was demonstrated that context-induced alcohol-seeking was accompanied by an increase in c-Fos mRNA and c-Fos protein expression, in the DH, particularly in the CA3 subregion, in rats (Dayas et al., 2007; Felipe et al., 2021; Marinelli et al., 2007). The hippocampus has also been shown to be involved in relapse behaviours in humans, for instance in studies showing that drug-associated stimuli which plays in triggering relapse following abstinence in patients, activate the hippocampus, as well as several other regions (Kilts et al., 2001; Schneider et al., 2001).

The prelimbic (PL) region of the prefrontal cortex is also implicated in reinstatement of drug seeking (Kalivas & Volkow, 2005). McFarland and Kalivas (2001) reported that inactivation of PL using local infusions of the GABA agonists baclofen/muscimol, or infusions of the dopamine receptor antagonist fluphenazine, prevented primed reinstatement (i.e. priming injection of cocaine to reinstate extinguished cocaine-seeking behaviour) of cocaine seeking in rats. Such studies are in synergy with studies conducted in humans, that have detected greater responses to salient drug stimuli in the dorsal PFC (the possible homologue of PL), dorsal striatum, thalamus, ACC, and posterior cingulate cortex (PCC) were associated with an increased risk of relapse across nicotine, cocaine, alcohol, and opioid dependence (Courtney et al., 2016).

There is also evidence of a role for the OFC in drug-related reinstatement and/or relapse (Costa et al., 2023; Schoenbaum & Shaham, 2008). In rats, inactivation of lateral, but not medial, OFC was found to decrease the context-induced reinstatement of cocaine seeking (Lasseter et al., 2009). Likewise, Fuchs and colleagues (2004) also demonstrated that the OFC

modulate cocaine-seeking, with conditioned cue-induced reinstatement controlled by lateral OFC (lOFC) and cocaine-primed reinstatement by the medial OFC (mOFC), suggesting that prolonged cell loss in OFC subregions may modulate the propensity for cocaine seeking in a subregion-specific manner in rats. In addition, exposure to cues previously associated with heroin use often provokes relapse after prolonged withdrawal periods. Fanous and colleagues (2012) have demonstrated that Fos-expressing neuronal ensembles in the OFC has been shown to mediate cue-induced heroin seeking in rats. In humans, heroin cues activate the OFC in individuals who abuse herion, and that this activation correlates with drug craving (Langleben et al., 2008; Sell et al., 2000), suggesting that OFC activation in these individuals could also be associated with relapse. In addition, Daglish et al. (2003) provided additional imaging evidence of craving in individuals with heroin addiction show that both drug and non-drug stimuli activate brain attentional and memory circuits in the anterior cingulate (ACC) and OFC.

Studies also suggest that the dorsal striatum plays a crucial role in relapse and reinstatement (Rubio et al., 2015; See et al., 2007; Yager et al., 2019). Wang and colleagues (2010) found that found that alcohol induces long-term facilitation of the activity of NR2B-containing NMDA receptors (NR2B-NMDARs) and this alcohol-mediated induction of long-term facilitation of NR2B-NMDAR activity is centred in the DMS. In the same study, they also demonstrated that NR2B-NMDARs inhibition in the DMS reduces operant self-administration of alcohol and decreases alcohol-priming-induced reinstatement of alcohol seeking in rats (Wang et al., 2010). Using an outcome-specific reinstatement paradigm, Yin and colleagues (2005) investigated the effect of inactivating pDMS on the reinstatement of lever pressing by a single presentation of the outcome. Rats received a reinstatement session where responding was extinguished on both levers (i.e. the levers were available but presses on it

were not reinforced) for the first 20 minutes. Then rats were given a single free delivery of one of the outcomes and they found that inactivation of the pDMS using muscimol infusion impaired the performance of rats during the reinstatement test.

Further evidence implicating the mesolimbic DA system in the reinforcing effects of drugs includes findings that lesions of the NAc, the VTA, and the ventral pallidum severely attenuate cocaine self-administration in rats (Hubner & Koob, 1990; Roberts & Koob, 1982; Roberts et al., 1980). There is also evidence suggesting a role for the ventral striatum in context-induced reinstatement, because reversible inactivation of either the NAc core or shell (within the ventral striatum) was found to block drug-induced reinstatement in rats (McFarland & Kalivas, 2001). Kalivas and colleagues have also demonstrated a key role for glutamate projections from the dorsal PFC to the core of the NAc in the precipitation of relapse to drug seeking in general (Kalivas, 2004; Kalivas & McFarland, 2003), which they suggested served as the final common pathway for all events that induce relapse. Glutamatergic agonists given into the NAc induce reinstatement in rats (Cornish & Kalivas, 2000), whereas antagonists (Bäckström & Hyytiä, 2007) and mGLU 2/3 receptor agonists, which reduce glutamate release, given systemically or into the NAc (Bossert et al., 2006) block cue-induced reinstatement in rats. This suggests that changes in glutamatergic functioning plays a critical role in the reinstatement of drug seeking.

Taken together, these studies in animals and humans suggest that the circuitry that underpin drug-and context-induced reinstatement is complex, and includes hippocampal, cortical, amygdala, and striatal structures.

1.8 Summary: Chapter 1

Studies in animal learning and behavioural neuroscience suggests that reward-based decision making is governed by two forms of action control: a goal-directed control which appears to be motivated by and directed toward a specific outcome and a habit learning process which is instigated by a particular stimulus or cue and are relatively inflexible in the face of context changes. The study of associative learning can be traced back at least to the early 1900s and has provided many important insights into the causes and consequences of various behaviours. However, abnormalities in behaviours have been identified as a feature of many neuropsychiatric disorders like SUD and OCD. In fact, human and animal-based studies suggest that relapse to compulsive behaviours is provoked by exposure to certain contexts. For example, an individual in recovery from alcohol use disorder, might relapse to compulsive behaviours like drinking upon visiting their favourite bar.

Reinstatement and renewal have long been measured in the laboratory as a proxy of relapse to action, but the way in which this has been achieved has been highly simplified relative to the real-world environment in which relapse occurs. This is true in multiple ways, but the way in which this is of particular interest to the current thesis is due to the absence of choice. That is, almost all prior studies of reinstatement and renewal have involved a single response for a single outcome. Reinstatement under these circumstances is shown to occur when animals have unsignalled access to the outcome in question, but increased responding also occurs when animals are exposed to certain contexts. Reinstatement itself has been argued to be a context-dependent effect. Here I ask whether the selective reinstatement that occurs when animals are given unsignalled access to outcomes and has a choice between two responses is also contextually driven, both with regards to the vigor of the response and its

selectivity to the action that previously earned the outcome. I hypothesize that selective reinstatement will be contextually driven, such that it will be reduced or abolished when tested in a context other than that which extinction occurred in. Moreover, I hypothesise that the reduction in responding will also mean that the selectivity of the response is lost.

Finally, I will investigate neural activation in several brain regions relevant to relapse using c-Fos immunohistochemistry to determine which region (mOFC, lOFC, pDMS, or DH) is most likely to underlie the contextual regulation of reinstatement in a choice-based paradigm. The results of these experiments will provide new information about how general certain principles of learning are, whether they can be extended to situations in which organisms have a choice, and will identify the putative brain region(s) involved in context-dependent selective reinstatement.

1.9 Aims and hypotheses of Chapter 3

I will employ the same outcome-selective reinstatement paradigm used by Ostlund and Balline (2007) described above, except that the physical contexts will be altered during extinction and test. Specifically, lever press training will take place in Context A for all groups, whereas extinction and testing will take place in either Context A or B, yielding four groups in total: groups AAA, ABB, ABA, and AAB.

The specific aims of the experiments presented in Chapter 3 are listed below:

- To determine whether choice-based reinstatement is context-specific
- To determine the neural correlates of contextually mediated choice-based reinstatement

I hypothesise that:

- Choice-based reinstatement will be context specific.

- Neural correlates for the contextual modulation of choice-based reinstatement will be identified in mOFC, lOFC, pDMS, and/or DH.

Intact outcome-selective reinstatement will be indicated by greater responding on the reinstated lever than the nonreinstated lever (Reinstated > Nonreinstated), and impaired selective reinstatement will be indicated by equivalent responding on both levers (Reinstated = Nonreinstated). If selective reinstatement is context-dependent, it should be intact for group AAA, for whom the context does not vary, and should be impaired, for group ABB for whom training and testing occurs in different contexts. If it is context-independent, however, it should be intact in both groups. I additionally included 'renewal' groups AAB and ABA, for whom the contexts were switched between extinction and test. Based on previous demonstrations of AAB and ABA renewal in instrumental conditioning (Bouton et al., 2011), I expected that responding would increase for these groups when placed into the test context in a manner that should interfere with the selective reinstatement effect. That is, because reinstatement depends on the reduction in responding that occurs as a result of extinction learning, then removing the influence of extinction learning via renewal should increase responding and preclude its observation. Thus, selective reinstatement was expected to be impaired for these groups. Experiments 1 and 2 were conducted identically, except that rats were tested immediately after extinction in Experiment 1, in line with the procedures employed by Ostlund and Balleine (2007), whereas rats were tested using more traditional extinction parameters (i.e. two extinction sessions and tested one day later) in Experiment 2, to determine the generality of the observed effects.

Finally, because relatively little is known about the neural mechanisms underlying outcome-selective reinstatement, I aimed to identify its potential neural correlates by examining expression of the immediate early gene and activity marker c-Fos in various brain regions. One brain region that selective reinstatement has been demonstrated to depend upon is the pDMS (Yin, Ostlund, et al., 2005) and one region it does not depend upon is the mOFC (Bradfield et al., 2015; Bradfield et al., 2018). The posterior dorsomedial striatal network is engaged in the acquisition and early performance of drug seeking and relapse after abstinence and an area important in the performance of goal-directed behaviours (Everitt & Robbins, 2013; Yin, Ostlund, et al., 2005). Likewise, OFC, an area essential in decision-making and compulsive behaviours, acts as a neural phenotypic marker for substance abuse and known to direct stimulus and context-induced drug-seeking behaviour in animal models of drug relapse (Ahmari et al., 2013; Bianchi et al., 2018; Bradfield et al., 2015; Gremel & Costa, 2013). Thus, I included both regions in my analysis with the expectation that c-Fos expression would reflect performance in the pDMS but not the mOFC. I additionally conducted exploratory analyses of c-Fos expression in the lOFC, given its central role in a varied number of reinforcement learning paradigms, as well as the DH given its central role in contextual representation and learning.

CHAPTER 2

NEUROINFLAMMATION AS A CANDIDATE MECHANISM FOR DECISION-MAKING DEFICITS IN COMPULSIVE DISORDER

2.1 What system is controlling actions? Goal-directed versus habitual action control

The dual control theory of instrumental actions was introducted in the previous chapter. Here I will explore the behavioural and brain mechanisms of goal-directed and habitual action control in more depth, as an introduction to the experiments presented in Chapter 4. This is because the experiments in Chapter 4 explore striatal neuroinflammation in a rat model as the candidate mechanism for the disruption in the balance between goal-directed actions and habits that occurs in compulsive disorders (although exactly how this occurs is the question of much debate – see section 2.4 below). Therefore, the experiments will test this more generally rather than investigating the effects on outcome-selective reinstatement specifically. This will be achieved by adding two additional behavioural assays to the experiments in this chapter: outcome devaluation to investigate goal-directed action, and specific Pavlovian instrumental transfer (sPIT) to examine cue-induced action selection.

2.2 The balance between goal-directed actions and habits

When humans and animals are given a choice between multiple actions to achieve multiple outcomes, often in a complex, messy, and ever-changing environment, their behaviour typically remains flexible and goal-directed. On the contrary, after numerous repetitions of the same action to achieve the same outcome or goal, individuals start depending on more automatic and reflexive behaviour, acting in a habitual manner. As such, adaptive everyday behaviour is modulated by the balance between the goal-directed and the habitual systems. While habitual behaviours allow for efficiency, considerably easing the cognitive load necessary for routinized actions, they are also inflexible which can at times lead to maladaptive responses. For example, an individual might habitually take a wrong turn down

the road that leads to their work when driving to the shops on the weekend or might enter their bank PIN into the microwave instead of the time.

It has been argued that goal-directed and habitual control contribute to instrumental conditioning concurrently, although the balance between each controller depends on several factors (de Wit & Dickinson, 2009). One of the best-known factors is practice or overtraining; early in training the response is thought to be goal-directed and reflects knowledge of a R-O association. Then the response is thought to gradually come under the control of a S-R association as it transitions to a habit following extended training (Adams, 1982; Dickinson, 1994; de Wit & Dickinson, 2009). Another factor thought to influence the transition from R-O to S-R control is the local correlation of responses and outcomes. Specifically, Dickinson and colleagues suggest that where there is a high correlation between, say, pressing a lever and the likelihood of receiving a grain pellet, this will strongly encode the R-O lever press-pellet association in memory, favouring goal-directed control, but where this correlation is low the R-O connection is weak such that responding is primarily elicited by the reinforcement of responding in the presence of the stimuli, leading to habitual control. This view is consistent with evidence that ratio schedules, in which animals receive more outcomes the more they press the lever such that R/O correlations are high, typically encourage goal-directed control. Interval schedules, on the other hand, are set up such that animals will only receive one outcome per set interval (e.g. every 30 seconds on an RI30 schedule), regardless of how much they lever press, such that R/O correlations and these tend to promote habitual responding (DeRusso et al., 2010; Dickinson et al., 1983; Dickinson, 1985). A final factor influencing the type of control is the performance of single versus multiple instrumental actions (Packard & Goodman, 2013). That is, instrumental behaviour appears resistant to shifting toward habitual control when multiple R-O associations are learned, possibly due to the continual

comparison of the sensory-specific characteristics of the outcomes, which keeps organisms attending to these features such that the outcome remains central to the association governing responding (i.e. the R-O association: Colwill & Rescorla, 1986; Holland, 2004; Kosaki & Dickinson, 2010).

2.3. Measuring goal-directed action in the laboratory

In Chapter 1, I noted that it is impossible to determine whether an organism is acting under goal-directed or habitual action control through simple observation of them performing an action, and I briefly described outcome devaluation as a commonly used methodology to distinguish between these controllers. Here I will describe this procedure in more detail, using the specific variation that I will employ in Chapter 4, as well as sPIT which is a measure of the selection of actions in accordance with cues. To briefly recap, Balleine and Dickinson (1998, 2002) conceived the following criteria for goal-directed actions: Such actions must rely upon 1) knowledge of the contingency between the response and their outcomes (R-O), and 2) the current motivational value of the outcome. Instrumental actions that do not fulfil these two criteria are said to be habitual.

The outcome devaluation paradigm is shown in Figure 5. This procedure is widely considered as the gold standard test of goal-directed action because animals that demonstrate intact devaluation exhibit the ability to respond in accordance with each of the two criteria of goal-directed action. Although there are a variety of ways in which outcome devaluation can be performed, I will here describe a commonly used two action, two outcome procedure that will be the procedure I employ in the experiments in Chapter 4 (Experiments 3 and 5). Animals are typically mildly food deprived prior to the start of the procedure so that they are motivated to press the lever for a food reward.

Figure 5. Schematic representation for outcome devaluation procedure. Stage 1: Lever Press training (left panel), rats learn to press two levers for two unique outcomes (counterbalanced, but shown here as left lever - pellet, right lever - sucrose). Rats are then pre-fed to satiety on one of these outcomes (here pellets) to reduce its value (Stage 2, middle panel) and then given a choice between levers in the absence of food outcomes on Stage 3: test (right panel). Typically, rats will respond selectively on the still valued lever (here the right lever, associated with the still-valued sucrose) and avoid the devalued lever (here the left lever associated with the devalued pellets).

As shown in Figure 5 (left) animals are first trained to perform two different actions (right and left lever press), for two different outcomes (sucrose solution and pellets). Following several days of training (often one lever press training session per day for 8 days), the animal is then either fed to satiety on one of the outcomes, shown as pellets in the middle panel of Figure 5, which reduces the value of that outcome relative to the other, still-valued outcome (Balleine & Dickinson, 1998). An alternate method that is often used to devalue the outcome is pairing it with an aversive event, for instance by injecting lithium chloride (LiCl) after consumption, which induces nausea and causes the animal to feel ill (Adams, 1982). This devaluation method is used more frequently in studies of habits as it does not involve a motivational shift (e.g., from hungry to sated) which, as discussed in Chapter 1 as forming part of a context shift, can promote goal-directed control. Following devaluation, the effects of the

manipulation are tested by assessing how readily rats will press each lever in the absence of the outcomes themselves (i.e., in extinction). Animals that are goal-directed will respond selectively on the lever that was associated with the valued outcome during training and will avoid the lever associated with the devalued outcome. This is because responding in this manner (Valued > Devalued) demonstrates that animals are acting in accordance with the current value of the outcome and are recalling from training which lever earned which outcome (i.e., the R-O contingency) from training – thus fulfilling the two criteria of goal-directed actions (Balleine & Dickinson, 1998).

The other behavioural assay I will use in Chapter 4 to investigate action selection is known as sPIT, this time as it is influenced by the presence of food-predicting cues.

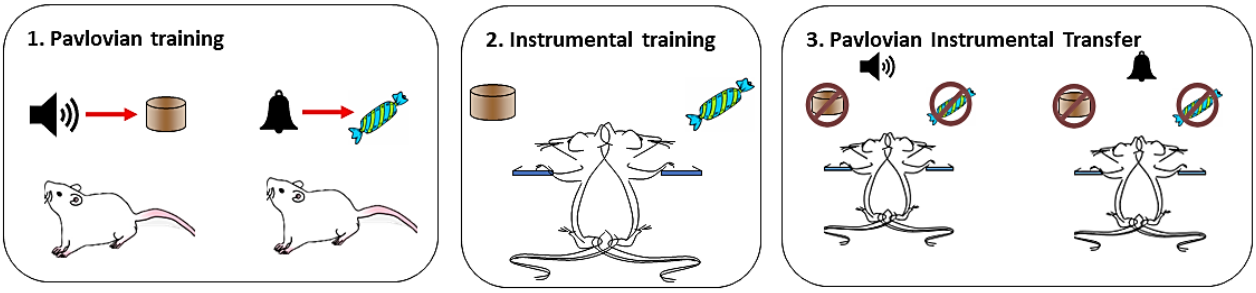

Figure 6. Schematic representation for specific Pavlovian instrumental transfer design. Stage 1: Pavlovian training (left panel), rats are presented with two auditory stimuli (a white noise and a tone) that predict the delivery of unique food rewards (pellets and sucrose, counterbalanced but here shown as white noise-pellets, tone-sucrose). Stage 2: Instrumental training (middle panel), rats are trained to press a left and right lever to receive the same food rewards (counterbalanced, but here shown as left lever- pellet, right lever- sucrose). Stage 3: 'Pavlovian Instrumental transfer' test, stimuli and levers are presented concurrently for the first time. Food outcomes are not presented. Typically, stimuli should elicit responding on the lever associated with the "same" outcome. According to the contingencies presented here, white noise presentations should elicit left lever responses, as both are associated with pellets, and tone presentations should elicit right lever responses, as both are associated with sucrose.

The sPIT procedure is shown in Figure 6. In the first Pavlovian conditioning stage, animals are typically presented with two distinct stimuli paired with two distinct food outcomes. In the left panel of Figure 6 these are represented as a white noise and a tone paired with pellets and sucrose to produce two unique S-O pairings: white noise-pellets and tone-sucrose, or vice versa, counterbalanced. This stage is followed by an instrumental conditioning phase in which the stimuli are not presented, but the same food outcomes could now be uniquely earned by two responses (e.g., left lever - pellets and right lever - sucrose, or vice versa, counterbalanced). On test, rats are once again given a choice between levers without the outcomes, and when each stimulus is presented it should elicit a response on the lever associated with the same outcome as that stimulus. That is, in Figure 6 the white noise should elicit presses on the left lever as both are associated with pellets, and the tone should elicit right lever presses as both are associated with sucrose.

I will also employ outcome-selective reinstatement in the experiments in Chapter 4, which I have already explained at length in Chapter 1 and shown in Figure 3. This time, however, contexts will be kept consistent as the manipulation in question in a brain manipulation (striatal neuroinflammation) rather than a behavioural manipulation.

Aside from the behavioural assays mentioned above, I will also employ a progressive ratio design in Chapter 4. A progressive ratio schedule of reinforcement is defined by an increasing response requirement for reinforcer delivery over successive sessions (DeLeon et al., 1997). The progressive ratio schedule was first introduced by Hodos (1961) where rats learned to press the lever for milk rewards. It is a common test of motivation in rodents and this task probes the ability of an organism to maintain instrumental responding (such as lever pressing in this thesis) under increasing work demands, for instance a single lever press might initially

earn a reward, then it will take 5 presses, then 10, and so on. The amount of effort an animal is willing to expend in pursuit of appetitive reinforcement, expressed as the maximum number of responses to obtain a single reward, is referred to as the 'breakpoint' (Stewart, 1975). This suggests an analogy in addiction studies in animals and humans which is marked by both increasing intakes of the drug and increasing motivation to obtain the drug (craving). Such schedules have been used to study effort exertion across a number of species including rats (Hailwood et al., 2018), mice (Poyraz et al., 2016), nonhuman primates (Griffiths et al., 1979), and humans (Roane et al., 2001).

Examining and understanding the underlying mechanisms involved in these two different action control systems is essential because it provides valuable insights into the neurobiology and/or changes in their balance associated with neuropsychological disorders, such as SUD and OCD. Using several behavioural tests will allow us to determine if neuroinflammation in pDMS would likely affect multiple types of action control, or whether any alterations are specific to a particular kind of action control.

2.4 Is compulsion goal-directed or habitual?

As explained in the introductory sections of the previous and current chapters, although it is not in dispute that compulsive disorders disrupt the balance between goal-directed and habitual action control, the precise way in which this occurs is the centre of much debate.

Disorders of compulsion such as drug addiction (Everitt & Robbins, 2016) and OCD (Gillan et al., 2011; Gillan & Robbins, 2014) have been proposed to result from an overreliance on habits (Robbins & Costa, 2017) associated with behavioural inflexibility in tandem with the underutilization of goal-directed behaviour (Balleine et al., 2015). For instance, habits are governed by associations that do not include a representation of the outcome, S-R

associations, and some have seen a parallel in people who suffer from SUD, for example, who often persist on seeking and taking drugs despite the clinically significant distress to oneself and others and the fact that their behaviours lead to harmful consequences (Hogarth et al., 2013).

Several studies have provided empirical evidence for such a theory. Ersche et al. (2016) trained participants with cocaine dependence to perform an action such as earning points toward a monetary reward or avoiding an unpleasant electrical shock. They then reduced the value of previously reinforcing outcomes by either discontinuing point allocation for certain outcomes in the appetitive task, or physically disconnecting participants from the electrical stimulator in the avoidance task. They found that healthy controls ceased performing the actions following devaluation, but that participants with cocaine dependence continued to perform them, showing an insensitivity to outcome devaluation that is indicative of habitual responding. Likewise, another study investigated the effects of alcohol on devaluation sensitivity for food reward (Hogarth et al., 2012). They recruited healthy participants that were randomly assigned to receive alcohol or placebo and were trained for instrumental responses for chocolate and water points. One of the outcomes were then devalued and they were given choice between the two responses in extinction. Although not suffering from alcohol use disorder, in this study the acute alcohol exposure did cause insensitivity to outcome devaluation suggesting it had caused a bias for habit learning. In rats, using a seeking-taking chained schedule of intravenous cocaine self-administration and outcome devaluation methods, Zapata et al. (2010) found that cocaine-seeking response was decreased following extinction of the taking response after limited but not extended training, hence providing direct evidence that cocaine seeking becomes habitual after a prolonged cocaine taking history.

On the other hand, there is also an argument that compulsive behaviour is driven by an excessive goal-directed control. For example, patients with OCD perform compulsive behaviour as an avoidance action to relieve the anxiety that arises from obsessive thoughts (Pauls et al., 2014) which implies that compulsive behaviour is conducted in a goal-directed manner (e.g., washing hands to relieve the fear of contamination). In line with this, Piantadosi and Ahmari (2015) have argued that compulsions are driven by an overwhelming 'urge' to act, which could still be indicative of a goal-directed behaviour. Another study conducted in rats also used an outcome devaluation procedure to determine whether behaviour is goal-directed. Olmstead and colleagues (2001) trained rats to respond on the seeking-taking chained schedule for a cocaine infusion. The taking response was then extinguished in the absence of the opportunity to perform the seeking response. This manipulation immediately reduced performance of the seeking response tested in extinction (in the absence of the taking lever), suggesting the cocaine seeking response was controlled by R-O association representing the contingency between seeking responses and the opportunity to perform an effective drug-taking response, rather than an S–R association.

It is worth noting that compulsivity may not be exclusively one or the other. That is, although compulsive behaviour may be explained by an imbalance of R-O (goal-directed actions) vs. S-R (habits) action control, this might manifest in some individuals as excessive goal-directed control and in others as excessive habitual control. It is further possible that both dysfunctions could be present within the same individual at different times. Regardless, the behavioural inflexibility that goes along with the aberrant goal-directed and/or habit formation can be debilitating for patients with compulsive disorder that are heavily affected by these cognitive deficits, and certainly requires urgent attention.

2.5 Neural mechanisms of goal-directed control

A large body of data has made significant progress in delineating the neural circuitry of goal-directed action, which is shown in Figure 7. In animals, many important studies have demonstrated that intact goal-directed action relies on the BLA and the DMS, with roles for prelimbic area (PL) and mediodorsal thalamus (MD) only during acquisition, as well as roles for the mOFC and NAc core only during performance. An intact DH is also necessary for goal-directed action, but only during and shortly after the initial learning of R-O associations. I will explain the findings that underlies each of these observations in more detail below.

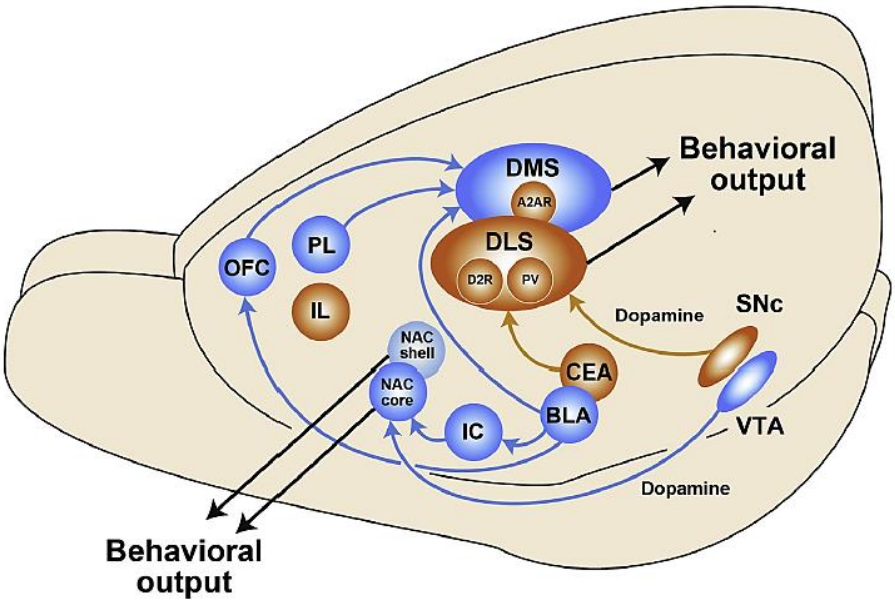

Figure 7. Brain circuitry thought to underlie habitual and goal-directed behaviour, as measured in animal models using outcome devaluation paradigm. The structures in orange play a role in habitual responding, whereas the structures in blue contribute to goal-directed action. Image adapted from Simmler and Ozawa (2019). ***Reproduced with permission.***

The fact that goal-directed actions rely on an intact BLA was demonstrated by Balleine and colleagues (2003), who showed that excitotoxic lesions of the BLA disrupted outcome devaluation performance in a procedure similar to that described above. Specifically, they found that sham animals selected the valued lever on test more often than the devalued lever (Valued > Devalued), animals with BLA lesions did not (Valued = Devalued). Later, the precise role of the BLA in goal-directed action was narrowed down to the encoding of a reduction in incentive value that occurs during devaluation of the outcome itself, because infusion of the N-methyl-D-aspartate (NMDA) receptor antagonist ifenprodil into the BLA prior to reward devaluation (i.e. sensory-specific satiety), but not prior to devaluation testing, impaired outcome devaluation (Parkes & Balleine, 2013). Using the sPIT design explained in Figure 6, Corbit and Balleine (2005) showed that lesions of the BLA impaired the ability of animals to show selective responding, that is, animals did not respond differentially during presentation of the same and different stimuli, thus disrupted sPIT.

Several other studies that have employed the same outcome devaluation procedure shown in Figure 5 have shown the critical importance of the DMS for goal-directed action control. First, Yin, Ostlund, et al. (2005) showed that lesions of the posterior but not the anterior DMS abolished devaluation performance. That is, intact pDMS functioning would drive lever selection to the lever that achieves the valued outcome, while inactivated pDMS was found to distribute responding to both valued and devalued levers acting in a habitual manner (i.e. Devalued = Valued). Moreover, they demonstrated that the DMS is critical for both the learning and the performance of goal-directed actions because both pre-training and post-training (pre-test) lesions or inactivations of this structure using infusions of the $GABA_A$ agonist muscimol or of the NMDA-antagonist AP5 of the posterior DMS (pDMS) impaired outcome devaluation performance expression (Yin, Knowlton, et al., 2005; Yin, Ostlund, et al.,

2005). In fact, the pDMS is the only brain structure that has, to date, been demonstrated to be critically involved in both the learning and performance of goal-directed actions and it is for this reason that this structure has been purported to be the neural locus of goal-directed action. The striatum is ideally placed for such a function, as it receives direct inputs from other structures critical to goal-directed action, including the PL and BLA – and the disconnection of these structures from the pDMS also disrupts goal-directed action. Further research has indicated that it achieves this role by acting as a critical interface for integration of information processing from other neural regions such as prefrontal and orbital regions (Voorn et al., 2004) to coordinate motor output (Balleine et al., 2007; Graybiel, 2005). Moreover, the pDMS works in concert with the BLA to produce goal-directed actions, and this has been shown directly by a study that found devaluation performance to be abolished following the pharmacological disconnection between the BLA and the DMS during initial training and immediately before devaluation testing (Corbit et al., 2013). As such, the pDMS is perfectly placed to integrate higher-order information from cortical structures with emotional information from the BLA (among other things) and to use this information to orchestrate the selection of a specific action or sequence of actions. This is a key reason why the pDMS will be the target structure in the current thesis. In the case of sPIT, for control animals with an intact pDMS, presentation of a stimulus during the sPIT test drove responding on the lever that had been associated with the same food outcome, despite the stimulus and lever never previously having been experienced together. Animals without a functioning pDMS demonstrated impaired performance on this task and pressed both levers equally (Corbit & Janak, 2010). This implies that a functioning pDMS is critical for the ability to accurately select an action in a stimulus-driven manner.

The respective roles of the PL and MD in goal-directed learning but not performance was shown in studies showing that pretraining lesions of each structure abolished sensitivity to outcome devaluation, but animals were spared this deficit when administered post training (pre-test) PL/MD lesions (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Corbit et al., 2003; Coutureau et al., 2009; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009). Again, the connection between these two structures was demonstrated to be important for goal-directed learning also, because excitotoxic lesions of each structure in contralateral hemispheres, paired with an electrolytic lesion of the corpus callosum to prevent these structures communicating across the two hemispheres, also prevented outcome devaluation learning (Bradfield et al., 2013). Projections from PL to pDMS have also been shown to be important for goal directed learning using a similar procedure (Hart et al., 2018).

Another brain region that is important for goal-directed action control is the OFC. Although excitotoxic lesions and chemogenetic inactivations of the lOFC have been shown to leave outcome devaluation intact (Lichtenberg et al., 2021; Ostlund & Balleine, 2007), implying no role for this subregion in goal-directed actions, excitotoxic lesions of the mOFC impaired devaluation (Bradfield et al., 2015; Bradfield et al., 2018) and chemogenetic activation of this region facilitated it (Gourley et al., 2016). Moreover, post-training pre-test chemogenetic inactivations of the mOFC were shown to impair devaluation (Bradfield et al., 2018), suggesting a specific role for this region in the performance rather than the learning of goal-directed actions.

NAc has also been shown to be important for the performance of goal-directed actions. In fact, Corbit et al. (2001) demonstrated that, in rats, excitotoxic lesions of the NAc core impaired the expression of outcome devaluation but not another behavioural measure of

goal-directed action – contingency degradation. Specifically, during contingency degradation the two levers continued to earn their respective outcomes (e.g., left lever-pellets, right lever-sucrose) but one of these outcomes was also delivered freely – i.e., unearned by any lever press. This served to degrade the contingency between the lever and that outcome. For example, if pellets were delivered freely, the rat no longer needed to press the left lever for pellets and the left lever-pellet contingency was degraded. By contrast, animals still needed to press the right lever for sucrose, such that the right lever-sucrose contingency remained nondegraded. Despite their impaired devaluation performance, animals with NAc core lesions were able to successfully learn to stop pressing the degraded lever whilst still pressing the nondegraded lever, suggesting that they could learn the R-O contingencies that underscores goal-directed action control. The impairment in devaluation performance suggests that they simply couldn't perform goal-directed actions. In a separate study, (Corbit & Balleine, 2011) found that devaluation was left intact by lesions of the NAc shell, but that sPIT was disrupted by lesions of the NAc shell but not by lesions of the NAc core. Together, these results suggest that an intact NAC core is necessary for the performance but not learning of goal-directed actions, and that NAC shell is not necessary for goal-directed actions but is necessary for cue-guided action control.

2.6 Neural mechanisms of habits

In contrast to the regions referred to above, the infralimbic cortex (IL), central nucleus of the amygdala (CEA), and dorsolateral striatum (DLS), have all been implicated in the development of habitual responding. This is based on studies showing that the temporary inactivation of IL restored sensitivity to outcome devaluation in a study in which control animals with an intact IL were insensitive to it, demonstrating that impaired IL function caused

animals to switch from habitual back to goal-directed action (Coutureau & Killcross, 2003; Haddon & Killcross, 2011; Killcross & Coutureau, 2003). Bilateral lesions of the anterior CEA, but not the posterior CEA, also caused overtrained rats to revert to goal-directed action whereas animals with sham lesions performed habitually (Lingawi & Balleine, 2012). Likewise, studies show that excitotoxic lesioning of the DLS in mice and rats shifts habitual reward seeking into goal-directed actions and does not affect goal-directed behaviour (Gremel & Costa, 2013; Yin et al., 2004).

2.7 Disruption of striatal function in individuals with compulsive disorders

As stated above, in rats at least, the pDMS has been identified as the neuroanatomical locus of goal-directed action control, as it is the only brain structure that appears to be critical for both the learning and the performance of goal-directed actions. This is the first reason why the current thesis will focus on the pDMS as the candidate structure in which dysregulation occurs to produce the observed disruption between goal-directed action control and habits in individuals with compulsive disorders.

The second reason for the focus on this structure is because it is translationally relevant: aberrant striatal activity has been consistently identified in the brains of individuals with neurologic and neuropsychiatric disorders, including compulsive disorders, for which goal-directed action control is impaired (Cox & Witten, 2019; Friedman et al., 2017). One neuroimaging study revealed higher metabolic activity in the striatum of OCD patients compared to healthy controls, and metabolic normalization following a successful behavioural or SSRI treatment (Baxter et al., 1992; Saxena et al., 1999). Similar studies have also found increased the activity and metabolism in both the caudate and the putamen in OCD patients compared to controls during a resting state (Brennan et al., 2013; Saxena &

Rauch, 2022; Menzies et al., 2008), and a separate study revealed aberrant hyperactivity in cortico-caudate pathway in individuals with OCD relative to healthy controls (Apergis-Schoute et al., 2018). Caudate abnormalities are also found in the brains of individuals with disorders other than OCD. For example, Cai et al. (2016) detected an increased volume in caudate of individuals with internet gaming disorder. Furthermore, participants who had developed alcohol dependence or heavy drinker participants showed higher alcohol cue-induced activation of the dorsal striatum (Vollstädt-Klein et al., 2010). Moreover, neuroimaging studies reveal planning and cognitive impairments in patients with OCD and SUD, which were associated with activity in the striatum(for review Everitt & Robbins, 2013; Menzies et al., 2008). Together, these studies suggest that disrupted caudate activity could be the cause of disrupted goal-directed action in compulsive individuals.

Studies of healthy and disordered individuals also reveal why disruptions to striatal activity (and caudate activity in particular) might lead them to dysregulate their action selection. A study published by van Timmeren et al. (2020) found that abstinent individuals with AUD showed intact PIT and outcome devaluation (indicating that abstinence might reinstate these effects) which were mediated by activity in the caudate. Another study showed that dorsal striatal activity in humans has linked with the degree of motivation to work for a particular reward (Koepp et al., 1998; Volkow et al., 2002; Zald et al., 2004). Specifically, positron emission tomography (PET) studies showed elevation in dopamine release in the dorsal striatum (as measured by displacement of endogenous dopamine by radioligands) when participants were presented with potential rewards, such as the opportunity to gain money (Koepp et al., 1998; Zald et al., 2004) or when presented with food stimuli while in a state of hunger (Volkow et al., 2002). Should these signals become dysfunctional, it is easy to imagine that it could lead to elevated motivation to seek particular rewards (e.g. drugs) on the one

hand, and decreased motivation to seek out 'healthier' rewards (e.g. keeping a job) on the other.

2.8 The role of the striatum in compulsive-like actions in animal studies

In addition to the central role for caudate/DMS in goal-directed action, several animal studies have revealed other aspects of DMS function that could relate to its dysregulation in compulsive and compulsive-like actions. For example, neuronal activity in the DMS has been shown to reflect aspects of choice performance not necessarily considered in devaluation studies, such as timing and contextual factors (Emmons et al., 2017; Parker et al., 2016; Stalnaker et al., 2016). Additionally, just as it is in humans, dorsal striatal activity in animals has been linked with the degree of motivation to work for a particular reward (Palmiter, 2008), the ability to perform previously learned action sequences (McDonald & White, 1993; Miyachi et al., 1997), task switching (Baunez & Robbins, 1999; Quinlan et al., 2008), and reversal learning (Clarke et al., 2008).

Other animal studies have produced more direct evidence of dysregulation in the striatum being linked to compulsive like actions. Wyvell and Berridge (2000) found that amphetamine microinjection into the NAc shell heightened the ability of a Pavlovian reward cue to initiate enhanced instrumental performance for sucrose reward. Using an animal model *Sapap3*-knock out (KO) mouse, who lack the postsynaptic density protein SAPAP3, Welch et al. (2007) expressed the behavioural phenotype of anxiety and compulsive grooming, leading to facial hair loss and skin lesions. *Sapap3*-KO mice also show impairments in adapting to a new contingency in Pavlovian (van den Boom et al., 2019) and in instrumental (Benzina et.al., 2019; Manning et al., 2019) paradigms. SAPAP3 protein is found at excitatory synapses, but not inhibitory, and is highly enriched in striatum relative to other SAPAP gene family members

(Kim & Sheng, 2004; Welch et al., 2007). Moreover, OCD-like behaviour was found to be improved by the intra-striatal injection of lentiviruses expressing SAPAP3, suggesting that it was altered functioning of this protein in the striatum in particular that contributed to repetitive OCD-like behaviours (Welch et al., 2007). A study by Burguière et al. (2013) further revealed the potential mechanisms of dysfunction in the *Sapap3-KO* model, who they found to express hyperactivity in the DMS, whereas Ade et al. (2016) discovered that they express an imbalance between direct and indirect pathway neuron activity in the DLS which could have resulted from abnormal cortical top-down control, mediated through changes at corticostriatal synapses. Together, these results indicate that defects in excitatory transmission at cortico-striatal synapses may underlie some aspects of OCD.

As reviewed in section 2.5, animal models of behaviour reveal a key role for the intact pDMS in goal-directed action control, and as reviewed in section 2.4, the balance between goal-directed and habitual actions becomes disrupted in individuals with compulsions. The studies reviewed in the previous and current section further demonstrate that abnormal activity in this part of the brain is observed in individuals who display compulsive or compulsive-like actions. This suggests, therefore, that dysregulation in the pDMS may be causing the behavioural deficits, although the evidence for this conclusion from human studies is purely correlative, and this this has yet to be studied directly in animals.

2.9 Neurotransmitters involved in the neuropathophysiology of compulsive disorders

Neurotransmitters are electrochemical signalling molecules that allow neurons to communicate with each other throughout the body, and they play important functions such as human development, synaptic plasticity, and ultimately shape network-wide communication (Hansen et al., 2022; Niyonambaza et al., 2019). Neuroscience research on

compulsive disorders including SUD and OCD has shown that numerous different brain chemicals, known as neurotransmitters, could be implicated in SUD and OCD. Other studies have shown that the balance between goal-directed and habitual strategies is mediated by various neurotransmitter including glutamate, dopamine, and serotonin (Giangrasso et al., 2023; Voon et al., 2020; Wickens et al., 2007; Worbe et al., 2016).

Studies of individuals with SUD and OCD, and of preclinical models of OCD, have discovered abnormal levels of glutamate, the major excitatory neurotransmitter in the central nervous system, in the cortico-striato-thalamo-cortical (CSTC) circuits suggesting that this could contribute to its symptoms (Karthik et al., 2020; O'Brien et al., 2018; Olive et al., 2012; Pittenger et al., 2011). Supporting this notion, elevated striatal GLU levels are observed in people with OCD (Rosenberg et al., 2000). Dopaminergic system alteration has also been gradually thought to play a role in the development of both SUD and OCD (Dong et al., 2020; Dreher et al., 2009; Johnson & Kenny, 2010; Koo et al., 2010); dopamine is a type of monoamine neurotransmitter and is an important brain chemical that affects both motor functions and motivational behaviours and regulates cognitive abilities, including feeling, thinking, understanding, and reasoning in physiological processes (Pine et al., 2010). Another neurotransmitter heavily implicated in compulsive disorders is serotonin. Serotonin helps regulate many body and brain functions, including mood, bowel movements, and sleep, among others, and changes in the serotonergic system may play a pivotal role in the remediation of SUD/OCD symptoms (Hatakama et al., 2022; Muller & Homberg, 2015; Nikolaus et al., 2016; Ketcherside et al., 2013; Perani et al., 2008; Schmidt et al., 1997) The role of serotonin in such disorders is also supported by the fact that selective serotonin reuptake inhibitors are currently the frontline treatment for OCD and certain types of SUD (Dell'Osso et al., 2005; Lochner & Stein, 2014; Fluyau et al., 2022; Pittenger & Bloch, 2014),

although it has been suggested that the mechanism of action for these drugs is not serotonin itself (Moncrieff et al., 2023).

Despite the extensive research done in these neurotransmitter systems that current pharmacological treatments have been targeting, these pharmacological treatments are far from perfect. In fact, treatment response is highly variable, where 40–60% of patients exhibiting a lack of significant response to serotonin reuptake inhibitors (Bloch et al., 2006; Erzegovesi et al., 2001) and 45-89% of patients treated with serotonin reuptake inhibitors have a reoccurrence of OCD symptoms after medication discontinuation (Pato et al., 1988; Simpson et al., 2004). This suggests the existence of an underlying pathological process that is unresolved by current medications and highlights the need to clearly identify the neurobiological causes of compulsive disorders to enable the development of more effective treatments, which is the second main aim of the current thesis.

2.10 A glial perspective - Neuroinflammation

Much recent research aimed at understanding the neuropathophysiology of various neurodegenerative and neuropsychiatric disorders has focused on neuroinflammation as a potential mechanism of the underlying brain dysfunction. With regards to peripheral inflammation, the first things that might come to mind tends to be swelling, redness, and/or pain. In addition to these observable changes, however, inflammation is governed by a highly complex network of cellular and molecular mechanisms. Neuroinflammation occurs in the brain and, due to the lack of pain receptors within the brain, is not associated with pain but rather is thought to cause abnormalities in behaviour. It is also a complex endogenous process that is a vital host response to the loss of cellular and tissue homeostasis.

Although originally targeted as a major mechanism associated with multiple sclerosis (MS), as our knowledge of the brain's immune system has become more detailed, research on neuroinflammation has also began to pervade the study of many other diseases and disorders. For instance, it has become a common denominator and a possible mechanism of cognitive dysfunction and neurodegeneration in complex diseases like Alzheimer's disease (AD) (Agostinho et al., 2010), Parkinson's disease (PD) (Hirsch & Hunot, 2009), as well as autism spectrum disorder (ASD) (Onore et al., 2012), schizophrenia (Murphy et al., 2021), bipolar disorder (Theoharides et al., 2011), major depressive disorder (MDD) (Woelfer et al., 2019), SUD (Namba et al., 2021), and OCD(Gerentes et al., 2019).

Together, these diseases and disorders are all associated with a range of cognitive impairments, with each affecting the individual's ability to exert cognitive control of their behaviour and make effective choices. For instance, individuals are thought to progress from a diagnosis of mild cognitive impairment to Alzheimer's disease when they are unable to perform certain tasks described on the "Activities of Daily Living" Scale (Edemekong et al., 2023; Potashman et al., 2023; Reisberg et al., 2001), which involves tasks such as cooking, cleaning, grooming, and navigating to desired locations. For individuals with SUD, the lack of cognitive control manifests as they are unable to flexibly switch from, or stop performing an action like seeking drugs or taking drugs, even when that action is leading to adverse consequences. Likewise in OCD, compulsively performing an action such as washing hands or checking a door lock can take many hours out of an individual's day, seriously impeding their ability to participate in other aspects of life, yet they cannot stop. Nevertheless, despite the commonality of neuroinflammation among these disorders and the prevalence of deficits in cognitive control for each of them, no causal link between neuroinflammation and impaired cognitive control has ever been empirically demonstrated.

2.11 The role of glia in neuroinflammation

Neuroinflammation is a part of the immune response in the central nervous system (CNS) and it is a necessary process for the normal healthy functioning of the brain. An immune response might occur if there is an infection, injury, stress, or some other factor and is carried out by three major types of glial cells in the CNS namely astrocytes, microglia, and oligodendrocytes which each perform distinct functions (Purves et al., 2001). As reviewed in more detail below, if, for example, a foreign substance is detected in the brain, for example, microglia and astrocytes might change from their resting/homestatic state to an active state, in which their morphology and function is altered. In doing so, these cells can then engulf the foreign substance, as well as secrete pro-inflammatory cytokines (or anti-inflammatory cytokines if the goal is to reign in an inflammatory response) to control the activity of other glial cells (Leng & Edison, 2021). Although neuroinflammation is usually intended to be protective in the CNS, it can become a problem when the triggered neuroinflammation is unregulated and starts persisting chronically.

Rudolf Virchow coined the term glia in 1856 in his book “Cellular Pathology” (Jacobson, 1991) to describe the whole non-neuronal compartment of the CNS (Prinz et al., 2019). At that time, these unusual cells were given the name “Nervenkitt” in German which means nerve glue. The name “glial cell” was derived from the ancient Greek word “glía” which means “glue” in English. Although the glial elements were documented first in 1838 by Robert Remak where he described a sheath around single nerve fibres (Remak, 1838) and in 1851 by Heinrich Müller where he discovered radial fibres in the retina (which later became known as Müller glial cells), the first in-depth examination of neuroglia was conducted by Camillo Golgi in early 1870s (Golgi, 1873, 1903).

In 1893, Michael von Lenhossek then introduced the term 'astrocyte' in describing the star-shaped cells in the CNS. Santiago Ramón y Cajal' initial observations of the cells in 1913 that glia might be insulators for the electrical activity of neurons using a gold chloride-sublimate staining technique that he developed (Parpura & Verkhratsky, 2012). In 1918, Cajal's student Pío del Río-Hortega identified two other principal classes of glial cells, namely microglia and oligodendrocytes, using the metallic impregnation technique that he developed, suggesting a potential phagocytic function and responsible for myelination in the CNS (Pérez-Cerdá et al., 2015). From these observations, early descriptions of these cells described them as having a purely passive support/structural role to the neurons' active role in the brain (Pasik and Pasik, 2004). However, with the advent of technology and advanced neuroscience techniques/tools, scientists have found that the role of these glial cells is much more extensive and complex (Araque et al., 2001).

2.11.1 Microglia

Microglia are commonly referred to as the brain's resident tissue macrophages, as they are specialized cells with powerful influence on homeostasis and tissue repair (Li & Barres, 2018; Michell-Robinson et al., 2015). As the brain's macrophages, microglia act as a first line of defence to infectious agents and injury. Specifically, in non-inflammatory conditions, microglial cells are said to be in a 'resting state' with ramified morphological state with processes constantly surveying the surrounding environment for pathological stimuli such as stress, infection, injury, or diseases. As shown in Figure 8, microglia become activated in response to pathological stimuli. What this means is that they transform from a ramified into an amoeboid state, with a swollen cell body with retracted processes, as well as proliferating and migrating to the site of injury (Weitz and Town, 2012). Upon activation, they can destroy

invading pathogens, remove debris, and promote tissue repair by secreting growth factors, thus protecting the brain from possible damage and enable the return to tissue integrity (Kreutzberg, 1995).

Although microglial cells are the primary mediators of an immune response in the CNS, they require an initial signal to respond in the form of cytokine signalling after an injury. Once there is an injury or tissue damage, cytokines release gets stimulated which increases the expression of mRNA and protein expression of several inflammatory cytokines/markers, which then attract microglia to the site of injury and cause a response (Benveniste, 1997; Chen et al., 2012; Stence et al., 2001). However, accumulating evidence now suggests that activated microglial responses can be detrimental as well as beneficial after CNS injury. Once activated, microglia are thought to release a variety of inflammatory and cytotoxic mediators contributing to cell damage and cell death leading to exacerbated damage (Kraft & Harry, 2011; Lai & Todd, 2006; Wood, 1995). Recent studies showed that microglia can either be classified as the M1 subtype, which are typically considered pro-inflammatory microglia, or the M2 subtype, which are typically considered anti-inflammatory microglia (Guo et al., 2022). M1 phenotype produces high levels of pro-inflammatory cytokines and oxidative metabolites such as IL-12, TNF-α, IL-6, IL-1β, and nitric oxide (NO) that can effectively promote persistent tissue inflammation while M2 phenotype are activated in response to IL-4 or IL-13 (Nguyen et al., 2011), which are thought to suppress inflammation, tissue repair, and promote wound healing (Colton, 2009). It has been recently reported that local microglia assume a M2 phenotype at an early stage, peaking at around 5 days from injury, but then gradually transforming into a M1 phenotype at the sites of injury in ischemic stroke and traumatic brain injury (Hu et al., 2012). Although some researchers believe that the classification method of

M1/M2 phenotype has limitations, given that the microglia polarization process is complex and diverse (Butovsky & Weiner, 2018; Ransohoff, 2016; Wang et al., 2023).

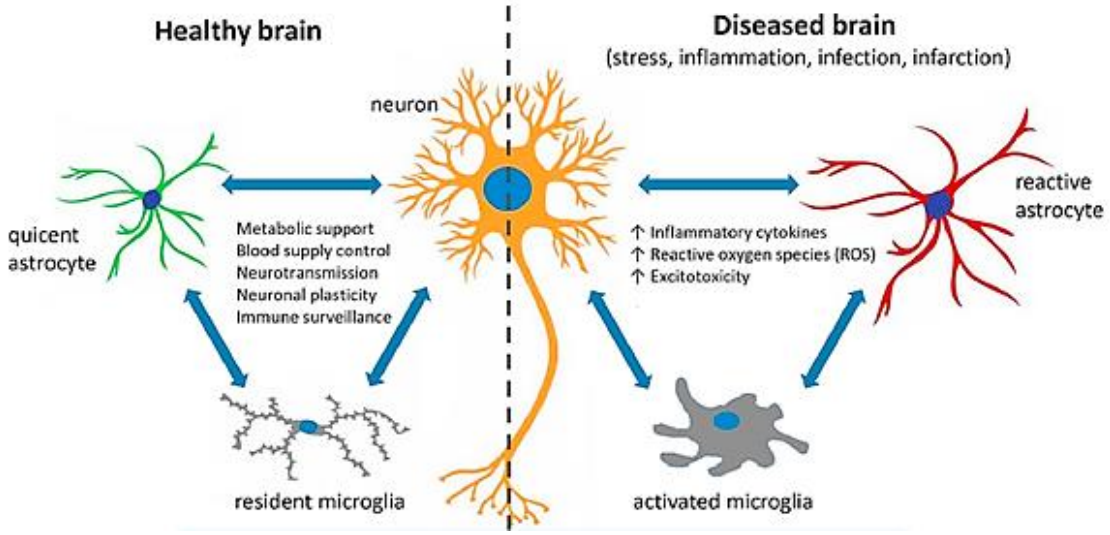

Figure 8. Schematic diagram of neuroimmune crosstalk between neurons, microglia and astrocytes in the brain under normal (left) and pathological conditions (right). Image adapted from Salvesen et al. (2019). ***Reproduced with permission.***

In addition to this role in the immune system, microglia have additional functions such as maintaining synaptic homeostasis (Paolicelli et al., 2011), promoting neurogenesis, and neuronal growth (Matsui & Mori, 2018; Wu et al., 2015), and responding to neurotransmitter release to aid their surveillance role (Pocock & Kettenmann, 2007). For example, electrophysiological recordings of cultured rat microglia found that glutamate induced microglial activation and resulted in a neurotoxic microglial phenotype (Taylor et al., 2005), while GABA receptor stimulation on cultured microglia was found to attenuate cytokine release (Kuhn et al., 2004), which could implicate that modulation of microglial cells in response to glutamate and GABA release may constitute a means to control microglial

activation. Importantly for the current thesis, another key physiological role performed by microglia is in brain plasticity. Evidence for this was produced by a study performed by Parkhurst et al. (2013), where they generated transgenic mice which allowed them to specifically manipulate of gene function in microglia. These animals' express tamoxifen-inducible Cre recombinase in microglia under the control of the endogenous CX_3CR1 promoter, followed by an IRES-EYFP element. To test the functionality of CreER, they crossed CX_3CR1^{CreER} mice to Rosa26-stop-DsRed reporter allele mice ($R26^{DsRed}$) to generate $CX3CR1^{CreER/+}$:$R26^{DsRed/+}$ animals. In the absence of tamoxifen, few microglia were found (0.3%) but 5 days after tamoxifen treatment, 93.9% of microglia were expressed in the mice brain. They found that mice depleted of microglia showed decreased performance in multiple learning tasks and a significant loss of motor-learning-dependent synapse formation, suggesting an important physiological function of microglia in learning and memory.

2.11.2 Astrocytes

Another abundant type of glial cell involved in the neuroinflammatory response is astrocytes. Astrocytes form the blood-brain barrier (BBB) and, like microglia, become activated in response to inflammatory stimuli (Heithoff et al., 2021; Soung & Klein, 2019). These cells are the most abundant glial cells in the CNS (Kettenmann & Ransom, 2005) and, also like microglia, they play important roles in the brain that go beyond an immune response, including the modulation of the metabolism of neurotransmitters and ion homeostasis, as well as participating in the tripartite synapse (Kimelberg, 2010; Kimelberg & Nedergaard, 2010; Zhang, 2001). Astrocytes are also becoming recognized as active participants in the construction of synaptic circuits (Chung et al., 2015).

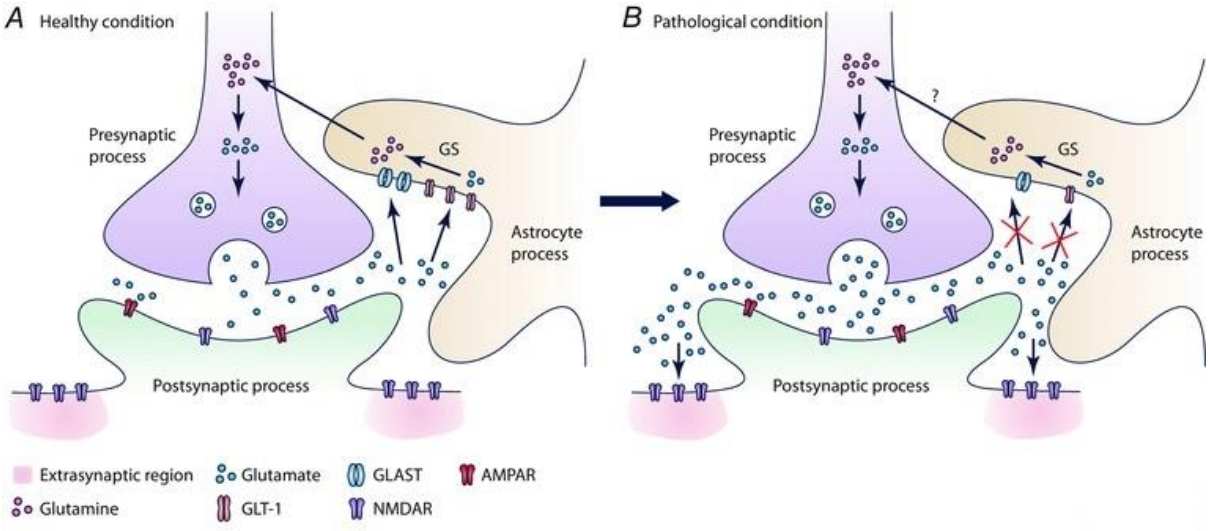

Figure 9. The role of the tripartite glutamatergic synapse in the brain under healthy (left) and pathological conditions (right). Image adapted from Blanco-Suárez et al. (2017). ***Reproduced with permission.***

As can be seen from Figure 9, the tripartite synapse is so-called due to the astrocyte forming the third part of the synapse along with the presynaptic terminal and the postsynaptic process (Araque et al., 1999). It is through their participation in the tripartite synapse that astrocytes can influence essential and pivotal role in information processing in the brain, primarily through the modulation of glutamate transmission (Perea et al., 2009). Such modulation is achieved via the numerous glutamate transporters that are found on astrocytic processes, which function to rapidly clear and metabolise glutamate (Allen & Eroglu, 2017). This is important because glutamate can be excitotoxic if it accumulates.

Astrocytes also express glutamate receptors (Duan et al., 1999), such that in response to extracellular glutamate release, astrocytes display 'excitability' as evidenced by increases in intracellular Ca^{2+} (Suzuki et al., 2011) which then trigger downstream signalling cascades that modify local neuronal signalling (Guerra-Gomes et al., 2018; Semyanov et al., 2020). The activity of astrocytes is further modulated through the release of various gliotransmitters (Li

et al., 2013) including adenosine triphosphate (ATP), adenosine), D-serine, and others (Harada et al., 2016). Studies have shown that, astrocytic excitability is also linked to learning and behavioural changes. For example, Tanaka et al. (2013) generated a transgenic mouse model and examined the role of astrocytic Ca^{2+} signalling at the level of both the tripartite synapse and behaviour. This transgenic mouse system enabled them to induce the expression of the lacZ marker protein in approximately 90% of S100B-positive astrocytes in the hippocampal CA1 region of the transgenic mice. They found that IP3-mediated astrocytic Ca^{2+} activity regulates synaptic coverage by astrocytes in the hippocampal CA1 and affects spatial reference memory and remote contextual fear memory (Tanaka et al., 2013). Another study by Han et al. (2013) found enhanced cognitive performance and long-term potentiation of synapses in mice injected with human glial progenitor cells that differentiate into astrocytes and oligodendrocytes. Furthermore, a recent study from Kol and colleagues (2020) established that astrocytes, via selective modulation of CA1 neurons that project to the anterior cingulate cortex (ACC), play a critical role in the formation of remote memories. They used a chemogenetic approach to activate the Gi pathway in CA1 astrocytes and trained mice in contextual fear conditioning. They found that astrocytic Gi activation during memory acquisition impairs remote, but not recent, memory retrieval.

Because of their important role in the modulation of neurotransmission and synaptic plasticity, when astrocytes become activated as a result of being exposed to immunomodulatory signals, this has indirect consequences on astrocytic regulation of synaptic transmission (Cekanaviciute & Buckwalter, 2016). That is, upon injury, astrocytes undergo a series of morphological and functional changes and become ‘reactive’ (see Figure 8), which causes the strong upregulation of glial fibrillary astrocytic protein (GFAP – a protein that is typically found only in astrocytes) (Eng, 1985). When astrocytes are in reactive states,

they proliferate and have been shown to promote axonal repair, synapse formation, and scar-formation to encapsulate injury. However, scar formation can also disrupt neuronal communication, and gene transcriptome analysis of reactive astrocytes shows that A1 reactive astrocytes can upregulate many complement cascade genes that are destructive to synapses (Liddelow & Barres, 2017; Sofroniew & Vinters, 2010). Thus, the activation of astrocytes must also influence learning and behaviour, although what exactly this influence might be is only starting to be determined.

2.11.3 Oligodendrocytes

Although they will not be a focus of the current thesis, as they are not as central to the neuroinflammatory response as microglial and astrocytes, it is also worth briefly mentioning the third type of glial cell observed in the brain: oligodendrocytes. These cells comprise only 5%–8% of total glial cells, and they are the myelinating cells of the CNS (Boullerne, 2016; del Río-Hortega, 1921; Kuhn et al., 2019). They have also been associated in a broad range of white matter dysfunction, including those that have been recognized as contributing to behavioural disorders such as schizophrenia and bipolar disorder (Bellani et al., 2016; Edgar & Sibille, 2012). Recent studies have also demonstrated that oligodendrocytes are implicated in learning and memory, myelination and axonal support, and remodelling of neuronal circuits (Gibson et al., 2014; Moore et al., 2020; Saab et al., 2013; Simons & Nave, 2016; Zatorre et al., 2012). In response to any pathological stimuli, oligodendrocytes generate several immune mediators such as CXCL10, CCL2 and CCL3 known to modulate the activation state of microglia during inflammation and infection, indicating that oligodendrocytes actively recruit microglia to damaged tissues (Balabanov et al., 2007; Ramesh et al., 2012).

2.12 Evidence of neuroinflammation in compulsive disorder

The studies reviewed above reveal that glial cells can orchestrate a potent modulatory control over synaptic plasticity and neurotransmission, and influence behaviour and cognitive processes. Because these cells become activated, and their functions altered, during a neuroinflammatory event, this must have consequences for the modulation of plasticity, neurotransmission, and behaviour, suggesting that neuroinflammation could be the mechanism by which cognition and behaviour becomes distorted in compulsive disorders. Therefore, it is worth considering the current evidence that inflammatory events that may be occurring in the brains of individuals with compulsive disorders and in preclinical models of those disorders.

Arguably, the most direct evidence of neuroinflammation contributing to the neuropathology of compulsivity comes from postmortem studies of inflammatory gene transcripts. Post-mortem studies of autopsied individuals with SUD have revealed significant brain damage like brain shrinkage, white matter, and neuronal loss (Goldstein & Shelly, 1980; Harper, 1998; Harper & Blumbergs, 1982) and increased levels of inflammatory markers (Bachtell et al., 2017; Crews et al., 2013; Crews & Vetreno, 2014; He & Crews, 2008; London et al., 2015). Furthermore, examination of post-mortem tissue from the Australian brain bank has revealed decreased neuron density (15–23%) in the frontal cortex of alcoholics (Harper & Matsumoto, 2005). Moreover, such studies have identified structural and functional abnormalities within the brains of individuals with SUD possibly due to sustained glial functional alterations following chronic drug use which likely contribute to the behavioural outcomes associated with substance abuse (Coller & Hutchinson, 2012; Miguel-Hidalgo, 2009). For example, a previous study used quantitative analysis of astrocyte and microglia

markers demonstrated a marked elevation of microglial markers in striatum in individuals with a history of methamphetamine use compared to controls (Kitamura et al., 2010). Likewise, analysis of post-mortem tissue of cocaine abusers found evidence for increased microglial activation, particularly in the substantia nigra pars compacta (SNc) (Little et al., 2009) and elevated immunoreactivity for microglial Iba1 in the cingulate cortex of alcohol-dependent humans (He & Crews, 2008).

Using animal models, a study also showed that repeated injections of morphine in the rat brain increases microglial CD11b and astrocytic GFAP densitometry (Hutchinson et al., 2009). Similarly, Schwarz and colleagues (2011) demonstrated that acute injection of morphine rapidly increases mRNA expression of both microglial CD11b and astrocytic GFAP in the NAc, but not the hippocampus. Also, repeated amphetamine causes increased GFAP expression on astrocytes in the caudate-putamen but not the NAc or prefrontal cortex (Armstrong et al., 2004). In individuals with OCD, Piantadosi and colleagues (2021) found that people with OCD had significantly lower gene expression in both the OFC and the striatum related to excitatory synapses than people without OCD. It has also been reported that subgroups of patients with OCD show elevated proinflammatory cytokines that that include the basal ganglia (Endres et al., 2022).

Advanced techniques in neuroimaging have also produced evidence of elevated and sustained neuroinflammation in the brains of individuals with compulsive disorders. Attwells et al. (2017) used translocator protein (TSPO) positron emission tomography (PET) imaging in the brains of individuals with OCD, to identify evidence of neuroinflammation in the caudate (among other brain regions) relative to healthy controls. TSPO is a marker of the microglia activation, which as mentioned above, occurs during neuroinflammation. In fact, several

studies have validated TSPO as a marker of immune function, demonstrating a tight relationship between immunohistochemical measures of microglial activation and TSPO levels (Cosenza-Nashat et al., 2009; Liu et al., 2014). MRI-PET imaging has also revealed strong binding of a microglia radiotracer ligand in the striatum and other regions of the brain in individuals with a history of methamphetamine use compared to healthy controls, and lower levels of microglial activation were found to be associated with greater duration of abstinence (Sekine et al., 2008). Although not directly related to compulsivity, another recent study did indicate that disrupted functional connectivity between corticostriatal brain regions that subserve reward processing and other goal-directed behaviours was linked to neuroinflammation in patients with major depression, as identified by increases in C-reactive protein (CRP), another biomarker of inflammation (Felger et al., 2016).

Despite the fact that astrocytes are the most abundant type of glial cell in the mammalian brain, are central to the modulation of neurotransmission and synaptic plasticity, and are affected by drugs of abuse (Bull et al., 2015), there are currently no techniques available to directly quantify astrocyte activation in humans in vivo. This provides a challenge to attempt to provide a direct link between neuroinflammation and dysregulated goal-directed control. Moreover, the post-mortem and neuroimaging studies reviewed above provide convincing evidence that neuroinflammation is present in the brains of compulsive individuals, but they do not demonstrate that this is the cause of cognitive/behavioural disruption due to their correlational nature. It is possible that the observed neuroinflammation is a result of a third, unknown process that causes both the behavioural deficits and the neuroinflammation, or even that the neuroinflammation is simply an epiphenomenon. Questions regarding whether striatal neuroinflammation *causes* deficits in goal-directed action control can therefore only

be answered through the use of an animal model, in which neuroinflammation can be experimentally induced in the striatum and the consequences of that on goal-directed action.

2.13 Evidence from animal studies that neuroinflammation alters cognition and behaviour

Corkrum et al. (2020) have shown that optogenetic stimulation of dopaminergic axons in the NAc core, a key reward centre in the brain, has been demonstrated to increase intracellular calcium ion concentration in surrounding astrocytes, and that these responses are altered by amphetamine. They used a fiber-photometry system in freely behaving mice and monitored astrocyte Ca^{2+} levels in the NAc and used optogenetics to specifically stimulate dopaminergic afferents to the NAc. Using the psychostimulant drug amphetamine, the amplitude, rise time, and width of the dopamine-evoked astrocyte Ca^{2+} responses were augmented which is consistent with its known mode of action to increase synaptic dopamine. Together, these results suggest that astrocytes in the NAc respond with Ca^{2+} elevations to dopamine released by synaptic terminals from the VTA, and that these responses are regulated by amphetamine. Interestingly, they also found that the enhancement in locomotion activity evoked by amphetamine is modulated by astrocytes, suggesting that astrocytes contribute to the acute behavioural psychomotor effects of amphetamine.

Another study, published by (Scofield et al., 2016), also indicates that astrocytes modulate responses to cocaine. These authors employed AAV transduction in the NAc to express the hM3D (Gq) designer receptor exclusively activated by a designer drug (DREADD) under control of the GFAP promoter and used glutamate biosensors to measure NAc glutamate levels following intracranial or systemic administration of Clozapine N-oxide (CNO – a ligand used for remotely controlling selected neuronal and non-neuronal populations) and found that animals expressing Gq-DREADD in NAc core astrocytes yielded a transient increase in

extracellular glutamate concentration. Using a rat operant model of cocaine self-administration followed by extinction training and cued reinstatement, they also found that chemogenetically-mediated glutamate gliotransmission inhibited cue-induced reinstatement of cocaine seeking via metabotropic glutamate receptor 2/3. Given that glial cells directly influence neuronal activity by releasing neurotransmitters like glutamate and these extracellular glutamates affect synaptic plasticity responsible for relapse vulnerability, the study shows the possibility that stimulating metabotropic glutamate receptor 2/3 selectively by enhancing glial glutamate release at a specific site of pathology in the brain (i.e., the NAc core) may appear an attractive target for cocaine relapse prevention medication. The pre-clinical studies provided evidence that neuroinflammation, through the activation of astrocytes, alters neurotransmission and/or behaviour.

Drugs of abuse also interact with microglia. Studies on toll-like receptors' (TLRs'), which are strongly expressed in microglia, have determined a critical role in regulating neuroinflammation, and their expression is regulated by internal and external stimulating factors, including drugs of abuse (Alfonso-Loeches et al., 2010). Furthermore, methamphetamine has been found to elevate the levels IL-1 (Liu et al., 2012; Yamaguchi et al., 1991), a major proinflammatory cytokine primarily sourced by microglia (Rothwell & Luheshi, 2000) that is essential for synaptic plasticity and long-term potentiation, which in excessive levels can adversely affect learning and cognition (Rizzo et al., 2018; Wilson et al., 2002). Additionally, microglia dysfunction has also been implicated in OCD-like behaviour in mice. Chen et al. (2010) reported that the compulsive grooming behaviour of Hoxb8 mutant mice, a transgenic mouse proposed as a model for a human behavioural disorder, trichotillomania (compulsive hair pulling), which may be related to OCD (Chamberlain et al., 2006), results from a deficiency in microglia.

Together with the studies reviewed in the previous section, these findings provide evidence that neuroinflammation and processes related to it (e.g. the activation of astrocytes) is related to compulsion and compulsive-like action. Nevertheless, none of these studies have investigated *why* neuroinflammation leads to such actions - i.e., whether it impairs or alter cognitive control or goal-directed action selection. Moreover, almost all of the preclinical studies that do establish causality for brain regions such as the pDMS in impaired action selection have employed procedures such as lesions or inactivations of DMS that involve pervasive neuronal silencing or death (Corbit & Janak, 2010; Yin, Ostlund, et al., 2005). These features are almost never observed in the brains of individuals with compulsive disorders. In fact, several studies suggest that activity is aberrantly *increased* in the brains of such individuals, and several others have shown that caudate volumes are *larger* in compulsive individuals, which is the opposite of what might be expected if such individuals were experiencing a high degree of neuronal atrophy and death (Aylward et al., 1996; Cai et al., 2016). Such increases in activity and volume are unlikely to result from neuronal loss, but could be a consequence of neuroinflammation.

2.14 Summary: Chapter 2

Individuals who suffer from compulsive disorders lack cognitive control over their actions. As a result, their actions are not aligned with their overall goals, but it is also possible that they have multiple competing/conflicting goals, and/or can be too sensitive to external cues. The endogenous cause of the brain dysfunction that might lead to dysregulated cognitive control in compulsive individuals is unknown. Although research over the last couple of decades has done a relatively thorough job of revealing the neural network that underlies goal-directed action control, both in rodents and humans, these studies do not speak to how

this network becomes dysregulated in compulsive disorders. This is because such research is primarily achieved by lesioning, inactivating, or otherwise inhibiting the various brain structures and connections involved in goal-directed action control and observing the consequences of these manipulations for behaviour using assays such as outcome devaluation. However, the laboratory techniques used in these studies typically achieves a far higher level of neuronal disruption, atrophy, or death than that has ever been observed in post-mortem studies of compulsive individuals. Thus, the question remains as to what the endogenous cause of the disruption to this system might be. Neuroinflammation in the caudate/pDMS is an excellent candidate mechanism for several reasons. First, neuroinflammation is caused by chronic stress, alcohol, and drug use, as well as infection and injury – all conditions that are observed across compulsive disorders. Second, neuroinflammation has the capacity to disrupt the homeostatic function of glial cells, thus affecting synaptic plasticity and neurotransmission, which must have consequences for cognition and behavioural output. Third, pDMS is the neural locus of goal-directed action so once this brain region is disrupted, any information provided by other brain structures or on the immediate circuits controlled by the pDMS will be disrupted too. Finally, neuroinflammation within the caudate has been consistently observed in correlational studies of post-mortem brains of individuals with compulsive disorders, as well as in neuroimaging studies. Therefore, it is the aim of the current thesis, as explored in Empirical Chapter 4, to provide the first, causal evidence that neuroinflammation in the pDMS of rats disrupts cue-guided and goal-directed action selection. The specific aims and hypotheses of Chapter 4 are outlined below.

2.15 Aims and hypotheses of Chapter 4

The experiments in Chapter 4 aim to establish a causal link between neuroinflammation in the pDMS, and cue-guided and goal-directed action control. This will be done using stereotaxic surgery to induce local neuroinflammation into the pDMS of rats by directly injecting the gram-negative bacterial endotoxin lipopolysaccharide (LPS). LPS has been heavily studied and used as a proinflammatory agent but does not directly kill neurons (although neuronal death is a possible consequence of the induction of neuroinflammation, and this will be measured with post-mortem staining for neurons using NeuN). The behavioural paradigms that will be employed are (1) sPIT, (2) outcome devaluation, and (3) outcome-selective reinstatement. The results of the sPIT test will provide a measure of cue-guided action selection, as will outcome-selective reinstatement except that the outcome is the cue. The results of outcome devaluation will provide a measure of goal-directed action selection. Based on the central role of the pDMS in action selection, I hypothesised that neuroinflammation in pDMS would likely affect multiple types of action control, necessitating the inclusion of each of these behavioural assays to determine the exact nature of behaviour affected. The second experiment in this Chapter followed on from the results of Experiment 3 and aimed to determine whether neuroinflammation in the pDMS facilitated motivation generally, or goal-directed action control specifically. The immunohistochemical results of Experiments 3 and 4 suggested a particular role for the astrocytes in the modulation of behavioural effects, and this was tested directly in Experiment 5 using a chemogenetic disruption of astrocytic signalling within the pDMS and again observing the behavioural consequences of this for sPIT, outcome devaluation, and outcome-selective reinstatement.

The specific aims of this Chapter are as follows:

- To establish causal evidence that neuroinflammation in the pDMS impairs cue-guided and goal-directed action selection.
- To quantify the extent of pDMS neuroinflammation by using immunohistochemical markers.
- To distinguish the relative contributions of astrocytes in pDMS to decision-making.

I hypothesise that:

- Local neuroinflammation in pDMS will produce impairments in action selection.
- Neuroinflammatory markers [Glial fibrillary acidic protein (GFAP) for astrocytes, and ionized calcium binding adaptor molecule 1 (IBA1) for microglia] will be increased in the pDMS of LPS-injected rats relative to Sham controls, and their expression will negatively correlate with performance on goal-directed decision-making assays, indicating that increased neuroinflammation is associated with poorer performance on these tasks. No such correlations are predicted for Sham controls.
- Chemogenetic disruption of astrocytic signaling is expected to impair action selection in the same manner as neuroinflammation.

CHAPTER 3

OUTCOME-SELECTIVE REINSTATEMENT IS PREDOMINANTLY CONTEXT-INDEPENDENT, AND ASSOCIATED WITH C-FOS EXPRESSION IN THE POSTERIOR DORSOMEDIAL STRIATUM

INTRODUCTION

The increase in responding that is observed after a period of treatment or intervention, such as a return to drug seeking following treatment for SUD, is commonly modelled in animals through procedures such as renewal and reinstatement. Such models are essential because they allow researchers to gain a deeper understanding of the behavioural and brain mechanism of relapse using techniques that are not viable for use in human studies. In these procedures, the animal is typically first trained to administer a drug, food, or other rewarding substance, which is earned by performing a response such as lever pressing. Treatment is then modelled via a process known as 'extinction' during which responding no longer earns the desired outcome until it subsequently declines. Reinstatement is observed if the animal is later subject to an unsignalled, unearned delivery of the outcome, causing responding to re-emerge (de Wit & Stewart, 1981; Stretch & Gerber, 1973). Renewal (or context-induced reinstatement), on the other hand, is the increase in responding that is observed if the animal is placed into a context other than that in which extinction took place (Bouton et al., 2011; Delamater, 1997).

Although renewal and reinstatement are useful models, they do not fully capture the richness of the relapse environment. This is because the majority of studies using these models require animals to make a single, active response for a single outcome. In the 'real world', however, an individual performing a single response for a single outcome in a uniform environment is rare. Rather, as noted in a recent review (Vandaele & Ahmed, 2021), people are far more likely to be faced with scenarios in which they can choose between multiple actions that have multiple outcomes. A person who both drinks and smokes, for example, will have many context and response-bound associations with both behaviours (e.g. at bars, the

balcony at home, garden at work etc). Thus, it is the aim of this study to begin to capture some of this complexity at a preclinical level, by determining how selective reinstatement in a choice-based procedure is influenced by context. Specifically, I ask whether increasing multiple responses for multiple outcomes, rather than selective responding for a single outcome, is more likely after a change in physical context. For example, would a person who has been through treatment and thus abstinent from both alcohol and cigarettes, but then relapses on one of these drugs in their local bar also be more likely to relapse on the other? And are they more likely to relapse on both in this context than in if they were in another, more neutral context? In order to answer this question whilst avoiding the potentially confounding effects that drugs have on the physical and/or mental state of the animals, I used food rather than drug outcomes for the current study.

The phenomenon of renewal was first demonstrated in Pavlovian (i.e. S-O) conditioning (Bouton & Bolles, 1979), and later replicated in instrumental (i.e. R-O) conditioning (e.g. Bouton et al., 2011). There are several ways in which renewal can occur, but ABA renewal is the most common and most robust. The ABA renewal effect is thought to occur because it reduces the ambiguity that results from the extinction procedure, after which the cue or action has been both paired with the outcome and with nothing. If, however, the cue/action was consistently paired with the outcome in Context A and with nothing in Context B, then this contextual information can be used to reduce this ambiguity such that the animal responds as if again expecting the outcome when it is returned to Context A (e.g. Bouton et al., 1994; Bouton et al., 2021; Bouton et al., 2011). Other forms of renewal have also been demonstrated in instrumental conditioning paradigms, such as AAB and ABC renewal.

Reinstatement, like renewal, is thought to be a contextually-mediated phenomenon (Delamater, 1997). Specifically, when the outcome is delivered on test in a manner that is unsignalled – i.e. unpaired with the response – this is thought to imply that the outcome is once again available within that context which increases the propensity to respond. Consistent with this idea, reinstatement is reduced if the outcome is presented in a context different to that of initial training or test (Baker et al., 1991). However, an alternative account has been proposed in which the outcome itself could provide the 'context' of reinforcement. For instance, when rats learn to press a lever for pellets, they will often retrieve and consume a pellet then shortly afterwards perform their next lever press. This is thought to lead to the formation of pellet-lever press (i.e. O-R) associations as well as the more traditionally considered lever press-pellet (i.e. R-O) associations. When the pellet is later delivered on test in the absence of a preceding lever press, it could activate these O-R associations in such a way the outcome acts as a stimulus that drives, or sets the occasion for, the response regardless of the physical context (Bouton et al., 2021).

As reviewed in Chapter 1, selective reinstatement in a two action, two outcome paradigm has been explicitly demonstrated to rely on O-R associations by Ostlund and Balline (2007). For these associations, the outcome is thought to function as a stimulus, suggesting that responding during selective reinstatement is more akin to habitual responding which also relies on S-R associations, than goal-directed actions that rely on R-O associations (Balleine & Dickinson, 1998). This is notable for the current study, because habits have been shown to depend on the context in which they are learned (Bouton et al., 2021; Bouton et al., 2011) whereas goal-directed actions have been demonstrated to be relatively context-independent (Bradfield et al., 2020; Thrailkill & Bouton, 2015). Thus, if context-specificity is a general

property of S-R associations, we might expect outcome-selective reinstatement to also be relatively context-specific. Alternatively, it is possible that O-R associations do not function in the same way as other S-R associations, and are in fact independent of their learning context, consistent with the suggestion by Bouton et al. (2021) that it is the outcome itself that provides the 'context' for reinstatement.

The current study will test these opposing predictions. I will employ the same outcome-selective reinstatement paradigm used by Ostlund and Balline (2007), except that the physical contexts will be altered during extinction and test. Specifically, lever press training will take place in Context A for all groups, whereas extinction and testing will take place in either Context A or B, yielding four groups in total: groups AAA, ABB, ABA, and AAB. Experiments 1 and 2 were conducted identically, except that rats were tested immediately after extinction in Experiment 1, in line with the procedures employed by Ostlund and Balline (2007), whereas rats were tested using more traditional extinction parameters (i.e. two extinction sessions and tested one day later) in Experiment 2, to determine the generality of the observed effects.

Finally, because relatively little is known about the neural mechanisms underlying outcome-selective reinstatement, I aimed to identify its potential neural correlates by examining expression of the immediate early gene and activity marker c-Fos in pDMS, the brain region that selective reinstatement has been demonstrated to depend upon (Yin, Ostlund, et al., 2005), and mOFC, one region it does not depend upon (Bradfield et al., 2015; Bradfield et al., 2018). Thus, I included both regions in my analysis with the expectation that c-Fos expression would reflect performance in the pDMS but not the mOFC. I additionally conducted exploratory analyses of c-Fos expression in the lOFC, as well as the DH.

Experiment 1: Outcome-selective reinstatement is context-independent, but extinction learning is not, when tested immediately following extinction.

The aim of Experiment 1 was to determine whether outcome-selective reinstatement is context dependent, and to investigate the potential neural mechanisms of this effect. The design for this experiment is in Figure 10. All rats were trained to lever press in Context A, the identity of which was counterbalanced. Half of the rats in each group were trained to press a left lever for pellets and a right lever for a sucrose solution, and the other half were trained on the opposite contingencies (counterbalanced). All rats then received 30 minutes of extinction during which both levers were extended but no outcomes delivered. For groups AAA and AAB, this extinction session occurred in the same context as lever press training (Context A) whereas for groups ABB and ABA it occurred in a context that had different wallpaper, floor texture, and odour (Context B). Following extinction, rats were briefly put back into their home cage for 5 minutes to allow the experimenter to change the context adorning the operant chamber, then immediately transferred back into the operant chamber for testing.

Testing occurred in either Context A (groups AAA and ABA) or B (groups ABB and AAB). No outcomes were delivered in the first 3 minutes of the test session to allow us to measure whether there were any increases in responding as a result of the alterations in context alone – i.e. to measure renewal prior to reinstatement. Following this 3-minute period, rats received sucrose, pellet, pellet, sucrose, presentations in that order, each separated by 4 minutes of extinction. Baseline lever pressing was recorded for the 2 minutes prior to each outcome delivery, and selective reinstatement was measured as the number of lever presses on the reinstated lever compared to presses on the nonreinstated lever in the 2 minutes post-

outcome delivery. I expected that selective reinstatement (Reinstated > Nonreinstated) would be intact in group AAA, but impaired (Reinstated = Nonreinstated) in all other groups.

Two hours after the start of the reinstatement test animals were perfused with 4% paraformaldehyde, their brains removed, and sections from the mOFC, lOFC, pDMS, and DH were extracted and immunostained for expression of the immediate early gene and neuronal activity marker c-Fos. It was expected that c-Fos expression in the pDMS would be higher in groups expressing intact outcome-selective reinstatement than those for which it was impaired, whereas it was expected to be equivalent in the mOFC in all groups. Because the role of lOFC and DH in selective reinstatement is unknown, these analyses were exploratory, but it was expected that c-Fos expression in DH would differ in groups that experienced a context change on test day (groups AAB and ABA) relative to those that did not (groups AAA and ABB).

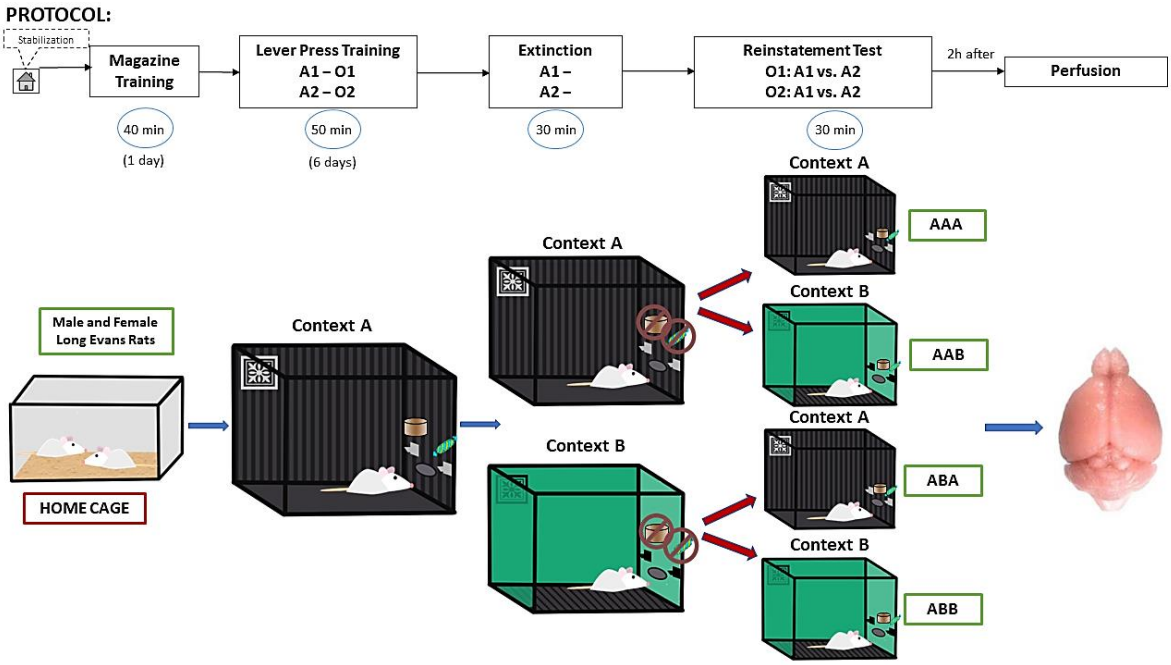

Figure 10. Representation of the experimental design. Briefly, animals were first trained to press left lever-pellets, right lever-sucrose, or vice versa (counterbalanced) in Context A. Next, lever pressing was extinguished in either the same context (A) or different context (B). Subsequently, reinstatement responding was assessed in context A or B, yielding 4 groups in total: AAA, ABB, ABA, and AAB.

MATERIALS AND METHODS

Animals

A total of 20 male and 20 female Long-Evans rats were used for Experiment 1 (n = 11 (AAA), n = 10 (ABB), n = 10 (ABA), and n = 9 (AAB), N = 40). Male and female rats were assigned evenly to each group. The slightly uneven group numbers in AAA and AAB in Experiment 1 were due to one animal being incorrectly assigned to group AAA instead of AAB on test. All animals were purchased from the Australian Research Centre, Perth, Australia, and were housed in groups of 2-4 in transparent amber plastic boxes located in a temperature- and humidity-controlled room with a 12-h light/dark (07:00–19:00 h light) schedule. Experiments were conducted during the light cycle. Rats were aged between 10-15 weeks and weighed between 190-250 g (female) or 290-380 g (male) at the beginning of the experiment. Before the experiments, all animals were habituated to the housing area for a week, during which they had free access to food and water. During behavioural training however, animals were maintained at ~85% of their free-feeding body weight by limiting their food intake to 8-12g of their maintenance diet per day. All procedures were approved by the Ethics Committees of the Garvan Institute of Medical Research, Sydney.

Apparatus

All behavioural procedures took place in six identical sound attenuating operant chambers (Med Associates, Inc.,) that were enclosed in sound- and light-attenuating cubicles. Each chamber was equipped with a recessed food magazine, located at the base of one end wall, through which 20% sucrose solution (0.2 ml) and food pellets (45 mg; Bio-Serve, Frenchtown, NJ) could be delivered using a syringe pump and pellet dispenser, respectively. Pellet and sucrose outcomes were delivered to the same food magazine, in separate compartments to

prevent pellets becoming wet. An infrared light situated at the magazine opening was used to detect head entries. Illumination was provided by a 3-W, 24-V house situated at the top-centred on the left end wall. The apparatus was controlled and the data were recorded using Med-PC IV computer software (Med Associates, Inc.).

Contexts

Two contexts were used that differed along visual, olfactory, and tactile dimensions. In one context, laminated sheets of black and white vertical stripes were mounted on the hinged front door and transparent wall of the chamber, a smooth black plexiglass sheet was positioned on the floor, and a paper towel with 1ml of 10% vanilla essence (Queen Fine Foods, Queensland, Australia) was placed in the bedding. In the second context, the hinged front door and wall were left clear, with a stainless-steel grid floor and a paper towel placed in the bedding, which had 1ml of 10% coconut essence (Queen Fine Foods, Queensland, Australia) added. Paper towels were changed prior to every session. The identities of Contexts A and B were fully counterbalanced across animals, such that Context A was the stripey-walled, smooth-floored, vanilla-scented context and Context B was the clear-walled, grid floor, coconut-scented context for half of the animals, and the remaining animals received the opposite arrangement.

Magazine training

Magazine training took place on day 1 in Context A. For these sessions, the house light was turned on at the start of the session and turned off when the session was terminated. No levers were extended. During the session, 20 deliveries of pellets and 20 deliveries of 20% sucrose solution were delivered on independent RT60 schedules, after which the session terminated.

Lever press training

Lever press training took place over 6 days (days 2-7) in Context A. Each session lasted for 50 minutes and consisted of two 10 minutes periods on each lever (i.e., four x 10 minutes sessions in total) separated by a 2.5 minutes time-out period in which the levers were retracted and the houselight switched off. Lever press periods terminated early if 20 outcomes were earned such that rats could earn a maximum of 40 pellets and 40 deliveries of sucrose solution per session. For half of the animals, the left lever earned pellets and the right lever earned sucrose, and the other half received the opposite arrangement (counterbalanced). For the first 2 days of lever press training, lever presses were continuously reinforced. Animals were shifted to a random ratio (RR)-5 schedule for the next 2 days (i.e. each lever earned an outcome with a probability of 0.2), then to a RR-10 schedule (i.e. each lever earned an outcome with a probability of 0.1) for the final 2 days.

Habituation

Rats were pre-exposed to Context B on day 8, following the last lever-press training session and prior to extinction training. This served to familiarize the animals to this context and reduce neophobia. Pre-exposure sessions lasted 40 minutes, during which no levers were extended and no food was delivered

Extinction

Rats were assigned to groups AAA, ABB, ABA and AAB after being matched for responding on the last day of acquisition training. For groups AAA and AAB, extinction training occurred in Context A. For groups ABA and ABB, extinction was conducted in Context B. Extinction sessions were 30 minutes long during which the houselight was turned on, both levers extended and lever presses recorded, but no outcomes were delivered. Following termination of the extinction session, rats in Experiment 1 were put back into their home cage for 5

minutes to allow the experimenter to make any of the necessary context changes prior to reinstatement testing.

Outcome-selective reinstatement test

After 5 minutes in their home cages, rats were placed back into the operant chamber that was now adorned in the correct context for test. On test, both levers were available for the entire session and rats received 4 reinstatement trials separated by 4 minutes each. Each reinstatement trial consisted of a single free delivery of either the sucrose solution or the grain pellet. All rats received the same trial order: sucrose, pellet, pellet, sucrose. Responding was measured during the 2 minutes periods immediately before (Pre) and after (Post) each delivery. The reinstatement test session lasted for 30 minutes.

Tissue preparation and immunofluorescence

Two hours after the start of the reinstatement test, rats were deeply anesthetised via CO2 inhalation and perfused transcardially with cold 4% paraformaldehyde in 0.1 M phosphate buffer saline (PBS; pH 7.3-7.5). Brains were rapidly and carefully removed and postfixed in 4% paraformaldehyde overnight and then placed in a PBS solution containing 30% sucrose. Brains were sectioned coronally at 40 µm through the OFC, pDMS and DH defined by Paxinos and Watson (2014) using a cryostat (CM3050S, Leica Microsystems) maintained at approximately -20˚Celsius. The sectioned slices were immediately immersed in cryoprotectant solution and stored at -20˚Celsius. Five representative sections from each region of interest (mOFC, lOFC, pDMS, and DH) were selected for each rat. Sections were first washed three times (10 minutes per wash) in PBS to remove any exogenous substances. The sections were then incubated in a blocking solution comprising of 3% Bovine Serum Albumin (BSA) + 0.25% TritonX-100 in 1x PBS for one hour to permeabilize tissue and block any non-specific binding. Sections were then incubated in anti-c-Fos primary antibody (1:500, Synaptic Systems Catalog #226 003) as

an ‘activation marker’ (c-Fos is an immediate early gene that is expressed following neuronal activation). c-Fos was diluted in blocking solution for 72 h at 4°C. Sections were then washed 3 times in 1 × PBS and incubated overnight at 4°C in donkey anti-rabbit AlexaFluor-488-conjugated secondary antibody (1:1000, Invitrogen, Catalog #A21206). Every section was mounted on glass slides and were coverslipped using the mounting agent Vectashield and left to dry overnight in darkness. For quantification of c-Fos, a single image was taken of the mOFC/lOFC, pDMS, and DH CA1 per hemisphere of each slice (10 images in total per brain region of rat) on a Fluorescence Microscope (Zeiss) using a 10x air objective. Regions taken for each section were identical (2048 x 2048 pixels). Images were quantified using imaging software (ImageJ, Fiji Cell Counter). Briefly, background subtraction was applied to remove background noise. Images were then converted to binary, and thresholding was used to isolate stained cells. Finally, the Analyze Particles tool was used to quantify the number of cells based on a minimum particle size of 80 pixel units.

Data and Statistical analysis

Lever press and magazine entry data were collected automatically by Med-PC (version 5) and uploaded directly to Microsoft Excel using Med-PC to Excel software. Lever press acquisition and extinction data were analysed using repeated measures (Group x Session) ANOVA controlling the per-family error rate at $\alpha=0.05$. For a more fine-grained analysis of test data, I used planned, complex orthogonal contrasts controlling the per-contrast error rate at $\alpha=0.05$ according to the procedure described by Hays (1973). If interactions were detected, follow-up simple effects analyses were calculated to determine the source of the interaction. Data were expressed as mean ± standard error of the mean (SEM) and averaged across counterbalanced conditions. Values of $p < 0.05$ were considered statistically significant.

Statistical softwares SPSS and PSY were used to carry out these analyses. Full data, statistical analyses, and results are shown in Appendix A.

RESULTS

Behavioural Results

Lever press acquisition is shown in Figure 11A, averaged across left and right levers. It is clear from this figure that all animals in Experiment 1 acquired the lever press response, and groups did not differ on their acquisition. This is supported by a main effect of day $F(1,36) = 41.459$, $p = .00001$, no main effect of group and no day x group interaction $Fs < 1$.

Responding during the 30 minutes extinction session is shown in Figure 11B. This figure shows that all animals reduced responding over this session, and that this did not differ between groups, $F(1,36) = 2.263$, $p = .098$. This is supported by a main effect of minute (Greenhouse-Geisser corrected for violating sphericity), $F(7.337,36) = 4.725$, $p = .000$ that did not interact with group, $F(22.012, 36) = 1.278$, $p = .185$.

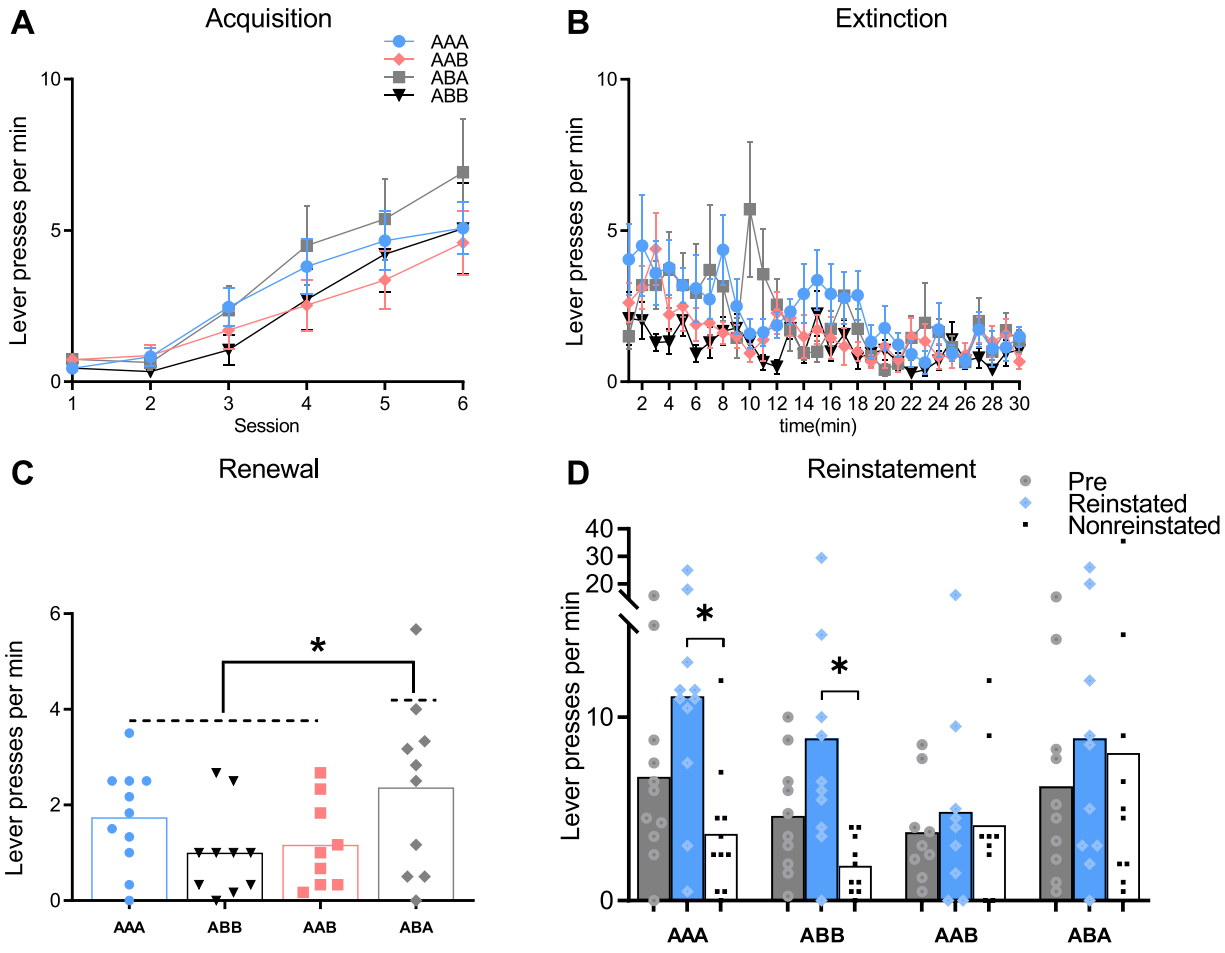

*Figure 11. Lever presses per min (± SEM) during acquisition (A) and extinction (B). (C) Lever presses per min (± SEM) during first 3 minutes of the reinstatement test, prior to outcome delivery. (D) Lever presses per min (± SEM) during the reinstatement test. * p < .05*

Responding during the first 3 minutes of reinstatement testing is shown in Figure 11C. Any increase in responding detected during this period can only be a result of context effects (i.e. 'renewal') and not reinstatement, because no outcomes were delivered during this period. Figure 11C shows that responding was highest in group ABA relative to the rest of the groups. Statistical analysis confirmed that this was the case (i.e. ABA > average [AAA/ABB/AAB]), $F(1,36) = 5.596$, $p = .024$. By contrast, responding in group AAB did not differ from groups AAA/ABB, $F < 1$, and groups AAA and ABB also did not significantly differ from each other,

F(1,36) = 1.904, p = .176. These results suggest that there was an effect of renewal in group ABA but not in group AAB.

Performance during the reinstatement test is shown in Figure 11D. There was no general reinstatement/main effect of post-outcome delivery responding, i.e. more responding post-outcome delivery than pre-outcome delivery on test, F(1,36) = 2.956, p = .094, that did not interact with groups, all Fs < 1. Although it is clear from this figure, that outcome-selective reinstatement was intact (Reinstated > NonReinstated) for groups AAA and ABB, and impaired (Reinstated = NonReinstated) for groups ABA and AAB. This is supported by a main effect of reinstatement F(1,36) = 10.213, p = .003, that did not interact with the AAA vs. ABB comparison, F < 1. Nevertheless, selective reinstatement was impaired for groups AAB and ABA, as demonstrated by a significant group (AAA/ABB vs AAB/ABA) x reinstatement interaction, F(1,36) = 6.691, p = .041. This interaction is supported by significant simple effects demonstrating greater responding on the reinstated than the nonreinstated lever in groups AAA, F(1,36) = 9.958, p = .003, and ABB, F(1,36) = 7.774, p = .008, but no evidence of differential responding on either lever in groups ABA and AAB, both Fs < 1.

Results of the c-Fos analysis

Representative photomicrographs demonstrating the extent of c-Fos expression in the mOFC are shown in Figure 12A, in the lOFC are shown in Figure 12B, in the pDMS are shown in Figure 12C, and in the DH (roughly CA1 region) are shown in Figure 12D. Total c-Fos counts for these regions shown in Figures 12E (mOFC and lOFC), 12F (pDMS), and 12G (DH), respectively. Statistical analyses revealed c-Fos expression did not differ between groups in mOFC/lOFC or DH CA1 (p > 0.05). My analysis did detect higher c-Fos expression in the pDMS for groups that demonstrated intact outcome-selective reinstatement on test (i.e. groups AAA and ABB) than for groups that did not (i.e. groups AAB and ABA), supported by a complex

contrast (AAA/ABB vs AAB/ABA) demonstrating a main effect of group, F(1,36) = 32.394, p = .00001. Together, these results suggest that higher levels of neural activity in the pDMS, but not mOFC, lOFC, or DH, was associated with intact outcome-selective reinstatement.

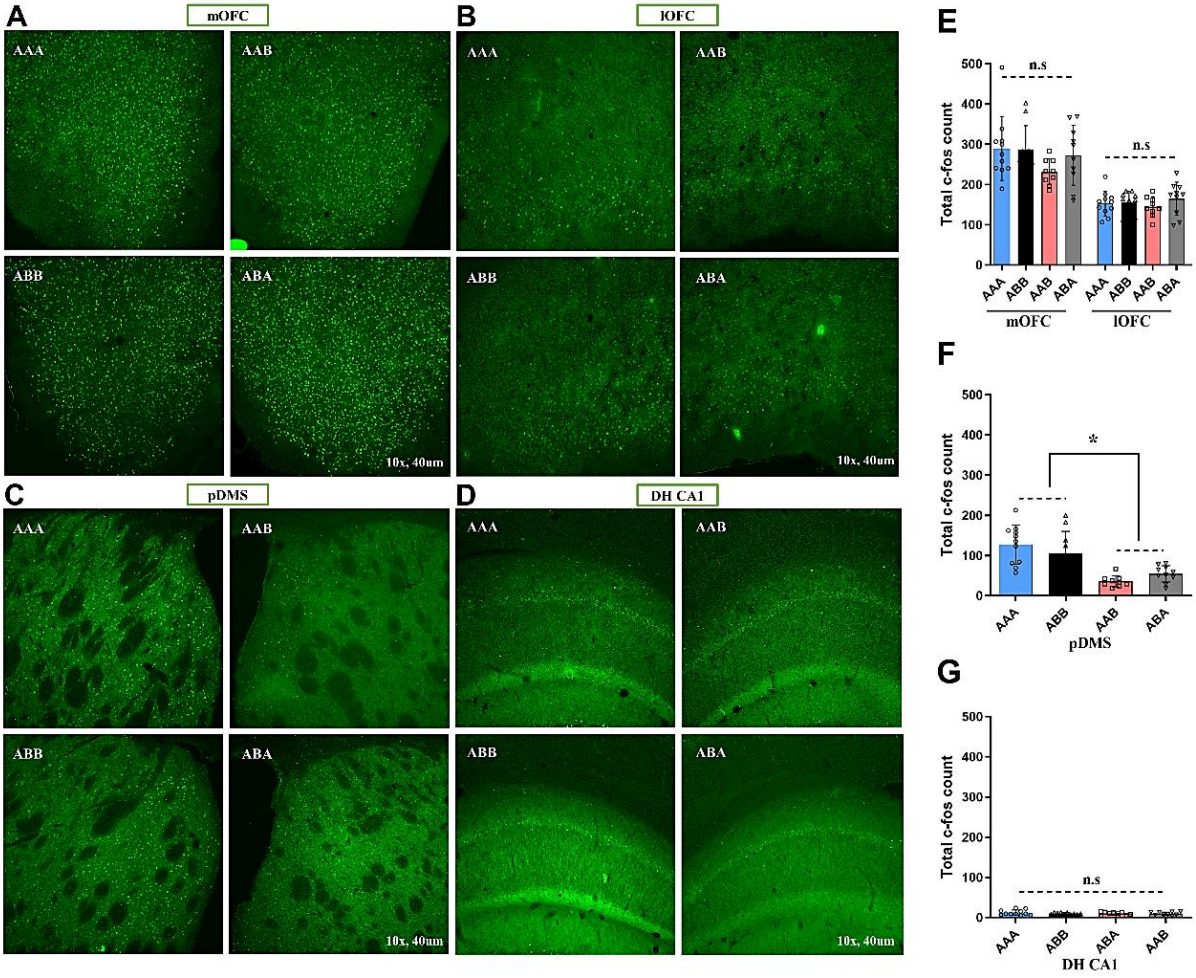

*Figure 12. Representative immunofluorescence images of c-Fos levels in medial/lateral orbitofrontal cortex (A-B), posterior dorsomedial striatum (C), and dorsal hippocampus CA1 (D) for Experiment 1. E) Total c-Fos counts (± SEM) for medial/lateral orbitofrontal cortex, F) Total c-Fos counts (± SEM) for posterior dorsomedial striatum, G) Total c-Fos counts (± SEM) for dorsal hippocampus CA1 region. * p < .05*

Experiment 2: Outcome-selective reinstatement and extinction learning are both context-independent in an instrumental choice paradigm after multiple days of extinction training.

In contrast to my expectations, the results of Experiment 1 suggest that outcome-selective reinstatement was only partially context-specific. This is because it was impaired in groups

AAB and ABA but was intact in groups AAA and ABB, despite group ABB being tested in a context (B) in which O-R pairings had never been experienced. The major difference between groups for which selective reinstatement was intact (AAA and ABB) versus those for which it was impaired (AAB and ABA) was that extinction and testing occurred in the same context for the two former, but not the two latter, groups. Together, therefore, the results of Experiment 1 suggest that although the selective reinstatement effect appears to be independent of the context in which O-R associations are learned, the extinction learning upon which selective reinstatement relies is context-specific.

One potential problem with this conclusion, however, is the fact that I did not observe a renewal effect in group AAB. That is, if extinction learning was specific to the context in which it was learned, then it should not have transferred to Context B on test for this group such that renewal – consisting of elevated responding relative to groups AAA and ABB in the first 3 minutes of test (prior to outcome delivery) – should have been observed here, but it wasn't. This failure to detect AAB renewal is notable for two reasons. First, as the current study is the first to my knowledge to investigate renewal in a paradigm involving instrumental choice, it could suggest that AAB renewal is not (but ABA renewal is) replicable in such a paradigm. Second, because selective reinstatement was impaired for group AAB despite the absence of a renewal effect, it could suggest that this impairment was independent of renewal rather than a consequence of it. It was the aim of Experiment 2 to investigate these questions.

An important difference between Experiment 1 and prior studies that have detected AAB renewal (Bouton et al., 2011; Bouton and Ricker, 1994; Tamai and Nakajima, 2000) is that I have here conducted extinction and testing on the same day rather than on separate days. Although I chose this procedure based on the parameters used by Ostlund and Balline (2007) almost all prior demonstrations of renewal and reinstatement have involved multiple days of

extinction training, and testing on a separate day. It is possible that such a procedure could allow for better consolidation of the extinction context-no outcome association, resulting in more robust renewal effects on test. Thus, I decided to adopt these more traditional parameters in Experiment 2 in an attempt to increase the possibility of observing AAB renewal on test, and to determine if this led to impaired selectivity of reinstatement.

The design of Experiment 2 was identical to that of Experiment 1, except that rats were given 2 x 30 minutes extinction sessions over two days, and tested one day later. This time, I expected to observe a renewal effect in both groups ABA and AAB, as indicated by enhanced responding relative to groups AAA and ABB in the first 3 minutes of test. I further expected to replicate the findings that selective reinstatement was impaired for groups AAB and ABA relative to groups AAA and ABB.

MATERIALS AND METHODS

Animals

A total of 30 male and 30 female Long-Evans rats (n = 15 per group, N = 60) were used for Experiment 2. Male and female rats were distributed evenly between groups (n = 7 or 8 females, and n = 7 or 8 males per group). Animals were housed, food deprived, and maintained as described for Experiment 1. All procedures were approved by the Ethics Committees of the Garvan Institute of Medical Research, Sydney.

Apparatus and Contexts

All Apparatus and Contexts were as described for Experiment 1.

Behavioural Procedures

All behavioural procedures were conducted identically to that described for Experiment 1, except that rats were given 2 x 30 minutes extinction sessions for Experiment 2, which were

conducted on different days (i.e. Days 9 and 10 of the experiment, following magazine training, lever press training, and habituation to Context B). Reinstatement testing occurred one day later, on Day 11, identically to the manner described for Experiment 1.

Tissue preparation and immunofluorescence

All tissue preparation and immunofluorescence procedures were as described for Experiment 1.

RESULTS

Behavioural Results

Lever press acquisition is shown in Figure 13A, averaged across left and right levers. As is clear from this figure, all animals acquired the lever press response, and this did not differ by group. This is supported by a main effect of day $F(1,56) = 108.711$, $p = .000$, no main effect of group, $F < 1$ and no group x day interaction $F < 1$. Responding during the two 30 minutes extinction sessions is shown in Figures 13B-C. There was evidence of between-session extinction on both days, and this did not differ between groups, $F(1,56) = 0.937$, $p = .429$ (Extinction 1), $F(1,56) = 1.257$, $p = .298$ (Extinction 2). For the first extinction session, there was a main effect of minute (Greenhouse-Geisser corrected for violating sphericity), $F(8.864,36) = 15.64$, $p = .00001$ that did not interact with group, $F(26.592, 56) = 1.163$, $p = .15$ and a main effect of minute for the second session (Greenhouse-Geisser corrected for violating sphericity), $F(11.996,56) = 3.862$, $p = .00001$ that did not interact with group, $F < 1$. There was also a between-session extinction effect that did not differ by group, $F(1,56) = 1.155$, $p = .335$, as evidenced by a main effect of day, $F(1,56) = 100.276$, $p = .00001$, and no group x day interaction, $F < 1$.

Performance during the first 3 minutes of reinstatement testing is shown in Figure 13D. Note that data for one rat from group ABB was removed from this analysis due to fulfilling the outlier criteria of responding at a rate greater than three standard deviations above the mean. From this figure it is clear that, once again, there was a robust renewal effect in group ABA but not in group AAB. Statistically, group ABA again responded more than the other groups (i.e. ABA > average [AAA/ABB/AAB]), $F(1,55) = 6.452$, $p = .016$, whereas responding in group AAB did not differ from groups AAA/ABB, $F < 1$, nor between groups AAA and ABB, $F < 1$. This result indicates that I was once again unable to demonstrate AAB renewal in this multiple action, multiple outcome paradigm, even when I employed more traditional extinction/renewal parameters.

Performance during reinstatement testing is shown in Figure 13E. There was a general reinstatement/main effect of post-outcome delivery responding on test, $F(1,56) = 15.989$, $p = .000$, that did not interact with groups, all $Fs < 1$. From this figure, and in further contrast to expectations, selective reinstatement was intact for all groups, including groups AAB and ABA that received extinction training and testing in different contexts. There was a main effect of selective reinstatement (Reinstated > Nonreinstated), $F(1,56) = 35.94$, $p = .000$, which did not interact with any group differences, all $Fs < 1$. I was so surprised by this result that I added n = 5 animals to each group (after initially replicating the group sizes of n = 10 from Experiment 1) to ensure that I was not underpowered to detect any small but significant effects between groups. However, the addition of these animals only strengthened my observations.

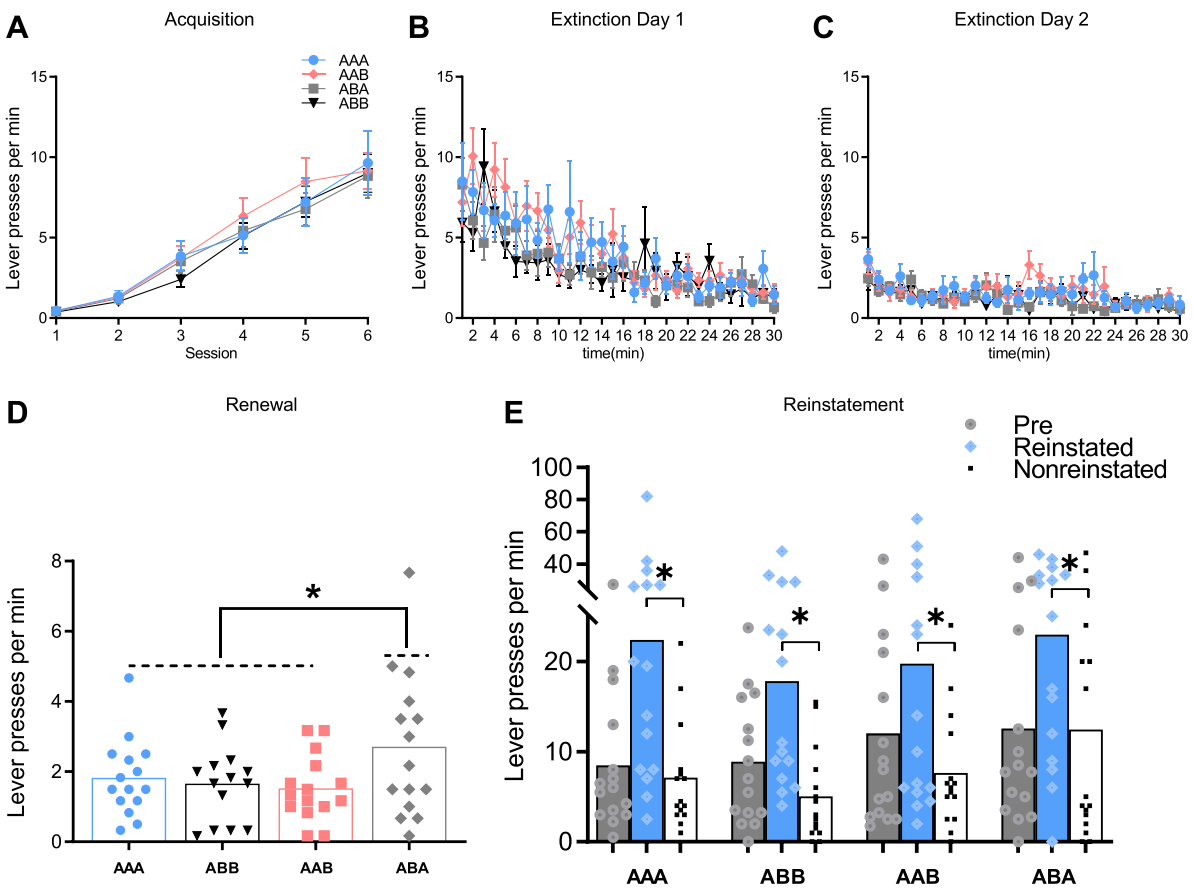

*Figure 13. Lever presses per min (± SEM) during acquisition (A) and extinction (B-C). (D) Lever presses per min (± SEM) during first 3 minutes of the reinstatement test, prior to outcome delivery. (E) Lever presses per min (± SEM) during the reinstatement test. * p < .05*

Together, these results demonstrate that outcome-selective reinstatement is entirely context-independent after multiple days of extinction training, and that AAB renewal is not replicable in a two action, two outcome, instrumental paradigm, at least with the parameters employed here. Moreover, the results of Experiment 2 appear to confirm that outcome-selective reinstatement and renewal effects are distinct phenomena. This is because in Experiment 1, selective reinstatement was impaired in group AAB despite the absence of a renewal effect, whereas in Experiment 2, selective reinstatement was intact in group ABA despite the presence of a renewal effect.

Results of the c-Fos analysis

As shown in Figure 14A-G, c-Fos expression did not differ between groups in any of the brain regions investigated for this experiment, all Fs < 1.

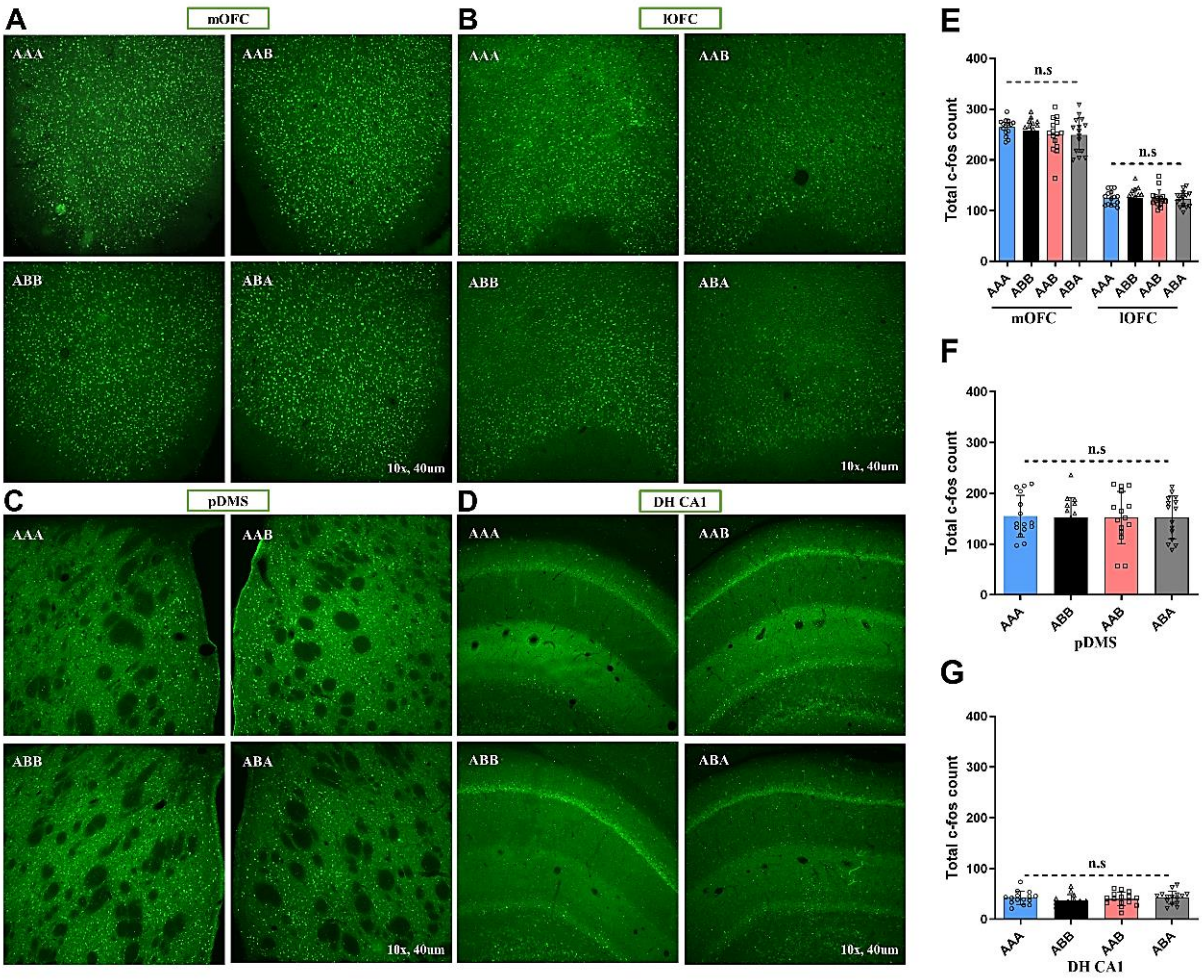

*Figure 14. Representative photomicraphs of c-Fos levels in medial/lateral orbitofrontal cortex (A-B), posterior dorsomedial striatum (C), and dorsal hippocampus CA1 (D) for Experiment 2. E) Total c-Fos counts (± SEM) for medial/lateral orbitofrontal cortex, F) Total c-Fos counts (± SEM) for posterior dorsomedial striatum, G) Total c-Fos counts (± SEM) for dorsal hippocampus CA1 region. * p < .05*

DISCUSSION

The experiments reported in this chapter reveal that the selective reinstatement of an action is partially context-dependent, only when tested immediately following extinction. By contrast, when tested after multiple days of extinction, outcome-selective reinstatement is

entirely context-independent. Moreover, the context-specificity of reinstatement appears to be independent of increases in responding related to the context switch alone: - i.e. renewal. This is because impaired selectivity of reinstatement (i.e. Reinstated = Nonreinstated) was observed in group AAB in Experiment 1 despite the absence of a renewal effect in this group, whereas intact selectivity of reinstatement (i.e. Reinstated > Nonreinstated) was observed in Experiment 2 in group ABA, despite the presence of renewal. Finally, my results suggest that selective reinstatement is associated with neural activity in pDMS, but not the OFC or DH, because only in the pDMS did c-Fos expression reflect the intact/impaired nature of outcome-selective reinstatement.

For the most part, these results were not as predicted because I had hypothesised that outcome-selective reinstatement would be context-dependent, due to its reliance on O-R associations that are similar to S-R associations which have been conclusively demonstrated to be context dependent. Nevertheless, it is clear from the current results that O-R associations that underlie outcome-selective reinstatement can be expressed independently of their physical context. That is, in Experiment 1 and 2, group ABB demonstrated intact selective reinstatement despite the response and outcome never having been experienced in Context B prior to test. This could suggest that O-R associations are not simply a special type of S-R association, but rather are their own category of association, one that is context-independent.

Current results also reveal novel information about the nature of extinction in a multiple action/outcome design. That is, whether extinction occurred immediately prior to, or in the days before, testing affected the selectivity of responding. Specifically, when extinction and reinstatement occurred on the same day, switching context between each phase caused reinstatement not to be specific to the outcome delivered. But when extinction and

reinstatement occurred on different days, responding was outcome-specific regardless of the context in which the test is conducted. These results suggest that extinction learning is initially context-dependent but becomes context-independent over time. There is some evidence in the literature that is consistent with such a notion; Bradfield and colleagues (2020) have published that in instrumental choice situations, performance is context dependent for a very short period of time immediately after learning but becomes context independent when learning is better-established.

Other unexpected results of this chapter were that outcome-selective reinstatement does not appear to be related with the cellular activity in the mOFC/lOFC, or DH CA1, but is related with activity in pDMS, as measured by increased c-Fos expression. This latter finding was as expected because a previous paper has shown that lesions of pDMS abolish outcome-selective reinstatement relies (Yin, Ostlund, et al., 2005). Although somewhat disappointing, this positive result in pDMS at least confirmed that the measurements were sensitive and it was not an overall failure of protocol. As reviewed in Chapter 2, there are many other brain regions involved in reinstatement and relapse-like behaviour, so future studies may want to explore whether basolateral amygdala or prelimbic cortex (among others) might play a role in outcome selective reinstatement.

In summary, these results suggest that a) outcome-selective reinstatement is predominantly context-independent, and b) outcome-selective reinstatement performance is associated with neural activity in the pDMS, but not the mOFC, lOFC, or DH. If these findings are considered for their implications for SUD, as per the rationale for this study, they might suggest that an individual who has a co-morbid addiction, such as alcohol and cigarettes, if they experience a short period of abstinence and relapse on one outcome in a context where

abstinence has not occurred (e.g. they have been abstinent at home and they go to the pub and have a cigarette), they are likely to relapse on both outcomes (alcohol and the cigarette). Alternatively, because there was no general reinstatement for Experiment 1, it is possible that a person might not relapse at all. If, however, relapse on one outcome occurs in the abstinence context, or if abstinence occurs over a longer period, it is more likely to be specific to the outcome that is experienced.

CHAPTER 4

NEUROINFLAMMATION IN THE POSTERIOR DORSOMEDIAL STRIATUM FACILITATES GOAL-DIRECTED ACTION THROUGH AN ASTROCYTE MEDIATED MECHANISM

INTRODUCTION

Multiple studies have identified the neural circuitry of compulsive reward-seeking, but have failed to identify the endogenous mechanisms that drive dysfunction in these circuits. Neuroinflammation is a primary candidate, as it has been identified in the striatum of individuals with compulsive disorders such as SUD and OCD. As reviewed in Chapter 2, glial cells within the CNS are the primary cells responsible for a neuroinflammatory response and when such a response occurs, this alters the homeostatic role glial cells play in modulating brain plasticity and behaviour (Kol et al., 2020; Namba et al., 2021; Parkhurst et al., 2013; Tanaka et al., 2013). Although originally only associated with multiple sclerosis (MS), as our knowledge of the brain's immune system has become more nuanced, investigations of neuroinflammation has also began to pervade the study of many varied neurodegenerative and neuropsychiatric disorders. These disorders are all associated with a range of cognitive impairments, each of which affect an individual's ability to exert cognitive control over their behaviour and make effective choices. Together, these studies suggest that neuroinflammation may contribute to the diminished behavioural control observed in people with compulsive disorder.

Dysfunction of the pDMS (or its homologue: the caudate), an area identified as the neural locus for goal-directed decision-making, acts as a neural phenotypic marker for compulsion (Ahmari et al., 2013; Balleine & O'Doherty, 2010; Corbit & Janak, 2010; Gremel & Costa, 2013; Lipton et al., 2019; Yin, Ostlund, et al., 2005). Indeed, aberrant striatal activity and increased neuroinflammation has been consistently identified in the brains of individuals with neurologic and neuropsychiatric disorders, including compulsive disorders using neuroimaging or post-mortem immunohistochemistry (Cox & Witten, 2019; Friedman et al., 2017). However, such studies are inherently correlational and do not establish whether the

neuroinflammation observed is causal to the cognitive and behavioural deficits that accompany compulsive disorders. Thus, Aim 2 of the current thesis was to investigate whether neuroinflammation in the pDMS alters control over action selection – whether that control is guided by cues or goal-directed, and will further explore the precise glial mechanisms that might underlie such alterations. This aim will be investigated in three experiments presented in Chapter 4, each of which comprise multiple stages and tests. The schedules for Experiments 3 and 5 are shown in Figure 15A, and the schedule for Experiment 4 is in 15B.

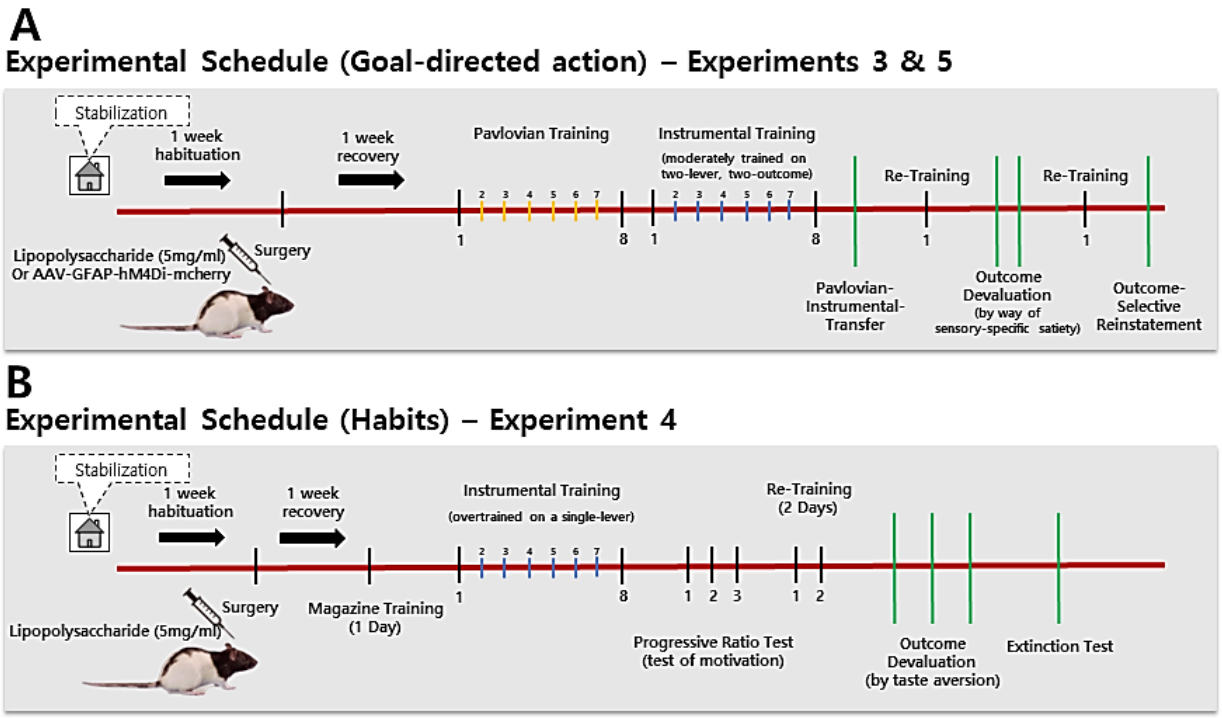

Figure 15. Schematic diagram as described in the "Materials and methods" section. Experiments 3 and 5 aim to establish causal evidence that neuroinflammation in the pDMS impairs cue-guided and goal-directed action selection, and to distinguish the relative contributions of astrocytes in pDMS to decision-making. Experiment 4 aims to investigate whether pDMS neuroinflammation increases motivation generally, or goal-directed action specifically.

For Experiment 3, I stereotactically injected LPS into the pDMS to induce a neuroinflammation and examined the performance of rats with an inflamed pDMS relative to saline-injected Sham controls on across several behavioural assays. Experiment 3 results revealed that, against expectations, neuroinflammation in pDMS facilitated performance on sPIT and devaluation tests (but not selective reinstatement) relative to Sham controls. However, because Sham animals did not display the basic behavioural effects when these facilitations were observed, animals were switched to a lower-fat/lower-protein lab chow and then retrained and retested to produce intact behaviour in Shams. After this switch, however, the facilitation in LPS animals was not maintained. These results indicated three possible interpretations: a) that pDMS neuroinflammation generally increased motivation, b) that extinction due to re-testing or increased time from LPS injection masked our ability to observe any facilitation of effects after the diet switch, or c) that pDMS neuroinflammation facilitated cue-guided and goal-directed action control more specifically.

It was the aim of Experiment 4 to distinguish between these possibilities. For this experiment, LPS or vehicle was again injected into the pDMS and animals were tested for outcome devaluation performance, but this time rats were overtrained on a single-lever, single outcome protocol on an interval schedule to encourage habitual responding. In addition, taste aversion conditioning was used rather than specific satiety in order to 'devalue' the sucrose outcome, because specific satiety has been demonstrated to maintain goal-directed control even after overtraining (Bouton et al., 2020), and here we wanted to investigate the effects of pDMS neuroinflammation under circumstances that would usually promote habits.

Rats were then given a progressive ratio test in which rats had to press a lever for a sucrose outcome at ever-increasing ratios. This is a common test of motivation in rodents and, if pDMS neuroinflammation increases motivation, then group Sham would be expected to reach 'breakpoint' (i.e. 5 minutes without responding) earlier than group LPS. Following this test, animals were retrained on lever pressing, then half of the animals received taste aversion training to the sucrose (i.e. pairings with lithium chloride injections to induce illness) to devalue it. All rats were then tested for their propensity to lever press in an extinction test. It was expected that group Sham would respond in a habitual manner (i.e. Valued = Devalued) whereas if goal-directed action was facilitated in group LPS they should respond in a goal-directed manner (i.e. Valued > Devalued). Importantly, this experiment was not subject to re-testing in extinction nor to a long lag between LPS injection and testing, so that any alterations in levels of responding could not be attributed to these factors. The results of Experiment 4 showed that LPS-induced neuroinflammation in pDMS did facilitated performance on progressive ratio testing as well as maintaining goal-directed action control when Shams were trained to be habitual.

Together, the results of Experiments 3 and 4 suggest that pDMS neuroinflammation both increases motivation and facilitates goal-directed action control. Once these behavioural alterations had been determined I next turned my attention to the question of the underlying mechanisms of these alterations. The immunohistochemical results of Experiments 3 and 4 detected elevations in the levels of both microglia and astrocytes, as might be expected in a neuroinflammatory event, but only the expression of astrocytes positively correlated with choice scores on which action selection was facilitated for LPS animals. No such correlations were detected for microglial expression. Moreover, co-localised NeuN/cFos that was taken as a reflection of basal activity in the circuit (i.e. was not timed to reflect any behavioural event)

showed the same correlational pattern as astrocyte expression, suggesting that astrocytes might be modulating neuronal activity to achieve these behavioural effects. Thus, in Experiment 5, I explored whether intact astrocytic signalling in the pDMS is necessary for goal-directed action using chemogenetics (designer receptor exclusively activated by designer drugs-DREADDs) under the GFAP promoter in pDMS to specifically target astrocytes. This experiment was conducted in the same manner as described for Experiment 3, with the 'designer drug' deschlorochlozapine (DCZ) administered prior to each test session. Results confirmed that intact astrocytic signalling in pDMS is indeed required for the observation of sPIT and outcome devaluation, but not outcome-selective reinstatement.

Experiment 3: pDMS neuroinflamation facilitates action selection under low motivation conditions.

MATERIALS AND METHODS

Animals and housing conditions

A total of 34 Long-Evans rats (15 male and 19 female), weighing 180–350 g, 10 weeks of age at the beginning of the experiment were purchased from the Australian Research Centre, Perth, Australia, and were housed in groups of 2-3 in transparent amber plastic boxes located in a temperature- and humidity-controlled room with a 12-h light/dark (07:00–19:00 h light) schedule. Experiments were conducted during the light cycle. Before the experiments, all animals were habituated to the laboratory settings for a week with full access to food and water and environmental enrichment which include plastic tunnel, shreds of paper, and wooden object to gnaw. Throughout the training and actual experiment, animals were maintained at ~85% of their free-feeding body weight by restricting their food intake to 8-14g of their maintenance diet per day. All procedures were approved by the Ethics Committees of

the Garvan Institute of Medical Research Sydney (AEC 18.34), and Faculty of Science, University of Technology Sydney (ETH21-6657).

Surgery

Animals were anaesthetized with isoflurane (5% induction, 2–3% maintenance) and positioned in a stereotaxic frame (Kopf Instruments). An incision was made into the scalp to expose the skull surface and the incisor bar was adjusted to align bregma and lambda on the same horizontal plane. Small holes were drilled into the skull above the appropriate targeted region and animals received bilateral injections by infusing 1 µl per hemisphere of LPS (5ug/ µl) via a 1-µl glass syringe (Hamilton Company) connected to an infusion pump (Pump 11 Elite Nanomite, Harvard Apparatus) into the pDMS (anteroposterior, −0.2mm; mediolateral, ±2.4mm (male), ±2.3mm (female); and dorsoventral, −4.5mm, relative to bregma). The infusion was conducted at a rate of 0.15 µl/min, and injectors were left in place for an additional 5 min to ensure adequate diffusion and to minimize LPS spread along the injector tract. The remaining control animals underwent identical procedures but with injection of sterile saline rather than LPS. A nonsteroidal anti-inflammatory/antibiotic agent were administered preoperatively and postoperatively to minimize pain and discomfort. Animals were allowed to recover for 7 days before the onset of any behavioural training.

Apparatus

All behavioural procedures took place in twelve identical sound attenuating operant chambers (Med Associates, Inc.,) and these chambers were located within individual cubicles. The ceiling, back wall, and hinged front door of the operant chambers were made of a clear Plexiglas and the side wall were made of grey aluminium. The floor was made of stainless steel grids. Each chamber was equipped with a recessed food magazine, located at the base

of one end wall, through which 20% sucrose-10% polycose solution (0.2 ml) and food pellets (45 mg; Bio-Serve, Frenchtown, NJ) could be delivered using a syringe pump and pellet dispenser, into separate compartments respectively. Two retractable levers could be inserted individually on the left and right sides of the magazine. An infrared light situated at the magazine opening was used to detect head entries. Illumination was provided by a 3-W, 24-V house situated at the top-centred on the left end wall opposite the magazine provided constant illumination, and an electric fan fixed in the shell enclosure provided background noise (≈70 dB) throughout training and testing. The apparatus was controlled and the data were recorded using Med-PC IV computer software (Med Associates, Inc.). The boxes also contained a white-noise generator, a sonalert that delivered a 3 kHz tone, and a solanoid that, when activated, delivered a 5 Hz clicker stimulus. All stimuli were adjusted to 80 dB in the presence of background noise of 60 dB provided by a ventilation fan. Outcome devaluation procedures took place in transparent plastic tubs that were smaller, but otherwise identical to the cages in which rats were housed.

Behavioural tests

In addition to the choice-based reinstatement paradigm employed in Chapter 3, the design for which is shown in Figure 3 (Chapter 1), for the experiments under Chapter 4 I additionally tested sPIT and outcome devaluation, which measure cue-guided and goal-directed action selection, respectively. The design for PIT is shown in Figure 6 (Chapter 2), and the design for outcome devaluation is shown in Figure 5 (Chapter 2).

Food restriction and Chow maintenance

One week following recovery from surgery, animals underwent 3 days of food restriction before the onset of lever press training. During this time animals received 10-14g of chow per

day, and their weight was monitored daily to ensure it remained at ~85% of their pre-surgery body weight.

For the initial Pavlovian and instrumental training, as well as the first round of testing for sPIT, devaluation, and reinstatement, the chow that rats were maintained on the higher-fat, higher-protein Gordons Specialty Feed (see Table 1). Following reinstatement testing, animals were switched to a lower fat, lower protein Irradiated Specialty Feed's chow (see Table 1) and re-trained and re-tested on each test. See below for details. See below for details.

Table 1. Nutritional information of the lab chow used during the experiment

	Gordons Specialty Feed	Irradiated Specialty Feed
Protein	23%	19%
Saturated Fat	21.3%	0.78%
Mono-unsaturated Fat	42.9%	2.06%
Poly-unsaturated Fat	30.7%	1.88%
Crude Fibre	5%	5.20%

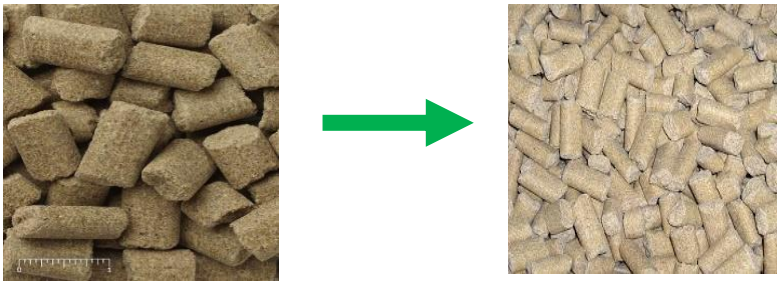

Figure 16. Representation of the food used during the experiment (Gordons Specialty Feed chow vs. Irradiated Specialty Feed chow).

Pavlovian training

For the first 8 days, animals were placed in operant chambers for 60 min during which they received eight 2 min presentations of two conditioned stimuli (CS; white noise or clicker) paired with one of two outcomes (sucrose solution or pellet) presented on a random time schedule around an average of 30 s throughout each CS presentation. Each CS was presented 4 times, with a variable intertrial interval (ITI) that averaged to 5 min. For half the subjects, tone was paired with sucrose and noise with pellets, with the other half receiving the opposite arrangement. Magazine entries throughout the session were recorded and reported for the 2 min prior to each CS presentation (PreCS) and the 2 min during each CS presentation.

Lever press training

Following Pavlovian training, animals were trained to press a left and right lever over 8 days which earned the same sucrose and grain pellet outcomes. Specifically, for half of the animals, the left lever earned pellets and the right lever earned sucrose, and the other half received the opposite arrangement (counterbalanced). Each session lasted for 50 minutes and consisted of two 10 minutes sessions on each lever (i.e., four x 10 minutes sessions in total) separated by a 2.5 minutes time-out period in which the levers were retracted and the houselight was switched off. Animals could earn a maximum of 40 sucrose and 40 pellets deliveries within the session. For the first 2 days, animals were trained on a continuous reinforcement schedule (CRF) in which each lever press produced a single outcome. Animals were then shifted to a random ratio-5 schedule for the next 3 days (i.e. each action delivered an outcome with a probability of 0.2), then to a RR-10 schedule (or a probability of 0.1) for the final 3 days. After 40 sucrose solutions and 40 pellets were delivered or 50 minutes had

elapsed, whichever came first, the session was terminated, levers were retracted, and house lights switched off.

Pavlovian Instrumental Transfer (Specific PIT) test

One day after the end of instrumental training, rats were tested for sPIT performance. For this test, responding on both levers was first extinguished for 8 min to reduce baseline performance. Subsequently, each CS was presented four times over the next 40 min in the following order: clicker-noise-noise-clicker-noise-clicker-clicker-noise. Each CS lasted 2 min and had a fixed ITI of 3 min. Magazine entries and lever pressing rates were recorded throughout the session and responses were separated into PreCS and CS periods (2 min each). Lever presses were recorded, but not reinforced.

Outcome Devaluation

One day after sPIT testing, rats were given 1 day of instrumental retraining on RR-10 in the manner previously described. On the following day, animals were given free access to either the pellets (20 g placed in a bowl) or the sucrose solution (100 ml in a drinking bottle) for 1 hr. The amount of pellets and sucrose solution consumed each day was measured. Animals were then placed in the operant chamber for a 10 min choice extinction test. During this test, both levers were extended and lever presses recorded, but no outcomes were delivered. The next day, a second devaluation test was administered with the opposite outcome (i.e. if animals were prefed on pellets the previous day they were now prefed on sucrose, and vice versa). Following pre-freeding animals were again placed into the operant chambers for a second 10 min choice extinction test. All test results are reported as averaged across these two tests.

Outcome Selective Reinstatement Test

Subsequent to devaluation testing, rats received one day of instrumental retraining on an RR-10 schedule for 1 day. The next day, animals were tested for outcome-selective reinstatement as described in Chapter 3, except that this time rats received a 15 min period of extinction to reduce baseline performance. Because rats in Experiment 3 had been subject to two tests in extinction already (i.e., sPIT and devaluation), they did not require the full 30 min of extinction prior to reinstatement testing. They then received four reinstatement trials separated by 4 min each as before, and each reinstatement trial consisted of a single free delivery of either the sucrose solution or the grain pellet presented in the following order: sucrose, pellet, pellet, and sucrose. Responding was measured during the 2 min periods immediately before (pre) and after (post) each delivery.

Switching maintenance chow, re-training and re-testing

As noted, I initially used a highly palatable home chow (high-fat/high-protein lab chow) for Experiment 3 which reduced performance in Sham controls. Following training and testing during which animals were given this chow, I switched to a smaller amount (6-8g) of less palatable home chow (lower-fat/lower-protein lab chow) to increase hunger and motivation to lever press for food, with the aim of improving test performance in group Sham. Then I sought to answer whether pDMS neuroinflammation still facilitated goal-directed action when Sham performance was improved.

Following the switch from Gordon's to Specialty feeds chow, rats were given an additional 4 days of Pavlovian training, and an additional 4 days of intrumental training, then tested for performance on sPIT, outcome devaluation, and outcome-selective reinstatement as before.

Tissue preparation

For post-mortem tissue analysis I used immunohistochemical markers GFAP to measure astrocyte expression, IBA1 to measure microglial expression, c-Fos as an activation marker, and NeuN to neurons.

One day after the outcome-selective reinstatement test, animals were sacrificed via CO2 inhalation and perfused transcardially with cold 4% paraformaldehyde in 0.1 M phosphate buffer saline (PBS; pH 7.3-7.5). Brains were rapidly and carefully removed and postfixed in 4% paraformaldehyde overnight and then placed in 30% sucrose. Brains were sectioned coronally at 40 µm through the pDMS defined by Paxinos and Watson (2014) using a cryostat (CM3050S, Leica Microsystems) maintained at approximately -20℃elsius. The sectioned slices were immediately immersed in cryoprotectant solution and stored in the -20 freezer.

Later, five representative sections from pDMS were selected for each rat. Sections were first washed three times (10 minutes per wash) in PBS to remove any exogenous substances. The sections were then incubated in a blocking solution comprising of 3% Bovine Serum Albumin (BSA) + 0.25% TritonX-100 in 1 x PBS for one hour to permeabilize tissue and block any non-specific binding. Sections were then incubated in anti-GFAP mouse primary antibody (1:300, Cell Signalling Technology Catalog #3670), anti-IBA1 rabbit primary antibody (1:500, FUJIFILM Wako Chemicals U.S.A. Corporation), and anti-NeuN chicken primary antibody (1:1000, GeneTex Catalog #GTX00837) diluted in blocking solution for 72 h at 4°C. Sections were then washed 3 times in 1 × PBS and incubated overnight at 4°C in goat anti-mouse AlexaFluor-488 secondary antibody (1:250, ThermoFisher Catalog #A-11001), donkey anti-rabbit AlexaFluor-568 secondary antibody (1:250, ThermoFisher Catalog #A10042), and goat anti-chicken AlexaFluor-647 secondary antibody (1:250, ThermoFisher Catalog #A-21449),

followed by a counterstain with 4',6-diamidino-2-phenylindole (DAPI; Thermo Scientific; 1:1000, diluted in 1x PBS). Finally, every section was mounted onto Superfrost microscope slides (Fisher Scientific) and were coverslipped (Menzel-Glaser) using the mounting agent Vectashield and left to dry overnight in darkness.

Separate brain sections of the pDMS were also processed and incubated in anti-c-Fos primary antibody (1:500, Synaptic Systems Catalog #226 003) and anti-NeuN chicken primary antibody (1:500, GeneTex Catalog #GTX00837) diluted in blocking solution for 72 h at 4°C to see how much activation during neuroinflammation. Sections were then washed 3 times in 1 × PBS and incubated overnight at 4°C in donkey anti-rabbit AlexaFluor-568 secondary antibody (1:500, ThermoFisher Catalog #A10042) and goat anti-chicken AlexaFluor-647 secondary antibody (1:500, ThermoFisher Catalog #A-21449), followed by a counterstain with DAPI (Thermo Scientific; 1:1000, diluted in 1x PBS). Sections were mounted and quantified using the same procedures described above.

Imaging and immunofluorescence analysis

For quantification of GFAP, IBA1, NeuN, and c-Fos, a single image was taken of the pDMS per hemisphere of each slice (10 images in total per brain region of each rat) on a Nikon TiE2 microscope using a 10x objective and Leica STELLARIS 20x air objective for representative images.

For cell counts: Images were quantified using imaging software (ImageJ, Fiji Cell Counter), whereby each fluorescent channel was split to isolate and count the cells of interest. Z-stacks were used instead of simply a single image plane. Briefly, the image was adjusted to 8-bit and background subtraction was applied to remove background noise. Thresholding was used to isolate positive stained cells and the threshold for contrast and brightness was adjusted for

all images until consistent between images (maximum: 255, minimum: 0). Images were then converted to binary and finally, the Analyze Particles tool was used to quantify the number of cells based on a minimum particle size of 16. ImageJ counted each cell between our parameters and presented it as a "count."

For co-localization of NeuN and c-Fos: Co-localization was measured for c-Fos and NeuN only to determine the rate of neuronal activation. Stacked images of each were converted into RGB colour images and made composite. The colour threshold was adjusted to select all of the red signal (which was the colocalization of c-Fos and NeuN), and the percentage area of the selected signal was measured and averaged for each brain using ImageJ.

Data and Statistical analysis

Data were collected automatically by Med-PC and uploaded to Microsoft Excel using Med-PC to Excel software. Pavlovian conditioning and lever press acquisition data was analysed using two-way repeated measures ANOVAs controlling the per-family error rate at $\alpha=0.05$. If conditions for sphericity were not met, the Greenhouse-Geisser correction was applied. To allow for a more fine-grained analysis of test data, all data for sPIT, outcome devaluation, and outcome-selective reinstatement were analysed using complex orthogonal contrasts controlling the per-contrast error rate at $\alpha=0.05$ according to the procedure described by Hays (1973). Data were expressed as mean ± standard error of the mean (SEM) and averaged across counterbalanced conditions. If interactions were detected, follow-up simple effects analyses ($\alpha=0.05$) were calculated to determine the source of the interaction. For immunohistochemical analysis, counts and intensity were compared between LPS and Sham groups using two tailed t-tests and correlated using GraphPad. Values of $p < 0.05$ were considered statistically significant. The statistical softwares GraphPad Prism, SPSS, and PSY

were used to carry out all these analyses. Full data, statistical analyses, and results are shown in Appendix B.

RESULTS

Histology: Neuroanatomical placements

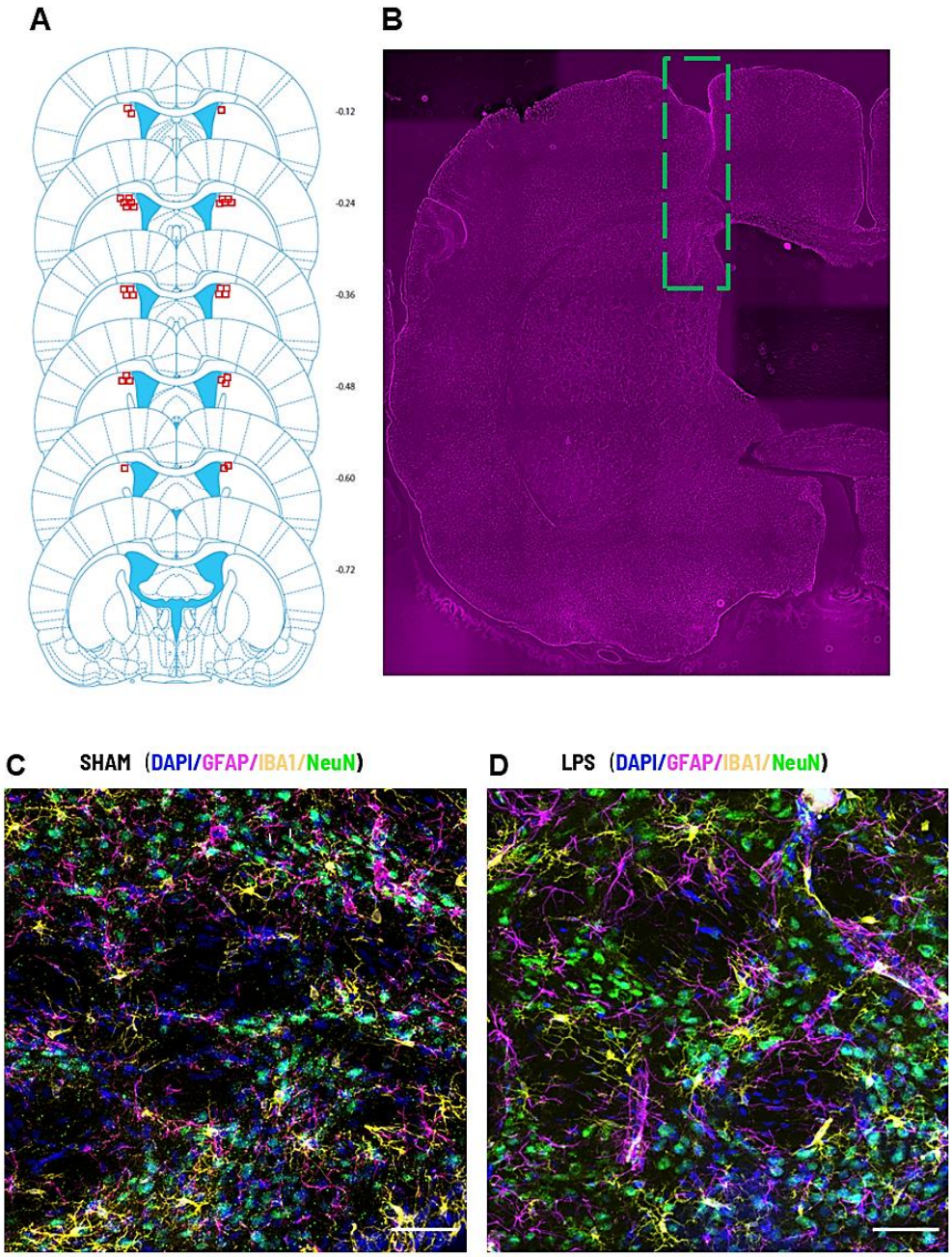

Figure 17. A representative image of the posterior dorsomedial striatum region. (A) Distribution and locations of the LPS injections included in the analysis. (B) GFAP-labelled demonstrating needle placement in a rat. Magenta

= Glial fibrillary astrocytic protein (GFAP) labelled astrocytes. (C) Saline-injected and (D) LPS-injected rat stained with DAPI/GFAP/IBA1/NeuN. Calibration: 42 µm.

Figure 17A shows the approximate placements each LPS injection, as determined by the co-localisation of GFAP and IBA1 expression around a track mark. A representative image is shown in Figure 17D (relative to saline-injected Sham control in Figure 17C – quantification of these markers is reported following the behavioural results below). Figure 17B shows a representative image of the target pDMS region for all placements. In total 4 rats were excluded from the final analysis because they either did not express any track marks indicative of neuroinflammation, or this trackmark was not in the target region. After exclusions, final numbers were N = 30, of which n = 14 were in group Sham and n = 16 in group LPS.

Behavioural Results: Neuroinflammation in pDMS facilitates goal-directed behaviours under low motivation conditions.

Animals in both groups acquired Pavlovian conditioning (Figure 18B) and this did not differ according to group ($F < 1$). That is, all animals learned to enter the food magazine more during the 2 min CS presentation than during the 2 min preCS period. This is supported by a main effect of CS period (preCS vs CS) $F(1,28) = 364.980$, $p = .000$, and of Day $F(7,196) = 32.398$, $p = .000$, and a Day x CS period interaction (preCS vs CS) $F(7,196) = 46.896$, $p = .000$. No main effect of group or any interactions with group was detected, $Fs < 1$. Both groups also equally acquired lever press responding, as shown in Figure 18C. This is supported by a main effect of day $F(7,196) = 53.28$, $p = .000$, no main effect of group and no day x group interaction, $Fs < 1$. LPS-induced neuroinflammation in the pDMS therefore does not appear to affect Pavlovian and instrumental learning *per se*.

Performance on the sPIT test is shown in Figure 18D. During the test, food outcomes are not presented. Typically, sPIT is observed when a stimulus associated with a unique outcome

(usually appetitive, such as a food outcome) enhances performance of an instrumental response that earns the same reward. From this figure, it appears that sPIT was intact for the LPS group but not Sham controls. That is, only group LPS responded more on the lever that earned the same outcome as the currently presented stimulus (i.e. Same > Different) whereas Shams responded equally on both levers (Same = Different). This was supported by a main effect of sPIT, $F(1,28) = 9.455$, $p = .005$, that interacted with group, $F(1,28) = 5.710$, $p = .024$. The interaction was comprised of a significant simple effect for the LPS group (Same > Different), $F(1,28) = 15.996$, $p = .000$, but no such effect for the Sham group (Same = Different), $F < 1$. There was also a main effect of post-baseline responding on test, $F(1,28) = 10.818$, $p = .003$, that did not interact with the group, $F(1,28) = 0.015$, $p = .903$.

Performance on the outcome devaluation test is shown in Figure 18E. Like sPIT, pDMS neuroinflammation facilitated performance on this task compared to group Sham. That is, although both groups responded in the expected direction this time – pressing the valued lever at higher rates than the devalued lever – this difference (Valued > Devalued) was larger for animals in the LPS group, as demonstrated by a significant group x devaluation interaction on the performance $F(1,28) = 4.878$, $p = .035$. This interaction consisted of a significant simple effect for both groups, but it was smaller for group Sham ($F(1,28) = 7.445$, $p = .011$) compared to group LPS ($F(1,28) = 31.060$, $p = .000$).

Performance during reinstatement testing is shown in Figure 18F. From this figure, it is clear that outcome-selective reinstatement was intact for both groups. That is, after each outcome was delivered, animals preferentially pressed the lever that had previously earned that outcome (i.e. pellet delivery elicited presses on the pellet lever and sucrose delivery elicited presses on the sucrose lever). In support, there was a main effect of reinstatement

(Reinstated > Nonreinstated) F (1,28) = 67.951, p = .000, which did not interact with any group differences, all Fs < 1.

Together, these results suggest that, in contrast to expectations, stimulus-guided and internally-guided goal-directed action control was facilitated by LPS-induced neuroinflammation in the pDMS, whereas outcome-guided decision-making was unaffected.

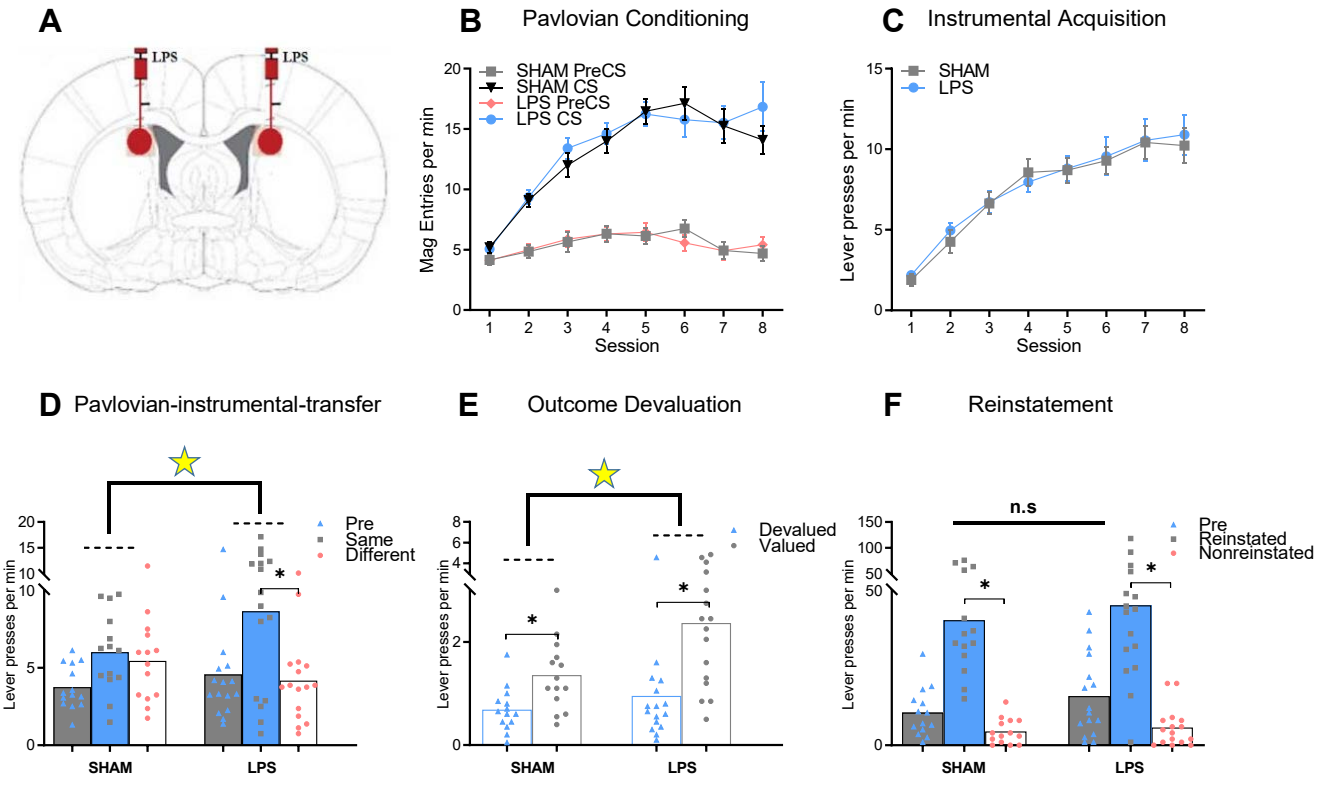

Figure 18. ***Neuroinflammation in posterior dorsomedial striatum facilitates goal-directed action under low motivation conditions****. (A) Representation of the LPS injections made into the posterior dorsomedial striatum. (B) Magazine entries per min (±SEM) during Pavlovian conditioning. (C) Lever pressing per min (±SEM) during instrumental conditioning. (D) Individual data plots and mean lever presses during the Pavlovian-instrumental transfer test, (E) outcome devaluation test, and (D) outcome-selective reinstatement test using Gordons Specialty Feed chow. *, ☆ denotes that the p-value was under 0.05. (n = 14 (SHAM), n = 16 (LPS), N = 30).*

Neuroinflammation in pDMS does not affect performance under high motivation conditions.

Once maintenance chow was switched to the lower-fat, lower protein Irradiated Specialty Feeds chow, animals in both groups maintained Pavlovian responding across retraining (Figure 19A). That is, all animals entered the food magazine more during the 2 min CS presentation than during the 2 min preCS period. This is supported by a main effect of CS period (preCS vs CS) $F(1,28) = 126.575$, $p < .0001$, and of Day $F(3,84) = 3.443$, $p = .020$, but no Day x CS period interaction ($F<1$), group ($F<1$), or any interactions with group ($F(3,84) = 2.147$, $p = .100$). Both groups also equally increased lever press responding across instrumental retraining, as shown in Figure 19B. This is supported by a main effect of day $F(3,84) = 15.87$, $p < .0001$, no main effect of group ($F<1$) and no day x group interaction ($F(3,84) = 1.446$, $p = .235$).

This time, both groups LPS and Sham showed intact PIT (Same > Different) when re-tested as shown in Figure 19C. This is supported by a main effect of PIT, $F(1,28) = 30.605$, $p = .000$ which didn't interact with group, $F < 1$. There was also a main effect of post-baseline responding, $F(1,28) = 18.666$, $p = .000$, that did not interact with the group, $F(1,28) = 0.394$, $p = .535$. Both groups also now displayed equivalent outcome devaluation performance (Valued > Devalued), as shown in Figure 19D. There was a main effect of devaluation, $F(1,28) = 12.378$, $p = .000$), which didn't interact with group $F < 1$. As before, selective reinstatement was intact for all groups as shown in Figure 19E. This is supported by a main effect of selective reinstatement (Reinstated > Nonreinstated), $F(1,28) = 57.780$, $p = .000$, which did not interact with group, $F < 1$.

These results suggest that when performance on each test is intact for Sham controls, pDMS neuroinflammation does not provide any further facilitation of each effect. Together with the results obtained when animals were fed Gordon's chow, these results could suggest

that rather than facilitating action selection specifically, pDMS neuroinflammation has simply increased motivation under low motivation conditions (i.e. when animals are receiving a high fat/protein home chow and are not highly motivated to food seek). Alternatively, it is possible that performance on the Sham animals was not at ceiling under low motivation conditions in Figure 18 above, but was in Figure 19, such that it was not possible to detect any further facilitation of performance when motivation was higher overall. It was the aim of Experiment 4 to distinguish between these possibilities.

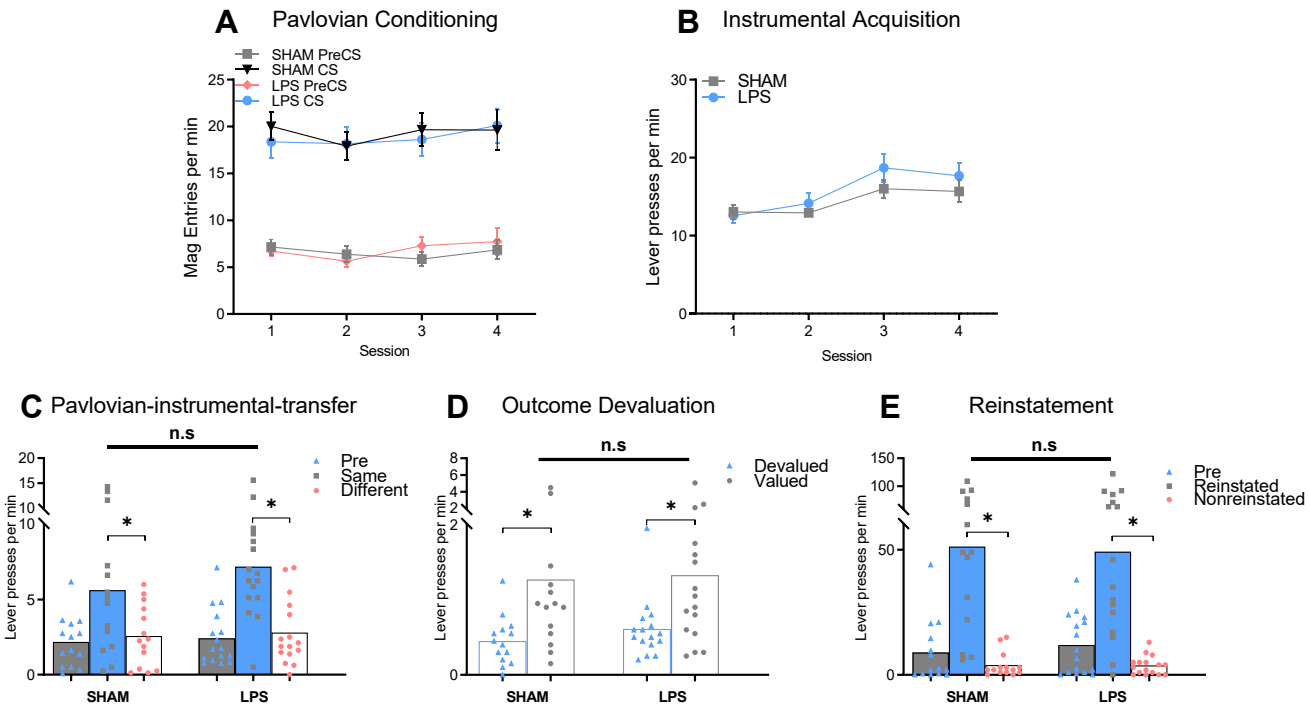

*Figure 19. (A) Magazine entries per min (±SEM) during Pavlovian conditioning. (B) Lever pressing per min (±SEM) during instrumental conditioning. Individual data plots and mean lever presses during the (C) Pavlovian-instrumental transfer test, (D) outcome devaluation test, and (E) outcome-selective reinstatement test using Irradiated Specialty Feed chow. * denotes that the p-value was under 0.05. (n = 14 (SHAM), n = 16 (LPS), N = 30).*

Quantification of immunohistochemical markers in posterior dorsomedial striatum.

Representative photomicrographs demonstrating the extent of GFAP, IBA1, NeuN, and c-Fos expression, and c-Fos/NeuN co-localization in the pDMS of Sham and LPS-injected rats are shown in Figures 20-23A-B, respectively. As shown in Figure 20C, the number of GFAP positive cells ($t=6.255$, $p < .0001$) was increased in LPS-injected rats relative to Sham controls. As shown in Figure 21C, the number of IBA1 positive cells ($t=8.742$, $p < .0001$) was increased in LPS-injected rats relative to Shams. Together, these results show that LPS injections caused the proliferation of both astrocytes and microglia, confirming that LPS was effective in producing a neuroinflammatory response that was still present at the time of analysis – 8 weeks after the initial surgery.

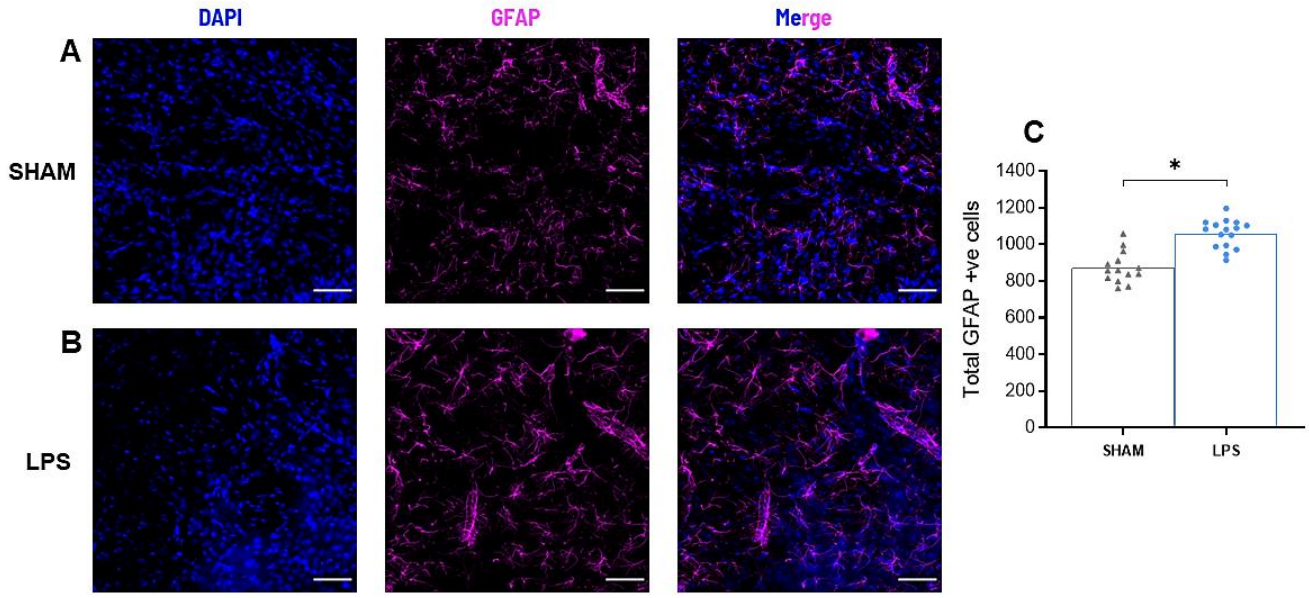

*Figure 20. A representative image of the pDMS region of saline-injected (A) and LPS-injected (B) rat stained with GFAP. (C) Number of cells positively immunostained for GFAP. * denotes that the p-value was under 0.05. (n = 14 (SHAM), n = 16 (LPS), N = 30)*

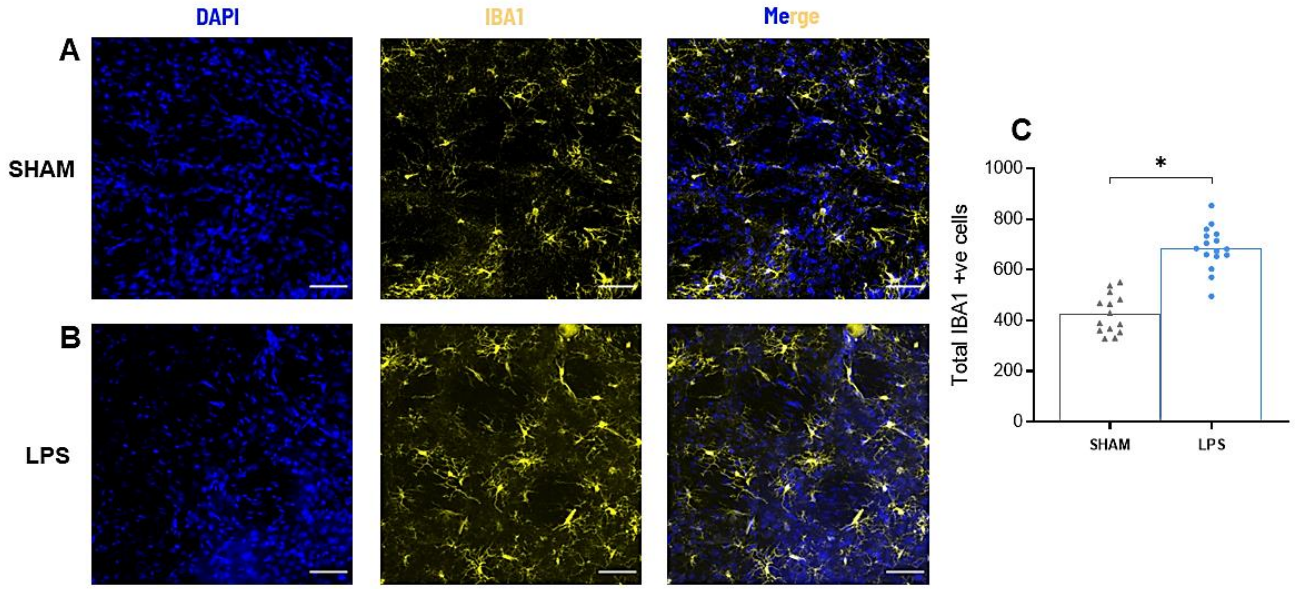

*Figure 21. A representative image of the pDMS region of saline-injected (A) and LPS-injected (B) rat stained with IBA1. (C) Number of cells positively immunostained for IBA1. * denotes that the p-value was under 0.05. (n = 14 (SHAM), n = 16 (LPS), N = 30)*

As shown in Figure 22C, the number of NeuN positive cells did not differ between groups, t=1.897, p = .0682. This demonstrates that LPS injection did not cause any significant neuronal death in this region. As shown in Figure 23C, however, LPS injections did increase cell activity, as demonstrated by an increase in the number of c-Fos expressing cells in the pDMS (t=5.519, p < .0001) in group LPS relative to group Sham. Moreover, neurons in particular appear to have increased their activity in LPS-injected rats, because the co-localised c-Fos-NeuN intensity (Figure 23D) was also higher (t=5.137, p < .0001) in LPS-injected rats.

Together, the immunohistochemical analysis confirms that LPS was successful in inducing neuroinflammation, and suggests that this inflammatory response also led to an increase in neuronal excitation.

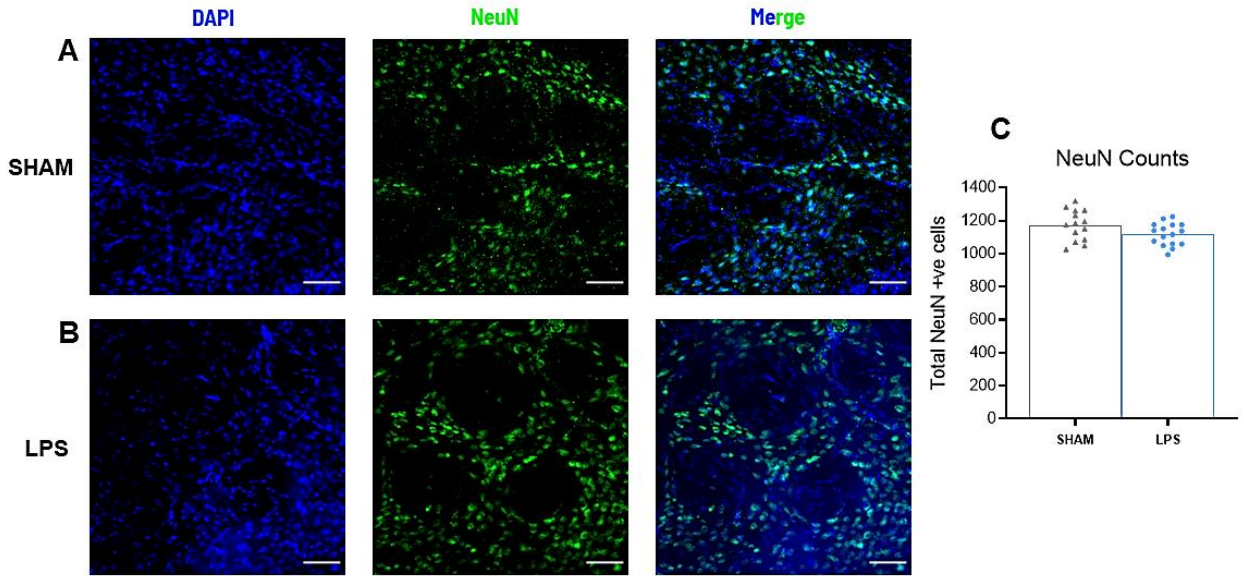

Figure 22. A representative image of the pDMS region of saline-injected (A) and LPS-injected (B) rat stained with NeuN. (C) Number of cells positively immunostained for NeuN. (n = 14 (SHAM), n = 16 (LPS), N = 30).

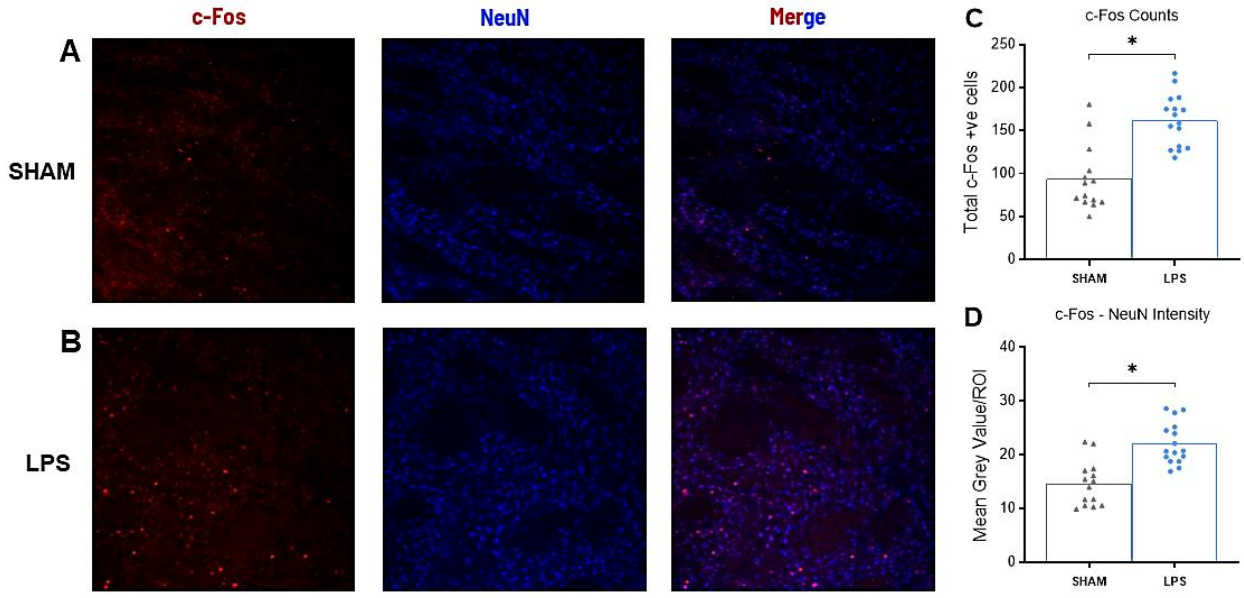

*Figure 23. A representative image of the pDMS region of saline-injected (A) and LPS-injected (B) rat stained with c-Fos and NeuN. (C) Number of cells positively immunostained for c-Fos. (D) c-Fos-NeuN intensity quantification. * denotes that the p-value was under 0.05. (n = 14 (SHAM), n = 16 (LPS), N = 30)*

Astrocytic (GFAP) expression and c-Fos-NeuN intensity, but not microglia (IBA1), positively correlated with sPIT and devaluation performance.

Test behaviours were next correlated with GFAP, IBA1, NeuN, and c-Fos expression, as well as c-Fos-NeuN intensity using the immunohistochemical results from Figures 20-23. To calculate this correlation, I used "PIT score", a "devaluation score", and a "reinstatement score" to ensure that any association detected was not driven by baseline differences in lever press responding *per se*, but rather by the animals selectivity of responding for one or the other levers. For these scores, I first calculated suppression ratio (SR) scores on each of the levers (i.e., the same and different levers for sPIT, the valued and devalued levers for devaluation, and the reinstated and non-reinstated levers for outcome selective reinstatement) according to the Equation 1:

$$1)\quad SR = \frac{Lever\ press\ rate\ on\ test}{(Lever\ press\ rate\ on\ test + Lever\ press\ rate\ during\ training)}$$

In this equation, "lever press rate during training" was taken as the average press rate on each lever across the last two days of lever press training relative to test. I then calculated the PIT score by subtracting the normalised scores on the different lever from the normalised scores on the same lever, such that a higher score indicated better sPIT performance. Likewise, for devaluation I subtracted the normalised scores on the devalued from those on the valued lever, such that a higher score indicated better devaluation performance, and I did the same thing for reinstatement, this time subtracting scores on the nonreinstated from scores on the reinstated lever, such that a high score indicated better reinstatement performance. Each of these scores were then separately correlated with GFAP, IBA1, NeuN/c-Fos expression (correlations with c-Fos and NeuN separately can be found in Appendix B, p. 271-273).

I first calculated correlations for the tests given under low motivation conditions, when rats were fed Gordon's chow. As shown in Figure 24, I found that GFAP counts significantly positively correlated with PIT, r = 0.3788, p = 0.0390 (Figure 24A) and devaluation scores, r = 0.3957, p = 0.0304 (Figure 24D) but not with reinstatement scores, r = -0.1550, p = 0.4135 (Figure 24G), suggesting that higher astrocytic expression in pDMS was associated with better cue-guided and goal-directed action control specifically on the two tests in which performance was facilitated by LPS, but not on reinstatement for which it was not. By contrast, IBA1 expression did not correlate with any behavioural measures on test [PIT, r = 0.3197, p = 0.0850 (Figure 24B), devaluation scores, r = 0.2385, p = 0.2043 (Figure 24E), reinstatement scores, r = -0.0710, p = 0.7091 (Figure 24H)], suggesting that microglial expression was not associated with any of the observed behaviours. I further found that c-Fos-NeuN intensity positively correlated with sPIT, r = 0.4029, p = 0.0273 (Figure 24C) and devaluation scores, r = 0.3757, p = 0.0408 (Figure 24F), and not reinstatement scores, r = -0.2031, p = 0.2817 (Figure 24I), suggesting that increased neuronal activity in the pDMS, like the increase in astrocyte expression, was associated with better cue-guided and goal-directed action control.

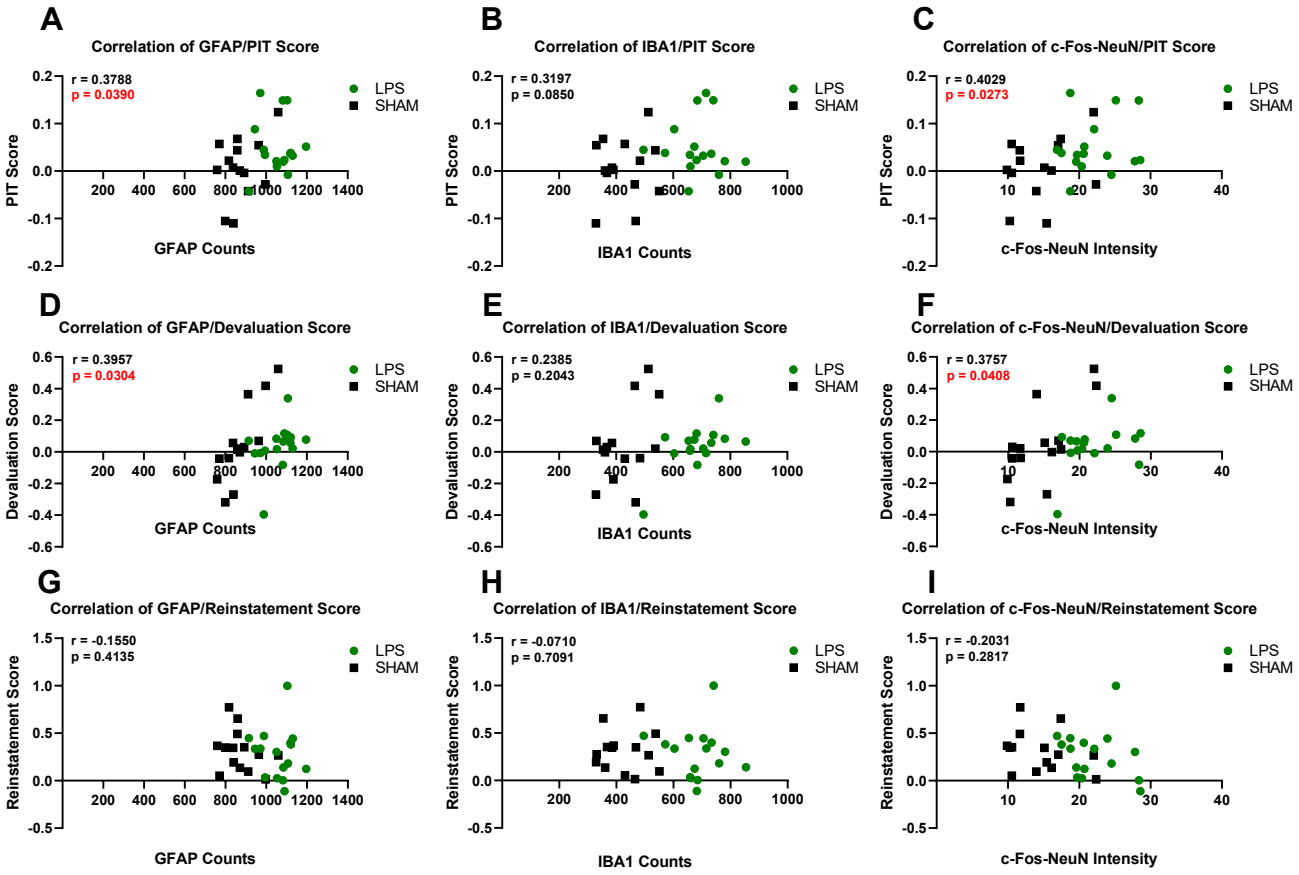

Figure 24. Correlation between GFAP and IBA1 expressions, and c-Fos-NeuN intensity and behavioural performances using Gordons Specialty Feed chow.

The behavioural performances using Specialty Feeds Chow were again correlated with GFAP, IBA1, NeuN, and c-Fos expressions, and c-Fos-NeuN intensity using the immunohistochemical results and newly calculated scores for each test. For these tests, on which performance did not differ between Sham and LPS groups, none of the immunohistochemical markers used correlated with any behavioural measures on test as shown in Figure 25.

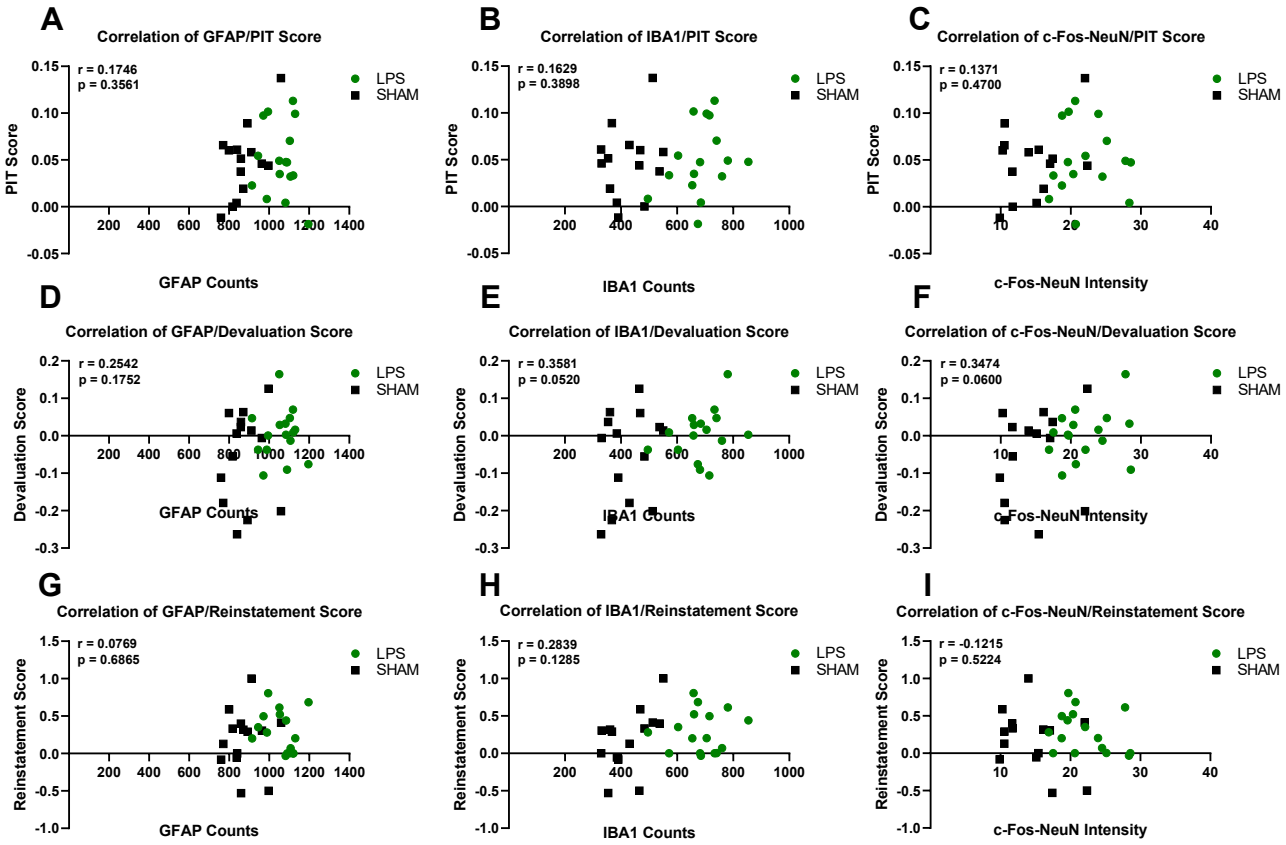

Figure 25. Correlation between GFAP and IBA1 expressions, and c-Fos-NeuN intensity and behavioural performances using Irradiated Specialty Feed chow.

Overall, astrocytic and co-localised c-Fos-NeuN was positively associated with performance on the only two tests in which a behavioural difference was observed – sPIT and devaluation under the Gordons chow. The direction of the results suggests that higher astrocytic expression and higher neuronal activation was associated with better performance on each test, implying that the increases in each might have caused the behavioural facilitation in LPS animals. By contrast, microglial expression did not correlate with any behavioural measure on these experiments, suggesting that the alteration to microglial expression that occurred due to LPS expression likely did not cause the observed behavioural changes.

Experiment 4: Effects of LPS injection into pDMS on overtraining-induced habits

As noted, the fact that pDMS neuroinflammation facilitated sPIT and devaluation performance only when animals were fed a high-fat, high protein maintenance chow which reduced test effects in behavioural controls could suggest that pDMS neuroinflammation increases motivation generally, or that it facilitates goal-directed action more specifically. Experiment 4 was designed to tease apart these possibilities by testing animals on progressive ratio as a measure of motivation, and on devaluation but under procedures designed to induce habits in the Sham controls (i.e. single lever, single outcome on an interval schedule, devaluation by taste aversion) to determine if the LPS animals remained goal-directed when habits would otherwise be expected.

MATERIALS AND METHODS

Animals and Housing

A total of 27 male and 27 female Long-Evans rats (N = 54) were used for Experiment 4. Animals were housed, food deprived, and maintained as described for Experiment 3. All procedures were approved by the Ethics Committees of the Garvan Institute of Medical Research Sydney (AEC 18.34), and Faculty of Science, University of Technology Sydney (ETH21-6657).

Surgery

All surgical procedures were conducted identically to that described for Experiment 3.

Food restriction and Chow maintenance

For this experiment, animals received only 6-8g of the Irradiated Specialty Feeds chow per day to maintain high motivation conditions. They did not receive Gordon's chow at any point.

This was for two reasons, because a) if pDMS neuroinflammation increases motivation on progressive ratio, it should do so over and above any motivation observed in Sham controls, and b) overtraining is known to promote habits, and as I was intending to induce habits in the Sham controls I desired high motivation conditions such that animals pressed the levers at high rates to ensure such overtraining occurred.

Apparatus

All Apparatus were as described for Experiment 3.

Magazine Training

Following recovery from surgery to inject LPS or saline into the pDMS, animals received 3 days of food deprivation and were then given two sessions of magazine training. For these sessions, the house light was turned on at the start of the session and turned off when the session was terminated. No levers were extended. Sucrose solution was delivered at random 60 s intervals for 30 outcomes per session. The session terminated after 45 min or after 30 outcomes had been delivered, whichever came first.

Lever Press Training

Following magazine training, animals then received 8 days of instrumental training (two sessions per day) to press a single lever for sucrose solution delivery. Animals received three sessions of continuous reinforcement, four sessions of random interval of 15 s (RI-15), four sessions of RI-30, and four sessions of RI-60. Right and left lever assignment was counterbalanced across animals. Sessions ended, levers retracted and the houselight terminated when 30 reinforcements were earned or after 60 min, which ever came first.

Progressive ratio test

Following lever press training, animals underwent 2-h of progressive ratio (PR) testing each day for 3 days. A progressive ratio schedule requires the subject to perform an increasing number of lever presses for the next presentation of a reinforcer (Hodos, 1961). For the current study, the PR was set at n+5. This meant that animals initially received a sucrose reward for a single lever press, then for 5 lever presses, then n+5 lever presses until breakpoint – with breakpoint defined as 5 min of no lever pressing. The number of responses required to obtain each successive delivery of the sucrose reward was collected automatically by Med-PC.

Outcome devaluation

The day after progressive ratio testing, animals were given 2 days of instrumental retraining on an RI-60 schedule in the manner previously described. The following day, the sucrose solution was devalued using conditioned taste aversion method for half of the animals. That is, all animals were given ad libitum access to sucrose solution in clear plastic tubs for 30 min each day for 3 days. Immediately after the 30 mins, half of each type of lesion group received an intraperitoneal injection of lithium chloride (0.15 M LiCl, 20 ml/kg) to induce illness which the rat will associate with the outcome, effectively devaluing it, after which they placed back in their home cages. The remaining rats received 0.9% purified saline injections (20 ml/kg) and these animals comprised the valued groups. In total this manipulation yielded 4 groups: Sham-Valued, Sham-Devalued, LPS-Valued, LPS-Devalued. The amount of sucrose solution consumed each day was measured.

Extinction test

The day following the last day of LiCl pairings, all animals received a 5 min extinction test. The test began with the insertion of the same lever used during training and ended with the retraction of the lever. Lever presses were recorded, and no sucrose reward was delivered.

Tissue Processing and Fluorescent Microscopy

All tissue processing and microscopy were conducted identically to that described for Experiment 3.

Statistical analysis

Lever press and magazine entry data were collected automatically by Med-PC (version 5) and uploaded directly to Microsoft Excel using Med-PC to Excel software. Lever press acquisition and progressive ratio data were analysed using repeated measures (Group x Session) ANOVA controlling the per-family error rate at $\alpha=0.05$. To allow for a more fine-grained analysis of test data, I used planned, complex orthogonal contrasts controlling the per-contrast error rate at $\alpha=0.05$ for analyzing the outcome devaluation according to the procedure described by Hays (1973). The amount of sucrose consumed was analysed using Three-Way ANOVA repeated measures. If conditions for sphericity were not met, the Greenhouse-Geisser correction was used. Data analysis was conducted in the manner described for Experiment 3.

RESULTS

pDMS neuroinflammation increased both motivation and goal-directed action relative to controls.

Behaviour

All of the rats acquired lever pressing and the groups increased performance over days (Figure 26A). Although group LPS did appear to press the lever at slightly higher rates than Shams this was not significant. This is supported by a main effect of day F (14,546) = 72.65, p = .000, but no main effect of group (F (1,39) = 3.360, p = .074) and no day x group interaction (F (14,546) = 1.434, p = .133). Moreover, the overall numbers of action-outcome pairings (Figure 26B) and magazine entries (Figure 26C) did not differ between groups (all Fs <1).

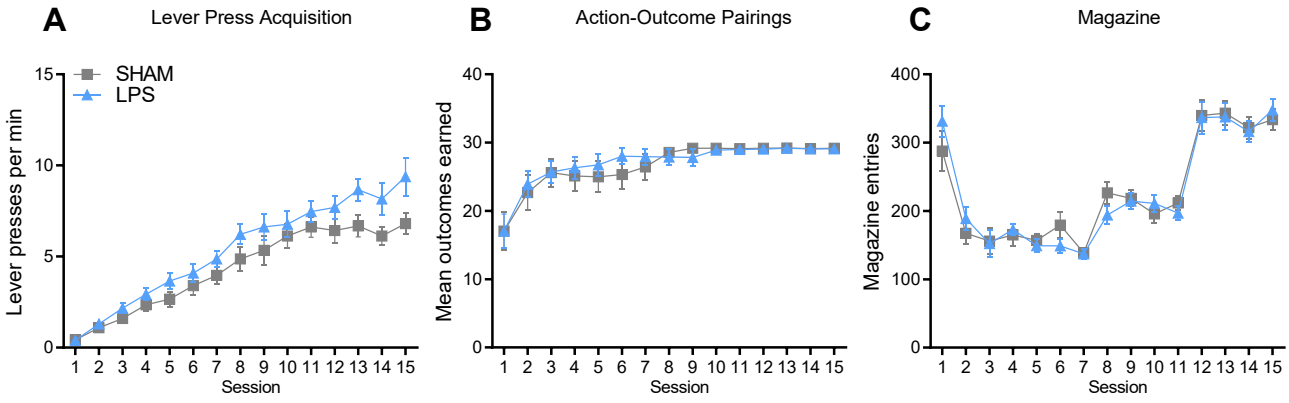

Figure 26. (A) Lever pressing per min (±SEM) during instrumental conditioning, (B) action-outcome pairings, and (C) magazine entries over 15 sessions. (n = 18 (SHAM), n = 23 (LPS), N = 41)

Breakpoint data during progressive ratio testing is shown in Figure 27A. As can be seen from this figure, rats in the LPS group consistently reached higher breakpoints than group Sham, indicative of high motivation for the reward. This is supported by a main effect of

sessions, F (2,78) = 32.78, p = .000, and of group, F (1,39) = 15.15, p = .0004, but no sessions x group interaction, F < 1. To ensure this wasn't simply an artefact of group LP pressing the lever slightly more at baseline (as shown in Figure 26A), I also calculated whether the group differences in progressive ratio persisted when performance was calculated as a percentage of baseline responding, with baseline taken as the average rate of lever pressing during the last four sessions (i.e. two days) of lever press training. As shown in Figure 27B, even when calculated this way, responding was higher in group LPS than in group Sham. This was supported by a main effect of sessions, F (2,78) = 35.36, p = .000, and of group, F (1,39) = 6.243, p = .0168, but no sessions x group interaction, F < 1.

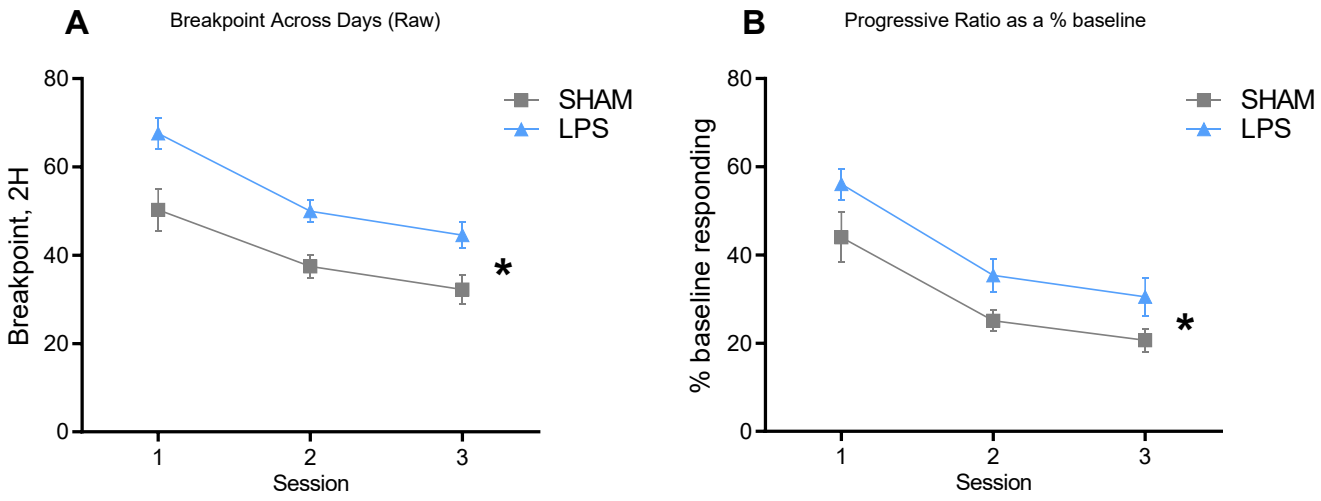

*Figure 27. (A) Breakpoint obtained during the 2-h, 3-day Progressive Ratio schedule. (B) Sum of the lever presses attained during the 2-h, 3-day progressive test displayed as a percentage of baseline responding. * denotes that the p-value was under 0.05. (n = 18 (SHAM), n = 23 (LPS), N = 41)*

The amount of sucrose solution consumed each day following taste aversion training is shown in Figure 28A. This graph shows that devaluation was successful in reducing consumption in both groups, because rats that received LiCl injections reduced their consumption over days whereas saline-injected rats continued to consume the sucrose

solution over days. This pattern did not differ according to group. This was supported by a main effect of devaluation (i.e., the groups injected with LiCl consumed less than saline-injected rats), $F(1,37) = 45.534$, $p = .000$, and days $F(2,74) = 106.707$, $p = .000$, and a significant devaluation-by-day interaction $F(2,74) = 90.436$, $p = .000$. No main effect of group or any interactions with group has been detected, $Fs < 1$. Together, these results show that both injected with LiCl reduced sucrose consumption across days, whereas saline-injected rats in each group did not, and this pattern was identical for Sham and LPS groups, indicating that LPS did not alter taste aversion learning *per se*.

Devaluation test performance is shown in Figure 28B. It is clear from this figure that although performance was habitual in group Sham, as expected, it remained goal-directed for group LPS. Specifically, averaged across groups there was more responding on the valued than the devalued lever, as supported by a main effect of devaluation, $F(1,37) = 14.996$, $p = .000$. However, there was also a group x devaluation interaction, $F(1,37) = 4.373$, $p = .043$. Simple effect analysis revealed the source of this interaction: only group LPS responded significantly more on the valued relative to the devalued lever, $F(1,37) = 20.198$, $p = .000$, whereas group Sham responded equally on both (Valued = Devalued), $F(1,37) = 1.417$, $p = .241$. Therefore, whereas Sham controls were habitual, LPS rats were goal-directed, suggesting that pDMS neuroinflammation does indeed facilitate goal-directed action in a manner that is dissociable from lever press rates. That is, although group LPS pressed the levers at equivalent rates to Shams during lever press acquisition (and if anything slightly higher rates), suggesting that levels of overtraining were the same in each group, only group LPS maintained goal-directed control over their actions.

Together, the results of Experiment 4 demonstrate that pDMS neuroinflammation does increase progressive ratio performance, as well as facilitates goal-directed action control

under conditions that would otherwise produce habits. Although unexpected, this does make some sense as motivation and goal-directed action control are not cognitively separable processes; increasing motivation for a specific food or outcome will, in turn, increase goal-directed control. Importantly, however, the facilitation of goal-directed control cannot simply be viewed as an increase in lever press rates as driven by increased motivation, because this increase should also have applied to LPS animals in the devalued group, but this group responded at very low levels overall. pDMS neuroinflammation does therefore facilitate goal-directed action control specifically.

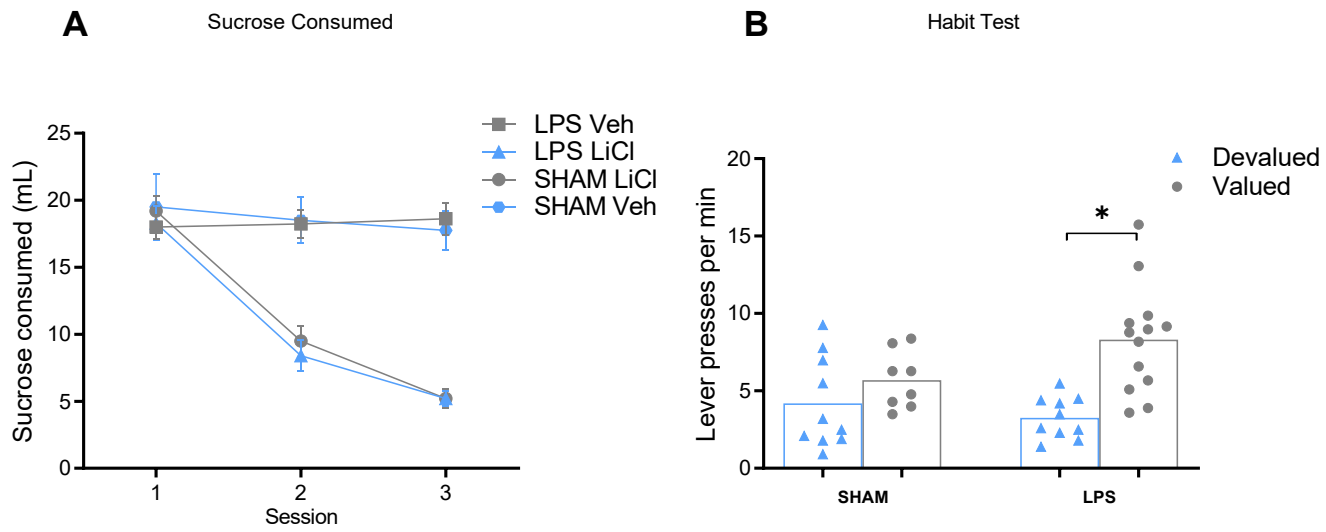

*Figure 28. (A) The amount of sucrose consumed during the 3 days of conditioned taste aversion. (B) Individual data plots and mean lever presses during the extinction test after the 3 days of conditioned taste aversion. * denotes that the p-value was under 0.05. (n = 18 (SHAM), n = 23 (LPS), N = 41)*

Astrocyte and microglia expression, and c-Fos-NeuN intensity was increased in LPS-injected rats relative to Shams

Histology

Sections of pDMS were immunostained following behavioural testing in the same way as described for Experiment 3, with GFAP and IBA1 to measure astrocyte and microglia

activation, respectively. Separate sections were also stained for c-Fos and NeuN. Following initial assessment for placements, 13 rats were excluded based on the absence of any notable astrocyte/microglial co-localisation around a track mark or a misplacement of that track mark outside of the pDMS. Thus, from an initial cohort of 54 rats, the final sample size was N = 41 rats, of which n = 18 were in group Sham and n = 23 in group LPS.

Following quantification of each immunohistochemical marker, and as shown in Figures 29A-B, there was increased GFAP ($t=5.380$, $p < .0001$) and IBA1 ($t=10.27$, $p < .0001$) positive cells in the pDMS of LPS-injected rats relative to Shams. Thus, LPS produced a clear astrocytic and microglial response, suggesting that it was successful in inducing neuroinflammation.

NeuN expression did not differ between groups investigated for this experiment, $p = .7405$, again suggesting that LPS did not induce neuronal death (see Appendix B, p. 295). However, as shown in Figure 29C, there was higher c-Fos-NeuN intensity ($t=6.433$, $p < .0001$) in the LPS group than the Sham group, suggesting that neuronal activation was increased in group LPS relative to group Sham.

Astrocyte, microglia, and c-Fos/NeuN positively correlated with breakpoint, but only astrocyte and c-Fos/NeuN but not microglial expression correlated with outcome devaluation.

Test scores were calculated again using Equation 1 to normalise scores to baseline responding (where baseline = average lever press rats on the last two days of lever press training), and were then correlated with GFAP and IBA1 expressions, and c-Fos-NeuN intensity using the immunohistochemical results from Figures 29A-C. Because animals were only trained to press a single lever for a single outcome in Experiment 4, no further calculation was necessary to determine test scores.

As shown in Figure 29D, GFAP counts positively correlated with breakpoint, $r = 0.3496$, $p = 0.0251$, as did IBA1, $r = 0.5922$, $p = 0.00005$ (Figure 29E) and c-Fos-NeuN intensity, $r = 0.4291$, $p = 0.0015$ (Figure 29F). This result suggests that increases in astrocytes, microglia and neuronal activity was associated with higher motivation as measured by progressive ratio testing.

For habit testing, however, GFAP correlated with devaluation scores, $r = 0.3566$, $p = 0.0221$ (Figure 29G), but IBA1 did not, $r = 0.1061$, $p = 0.5091$ (Figure 29H). Likewise, I also found that c-Fos-NeuN intensity corelated with habit test, $r = 0.3760$, $p = 0.0154$ (Figure 29I). These results suggest that increased astrocytic expression and c-Fos-NeuN intensity in the pDMS was related to better performance on the habit test, but microglial expression was not. The behavioural performances were also correlated with NeuN and c-Fos positive cells separately, data for which are shown in Appendix B, p. 300-302.

Taken together with the immunohistochemical results from Experiment 3, these correlations suggest that the increase in astrocytic expression in the pDMS in particular could be responsible for the observed facilitation of cue-guided and goal-directed action control in Experiments 3 and 4, possibly by increasing neuronal activity. As mentioned, neurons do not express the necessary receptor to respond to LPS directly, but microglia and astrocytes do, so that the observed increases in c-Fos observed in neurons must have been caused by microglia and/or astrocytic activation. The fact that microglial expression correlated only with enhanced motivation on breakpoint testing and no other behavioural measure, however, suggests that the increase in microglia was associated with a general increase in motivation but not with the selective facilitation of action control. Based on these results, therefore, astrocytes in the pDMS stood out as the primary candidate for mediating the effects observed in Experiments 3 and 4. This was tested in Experiment 5.

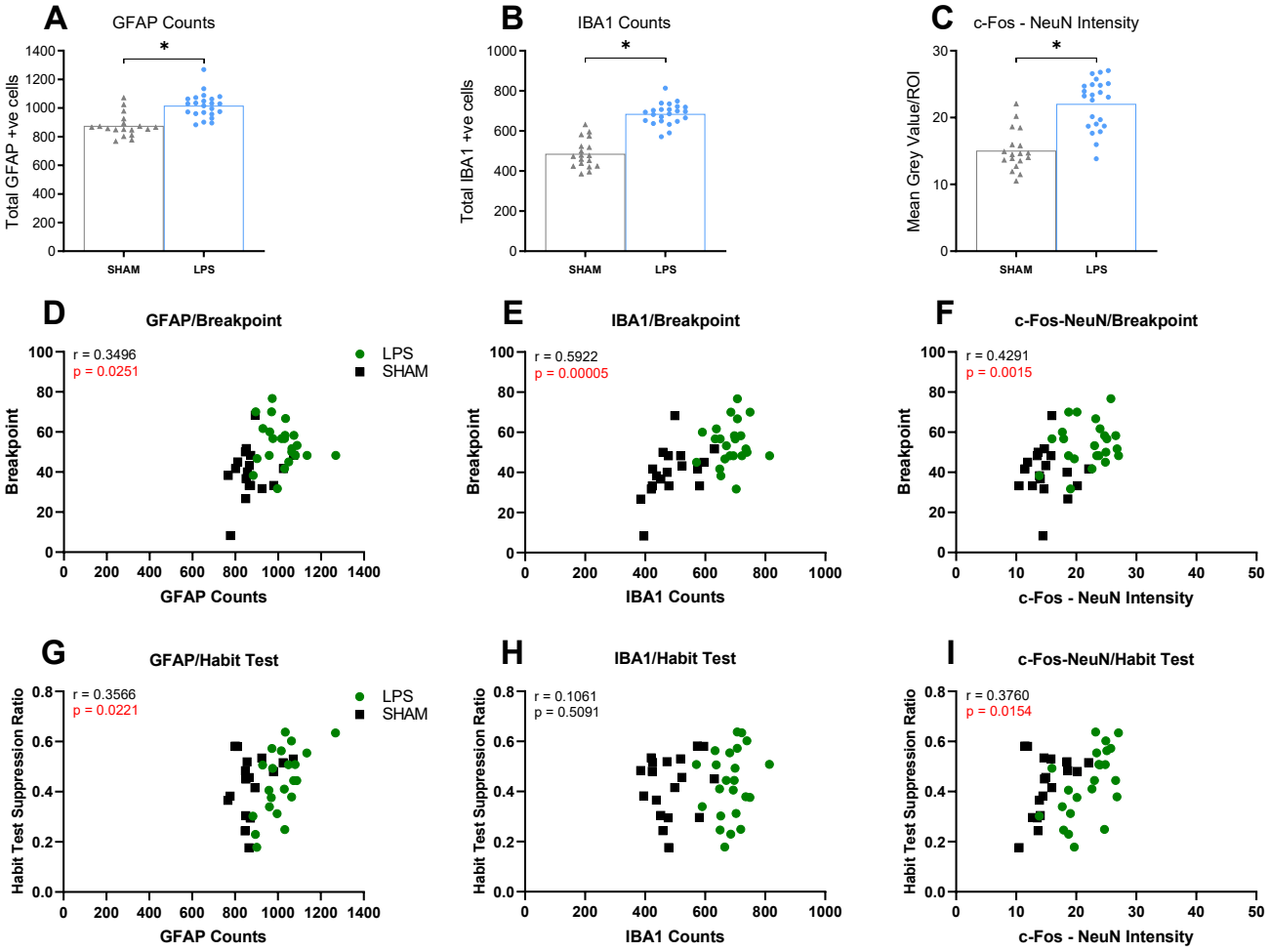

*Figure 29. Number of cells positively immunostained for (A) GFAP, (B) IBA1, and (C) c-Fos–NeuN intensity quantification. (D-I) Correlation between GFAP and IBA1 expressions, and c-Fos-NeuN intensity and behavioural performances. * denotes that the p-value was under 0.05. (n = 18 (SHAM), n = 23 (LPS), N = 41)*

Experiment 5: Chemogenetic manipulation of astrocytes

Experiment 5 aimed to test whether intact astrocytic functioning in the pDMS was required for rats to demonstrate cue-guided and goal-directed action control. To target astrocytes specifically, I used chemogenetics. Specifically, hM4Di DREADDs under the GFAP promoter. Although the mechanism by which hM4Di DREADDs might disrupt astrocytic function is still somewhat unclear, with some studies reporting them to excite astrocytes and others

reporting them to inhibit them at various temporal intervals (Kim et al., 2021; Kol et al., 2020; Nam et al., 2019), these DREADDs were preferable to the hM3Dq DREADDs under the GFAP promoter that we obtained from Addgene, as I found this AAV (AAV-hM3Dq-GFAP-mCherry) to significantly transfect cells other than astrocytes. The hM4Di AAV (AAV-GFAP-hM4Di-mCherry), on the other hand, had a high degree of co-localisation with astrocytes (>98%). Thus, I decided to use the hM4Di DREADD with the intention of determining its mechanism of action (i.e. excitation or inhibition of astrocytes) using c-Fos as I have previously. Unfortunately, and as reported below, the c-Fos antibody I previously used was discontinued but the supplier, and my several attempts to immunostain these sections for c-Fos were unsuccessful (despite the success of other stains – GFAP, IBA1, and NeuN). Therefore, although I was unable to determine the precise manner in which the activation of hM4Di receptors in astrocytes were affecting cellular activity generally and neuronal activity more specifically, other experiments in the laboratory using fibre photometry are being conducted to determine exactly how this might occur. Nevertheless, this experiment did produce several clear alterations in behaviour as a result of this manipulation, as reported below.

MATERIALS AND METHODS

Animals

A total of 20 male and 22 female Long-Evans rats (N = 42) were used for Experiment 5. Animals were housed, food deprived, and maintained as described for Experiment 3. All procedures were approved by the Ethics Committees of the Garvan Institute of Medical Research Sydney (AEC 18.34), and Faculty of Science, University of Technology Sydney (ETH21-6657).

Chemogenetics

The DREADD agonist deschloroclozapine (DCZ - TOCRIS a bio-techne brand CAS #: 1977-07-7) was acquired from National Institute of Health (NIH). DCZ was diluted with normal saline (SAL) (0.9% w/v NaCl) to a final injectable concentration of 0.1 mg/kg (at a volume of 1ml/kg). DCZ was always handled in dim/low light conditions (i.e. a single lamp in a darkened room) and freshly prepared on the morning of each test day.

Surgery

All surgical procedures were conducted identically to that described for Experiment 3, except that animals received bilateral injections of 1 µl per hemisphere of AAV-GFAP-hM4Di-mCherry. The infusion was conducted at a rate of 0.2 µl/min, and injectors were left in place for an additional 5 min to ensure adequate diffusion and to minimize DREADDs spread along the injector tract. The remaining control animals underwent identical procedures but with injection of AAV-GFAP-mCherry as control group.

Apparatus and Behavioural Procedures

All apparatus and behavioural procedures were conducted identically to that described for Experiment 3, except for outcome devaluation (specific satiety) where animals were given free access to either the pellets or the sucrose solution for 45 mins instead of 1 hr, after which DCZ was administered intraperitoneally (i.p) and rats returned to their home cage for 25-30 min prior to behavioural testing.

Tissue Processing and Fluorescent Microscopy

The extent of the expression was determined using the boundaries defined by Paxinos and Watson (2014). Sections were then stained with Living Colors® DsRed Polyclonal Antibody

(1:500, Takara Bio USA, Inc. Catalog #632496) to recognize the mCherry DREADDs expression, anti-GFAP mouse primary antibody (1:300, Cell Signalling Technology Catalog #3670) to check the co-localization, diluted in blocking solution for 72 h at 4°C. Sections were then washed 3 times in 1 × PBS and incubated overnight at 4°C in donkey anti-rabbit AlexaFluor-568 secondary antibody (1:500, ThermoFisher Catalog #A10042), goat anti-mouse AlexaFluor-488 secondary antibody (1:500, ThermoFisher Catalog #A-11001), followed by a counterstain with DAPI (Thermo Scientific; 1:1000, diluted in 1x PBS). Sections were mounted and quantified using procedures identical to those described above.

Statistical analysis

All statsitical analysis was conducted identically as described for Experiment 3.

RESULTS

Histological Placements

Figure 30A shows the representative placement of AAV transfection in the pDMS, Figure 30B shows a DAPI-stained section, Figure 30C shows the same section stained for GFAP, Figure 30D shows hM4Di expression in the same section, and Figure 30E shows these sections merged. As can be seen from Figure 30E, co-localisation of GFAP and AAV-hM4Di-GFAP-mCherry was very high, with approx. 95% overlap, suggesting high specificity of transfection for astrocytes.

Animals were excluded from the experiment if their AAV expression was not within the boundaries of the targeted region and/or the expression was minimal or not observed. In total, 11 rats were excluded from the initial cohort of 42, leaving a total sample size of 31 rats,

of which n = 8 were in group M4/mCherry + VEH, n = 11 in group mCherry + DCZ, and n = 12 in group M4 GFAP + DCZ.

Gi-coupled DREADDs targeting GFAP in pDMS selectively suppress cue-guided and goal-directed action control.

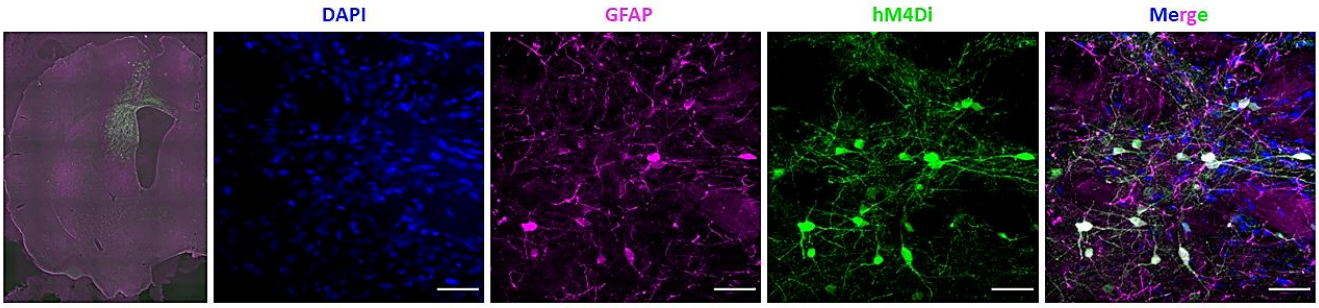

Figure 30. Representative images showing colocalization of mCherry from GFAP-hM4D-Gi-DREADD virus with the astrocytic marker. Calibration: 45 µm.

As in Experiment 3, rats were first trained and tested whilst being maintained on the higher fat/protein Gordon's chow. Animals with each type of AAV transfection acquired Pavlovian conditioning (Figure 31B) and this did not differ according to group (Fs < 1). That is, all animals learned to enter the food magazine more during the 2 min CS presentation than during the 2 min preCS period. This is supported by a main effect of CS period (preCS vs CS) F (1,28) = 742.205, p = .000, and of Day F (7,196) = 27.685, p = .000, and a Day x CS period interaction (preCS vs CS) F (7,196) = 48.789, p = .000. No main effect of group or any interactions with group has been detected, Fs < 1. Both groups also equally acquired lever press responding, as shown in Figure 31C. This is supported by a main effect of day F (7, 196) = 67.262, p < .0001, no main effect of group (F (2, 28) = 1.803, p = .183) and no day x group interaction (F (14, 196) = 1.281, p =.222). Viral transfection in the pDMS therefore does not appear to affect Pavlovian and instrumental learning per se.

Test performance for Pavlovian-instrumental transfer is shown in Figure 31D. As can be seen from this figure, this time the control groups GFAP-hM4Di/mCherry + Veh and mCherry + DCZ did (Same > Different), but the GFAP-hM4Di + DCZ animals did not (Same = Different), show a robust effect of Pavlovian-instrumental transfer. This was supported by a main effect of sPIT, $F(1,28) = 11.031$, $p = .003$, that interacted with group, $F(1,28) = 4.242$, $p = .049$. A significant simple effect for the groups mCherry + DCZ, $F(1,28) = 5.538$, $p = .026$, and GFAP-hM4Di/mCherry + Veh, $F(1,28) = 8.168$, $p = .008$, but no such effect for the GFAP-hM4Di + DCZ group (Same = Different), $F(1,28) = 0.112$, $p > 0.05$. There was no main effect of pre vs post-baseline responding on test, $F(1,28) = 1.215$, $p = .280$, that did not interact with the controls, $F(1,28) = 0.283$, $p = .599$, but there was an interaction with GFAP-hM4Di + DCZ x controls, $F(1,28) = 10.885$, $p = .003$, where groups mCherry + DCZ and GFAP-hM4Di/mCherry + Veh increase responding post-delivery, GFAP-hM4Di + DCZ animals decrease it.

Performance on the devaluation test is shown in Figure 31E. On this test, as it was for sPIT, devaluation was again intact (Valued > Devalued) in controls but was impaired in the GFAP-hM4Di + DCZ group for whom astrocytic signalling was temporarily disrupted. There was a main effect of devaluation, $F(1,28) = 11.907$, $p = .002$, comprised of a significant simple effect for GFAP-hM4Di/mCherry + Veh, $F(1,28) = 13.861$, $p = .001$, and a marginal significant simple effect for mCherry + DCZ, $F(1,28) = 3.400$, $p = .076$, but not the GFAP-hM4Di + DCZ group $F(1,28) = 0.003$, $p > 0.05$.

As in both previous experiments in this chapter, selective reinstatement was intact for all groups, as demonstrated by a main effect of selective reinstatement (Reinstated > Nonreinstated), $F(1,28) = 147.026$, $p = .000$, which did not interact with any group differences, all $Fs < 1$.

It is not clear why sPIT and devaluation were this time intact for control animals, whereas it was not for saline-injected Sham controls in Experiment 3, as all procedures were almost identical except for the injections of vehicle or DCZ prior to test. One possibility is that the i.p. injections caused stress in the animals, which somehow facilitated rather than impaired performance on test, although this would be quite unexpected. Nevertheless, because the activation of hM4Di receptors in astrocytes did not facilitate action selection relative to controls, this is not of major consequence. In fact, activation of these receptors actually impaired cue-guided and goal-directed action control, but as before outcome-guided decision-making was unaffected. Therefore, although the mechanism of the hM4Di activation in astrocytes in the current experiment is still unknown, behaviourally it did appear as though this receptor activation either silenced or otherwise reduced astrocytic activity to produce the observed effects.

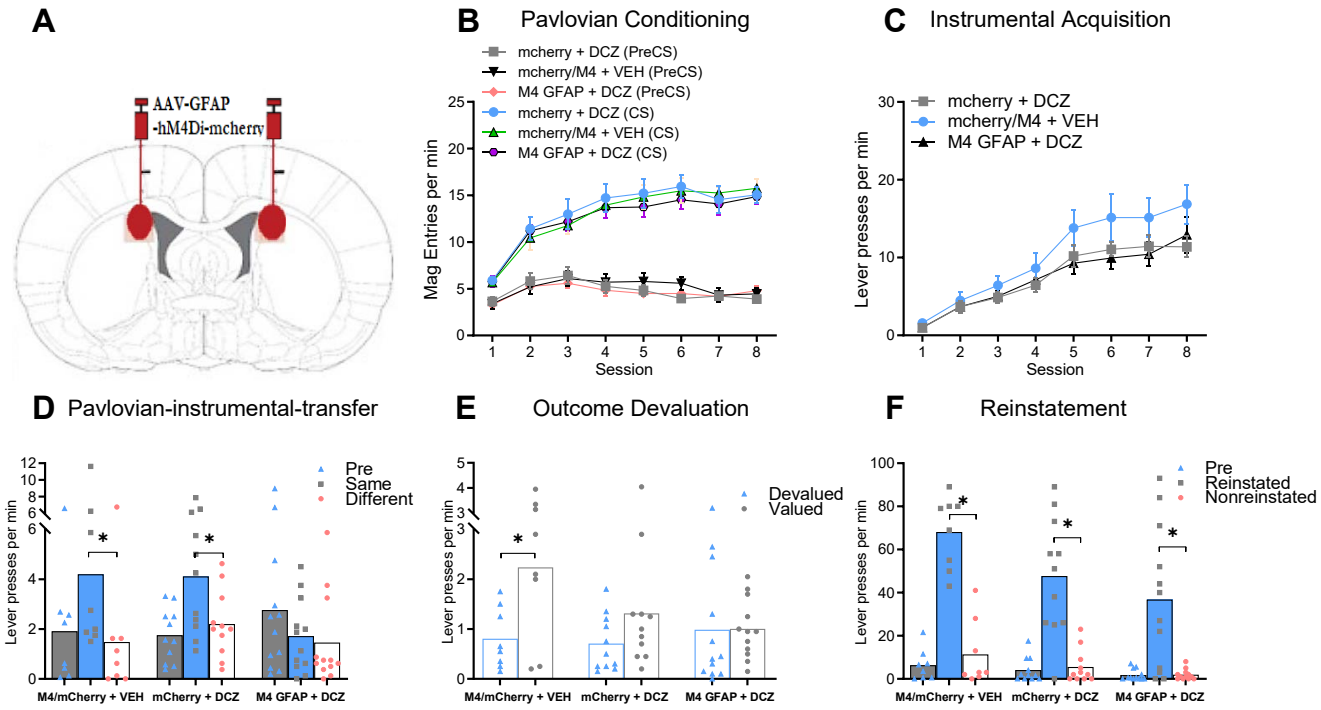

Figure 31. (A) Representation of the AAV-GFAP-hM4Di-mCherry injections made into the posterior dorsomedial striatum. (B) Magazine entries per min (±SEM) during Pavlovian conditioning. (C) Lever pressing per min (±SEM)

*during instrumental conditioning. Individual data plots and mean lever presses during the (D) Pavlovian-instrumental transfer test, (E) outcome devaluation test, and (F) outcome-selective reinstatement test using Gordons Specialty Feed chow. * denotes that the p-value was under 0.05 (n = 8 (M4/mCherry + VEH), n = 11 (mCherry + DCZ), n = 12 (M4 GFAP + DCZ), N = 31)*

In order to fully replicate the procedures of Experiment 3, I next switched animals to a smaller amount of the less palatable, Irradiated Specialty Feeds chow to increase motivation in controls and determine if the effects persisted. Once again, animals acquired Pavlovian conditioning (Figure 32A) and this did not differ according to group ($F < 1$). That is, all animals learned to enter the food magazine more during the 2 min CS presentation than during the 2 min preCS period. This is supported by a main effect of CS period (preCS vs CS) $F (1,28) = 282.571$, $p < .0001$, and of Day $F (3,84) = 8.018$, $p < .0001$, but no Day x CS period interaction ($F < 1$), group ($F < 1$), or any interactions with group has been detected ($F (6,84) = 1.680$, $p = .136$). Both groups also equally acquired lever press responding, as shown in Figure 32B. This is supported by a main effect of day $F (3,84) = 15.652$, $p < .0001$, no main effect of group ($F (2,28) = 1.837$, $p = .178$F) and no day x group interaction ($F (6,84) = 1.999$, $p = .075$).

Again, the control groups (groups GFAP-hM4Di/mCherry + Veh and mCherry + DCZ) showed intact sPIT but the GFAP-hM4Di + DCZ animals did not. This is supported by a main effect on sPIT, $F (1,28) = 14.731$, $p = .001$, that interacted with group, $F (1,28) = 4.947$, $p = .034$. The source of this interaction was revealed to be a significant simple effect for the groups mCherry + DCZ, $F (1,28) = 5.995$, $p = .021$, and GFAP-hM4Di/mCherry + Veh, $F (1,28) = 11.731$, $p = .002$, but no such effect for the Sham group (Same = Different) ($F < 1$). There was a main effect of pre vs post-baseline responding on test, $F(1,28) = 6.966$, $p = .013$, that did not interact with any groups, all $Fs < 1$.

Also, both control groups also displayed intact outcome devaluation performance (Valued > Devalued) as supported by a main effect of devaluation, $F(1,28) = 13.846$, $p = .001$, comprised of a significant simple effect for mCherry + DCZ, $F(1,28) = 16.464$, $p = .000$, and a marginal effect for GFAP-hM4Di/mCherry + Veh, $F(1,28) = 4.063$, $p = .053$, but not the GFAP-hM4Di + DCZ group, $F < 1$.

As before, selective reinstatement was again intact for all groups. This is supported by a main effect of selective reinstatement (Reinstated > Nonreinstated), $F(1,28) = 66.441$, $p = .000$, which did not interact with any group differences, all $Fs < 1$.

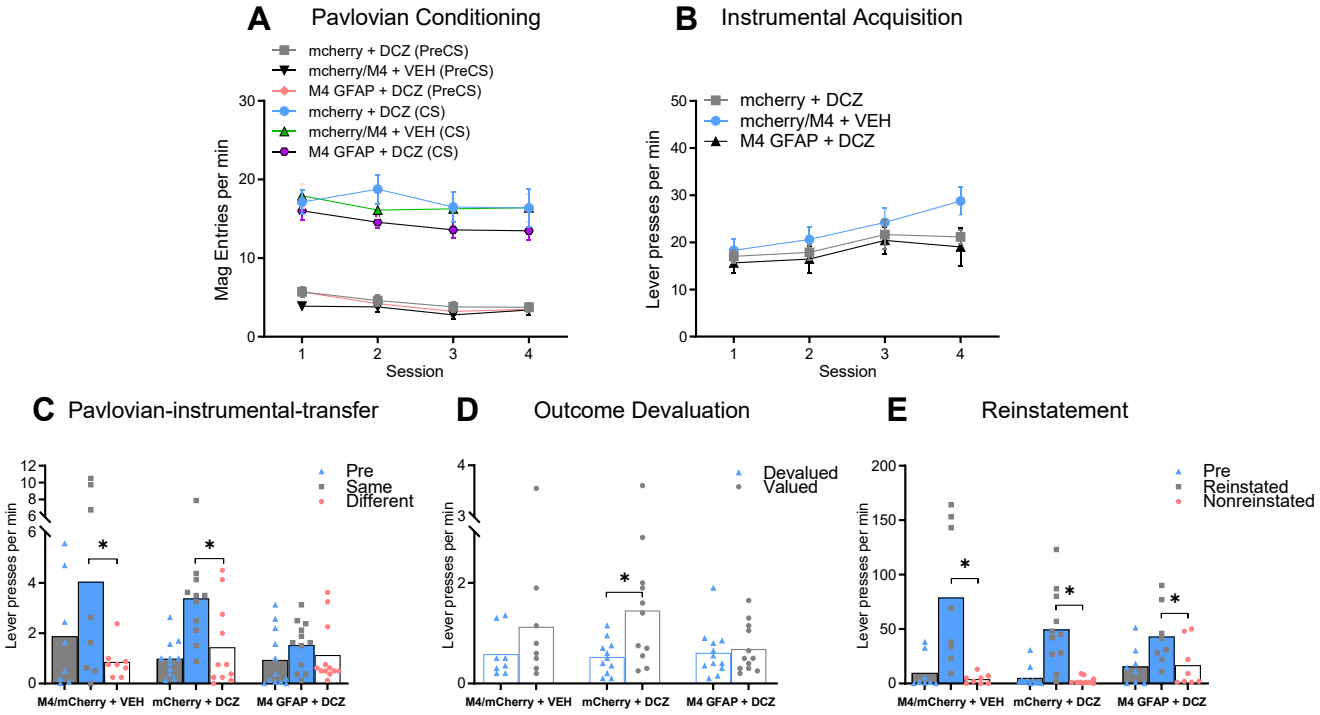

*Figure 32. (A) Magazine entries per min (±SEM) during Pavlovian conditioning. (B) Lever pressing per min (±SEM) during instrumental conditioning. Individual data plots and mean lever presses during the (C) Pavlovian-instrumental transfer test, (D) outcome devaluation test, and (E) outcome-selective reinstatement test using Irradiated Specialty Feed chow. Data were shown as individual plots and the mean ± S.E.M. * denotes that the p-value was under 0.05. (n = 8 (M4/mCherry + VEH), n = 11 (mCherry + DCZ), n = 12 (M4 GFAP + DCZ, N = 31)*

Overall, therefore, the results of Experiment 5 suggest that intact astrocytic functioning in the pDMS is necessary for cue-guided and goal-directed action selection, but is not necessary for outcome selective reinstatement. Together with the results of Experiments 3 and 4, this result suggests that neuroinflammation in the pDMS facilitates goal-directed action, and likely does so through astrocytic mediation of neuronal activity. This latter conclusion is still speculative (due to the failure of the c-Fos antibody to determine levels of neuronal activation in Experiment 5), however, and experiments are ongoing in the laboratory to determine if this is the case.

Discussion

Chapter 4 aimed to establish a causal evidence that neuroinflammation in the pDMS impairs goal-directed action in rats. To my knowledge, this is the first study to examine the effects of neuroinflammation in pDMS on cognitive control over actions. To do this, I first inject LPS, an endotoxin, into pDMS to induce local neuroinflammation in the brain. Once recovered, I tested the rats using battery of decision-making assays. I hypothesized that local neuroinflammation in pDMS will produce impairments in action selection. However, this hypothesis was disconfirmed by the data, as the result of Experiment 3, reveals that neuroinflammation in pDMS facilitates goal-directed reward-seeking. When animals were partially sated and control effects were small, transfer and devaluation were both enhanced in group LPS. Specifically, during transfer when cues and levers were presented together for the first time, group Sham responded equally on both levers whereas group LPS responded selectively on the lever that predicted the same outcome as the current cue. During devaluation testing, both groups responded more on the valued relative to the devalued lever, but this difference was larger for group LPS.

Experiment 4 tested whether pDMS neuroinflammation increases motivation generally, or goal-directed action specifically. When tested using a PR design, animals in group LPS reached consistently higher breakpoints than group Sham. Upon devaluation testing, group Sham demonstrated evidence of habits (Valued = Devalued) and group LPS demonstrated intact goal-directed actions (Valued > Devalued). Immunohistochemistry was performed to confirm neuroinflammation and to measure any neuronal death. Evidence shows that the facilitation in goal-directed action control was a result of increased astrocytic and neuronal activation in pDMS. In Experiment 5, astrocytes were selectively targeted by using chemogenetics under the GFAP promoter to inhibit local glial populations in pDMS. I found that chemogenetic inhibition of astrocytes in the pDMS selectively suppress the goal-directed behaviours. Together, these results suggest that LPS-induced neuroinflammation in pDMS increases both motivation and goal-directed action, likely through an astrocyte mediated mechanism.

There are several things to consider with regards to these results. First, it might superficially appear as though pDMS neuroinflammation somehow improved the performance of rats, or made them smarter. This is not necessarily the case, however, because perhaps the optimal way to act in low motivation conditions in Experiment 3 is not to demonstrate evidence of action control. Moreover, habits are adaptive, and the prevention of habit formation by pDMS neuroinflammation in Experiment 4 could be seen as an impairment rather than an improvement. Such interpretations are considered in detail in the general discussion below.

Second, the precise underlying mechanisms of the current results should be considered. Several studies have determined that neuroinflammation leads to neuronal excitability (Riazi et al., 2008; Schafers & Sorkin, 2008; Shimada et al., 2014), just as we discovered here. Current

results further suggest some synergy between the increases in astrocytic expression and neuronal excitability with the facilitation of behaviour, suggesting that astrocytic activation in particular is led to the increase in neuronal activity and alterations in behaviour. Moreover, the results of Experiment 5 are particularly intriguing in suggesting that disrupting the homeostatic function of astrocytes in pDMS disrupts action control. The potential mechanisms by which disrupted astrocytic signaling might affect neuronal excitability are also discussed in the general discussion.

Finally, there are several clinical implications, limitations, and suggestions for future studies based on the results of this chapter to be considered. For instance, there is the question of whether the neuroinflammation I induced in the current study was in its acute or chronic phase at the time of testing. Although the first behavioural test did not occur until 3 weeks after surgery, at which point some researchers suggest neuroinflammation has become chronic, this is not a unanimous suggestion, and it is possible that it was still acute. Furthermore, other important future directions involve the investigation of the consequences of neuroinflammation in brain regions other than just the pDMS given that individuals with compulsive disorders experience neuroinflammation across multiple brain regions (Attwells et al., 2017; Chen et al., 2023; Kohno et al., 2019). Moreover, determining how exactly I have disrupted the homeostatic function of Gi activation in astrocytes in the pDMS is critical given the disagreement in the literature about the physiological consequences of astrocytic activation of this pathway in astrocytes, with some articles claiming it to primarily excite them, and others claiming that it can inhibit their function (Erickson et al., 2021; Kol et al., 2020; Lines et al., 2020; Nam et al., 2019). Additionally, another consideration for future studies is to test whether pharmacological treatments currently in use such as anti-inflammatories is sufficient to rescue deficits in flexible decision-making and could be repurposed for broader

distribution among individuals who exhibit compulsion, such as SUD or OCD. Taken together, these results could suggest that goal-directed action control in rats could be particularly sensitive to striatal neuroinflammation, but, of course, it requires future studies to address it in detail.

CHAPTER 5

GENERAL DISCUSSION

This thesis investigated the behavioural and brain mechanisms of dysfunction in cognitive control over action selection in rats as it might apply to compulsive disorders. There were two specific aims:

1. To investigate how the selectivity of actions was affected by reinstatement after altering the physical context.
2. To investigate how neuroinflammation in the pDMS might alter cue-guided and goal-directed action selection, and to explore the neuronal and glial mechanisms that underlie such alterations.

The experiments reported in Chapter 3 addressed the first aim. Experiment 1 results indicated that outcome selective reinstatement was contextually mediated when reinstatement occurred immediately after extinction training. Specifically, the groups that received extinction and reinstatement in the same context (groups AAA and ABB) showed reinstatement that was selective to the lever that had previously earned the outcome during training (Reinstated > Nonreinstated). However, animals in the AAB and ABA groups, for whom extinction and reinstatement occurred in different contexts, responded non-selectively on both levers (Reinstated = Nonreinstated). This was despite only group ABA showing a renewal effect at baseline: responding more prior to the delivery of any outcomes. Experiment 2 was conducted identically to Experiment 1, except that rats were tested using more traditional extinction parameters (i.e., two extinction sessions and tested one day later) to determine the generality of the observed effects. This time, all groups showed intact outcome selective reinstatement. I also found that, across both experiments, c-Fos expression in pDMS was higher for groups in which outcome-selective reinstatement was intact, and reduced for groups in which it was impaired. No such pattern was observed in mOFC, lOFC, or DH CA1. Together, Chapter 3 results suggest that the selectivity of reinstatement is

primarily context-independent, except immediately after extinction training, and is associated with increases in cellular activity in the pDMS. These results led me to focus specifically on pDMS as the candidate structure of compulsivity in Chapter 4.

In Chapter 4, I wanted to directly investigate the potential brain mechanisms of goal-directed action in compulsive-like disorders. In particular, I chose to investigate whether neuroinflammation in pDMS altered action control, due to the fact that the pDMS is considered the neuroanatomical locus of goal-directed action, together with the fact that neuroinflammation in the caudate (homologue of the pDMS) is consistently implicated as dysregulated in compulsive disorders. To induce neuroinflammation, in Experiment 3 I injected the endotoxin LPS into the pDMS of rats, then determined the consequences of this for action selection across several assays. Contrary to expectations, LPS-injected animals initially showed a facilitation rather than impairment of action selection when control effects were reduced due to animals being fed a higher-protein, higher-fat home chow. Specifically, Sham controls did not show a selective Pavlovian-instrumental transfer effect, pressing both levers equally (Same = Different), but LPS-injected animals did (Same > Different). Then, although both groups did display an outcome devaluation effect (Valued > Devalued), this effect was significantly larger in group LPS. Unexpectedly, outcome selective reinstatement did not differ between groups and was intact (Reinstated > Nonreinstated) for both. Later, when animals were fed a lower fat, lower protein home chow and retrained and re-tested, all the test effects were intact for Sham controls and did not differ from group LPS. These results suggested that pDMS neuroinflammation might increase motivation generally or action selection more specifically, which was tested by Experiment 4. Results suggested that it does both: when tested for progressive ratio performance, animals in group LPS reached

consistently higher breakpoints than group Sham, whereas after training habits in Sham controls (Valued = Devalued), group LPS remained goal-directed (Valued > Devalued).

Immunohistochemical analyses of pDMS tissue from both experiments revealed that LPS-injections increased the expression of astrocytes and microglia, as well as c-Fos-NeuN intensity, suggesting that a) the LPS injections were effective in creating a neuroinflammatory response, and b) the neuroinflammatory response was associated with an increase in neuronal activity. To determine how these increases related to behaviour, I correlated the expression of each with test scores that had been adjusted to account for differences in baseline responding. I found that both astrocytic expression and c-Fos/NeuN intensity significantly correlated with test scores only on tests for which group LPS were facilitated relative to group Shams, whereas microglial expression correlated only with progressive ratio performance. This suggested that the facilitations in action selection were caused by neuronal excitation that resulted from the increases in astrocytic but not microglial expression. Experiment 5 tested this hypothesis by chemogenetically targeting hM4Di receptors in astrocytes specifically. Activating this Gi pathway in astrocytes abolished Pavlovian-instrumental transfer and devaluation effects (with selective reinstatement intact once again) suggesting that this manipulation may have caused neuronal inhibition. Unfortunately, my immunohistochemical analyses so far have been inconclusive due to a failure of the c-Fos antibody to work, but experiments are ongoing to directly determine how activation of the Gi-pathway in astrocytes is mediating cellular activity. Nevertheless, the behavioural results of this experiment do imply a specific role for astrocytes in the pDMS in cue-guided and goal-directed action selection. Together, the experiments in Chapter 4 suggest that cognitive control is altered as a result of neuroinflammation in pDMS, and that this dysregulation is mediated by the activation of astrocytes.

Overall, the experiments reported in this thesis support the following conclusions:

1. Outcome-selective reinstatement is predominantly context-independent and is associated with c-Fos expression in the pDMS.
2. pDMS neuroinflammation facilitates cue-guided and goal-directed action selection under low motivation conditions and when responding is otherwise habitual, as well as facilitating motivation more generally. It does not affect outcome-selective reinstatement.
3. Intact astrocytic signalling in the pDMS is necessary for accurate cue-guided and goal-directed action selection.

In the following sections, I will be discussing the results as two separate parts. The first half will discuss Aim 1 – the Chapter 3 of this thesis, followed by the second half of the section which will discuss Aim 2 – the Chapter 4 of this thesis. This will be followed by a brief conclusion section integrating the findings from each.

AIM 1 – Chapter 3:

Reinstatement is a widely known and studied phenomenon, however, the emphasis on those studies has typically been on Pavlovian learning (i.e., participants learn relationships between cues and outcomes) and the studies that do involve instrumental responses have been conducted in scenarios that involve a single active response. Therefore, the results provide the first insights into the context-specificity/independence of the reinstatement of an instrumental learning task involving choice.

Outcome-selective reinstatement is predominantly context-independent

Studies on Pavlovian and instrumental extinction and renewal confirm that extinction often results in new, context-dependent learning (Bouton et al., 2021). Current results support this conclusion to an extent, because the ABA renewal effect was present in both Experiments 1 and 2 in the 3 mins prior to outcome delivery, suggesting that the original learning that had occurred in context A had returned once rats were returned to that context. The lack of AAB renewal in both experiments speaks against the context-dependency of extinction learning, but again, this has always been reported to be less robust than ABA renewal and it is possible that there was simply a floor effect here.

What is clear from current experiments, however, is that unlike other forms of reinstatement, outcome-selective reinstatement itself is not context dependent. That is, across both experiments, we observed selective reinstatement to be intact for group ABB despite the response and outcome never having been experienced in Context B prior to test. This was in contrast to my speculations made both here and elsewhere (Abiero & Bradfield, 2021), that selective reinstatement would be specific to the context in which O-R associations are initially learned, based on the fact that S–R habits are generally context-specific (Bouton et al., 2011; Thrailkill & Bouton, 2015). This speculation relied upon the claim that O-R associations represent a special type of S-R association, in which the outcome functions as a stimulus (Ostlund & Balline, 2007). Current results appear to suggest, however, that O-R and S-R associations are distinct from each other, at least with respect to their dependence on physical contexts.

One possible reason for this distinction could be due to the nature of the 'stimuli' that enter into habitual S-R associations relative to the nature of outcomes acting as stimuli. For example, lever-associated stimuli, such as the sight and smell of the lever, might be encoded

as a part of the context in a way that outcomes are not. Indeed, levers in operant chambers are literally attached to the walls, whereas food outcomes can be lifted away from the food receptacle and consumed wherever the animal takes it. Thus, it is possible that O-R associations are encoded as being more distinct from their contexts, and thus might drive behaviour in a way that is distinguishable from (although still somewhat similar to) habits.

This finding that selective reinstatement is predominantly context-independent does raise the question, however, as to why prior studies have found (non-selective) reinstatement of a single instrumental action to be diminished by alterations in context (Baker et al., 1991). On possibility is that reinstatement under such circumstances is not underscored by O-R associations in the same way, or that the contextual stimuli and the outcome form a kind of configural representation that enters into the O-R/S-R association in a manner that does not occur in selective reinstatement, although why this would be the case is unclear. Another possibility is that the context might 'gate' the O-R association in a single action-outcome design, in a way that does not occur in a two action, two outcome design, although again, why this would be is unclear. A third possibility could be derived from suggestions (Adams, 1982; Holland, 2004) that training with a single action-outcome contingency results in the sensory properties of the outcome no longer controlling responding, which is controlled by its affective valence instead. By contrast, they suggested that training with two distinct action-outcome contingencies preserves the encoding of sensory properties. Thus, if we assume that affective valence is more likely to become attached to its context than the sensory properties of the outcomes are, then we would expect singular reinstatement to be more context-specific than selective reinstatement.

A final possibility is that some proportion of outcome-selective reinstatement responding remains goal-directed in a way that other types of reinstatement do not, and as reviewed in

Chapter 1, goal-directed actions tend to be more context-independent than habits. In Ostlund and Balleine's paper (2007), even though they concluded that the O-R association is more like an S-R than a 'goal-directed' R-O association, they did suggest that there may still a component of selective reinstatement responding that is goal-directed. This was based on the fact that devaluation did partially abolish the reinstatement effect, as well as the fact that selective reinstatement was partially diminished when O-R and R-O were inconsistent relative to when they were consistent. Thus, it is possible that the part of selective reinstatement effect that is contributed by the R-O association is the part that survived the change in context, and this is why selective reinstatement was intact in group ABB in Experiment 1 and in all groups in Experiment 2. The results of the experiments in Chapter 4 do argue against this interpretation somewhat, however, as they demonstrate that although the manipulations of pDMS function affect outcome devaluation performance they do not affect outcome-selective reinstatement, suggesting that the neural processes underlying each are likely dissociable.

Instrumental extinction learning in a choice paradigm appears to be initially context-dependent but becomes context-independent over time

Another potential issue raised by the current results is why selective reinstatement was impaired for groups ABA and AAB in Experiment 1, but not in Experiment 2, when the only differences between these experiments was the amount of extinction training (1 vs. 2 sessions, respectively) and the length of time from the last extinction session to test (5 min vs. 24 h, respectively). Because these two groups are the only two for whom extinction and testing occurred in different contexts, one seemingly straightforward way to interpret these findings would be to assume that although extinction learning did not transfer between contexts in animals tested immediately after brief extinction training, it did transfer in animals

trained and tested over multiple days. This would mean that renewal in both ABA and AAB groups interfered with the specificity of reinstatement for each. Indeed, the work of Bradfield et al. (2020) provides some precedent to the idea that instrumental learning is initially context-dependent but becomes context-independent over time, and further suggests that it is the additional time between training and test (as opposed to additional extinction training) that is the key variable in achieving such independence.

Applying this interpretation to current results is complicated, however, by the fact that selective reinstatement and renewal effects appeared to be independent of each other, suggesting that the observation of selective reinstatement was not entirely dependent on the transfer of extinction learning. However, my ability to fully interpret each of these effects as reflective of *learning* is limited, as I can only base my conclusions on the observable *performanc*e of the animals, the latter of which is not a perfect indicator of the former. This could explain, for example, why AAB renewal was not detected prior to the delivery of any outcomes, but post-outcome delivery performance was elevated to a level at which renewal interfered with the specificity of reinstatement. Moreover, it is possible that the change in experimental conditions from lever press acquisition, in which levers were trained separately, to extinction where both levers were presented simultaneously, provided an additional 'contextual' change that affected learning/performance, particularly in group AAB where renewal was expected but not observed. Future studies are therefore necessary to determine whether the contextual-impairment of selective reinstatement is an effect that is truly independent from renewal, and whether extinction learning is transiently context-dependent in instrumental choice learning as these results seem to suggest.

Neural mechanisms of outcome-selective reinstatement

Another area that requires further research is the precise neural circuitry underlying the selective reinstatement effect. Unfortunately, my exploratory c-Fos analyses were not particularly illuminating with regards to this question, as I was only able to confirm the previously demonstrated finding (Yin, Ostlund, et al., 2005) that neural activity in the pDMS is related to selective reinstatement. I was not able to form any similar conclusions for any of the other brain regions studied, including mOFC and lOFC, and DH CA1. The failure to find any differences in c-Fos expression in mOFC was expected, because a previous study has demonstrated that excitotoxic lesions of mOFC leaves outcome-selective reinstatement intact, suggesting that this region has no role in the behaviour. Therefore, this region was included as a positive control. The failure to detect any difference in lOFC was more surprising, however, given the number of studies that have implicated a role for this region in multiple types of choice behaviour (Elliott et al., 2000; Jollant et al., 2010; Mar et al., 2011) particularly when there is a contextual element to the study (Bradfield & Hart, 2020; Gremel & Costa, 2013). It is difficult to determine what a null effect here might reflect, however, particularly given the correlative nature of the analyses which may or may not imply a lack of any causal role for lOFC in selective reinstatement.

The failure to find any differences in c-Fos expression in the DH was even more surprising, given the central role of this region in spatial and contextual representations generally. I had, therefore, expected to at least observe some differences in accordance with context change. For instance, an increase in c-Fos expression in animals that experienced a change in context on test day (groups ABA or AAB), or in animals that experienced a change in context at any point (groups ABA, AAB, and ABB) relative to group AAA for whom the context was kept

consistent throughout the study. One potential reason for this lack of difference even related to context changes *per se* is that c-Fos expression in the DH appears to be particularly sensitive to novel contexts (Mendez et al., 2015; VanElzakker et al., 2008) and none of the contexts here were novel to the animals. This is because they had previously received magazine training in both contexts as well as a non-reinforced pre-exposure to the non-training context. Another possibility is that any differences in c-Fos in the DH was masked by the overall low levels of c-Fos expression in this brain region, making it difficult to detect any group differences. Nevertheless, it is worth noting once again that it is difficult to interpret a null effect, particularly in a correlative analysis such as this, so we cannot make any inferences about the cognitive mechanisms that might have led to this lack of c-Fos expression in the DH.

Another consideration with regards to these null effects is that, if I had co-localised the c-Fos with NeuN as I did in Chapter 4, it could reveal whether it was the neuronal activity specifically that was altered in pDMS when reinstatement was intact. At the time of conducting this study I was not aware that glial cells could also express c-Fos, and this is something I only became aware of later, when studying neuroinflammation. Therefore, it is possible that the c-Fos expression observed was in a mixture of cell types, including different types of glia and different types of neurons (e.g. excitatory vs. inhibitory), which could have masked any specific differences that may have been detected had cell populations been explored separately. Moreover, it is also worth noting that I did correlate c-Fos expression with performance in Chapter 3 in the same way as I did for various immunohistochemical markers in Chapter 4, but I did not report these findings because they did not yield any interpretable correlations.

Overall, as very little is known about the neural circuitry of outcome-selective reinstatement, there is fertile ground for future studies to investigate this. Although my exploratory analysis failed to display any conclusive results, there are plenty of other brain regions and/or circuits that qualify as excellent candidates for these investigations. In particular, I suggest that researchers explore regions detailed in Chapter 1 for their role in relapse and relapse-like behaviours, such as the BLA, prelimbic and/or infralimbic cortices, and/or ventral striatum, each of which also have a central role in the mediation of choice behaviour. Moreover, as mentioned, such explorations may wish to use measures more sensitive than simple c-Fos expression to determine the roles of these regions, potentially targeting specific cell types or neuronal ensembles.

Clinical implications of the findings in Chapter 3

In Chapter 1 I expressed a desire to contribute to the creation of a richer and more complex model of relapse than the single action, single outcome models currently available, so I will here conclude what my findings contribute to this understanding. Although I recognise that there are many steps that must be tackled before the work here can be thought to directly implicate certain behavioural features of humans with compulsive disorders, if I assume some degree of translatability that can be applied, then based on my findings we might predict that the likelihood of relapsing on two outcomes is higher when the abstinence has been brief and relapse occurs in a context other than the abstinence-associated context. Current results further imply that relapse should be more outcome-specific after longer periods of abstinence, regardless of context. To give the same example as before, if an individual has been abstinent from both smoking and drinking for a short time, and they relapse to smoking (or even breathe in passive smoke) as soon as they return to their local bar, they are also

more likely to relapse on alcohol. If that individual has been abstinent for longer, however, their relapse is more likely to be specific, regardless of where they are. It is important to acknowledge, however, that such an implication is limited on the basis of the particular parameters employed in the current study (e.g. 6 days of initial training, short periods of extinction, etc), and other parameters may well produce different implications, as explored in the next section.

Limitations and future studies based on the results of Chapter 3

First, I would like to acknowledge that most of the extinction/abstinence using pre-clinical models and even in the experiments I did is forced, in the sense that it is arbitrarily imposed on the animals by the experimenter, while in humans, extinction/abstinence is often chosen, possibly to avoid negative consequences or obtain alternative rewards. Therefore, in order to make my study more ecologically valid, a better home-cage extinction/abstinence model that more closely mimics the human condition should be developed to fully capture the complex nature of human abstinence. How exactly animals might be given a 'choice' to abstain or not is not clear, however, nor is whether any animals might actually make this choice.

Also, future studies on the context-specificity of outcome-selective reinstatement might want to investigate should how overtraining the initial learning (here lever pressing) might make a difference. This is because people who are compulsive learn to perform their compulsions repetitively, many times often over many years, meaning that they perform these actions vastly more than the rats performed lever pressing in the 6 days of training used in the current thesis. Future studies might therefore wish to repeat the current study but to give animals several weeks or even months of initial lever press training to determine the consequences for context-specific outcome-selective reinstatement. Likewise, future studies

might wish to repeat the current study, but after varying the extinction training in different ways. For example, one suggestion might be to test reinstatement a couple of weeks after extinction training to see if the responding is still selective over time and/or whether there's some kind of summation with spontaneous recovery.

Another suggestion for future studies that would be particularly important for those wishing to extrapolate information about the specificity of relapse to SUD might be to repeat the current study with drug outcomes. In particular, there are certain drugs that are known to be consumed together often, such as cocaine and alcohol (Pergolizzi et al., 2022) or nicotine and caffeine (Swanson et al., 1994), and it is possible that the specific characteristics of these drugs, both individually and as consumed together, could alter the propensity to relapse on one when the other is consumed. Thus, future studies may wish to repeat the current study, but with drug outcomes instead of food (and/or a combination of each, possibly as controls – e.g. is cocaine or alcohol likely to cause co-relapse in animals trained with both relative to animals trained on cocaine and sucrose). Finally, and as mentioned in detail above, more research is needed to determine the circuits/brain areas essential for extinction of choice behaviours as well as outcome-selective reinstatement.

AIM 2 – Chapter 4:

Chapter 4 aimed to establish the first causal evidence that pDMS neuroinflammation, shown here through the increased number of astrocytes and microglia in LPS-injected rats, alters cue-guided and goal-directed action selection in rats. Although unexpected, the results of Experiments 3-4 are thought-provoking, as they suggest that rather than impairing goal-directed action as might be expected, pDMS neuroinflammation appears to intensify it. That is, pDMS neuroinflammation causes animals to be goal-directed under circumstances for

which this might not normally occur, such as when fed a high fat, high protein home chow, or when animals are otherwise trained to be habitual (through the use of a single lever, single outcome, random interval schedule). The fact that outcome-selective reinstatement remained intact in each experiment was surprising, particularly given the results of the c-Fos analysis in Experiment 1 implicating a role for pDMS, but this could possibly be a ceiling effect. That is, outcome selective reinstatement was particularly robust and observed in Sham controls in Experiment 3 even when sPIT and devaluation were not, suggesting that performance on this test was at its physical limit beyond which any further facilitation could not be observed. Alternatively, it is possible that, unlike pDMS lesions, pDMS neuroinflammation in this region simply does not alter cue-guided action selection when the cue is an outcome. The results of the correlational immunohistochemical analysis in each of these experiments suggest that it was the activation of astrocytes in particular that is responsible for the facilitation of action control. Although, microglia and astrocytes have very dynamic responses to insult and injury, and their responses are likely to change overtime after LPS treatment. But the fact that the number of astrocytes is related to sPIT and outcome devaluation could possibly mean that astrocytic response is much more stable than microglia. The results of Experiment 5 showed this directly, demonstrating that intact astrocytic functioning in pDMS is indeed necessary for accurate cue-guided and goal-directed action selection.

In contrast to the findings of the current study, previous rodent studies that have inactivated the pDMS have found impairments in each type of action control, as measured by sPIT, and outcome-selective reinstatement, and outcome devaluation (Corbit & Janak, 2010; Gremel & Costa, 2013; Yin, Ostlund, et al., 2005). Based on the immunohistochemical analyses, this does make some sense however, as each of the prior studies caused significant

neuronal silencing or death, whereas the present study found no evidence of neuronal death. That is, there was no significant difference in expression of NeuN in animals injected with LPS compared to Sham controls. Moreover, in the current study I detected an *increase* in c-Fos expression in neurons in LPS animals, suggesting that neuroinflammation had caused excitation in pDMS neurons. This finding is consistent with prior findings suggesting that neuroinflammation causes neuronal excitation (Riazi et al., 2008; Schafers & Sorkin, 2008; Shimada et al., 2014), and although this has been argued to lead to eventual neuronal atrophy and death (due to over-excitation, Qin et al., 2021; Tansey & Goldberg, 2010), it is possible that the two months between surgery and perfusions in the current study was not sufficient for such an effect to occur. It is possible that if the neuroinflammation were left for longer, some neuronal death would have been observed.

This does raise the question as to whether the neuroinflammation observed in the current study was acute or chronic, and this is not necessarily a straightforward question to answer. Some researchers have claimed that acute neuroinflammation is that which is remedied within two weeks (O'Neill et al., 2021), whereas others have suggested that neuroinflammation lasting longer than two weeks could still be considered acute (Yang et al., 2015). For Experiments 3 and 4, rats were given one week following initial surgery to recover before any behavioural training occurred, and then animals had 16 days of Pavlovian and/or instrumental training prior to any testing. Therefore, neuroinflammation was present in all rats for at least 3 weeks prior to the first round of testing, suggesting that the damage they sustained was potentially more akin to chronic than acute neuroinflammation. This is supported by fact that the neuroinflammatory response was still observable upon post-mortem analysis which occurred 8-10 weeks after the initial surgeries. Nevertheless, such a conclusion must be approached with caution, and it must be considered that rats that had

neuroinflammation for even longer time frames (e.g. 6 months), their behavioural responses could have been quite different. Moreover, it is likely possible that inflammation and glial state is changing across the behavioural tasks which is difficult to capture in real time.

Facilitation of action selection: Is it really a cognitive improvement?

First, it is worth considering what exactly this pattern of results might mean. In studies for which the opposite pattern of results to that in Experiments 3-4 is typically observed, for instance a pDMS lesion or inactivation study in which control animals show intact specific PIT (Corbit & Janak, 2010) or devaluation (Yin, Ostlund, et al., 2005) but pDMS inactivated animals do not, this is usually interpreted as an impairment in the inactivated group. Therefore, it is tempting to apply a similar interpretation here and suggest that where Sham animals are somehow 'impaired' whereas animals with pDMS neuroinflammation are not. Such an interpretations could even be taken a step further, to suggest that pDMS neuroinflammation somehow improves cognition and/or performance on these tests. Indeed, such an interpretation cannot be entirely ruled out, particularly with regards to the results of Experiment 3 in which the feeding of the high fat, high protein chow may be viewed as having 'impaired' the performance of Shams. Despite the differences observed on the initial specific PIT test, responding during Pavlovian conditioning and instrumental acquisition did not differ according to group. This suggests that Sham and LPS animals could perform lever-pressing and magazine entries at similar rates, such that the deficit in Shams on test was not a result of locomotor or other performance-related issues. Rather, it is like that, under such low motivation conditions, the presentation of the stimuli on test was not sufficient to elevate responding on the lever associated with the same outcome. There are other possible interpretations of this effect, for instance that Sham controls did not learn the S-O associations or R-O associations sufficiently or were unable to discriminate between them.

The fact that Sham controls showed intact devaluation and outcome-selective reinstatement under the same conditions, however, suggests that R-O (and O-R) associations were intact and discriminable. Although it remains possible that S-O associations were specifically affected by these conditions, this seems unlikely given that such associations are typically highly robust.

The results of Experiment 4 are a little more difficult to view in this manner. With regards to progressive ratio testing, it is not entirely clear how the increase in breakpoint in LPS animals might be viewed as a reflection of intact performance in these animals versus an impairment in Shams. Even more difficult to understand within such a framework is the results of the habit test, because under these experimental conditions, the habits expressed by Shams is the typical result and should therefore be taken as 'normal' behaviour, whereas goal-directedness as observed in group LPS is the anomaly. Moreover, it is worth remembering that although I have detailed studies in Chapter 2 that have suggested that compulsive individuals over-rely on habits relative to healthy controls, for most individuals habits are useful for adaptive behaviours such that the inability to express habits where appropriate could actually be maladaptive. For instance, it has been argued that individuals with Parkinson's disease are perform actions particularly slowly because they lose their ability to perform in a habitual manner and are instead entirely goal-directed (de Wit et al., 2011; Mi et al., 2021; Redgrave et al., 2010). Also, given that compulsive disorders involve the inability to stop performing actions despite negative consequences, the progressive ratio result could be seen as a kind of intact performance that is akin to that displayed by compulsive individuals who persist despite negative consequences, because LPS animals also persisted when they were not getting any reward, and were likely are getting increasingly frustrated. I would also like to note that the conditioned taste aversion method used in

Experiment 4 did generalize outside of the context for LPS-injected animals, who showed an intact devaluation effect in Figure 28B, but not for Shams, who did not. Therefore, it is possible that the effect of LPS injections in pDMS was to facilitate the generalization of taste aversion learning across contexts relative to Shams, and this is why only the LPS animals demonstrated devaluation. Given the fact that pDMS LPS facilitated goal-directed action in Experiment 3 also (Figure 18E), in which specific satiety was used as the method of devaluation, it seems more parsimonious to assume that it facilitated goal-directed action here rather than context generalization.

There is a clinical inference that could be taken from these findings, however, in which the notion that neuroinflammation in the pDMS (or in its homologue the caudate) causes an improvement in goal-directed action could make sense. That is, perhaps when an individual sustains an infection or injury that causes neuroinflammation in the pDMS it is somehow useful for that individual to become more goal-directed in their actions so that they can seek to avoid getting into the situation that led to their injury or infection in the first place. Indeed, perhaps where there is an acute inflammatory response this is an adaptive way in which to behave. Over the longer term, however, the over-reliance on goal-directed processes and lack of ability to form habits could become maladaptive. For instance, in Experiment 3, the lack of motivation and accurate action selection in control animals is perhaps the accurate way to behave when a high-fat, high-protein 'home' chow is available, and the fact that LPS injected animals do not behave that way could be viewed as an overreliance on, or excessive use of, goal-directed action control in the way that has also been argued to underlie compulsive actions (Bradfield et al., 2017; Hogarth, 2020, 2022). If translatable, pDMS neuroinflammation causing the seeking of certain goals under typically low motivation conditions could be the underlying psychological process that leads compulsive individuals to

do the same, for instance drug-seeking when in poor health, or gambling when out of money. In this way, the action has not become disengaged from its outcome, as is observed in habits, but the outcome is so motivational to the animal that it is sought out despite the low motivation conditions.

One potential reason for the overreliance on goal-directed action control is that the value of the outcome might become inflated in individuals with pDMS/caudate neuroinflammation. This has been argued to be the case for individuals with SUD, for example, who might be driven by a greater expected value of the drug driving goal-directed drug seeking. This is supported from previous studies that dorsal striatal activity in humans and animals is linked with the degree of motivation to work for a particular reward (Koepp et al., 1998; Palmiter, 2008; Volkow et al., 2002; Zald et al., 2004). Another reason is that its outcome value be augmented by stress and withdrawal — effects amplified in those with neuropsychiatric symptoms and drug use coping motives. A study by Hutcheson et al. (2001) found that rats immediately increased their heroin seeking in extinction when shifted to a state of heroin withdrawal, demonstrating that withdrawal raised the expected value of heroin as a goal. Although previous studies have suggested that behavioural and pharmacological stress induction procedures reliably increase the reliance on habits (Schwabe & Wolf, 2009), as well as increasing single lever drug seeking and taking (Sommer et al., 2008; Spanagel et al., 2014), these results are not proving to be easily replicable (Smeets et al., 2023), possibly because stress could favour enhanced goal-directed control under some circumstances.

The facilitation of cue-guided action selection in sPIT could be viewed through a similar lens. This is because increased sensitivity to Pavlovian cues (Hoang et al., 2023) and the overwhelming ‘urge’ to act (Piantadosi & Ahmari, 2015) have both been shown to promote unhealthy behaviours in people with compulsive disorders. For example, an early study by

Monti and colleagues (1987) found that college students who are heavy drinkers were more inclined to choose an alcoholic drink when exposed to an alcohol cue. Another study also found that methamphetamine itself is sufficient to produce the heightened control that reward cues have over behaviour using a sPIT design (Hoang et al., 2023). Ahmari and colleagues (2013) have also generated a persistent OCD-like behaviour in mice through repeated stimulation of the OFC-ventral striatal pathway, suggesting that over-excitation of the ventral striatum (mirroring the excitation I observed in pDMS following neuroinflammation) is associated with compulsive-like actions. Together with current results, these findings could suggest that neuroinflammation in the striatum of individuals with SUD could cause specific and intense craving in these individuals, which may provoke and sustain the instrumental behaviours of drug seeking and taking in a goal-directed manner (Everitt, 2014; Grant et al., 1996; Robbins & Everitt, 2002). In this way, therefore, it is possible to see how the supposed 'improvements' in behavioural control as a result of pDMS neuroinflammation might actually be a contributing factor to compulsion and compulsive-like action selection.

Changes in glial and neuronal cell activation

The fact that animals injected with LPS were found to have a higher intensity of c-Fos-NeuN co-localization (Figure 23D, Figure 29C), indicating increased neuronal activity in these animals compared to controls, is interesting because neurons do not have the requisite receptors to directly respond to LPS. That is, LPS is considered an agonist of the toll-like 4 receptors (Calvo-Rodriguez et al., 2020; Moresco et al., 2011), which are found only on glia but not neurons (Lehnardt, 2010), and binding of LPS to these receptors activate nuclear factor kappa B (NFκB) leads to robust increases in production and release of pro-inflammatory cytokines, including IL-1β and TNF-α (Quan et al., 2000). Therefore, the excitation of neurons

could not have been caused directly by the injection of LPS but must have been achieved indirectly through the modulation of neurons by glia, possibly through cytokine release.

Current results indicate that the excitation of neurons leading to alterations in behaviour was most likely linked to the activation of astrocytes. This could have occurred through increases in glutamatergic transmission, which has previously been observed as a result of astrocytes activation (Mahmoud et al., 2019; Newman, 2003). One mechanism by which astrocyte activation might increase glutamate transmission is through its reduced ability to clear glutamate from the synaptic cleft via neurotransmitter uptake transporters that are expressed on astrocytes (e.g. glutamate transporter 1 [GLT-1] and glutamate aspartate transporter [GLAST]) (Perego et al., 2000). As a result of this failed uptake, more extracellular glutamate is available within the extracellular space and thus causing the activation of glutamatergic receptors. Also, the glutamate release from astrocytes includes the release of ATP, D-serine and GABA, giving the astrocyte the possibility to directly modulate synaptic transmission that could lead to complex astrocyte-neuron interactions in regulating behaviour (Allen, 2014; Araque et al., 2014; Koyama, 2015).

Although it is a less likely explanation given the results of the correlative analyses in Experiments 3 and 4 as well as the behavioural outcomes of Experiment 5, an alternate mechanism by which glial activation could have caused the increase in the neuronal excitation is via microglial activation. This is because microglia has the ability to detect and catabolize synaptic adenosine triphosphate, which can have the effect of reducing the amplitude of action potentials. As microglia become activated and their processes retract, they are no longer capable of performing this function such that action potentials can occur at higher amplitudes (Badimon et al., 2020). Higher amplitude action potentials received by the post-synaptic neuron could therefore generate higher excitatory post-synaptic potentials, which

could summate with others to increase the likelihood of the that neuron also generating an action potential, causing a net excitatory effect.

It is also worth considering how the observed neuronal excitation must have also underscored the alterations in behaviour in the context of the broader neural circuit underlying cue-guided and goal-directed action control, which is relatively complex and involves several cortico-striatal and thalamic structures (see Chapters 1 and 2, for review). Glia themselves typically only have short processes and surveil their local regions, lacking the long-range projections necessary to contact this broad circuit. This suggests that behaviourally, glia could only be achieving any behavioural modifications by modulating neuronal responses, which have much longer-ranging projections. As this might apply to the current set of results, this suggests that pDMS neuroinflammation is indirectly causing neuronal excitation as modulated by glia, and that this excitation is sending more action potentials along the action selection circuit, likely to regions such as substantia nigra, ventral tegmental area, and globus pallidus, to achieve the observed facilitation in motivation and action control.

The current findings implicating a role for astrocytes in motivated action selection are particularly exciting, and could signal a new avenue for research as well as novel potential therapeutic targets. Although pDMS neurons have been associated with intact action control for some time now, astrocytes have been largely ignored in these kinds of tasks. The importance of astrocytes in modulating memory, synaptic transmission, and animal behaviour has been recently shown in different brain areas, such as the prefrontal cortex (Mederos et al., 2021), the amygdala (Martin-Fernandez et al., 2017), the hippocampus (Adamsky et al., 2018; Kol et al., 2020), and the hypothalamus (Kim et al., 2014). Current results expand these findings to show a direct role for intact astrocytic signaling in cue-guided

and goal-directed action selection. Current results further demonstrate that intact astrocytic functioning is necessary specifically at the times when the choices are being made, because chemogenetic activation of the Gi pathway in astrocytes occurred only prior to test and not training. This was not purely a performance effect: altering astrocytic function did not reduce overall rates of responding, and nor did it abolish all kinds of choice behaviour because this manipulation left outcome-selective reinstatement unaffected (Figures 31F and 32E). Therefore, altering astrocytic signalling does not affect the rat's ability to discriminate between levers or outcomes. Rather, the pattern of results is consistent with a more specific deficit in action control, either when guided by cues or by internal goals.

Current findings are further consistent with a similar study that found that activation of the astrocytes in the DMS using Gq-coupled DREADDs facilitate goal-directed reward-seeking behaviour (Kang et al., 2020). Furthermore, the fact that activation of the astrocytic Gq pathway in this study had the opposite effect on devaluation performance relative to the activation of the Gi pathway in astrocytes in the current study (i.e. facilitation in the former and an impairment in the latter, in Experiment 5) further suggests that the current manipulation led to a decrease rather than an increase in neuronal activity. Nevertheless, as mentioned, the answer to this question was unable to be answered in the current thesis and is the subject of ongoing investigations in the laboratory.

Deeper insight into the possible brain mechanisms of facilitated goal-directed action control in the current study

Peak et al. (2020; 2019) have previously argued that glutamatergic inputs to the dorsal striatum constitute 'learning pathways' in the broader basal ganglia circuitry. Indeed, studies have shown that glutamate uptake is impacted by altered GLT-1 activity and level resulting to an increase extracellular glutamate level which can contribute to excitotoxic damage (Pajarillo

et al., 2019; Roberts-Wolfe & Kalivas, 2015; Scofield & Kalivas, 2014). Numerous studies have found that an imbalance of excitatory and inhibitory synaptic transmission is often associated as a pathological mechanism and potential therapeutic target in numerous diseases, such as Alzheimer's disease (Leng & Edison, 2021), epilepsy (Jiang et al., 2022), autism (Matta et al., 2019), depression (Kaufmann & Menard, 2018), SUD (Erickson et al., 2019; Namba et al., 2021) and OCD (Piantadosi et al., 2021; Pittenger et al., 2011).

Another plausible mechanism that could support the effects seen in the present study is that astrocytes in the striatum respond to D1-receptive or D2-receptive cells in a mutually exclusive manner. D1-responsive astrocytes increase Ca^{2+} levels in response to D1 receptor stimulation and not to D2 receptor stimulation, and vice versa (Martin et al., 2015). Likewise, increased Ca^{2+} levels trigger astrocytes to release glutamate to modulate excitability of neurons in a selective manner, with calcium waves in D2-responsive astrocytes only increasing excitatory post synaptic currents in D2 responsive, but not D1 responsive, neurons (Martin et al., 2015). This foundational work demonstrates that astrocytes modulate neurons in a circuit specific (D1 vs. D2) manner, and future work should investigate precisely how this is achieved.

Limitations and future directions for Chapter 4

The experiments presented in Chapter 4 suggest that pDMS neuroinflammation could be the potential endogenous cause of the brain dysfunction that underlies the disruptions in action control displayed by individuals with compulsive disorders. However, further studies are needed to determine the details regarding how homeostatic astrocytes and their cascading molecular events within the pDMS contribute to action selection, as suggested by Experiment 5, as well as the precise circumstances under which this function becomes disrupted. For instance, as I mentioned briefly before, neuroinflammation over a longer

timeframe (e.g., up to 6 months or longer) than that studied here could have different consequences for behaviour.

As also mentioned previously, determining the physiological consequences of Gi activation in astrocytes in the pDMS is critical to determine exactly how I have here disrupted their homeostatic function. Given the repeated failure of the c-Fos antibody in my M4-transfected tissue, other experiments in the laboratory are currently recording from hM4Di-transfected astrocytes using an astrocyte-specific form of gCAMP using fibre photometry to determine if the activation of this pathway is primarily excitatory or inhibitory as my behavioural data suggest. This procedure allows us to record calcium transients of cells, which is necessary because unlike neurons, astrocytes are not electrically excitable. However, we can measure astrocyte signalling via alterations in intracellular Ca^{2+} levels (Perea et al., 2009), in a manner such that increases and decreases in such signalling can be interpreted as an increase or decrease in astrocytic signalling, respectively.

Such experiments are necessary because, although it is clear that activation of hM4Di receptors in neurons cause inhibition of cell function (Armbruster et al., 2007), there is disagreement in the literature about the consequences activation of this pathway in astrocytes, with some articles claiming it to primarily excite them, and others claiming that it can inhibit their function, at least temporarily (Erickson et al., 2021; Kol et al., 2020; Lines et al., 2020; Nam et al., 2019). Furthermore, to my knowledge all these previous studies have been conducted in the hippocampus or in cortical tissue, for which the cellular composition is quite different to that of the striatum. In particular, the primary projection cell type in the hippocampus and cortex is glutamatergic, with a small population of inhibitory interneurons (Han & Sestan, 2013; Zeisel et al., 2015), whereas striatal projection cells are GABAergic medium spiny neurons, with several small populations of interneurons (Tepper & Bolam,

2004). Therefore, the consequences of activating the Gi pathway in astrocytes in the striatum is likely quite different to the consequences of doing so in hippocampal and cortical regions.

I have also been participating in electrophysiology studies recording the action potentials of medium spiny neurons in pDMS tissue injected with LPS or saline. This work is occurring in collaboration with Prof. Chris Dayas and Dr. Lizzie Manning at the University of Newcastle. Following surgical recovery, in vitro slices have been removed from the pDMS and neurons patched to determine whether there is an increase in spontaneous excitatory postsynaptic currents (sEPSC) frequency and amplitude in medium spiny neurons within inflamed tissue. Although the sample size is currently too small for statistical certainty, early results are in the expected direction (i.e. neurons in inflamed tissue appear to have a higher resting membrane potential than neurons in Sham controls, making them more excitable). We are further determining the consequences of pharmacologic inhibition on these slices, where we can pretreat the brain slices with either fluorocitrate − an astrocyte inhibitor − or minocycline − a microglia inhibitor − to see the contributions of these glial cells in the mechanism of action of LPS on the pDMS and whether direct glia activation through LPS could lead to an elevated glutamatergic neurotransmission in the pDMS. The results will be of interest to indicate which particular neuroimmune cells may be critical regulators or local sources of glutamatergic transmission in the pDMS. Future studies might also wish to quantify the protein levels of the glial glutamate transporter GLT-1 and GLAST in the brains of saline- and LPS-treated animals, given that these are the major transporters that take up synaptic glutamate to maintain the optimal extracellular levels.

With regards to the clinical implications of the current findings, other important future directions involve the investigation of the consequences of neuroinflammation in brain regions other than just the pDMS. This is important for two reasons. First, individuals with

compulsive disorders experience neuroinflammation across multiple brain regions (Attwells et al., 2017; Chen et al., 2023; Kohno et al., 2019) and the consequences of this for action control is unknown. Second, it is important to know whether the effects observed in the current study are specific to the pDMS, or whether neuroinflammation in any brain region might produce the same effects. I speculate that this is unlikely, given the heterogeneity of function of different brain regions in goal-directed action control identified by inactivation studies (see Bradfield & Balleine, 2017; Simmler & Ozawa, 2019, for review), nevertheless it is important to demonstrate this empirically.

A final important future direction is to determine whether the alterations in goal-directed action control can be reduced or even reversed using pharmacological interventions such as anti-inflammatories. If this were the case, it could have important implications for the treatment and possibly even prevention of compulsion in humans.

CONCLUDING REMARKS

The results of Chapter 3 showed that the specificity of reinstated responding is largely independent of external environments. The results of Chapter 4 provided the first, causal evidence of altered action control as a result of neuroinflammation in DMS, and show the centrality of astrocyte function to such control. Together, the results of these two chapters provide novel information about the behavioural and brain mechanisms of compulsive disorders. It is important to note that the results of each of these chapters, although quite independent of one another, are related in the sense that each produced effects that were somewhat unexpected or differed from predictions. Specifically, the results of Chapter 3 showed that, against expectations, reinstatement of choice behaviour is largely specific regardless of which context it occurs in. The results of Chapter 4 showed that, in contrast to

the expected impairment of behaviour as a result of pDMS neuroinflammation, action control was actually facilitated in inflamed animals in a number of instances. Together, these unexpected results not only highlight the importance of doing empirical research rather than relying on intuition to make inferences about the relationships between environments, brain mechanisms, and behaviour, but particularly reveals the importance of doing causal studies to make such inferences. Future studies should continue to expand upon and extend current findings in the multiple ways outlined above, not only to continue to deepen our understanding of the behavioural and brain mechanisms of compulsive disorders, but to also determine new ways in which such disorders can be treated or prevented. Based on current results, particular anti-inflammatories could be investigated, as well as drugs that normalise the signalling of astrocytes in particular.

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APPENDICES

APPENDIX A

Experiment 1

Instrumental Training, 6 sessions

Input

Average of Averaged o	Column Labels					
Row Labels	1	2	3	4	5	6
AAA	**0.44**	**0.83**	**2.47**	**3.80**	**4.66**	**5.08**
42	0.55	0.92	3.08	6.14	5.03	3.90
44	0.10	0.08	0.00	0.03	0.70	3.15
50	0.40	0.05	0.15	0.10	0.28	0.18
51	0.58	2.53	6.80	6.81	8.40	6.97
53	0.66	0.15	3.49	5.00	6.80	5.88
55	0.60	1.10	0.58	0.50	1.93	2.78
62	0.50	0.18	1.96	7.20	9.01	10.59
68	0.39	0.15	0.70	1.58	1.43	3.93
74	0.00	1.15	3.83	7.66	7.85	6.58
76	0.50	0.15	2.14	2.13	3.40	4.15
78	0.60	2.64	4.46	4.70	6.43	7.78
AAB	**0.73**	**0.87**	**1.71**	**2.53**	**3.36**	**4.59**
41	0.80	1.90	3.13	6.76	6.33	7.78
43	0.83	1.22	4.18	3.99	4.03	3.95
52	0.58	1.86	3.08	4.53	3.35	2.10
56	0.53	0.05	0.28	0.23	0.28	0.53
63	0.98	2.53	4.30	4.91	9.00	8.81
66	0.50	0.15	0.03	0.40	0.65	4.00
71	0.34	0.08	0.30	0.90	2.45	3.85
73	0.00	0.00	0.03	0.13	0.58	1.45
77	2.03	0.03	0.08	0.90	3.60	8.88
ABA	**0.74**	**0.64**	**2.36**	**4.50**	**5.38**	**6.92**
47	0.57	0.03	1.08	2.43	2.08	3.35
49	0.50	0.10	0.23	0.70	0.75	1.43
54	0.50	0.08	1.84	7.74	9.33	15.35
58	0.63	0.40	0.08	0.05	0.78	0.58
59	2.03	0.13	0.00	0.25	1.85	3.35
65	0.50	1.59	7.45	7.81	10.32	9.73
69	0.73	1.07	5.23	11.90	12.07	12.85
70	0.39	0.08	0.50	1.25	2.80	1.60
75	1.01	0.83	3.30	7.20	6.63	7.38
79	0.55	2.08	3.93	5.67	7.21	13.55
ABB	**0.45**	**0.33**	**1.05**	**2.71**	**4.21**	**5.06**
45	0.53	1.34	1.95	4.20	4.00	5.48
46	0.50	0.08	0.10	0.10	1.98	6.48
48	0.58	0.08	0.08	1.24	5.31	3.40
57	0.50	0.00	0.05	0.03	0.03	0.13
60	0.98	1.19	5.25	10.57	12.97	17.27
61	0.00	0.00	0.10	0.65	0.80	2.35
64	0.68	0.20	1.30	4.24	6.85	4.05
67	0.03	0.15	0.15	2.35	3.25	3.90
72	0.03	0.13	1.10	3.03	6.83	5.93
80	0.73	0.18	0.45	0.70	0.13	1.62
Grand Total	**0.58**	**0.66**	**1.92**	**3.42**	**4.44**	**5.42**

Output

Tests of Within-Subjects Effects							
Measure: MEASURE_1							
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	
Day	Sphericity Assumed	793.765	5	158.753	41.459	0	* Main effect of day
	Greenhouse-Geisser	793.765	1.744	455.143	41.459	0	
	Huynh-Feldt	793.765	1.978	401.289	41.459	0	
	Lower-bound	793.765	1	793.765	41.459	0	
Day * Group	Sphericity Assumed	41.55	15	2.77	0.723	0.759	* No Day x group interaction
	Greenhouse-Geisser	41.55	5.232	7.942	0.723	0.614	
	Huynh-Feldt	41.55	5.934	7.002	0.723	0.631	
	Lower-bound	41.55	3	13.85	0.723	0.545	
Error(Day)	Sphericity Assumed	689.251	180	3.829			
	Greenhouse-Geisser	689.251	62.784	10.978			
	Huynh-Feldt	689.251	71.209	9.679			
	Lower-bound	689.251	36	19.146			

Tests of Between-Subjects Effects						
Measure: MEASURE_1						
Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	
Intercept	1776.508	1	1776.508	63.857	0	
Group	51.184	3	17.061	0.613	0.611	* No main effect of group
Error	1001.521	36	27.82			

Experiment 1

Extinction

Input

Column Lat - Average of LL																													
Row Labe -	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
⊟AAA	6.45	7.27	5.00	5.18	4.27	2.82	3.55	5.36	3.73	1.82	2.45	2.82	2.91	4.18	4.73	3.18	4.73	3.64	2.18	2.55	1.82	1.73	1.45	0.45	0.82	1.00	1.64	2.09	2.00	2.09
42	14	10	5	6	4	4	6	7	1	3	6	6	7	3	2	4	6	6	1	3	1	0	0	0	0	0	4	2	6	4
44	1	1	0	0	0	1	0	1	2	0	0	3	0	0	0	0	0	4	0	0	0	0	0	0	0	1	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
51	6	10	12	7	5	6	7	3	7	3	1	3	2	2	8	1	10	12	1	6	7	6	3	2	2	4	11	9	5	
53	0	2	3	2	0	1	0	2	2	0	0	3	0	1	1	1	1	0	0	1	0	1	3	0	0	1	0	0	1	0
65	6	0	3	3	4	3	3	6	5	3	6	6	9	3	3	1	2	0	0	2	0	0	2	2	2	4	4	0	3	3
62	26	39	20	8	10	3	6	22	19	7	2	1	4	17	8	5	7	3	4	1	4	3	0	0	0	2	3	1	7	
68	4	2	0	2	2	0	0	1	1	0	2	2	0	1	2	2	0	0	0	0	1	1	0	0	0	1	0	0	2	1
74	1	1	3	1	5	0	1	4	0	0	2	0	1	2	2	0	1	1	2	0	1	2	0	1	0	0	0	0	0	0
76	3	7	3	8	6	2	5	2	4	4	8	8	6	4	7	7	5	3	4	0	0	0	0	0	4	2	4	7	0	3
78	10	8	6	20	11	11	11	11	0	0	0	1	3	13	19	16	20	14	12	15	7	8	8	1	0	0	0	0	0	0
⊟AAD	2.22	2.78	3.00	2.00	2.67	0.67	1.11	1.78	1.67	1.00	0.44	1.89	1.33	1.56	1.44	1.00	0.89	0.67	0.33	0.33	0.22	0.89	0.67	0.78	0.56	1.22	1.33	0.67	0.89	0.56
41	4	8	8	5	7	0	3	5	6	2	0	9	6	12	6	0	6	2	1	0	0	5	2	5	0	7	2	1	5	3
43	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	1	1	0	0	0
52	3	5	6	3	3	0	0	5	4	4	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0
56	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0
63	3	1	0	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	1	1	
66	8	9	10	6	7	5	3	3	2	3	4	3	0	3	3	8	2	1	0	3	2	2	2	1	1	0	7	3	1	1
71	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	2	0	2	0	0	0	3	1	1	0	2	0	2	0	0	0	1	0	4	2	2	1	0	0	0	0
77	1	2	1	0	3	0	0	2	2	1	0	0	1	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0
⊟ABA	1.2	2.5	2	2.9	3.6	1.9	1.9	2.1	2.3	4.7	2.1	2.9	1.7	0.8	1.6	2.1	2.5	1.8	0.6	0.6	1.1	1.6	1.2	1.9	1.9	0.8	2.1	1.5	2.3	1.5
47	2	0	1	2	2	3	4	2	1	0	1	0	2	0	0	1	1	1	1	2	0	0	0	0	1	1	1	1	0	2
49	0	0	3	2	2	4	0	4	2	2	1	3	2	2	1	2	0	0	1	1	2	0	2	2	1	2	1	2	2	3
54	2	6	1	5	11	3	5	0	2	3	1	0	0	0	0	1	0	0	0	0	4	9	3	0	4	1	0	0	0	0
58	1	1	2	1	1	0	1	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	2	2	1	0	
59	3	5	1	3	4	2	3	4	0	1	4	1	2	1	3	10	4	2	2	3	3	2	0	5	3	1	0	0	0	2
65	0	0	1	2	1	1	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	0	4	4	4	10	2	1	0	2	15	6	14	7	0	6	2	4	0	2	0	0	0	0	0	6	6	1	14	5	12
70	0	2	0	2	0	0	1	0	0	1	0	1	0	2	1	0	2	1	1	0	0	1	0	3	1	3	1	0	3	0
75	0	0	1	0	0	0	0	0	0	0	1	0	2	0	1	0	0	0	0	0	1	0	1	0	2	2	0	0	2	0
79	4	7	6	8	5	4	4	9	14	25	7	9	0	3	5	3	15	13	0	0	1	4	4	3	0	0	3	5	3	6
⊟ADB	2.27	3.00	2.18	2.18	2.55	1.73	1.45	1.91	2.91	1.64	0.64	1.36	2.91	1.55	2.45	1.82	2.45	1.91	1.09	1.27	0.91	0.55	0.73	1.27	2.00	1.09	1.36	0.55	0.82	1.36
45	6	6	0	6	3	3	2	5	5	3	4	2	4	5	6	2	4	6	4	2	2	2	3	5	6	4	7	0	1	4
46	2	9	3	2	3	0	0	3	4	5	0	0	7	1	3	4	5	4	5	4	4	0	2	4	0	4	2	0	0	1
48	3	3.5	3.5	3.5	4	4	2.5	2	3.5	0	0	2.5	3	1	1.5	1.5	1.5	4	1	0	0	0	0	0	0	0	0	0	0	0
57	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	3	6	1	0	0	0	2	6	1	5	0	0	1	5	2	1	6	7	2	0	3	2	0	0	0	5	0	1	2	3
61	0	0	3	0	0	0	0	0	1	3	0	0	1	1	2	2	2	0	0	0	0	0	0	2	6	1	3	1	0	0
64	7	3	4	7	9	4	0	5	7	3	2	4	4	9	3	3	0	0	0	2	0	2	0	3	5	0	1	1	0	1
67	0	0	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
72	0	2	1	2	1	1	2	2	0	1	3	2	1	0	0	0	0	3	0	0	1	1	0	0	0	0	1	0	1	1
80	0	0	4	0	4	0	1	0	4	0	0	3	1	3	0	0	0	1	1	1	2	3	0	0	3	1	0	4	1	5
Grand Total	3.12	3.98	3.07	3.12	3.29	1.83	2.05	2.85	2.71	2.29	1.44	2.24	2.27	2.07	2.63	2.07	2.73	2.07	1.10	1.24	1.05	1.20	1.02	1.10	1.34	1.02	1.61	1.22	1.51	1.41

Average of RL																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	1.91	1.64	2.64	2.45	3.73	1.18	3.45	2.09	1.27	0.91	1.18	1.18	1.09	1.73	3.64	1.27	1.18	1.36	0.45	1.18	0.45	0.18	0.27	2.45	1.09	0.45	1.73	0.09	0.45	0.73
	2	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	1	0
	5	3	2	0	2	3	2	4	2	2	2	3	5	3	1	0	0	3	1	3	0	0	0	1	2	0	2	2	0	5
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	2	0	3	2	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	3	0	4	6	26	1	19	3	3	4	4	0	0	0	18	3	7	0	0	1	0	0	0	0	0	0	0	0	1	0
	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	1	1	2	3	2	1	1	3	3	2	3	1	0	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	2
	2	9	2	3	3	0	2	1	2	1	2	0	3	0	2	0	1	3	0	0	0	2	0	20	3	1	1	0	0	2
	1	3	12	10	5	6	13	13	4	0	2	2	2	16	15	8	2	7	1	8	2	0	0	6	4	4	14	0	0	0
	3	2	1	2	3	0	0	1	0	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	1	0	0	0
	0	0	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	3	1	1	1	0	0	0	0	0	0	0	0	0
	3.00	3.44	5.89	2.33	2.56	2.89	2.78	1.67	1.11	0.89	2.33	2.67	2.89	1.44	2.00	1.89	1.44	1.33	1.00	2.00	1.22	2.11	2.00	0.89	1.11	0.67	2.00	2.00	2.22	0.78
	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	9	8	8	2	1	4	2	0	1	0	0	1	1	3	3	0	0	6	3	3	5	11	1	5	4	2	3	4	7	3
	0	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	5	24	9	14	5	16	2	0	3	12	12	11	0	4	8	1	4	2	13	6	3	6	3	4	1	5	2	3	1
	1	1	1	2	2	4	3	1	2	1	4	2	2	0	0	3	2	0	0	1	0	0	1	0	0	0	1	2	1	0
	1	4	13	7	2	6	3	6	4	3	4	7	9	6	8	4	10	0	2	0	0	0	0	0	0	3	6	9	8	3
	1	0	0	0	1	0	1	4	0	0	1	3	0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	1	0
	9	11	6	1	1	6	1	1	3	0	1	1	3	3	2	0	2	0	1	0	4	9	0	0	0	2	0	0	0	0
	2.5	5.2	4.9	4.8	3.5	5.4	3	2.3	1.8	5.6	4.6	2	1.9	1	0.3	2.5	2.3	1.5	1.1	0.4	1.4	2.5	0.6	0.8	0.8	0.3	1.9	0.5	1.1	1
	3	4	6	0	1	2	2	0	3	1	3	7	2	2	0	2	5	6	3	1	1	1	0	0	5	1	10	2	6	2
	1	3	3	0	1	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	13	21	19	23	43	18	4	10	3	1	0	1	0	0	9	2	0	0	2	0	11	18	3	0	0	0	0	0	0
	0	0	1	3	0	3	0	0	4	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
	1	0	1	1	0	1	0	0	1	1	2	0	0	0	0	1	0	0	1	0	0	2	0	1	0	0	0	0	0	0
	5	27	7	20	5	1	4	13	0	45	33	12	12	5	0	1	7	5	7	0	0	1	0	0	0	0	0	0	0	0
	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	3	1	0	0	2	1	0	3	2	0	1	1	1	0	0	0	0	0	0	0	1	2	2	1	4	2	2	1
	7	5	6	4	5	1	3	4	0	1	0	2	2	2	9	8	4	0	0	0	2	3	2	5	1	1	5	1	2	7
	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	2.10	0.91	0.45	0.82	1.55	0.36	0.91	1.45	0.82	0.45	0.55	0.00	0.64	0.00	1.91	0.09	0.55	0.09	0.45	0.55	0.27	0.00	0.00	0.00	0.55	0.10	0.09	0.10	0.91	0.55
	2	1	0	1	1	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
	0.5	0	0.5	1	0	0.5	0	1.5	0	0	0	0	0	0	0.5	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	15	6	0	0	7	0	4	9	3	1	0	0	0	0	15	0	2	0	3	4	3	0	0	0	5	0	0	0	2	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	3	2	3	4	2	4	4	3	0	4	0	0	3	0	0	2	2	0	0	0	0	0	1	2	1	1	6	4	
	1	0	1	0	1	1	0	1	0	0	1	0	0	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	2	1
	2.37	2.71	3.32	2.56	2.83	2.37	2.51	1.88	1.24	1.93	2.10	1.39	1.56	1.02	2.00	1.39	1.34	1.05	0.73	1.00	0.80	1.12	0.66	1.05	0.88	0.39	1.39	0.63	1.12	0.76

Output

Tests of Within-Subjects Effects									
Measure: MEASURE_1									
Source		Type III Sum of Squares	df	Mean Square	F	Sig.			
Min	Sphericity Assumed	589.138	29	20.315	4.725	0		Main effect of Min	
	Greenhouse-Geisser	589.138	7.337	80.294	4.725	0			
	Huynh-Feldt	589.138	10.17	57.931	4.725	0			
	Lower-bound	589.138	1	589.138	4.725	0.036			
Min * Group	Sphericity Assumed	478.025	87	5.495	1.278	0.049		No Min x group interaction	
	Greenhouse-Geisser	478.025	22.012	21.717	1.278	0.185			
	Huynh-Feldt	478.025	30.509	15.668	1.278	0.152			
	Lower-bound	478.025	3	159.342	1.278	0.297			
Error(Min)	Sphericity Assumed	4488.487	1044	4.299					
	Greenhouse-Geisser	4488.487	264.14	16.993					
	Huynh-Feldt	4488.487	366.106	12.26					
	Lower-bound	4488.487	36	124.68					

Tests of Between-Subjects Effects								
Measure: MEASURE_1								
Transformed Variable: Average								
Source	Type III Sum o	df	Mean Square	F	Sig.			
Intercept	3810.915	1	3810.915	108.424	0			
Group	238.671	3	79.557	2.263	0.098		* No main effect	
Error	1265.333	36	35.148					

Experiment 1

Renewal

Input

Row Labels	Average of LL First 3 min			Average of RL First 3 min		
	1	2	3	1	2	3
AAA	**1.82**	**3.09**	**2.18**	**0.73**	**0.55**	**2.09**
42	10.00	3.00	2.00	0.00	0.00	0.00
44	0.00	1.00	0.00	3.00	2.00	7.00
50	0.00	0.00	0.00	0.00	0.00	0.00
51	2.00	9.00	10.00	0.00	0.00	0.00
53	0.00	0.00	0.00	1.00	1.00	4.00
55	1.00	1.00	0.00	0.00	0.00	0.00
62	3.00	6.00	2.00	1.00	0.00	3.00
68	2.00	3.00	0.00	1.00	2.00	1.00
74	0.00	1.00	0.00	2.00	1.00	7.00
76	1.00	4.00	9.00	0.00	0.00	1.00
78	1.00	6.00	1.00	0.00	0.00	0.00
AAB	**1.33**	**0.44**	**2.00**	**1.56**	**0.56**	**1.11**
41	5.00	0.00	9.00	0.00	0.00	0.00
43	0.00	0.00	1.00	5.00	1.00	4.00
52	0.00	1.00	0.00	4.00	1.00	0.00
56	0.00	0.00	0.00	0.00	0.00	2.00
63	0.00	0.00	0.00	1.00	1.00	0.00
66	7.00	1.00	7.00	1.00	0.00	0.00
71	0.00	0.00	0.00	0.00	0.00	1.00
73	0.00	0.00	0.00	1.00	0.00	3.00
77	0.00	2.00	1.00	2.00	2.00	0.00
ABA	**2.60**	**1.10**	**4.70**	**2.50**	**1.90**	**1.40**
47	0.00	0.00	2.00	1.00	0.00	0.00
49	0.00	0.00	0.00	0.00	0.00	0.00
54	2.00	0.00	1.00	5.00	6.00	1.00
58	2.00	0.00	1.00	0.00	0.00	0.00
59	4.00	4.00	9.00	0.00	0.00	3.00
65	1.00	2.00	1.00	9.00	6.00	5.00
69	5.00	2.00	10.00	1.00	1.00	0.00
70	3.00	1.00	2.00	5.00	4.00	2.00
75	0.00	0.00	0.00	3.00	2.00	2.00
79	9.00	2.00	21.00	1.00	0.00	1.00
ABB	**1.30**	**0.90**	**1.60**	**0.60**	**0.80**	**0.80**
45	1.00	2.00	2.00	0.00	1.00	0.00
46	0.00	3.00	2.00	0.00	1.00	0.00
48	4.00	1.00	9.00	0.00	1.00	1.00
57	0.00	0.00	0.00	0.00	0.00	0.00
60	0.00	0.00	0.00	2.00	0.00	0.00
61	1.00	0.00	0.00	0.00	0.00	0.00
64	2.00	0.00	0.00	0.00	0.00	0.00
67	1.00	1.00	0.00	4.00	4.00	5.00
72	1.00	1.00	2.00	0.00	0.00	2.00
80	3.00	1.00	1.00	0.00	1.00	0.00
Grand Total	**1.78**	**1.45**	**2.63**	**1.33**	**0.95**	**1.38**

Output

Number of Groups: 4
Number of Measurements: 1

Number of subjects in...
Group 1: 11
Group 2: 10
Group 3: 9
Group 4: 10

Between contrast coefficients

Contrast	Group...			
	1	2	3	4
B1	1	1	0	-2
B2	1	1	-2	0
B3	1	-1	0	0

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	6.716	1	6.716	4.433	* Renewal effect of ABA vs. Controls, p = .042
B2	0.263	1	0.263	0.173	* No renewal effect of AAB vs. controls, F < 1
B3	2.882	1	2.882	1.902	* No difference between control groups: AAA vs. AAB, p = .176
Error	54.547	36	1.515		

ABA vs. Rest

Number of Groups: 4
Number of Measurements: 1

Number of subjects in...
Group 1: 11 (1 = AAA)
Group 2: 10 (2 = ABB)
Group 3: 9 (3 = AAB)
Group 4: 10 (4 = ABA)

Between contrast coefficients

Contrast	Group...				
	1	2	3	4	
B1	1	1	1	-3	* ABA vs. Rest
B2	1	1	-2	0	* AAB vs. Rest
B3	1	-1	0	0	* AAA vs. ABB

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	8.479	1	8.479	5.596	* ABA renewal, p = .024
B2	0.263	1	0.263	0.173	* AAB renewal F < 1
B3	2.882	1	2.882	1.902	* AAA vs. ABB, p = .176
Error	54.547	36	1.515		

Experiment 1

Reinstatement

Input

Row Labe	Average of Pre Rein	Average of Pre NonRein	Average of Post Rein	Average of Post NonReins	Pre
AAA	**5.00**	**8.50**	**11.14**	**3.64**	
42	4.00	4.50	10.50	4.50	4.25
44	2.00	5.00	3.00	0.50	3.50
50	0.00	0.00	0.50	0.00	0.00
51	10.50	19.50	13.00	7.00	15.00
53	5.00	10.00	11.00	3.50	7.50
55	4.00	1.00	7.50	0.50	2.50
62	5.00	8.00	18.00	2.50	6.50
68	5.50	6.50	11.50	2.50	6.00
74	2.00	7.00	11.50	2.50	4.50
76	6.50	11.00	11.00	4.50	8.75
78	10.50	21.00	25.00	12.00	15.75
AAB	**2.56**	**4.89**	**4.83**	**4.11**	
41	3.50	12.00	9.50	3.50	7.75
43	2.50	3.50	1.50	3.50	3.00
52	0.50	0.50	0.00	0.00	0.50
56	0.00	2.50	0.00	0.00	1.25
63	0.00	7.50	3.00	12.00	3.75
66	6.50	10.50	16.00	9.00	8.50
71	1.50	3.00	4.00	3.50	2.25
73	3.50	1.50	5.00	2.50	2.50
77	5.00	3.00	4.50	3.00	4.00
ABA	**5.95**	**6.50**	**8.85**	**8.05**	
47	4.00	2.50	2.00	2.00	3.25
49	1.00	1.00	5.00	2.00	1.00
54	22.50	8.00	12.00	6.50	15.25
58	0.00	1.00	0.00	0.50	0.50
59	10.00	6.50	9.00	4.50	8.25
65	2.50	8.00	20.00	9.00	5.25
69	1.50	7.50	26.00	14.50	4.50
70	7.50	8.00	8.50	5.00	7.75
75	2.50	2.00	3.00	1.00	2.25
79	8.00	20.50	3.00	35.50	14.25
ABB	**4.00**	**5.25**	**8.85**	**1.90**	
45	5.00	7.00	10.00	0.50	6.00
46	2.50	4.50	5.50	1.00	3.50
48	9.00	11.00	14.50	2.00	10.00
57	0.00	0.50	0.00	0.50	0.25
60	7.00	6.00	29.50	4.00	6.50
61	0.00	4.00	6.50	4.00	2.00
64	5.50	4.00	6.00	2.50	4.75
67	7.00	10.50	9.00	3.50	8.75
72	1.00	2.00	4.00	0.00	1.50
80	3.00	3.00	3.50	1.00	3.00
Grand Total	**4.44**	**6.38**	**8.58**	**4.41**	

Output

AAA/ABB vs. AAB/ABA (i.e. control vs. renewal groups)

Number of Groups: 4

Number of Measurements: 3

Number of subjects in...

Group 1: 11	1 = AAA
Group 2: 10	2 = ABB
Group 3: 9	3 = AAB
Group 4: 10	4 = ABA

Between contrast coefficients

Contrast	Group...			
	1	2	3	4
AAA/ABB vs. B1	1	1	-1	-1
AAA vs. ABB B2	1	-1	0	0
AAB vs. ABA B3	0	0	1	-1

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
Pre vs. Post W1	2	-1	-1
Reinst vs. N W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
AAA/ABB vs. B1	1.014	1	1.014	0.016	* No main effect of AAA/ABB vs. AAB/ABA (i.e. controls vs. renewal groups)
AAA vs. ABB B2	65.990	1	65.990	1.037	* No main effect of AAA vs. ABB (i.e. no differences between control groups), p = .315
AAB vs. ABA B3	172.700	1	172.700	2.714	* No main effect of AAB vs. ABA, p = .108
Error	2291.081	36	63.641		
Within					
Pre vs. Post W1	31.543	1	31.543	2.956	* Responding post-outcome delivery no different to responding pre-delivery, p = .094
B1W1	4.185	1	4.185	0.392	* No interactions, all Fs < 1.
B2W1	0.045	1	0.045	0.004	
B3W1	6.870	1	6.870	0.644	
Error	384.151	36	10.671		
Reinst vs. N W2	317.287	1	317.287	10.213	* Main effect of reinstatement
B1W2	207.860	1	207.860	6.691	* Interaction with AAA/ABB vs. AAB/ABA, p = .014
B2W2	0.792	1	0.792	0.026	* No interaction with AAA vs. ABB
B3W2	0.014	1	0.014	0.000	* No interaction with AAB vs. ABA
Error	1118.440	36	31.068		

Simple effects

Number of Groups: 4

Number of Measurements: 3

Number of subjects in...

Group 1: 11

Group 2: 10

Group 3: 9

Group 4: 10

Between contrast coefficients

Contrast	Group...			
	1	2	3	4
AAA simple B1	1	0	0	0
ABB simple B2	0	1	0	0
AAB simple B3	0	0	1	0
ABA simple B4	0	0	0	1

*** Caution ***

B1 coefficients do not sum to zero

B2 coefficients do not sum to zero

B3 coefficients do not sum to zero

B4 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
Reinst vs. N W1	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
AAA simple B1	1698.502	1	1698.502	26.689	* Dummy
ABB simple B2	787.969	1	787.969	12.381	* Dummy
AAB simple B3	481.333	1	481.333	7.563	* Dummy
ABA simple B4	1782.552	1	1782.552	28.009	* Dummy
Error	2291.081	36	63.641		
Within					
Reinst vs. N W1	317.287	1	317.287	10.213	* Main effect of reinstatment
B1W1	309.375	1	309.375	9.958	* Simple effect significant for Groups AAA, p = .003, and ABB, p = .008
B2W1	241.513	1	241.513	7.774	
B3W1	2.347	1	2.347	0.076	* Simple effects not significant for Groups AAB and ABA, both Fs < 1.
B4W1	3.200	1	3.200	0.103	
Error	1118.440	36	31.068		

Experiment 1

Number of c-Fos in mOFC/lOFC/pDMS/DH CA1

mOFC

AAA	AAB	ABA	ABB
306.6700	185.8300	169.0000	263.9600
189.7500	217.6700	226.8000	261.0000
240.6000	211.5600	239.3300	255.3300
309.0000	233.2500	307.3750	283.6250
236.0000	260.0000	159.7500	213.2200
240.3750	283.0000	365.8330	251.6700
274.8300	196.6700	329.0000	274.1250
299.6000	232.3300	369.0000	283.4280
338.2000	260.2000	262.6700	402.6250
257.7100		297.0000	382.4300
491.1100			

lOFC

AAA	AAB	ABA	ABB
142.6700	99.8300	98.5000	118.7100
114.6000	133.5000	175.0000	117.8000
157.0000	139.7800	174.5000	171.8900
133.7100	168.0000	192.6250	184.2500
166.2900	161.5600	105.7500	112.6700
176.0000	183.6700	195.8330	163.3300
164.2900	141.0000	168.0000	183.7500
158.0000	122.8330	227.5700	173.7100
106.3300	151.5000	130.0000	161.6250
141.1670		177.7500	159.8600
219.2500			

pDMS

AAA	AAB	ABA	ABB
81.2500	37.0000	27.9000	77.8750
69.3000	23.9000	70.4000	51.6000
147.9000	34.0000	81.0000	183.3000
84.3333	67.0000	51.5000	200.5000
166.2900	43.5000	18.3333	98.7500
162.5000	29.5000	50.2500	47.4000
123.8333	29.3333	64.9000	79.0000
57.5556	19.3750	77.6000	55.5556
135.2857	42.0000	46.2500	138.7500
157.1667		58.1667	125.0000
212.8571			

DH CA1

Group A	Group B	Group C	Group D
AAA	AAB	ABA	ABB
9.6000	7.1250	12.5000	9.0000
6.1429	14.8750	13.8333	7.0000
9.0000	13.1111	15.7500	12.6667
7.0000	12.8333	5.7778	12.7500
9.2500	6.6250	6.0000	7.3750
5.2857	6.6667	11.0000	6.7500
17.0000	3.5714	8.2500	11.0000
9.5714	14.0000	13.3333	8.1667
22.6500	6.5000	5.7500	13.0000
23.8000			9.0000
15.3750			

Experiment 2

Instrumental Training, 6 sessions

Input

Average of Averaged ove	Column La					
Row Labels	1	2	3	4	5	6
AAA	**0.44**	**1.36**	**3.85**	**5.15**	**7.22**	**9.65**
3	0.20	0.30	0.20	0.05	1.93	2.58
7	0.55	1.28	5.15	10.65	10.88	22.56
23	0.33	1.97	5.40	7.99	8.59	10.38
27	2.06	4.23	11.09	11.80	16.84	20.73
31	0.53	0.10	0.08	0.25	0.35	1.96
33	0.15	0.55	1.23	2.77	5.35	5.00
34	0.23	2.40	9.45	6.25	15.86	13.28
42	0.08	0.23	0.13	0.15	0.10	2.12
45	0.23	1.58	6.52	9.69	12.94	23.07
68	0.20	0.68	3.66	9.57	10.76	13.67
72	0.45	2.99	6.12	5.38	5.00	5.18
79	0.98	3.31	6.69	6.76	9.47	10.22
82	0.05	0.50	0.35	0.25	0.25	1.31
83	0.10	0.08	0.13	0.10	0.48	2.91
90	0.50	0.23	1.50	5.53	9.45	9.81
AAB	**0.47**	**1.27**	**3.74**	**6.33**	**8.48**	**9.16**
4	0.43	0.20	0.43	1.60	4.35	8.48
8	0.38	1.28	1.90	4.25	4.80	3.88
25	0.23	1.19	5.01	5.60	6.08	8.35
26	0.55	2.19	4.86	7.93	11.61	14.09
28	0.48	1.64	3.93	3.70	2.43	3.23
29	0.95	3.26	8.45	16.35	17.26	15.28
35	0.50	0.88	4.08	5.26	8.05	10.25
41	0.30	0.10	0.13	0.25	1.52	3.35
44	0.60	2.51	5.89	11.36	21.00	16.14
47	0.35	0.10	0.81	2.40	3.43	5.88
77	0.35	1.27	3.93	9.06	12.84	13.63
80	0.38	1.68	9.25	12.57	12.11	9.33
81	0.43	0.60	0.90	3.40	9.50	10.05
85	0.15	0.38	1.13	3.48	3.15	4.58
86	0.98	1.80	5.40	7.73	9.08	10.91
ABA	**0.41**	**1.21**	**3.52**	**5.43**	**6.77**	**8.84**
2	0.15	0.15	0.20	1.13	5.05	14.84
6	0.05	0.05	0.15	0.13	0.05	0.13
16	0.60	0.93	2.35	4.65	5.35	4.63
24	0.18	0.73	2.63	4.70	4.95	4.33
36	0.40	0.75	3.35	7.82	8.70	12.64
37	1.01	5.27	6.82	8.20	8.90	10.80
38	0.15	0.38	1.68	5.29	5.03	8.68
39	0.30	1.18	5.01	7.88	9.20	14.64
43	0.30	1.61	3.50	4.45	4.35	3.43
46	0.25	0.83	4.43	3.33	9.08	8.75
49	0.40	2.92	9.62	15.75	15.52	15.31
67	0.45	1.01	5.51	7.09	9.92	13.55
78	0.28	0.43	1.03	3.98	7.01	6.13
84	0.20	0.03	0.13	0.08	0.28	0.81
88	1.38	1.98	6.45	7.03	8.15	13.88
ABB	**0.37**	**1.03**	**2.41**	**5.11**	**7.24**	**9.01**
1	0.15	0.10	0.28	0.13	0.05	0.10
5	0.15	0.03	0.30	0.10	0.78	3.77
15	0.25	0.20	1.05	4.23	5.13	6.08
21	0.43	0.50	1.56	9.38	11.96	11.76
22	0.25	2.14	5.33	6.60	9.73	13.00
30	0.28	1.93	5.38	5.38	6.70	9.81
32	0.20	0.20	0.35	2.85	7.26	12.23
40	0.25	0.98	3.94	3.90	3.88	4.73
48	0.25	1.74	3.25	10.42	8.98	8.05
50	0.30	0.75	1.95	6.56	10.25	4.38
69	0.25	0.18	0.38	1.47	5.23	7.58
70	0.50	1.74	5.25	8.20	11.40	12.43
71	1.04	4.05	3.65	7.69	12.09	15.25
87	0.75	0.50	1.55	4.68	6.30	9.92
89	0.53	0.38	1.90	5.10	8.88	16.13
Grand Total	**0.42**	**1.22**	**3.38**	**5.50**	**7.43**	**9.16**

Output

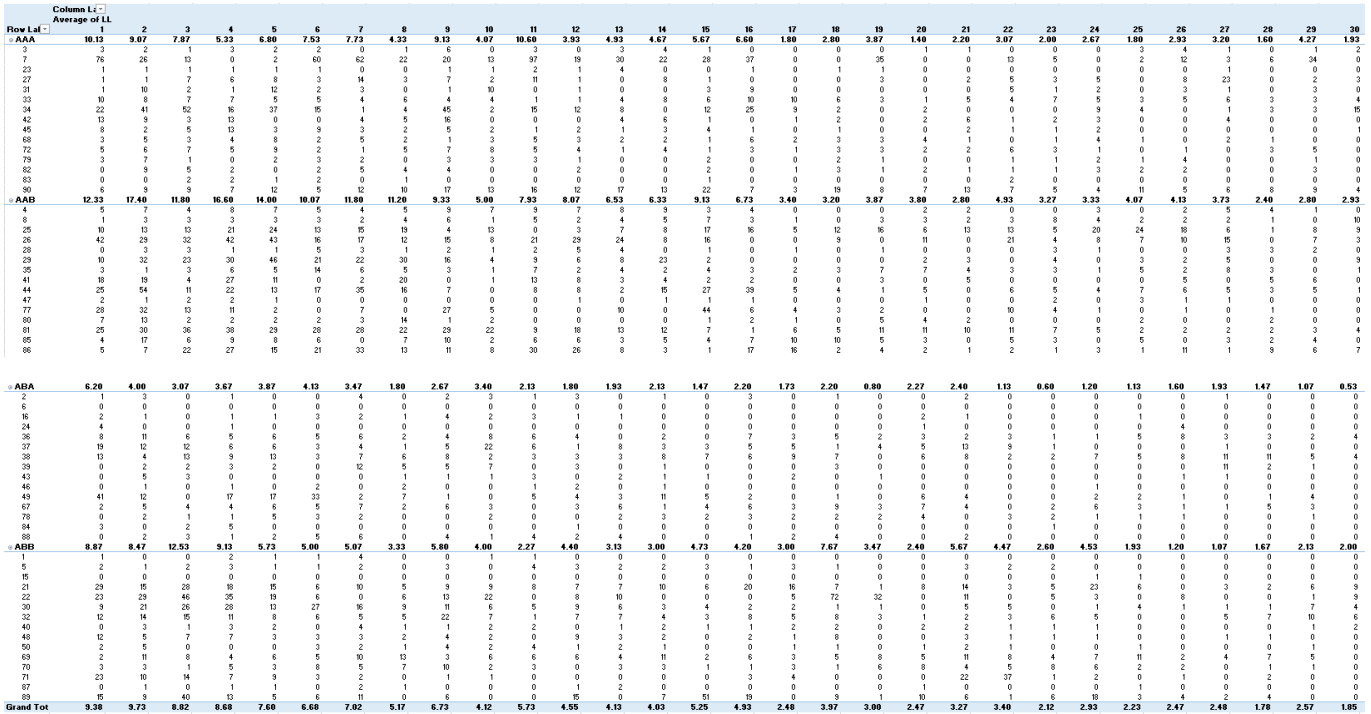
Tests of Within-Subjects Effects							
Measure: MEASURE_1							
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	
Day	Sphericity Assu	3599.295	5	719.859	108.711	0	* Main effect of Day
	Greenhouse-Ge	3599.295	1.92	1874.156	108.711	0	
	Huynh-Feldt	3599.295	2.094	1719.061	108.711	0	
	Lower-bound	3599.295	1	3599.295	108.711	0	
Day * Group	Sphericity Assu	39.03	15	2.602	0.393	0.98	* No Group x Day interaction
	Greenhouse-Ge	39.03	5.761	6.774	0.393	0.876	
	Huynh-Feldt	39.03	6.281	6.214	0.393	0.889	
	Lower-bound	39.03	3	13.01	0.393	0.759	
Error(Day)	Sphericity Assu	1854.091	280	6.622			
	Greenhouse-Ge	1854.091	107.547	17.24			
	Huynh-Feldt	1854.091	117.25	15.813			
	Lower-bound	1854.091	56	33.109			

Tests of Between-Subjects Effects					
Measure: MEASURE_1					
Transformed Variable: Average					
Source	Type III Sum of	df	Mean Squa	F	Sig.	
Intercept	7355.577	1	7355.577	153.094	0	
Group	25.988	3	8.663	0.18	0.909	* No main effect of group
Error	2690.587	56	48.046			

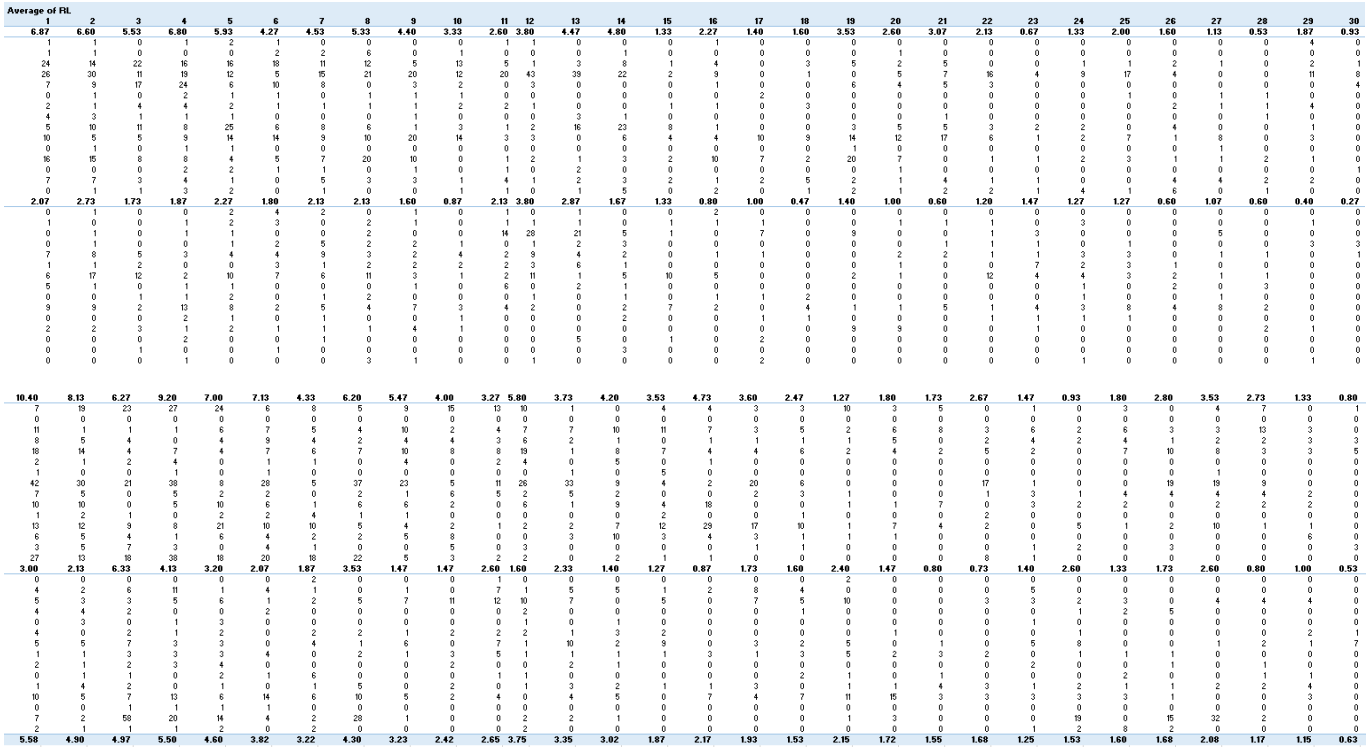
Experiment 2

Extinction, Day 1

Input



Column L	Average of LL																												
Row Lal	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
AAA	10.13	9.07	7.87	5.33	6.80	7.53	7.73	4.33	9.13	4.07	10.60	3.93	4.93	4.67	5.67	6.60	1.80	2.80	3.87	1.40	2.20	3.07	2.00	2.67	1.80	2.93	3.20	1.60	4.27	1.93
AAB	12.33	17.40	11.80	16.60	14.00	10.07	11.80	11.20	9.33	5.00	7.93	8.07	6.53	6.33	9.13	6.73	3.40	3.20	3.87	3.80	2.80	4.93	3.27	3.33	4.07	4.13	3.73	2.40	2.80	2.93
ABA	6.20	4.00	3.07	3.67	3.87	4.13	3.47	1.80	2.67	3.40	2.13	1.80	1.93	2.13	1.47	2.20	1.73	2.20	0.80	2.27	2.40	1.13	0.60	1.20	1.13	1.60	1.93	1.47	1.07	0.53
ABB	8.87	8.47	12.53	9.13	5.73	5.00	5.07	3.33	5.80	4.00	2.27	4.40	3.13	3.00	4.73	4.20	3.00	7.67	3.47	2.40	5.67	4.47	2.60	4.53	1.93	1.20	1.07	1.67	2.13	2.00
Grand Tot	9.38	9.73	8.82	8.68	7.60	6.68	7.02	5.17	6.73	4.12	5.73	4.55	4.13	4.03	5.25	4.93	2.48	3.97	3.00	2.47	3.27	3.40	2.12	2.93	2.23	2.47	2.48	1.78	2.57	1.85



Output

Tests of Within-Subjects Effects							
Measure: MEASURE_1							
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	
Min	Sphericity Assumed	6064.809	29	209.131	15.64	0	* Main effect of min
	Greenhouse-Geisser	6064.809	8.864	684.215	15.64	0	
	Huynh-Feldt	6064.809	11.241	539.549	15.64	0	
	Lower-bound	6064.809	1	6064.809	15.64	0	
Min * Group	Sphericity Assumed	1352.689	87	15.548	1.163	0.15	* No group x min interaction
	Greenhouse-Geisser	1352.689	26.592	50.869	1.163	0.264	
	Huynh-Feldt	1352.689	33.722	40.114	1.163	0.245	
	Lower-bound	1352.689	3	450.896	1.163	0.332	
Error(Min)	Sphericity Assumed	21714.977	1624	13.371			
	Greenhouse-Geisser	21714.977	496.378	43.747			
	Huynh-Feldt	21714.977	629.469	34.497			
	Lower-bound	21714.977	56	387.767			

Tests of Between-Subjects Effects						
Measure: MEASURE_1						
Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	
Intercept	24328.503	1	24328.503	159.746	0	
Group	428.248	3	142.749	0.937	0.429	* No group main effect
Error	8528.523	56	152.295			

Extinction, Day 2

Input

Column Labels / Average of LL																														
Row Labels	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
AAA	**4.07**	**3.00**	**2.13**	**3.93**	**0.93**	**1.27**	**1.00**	**1.27**	**1.80**	**1.67**	**3.20**	**1.73**	**1.13**	**1.07**	**1.47**	**2.00**	**2.33**	**0.80**	**1.13**	**2.13**	**3.73**	**5.00**	**1.60**	**0.67**	**1.33**	**0.80**	**0.87**	**1.80**	**1.20**	**0.80**
3	1	2	3	0	0	0	0	0	1	0	0	3	1	0	0	1	0	0	0	0	2	0	0	0	0	0	2	0	0	0
7	6	3	2	9	2	0	0	0	0	1	5	0	1	1	4	2	0	0	2	6	29	43	0	0	3	0	0	0	0	0
23	0	0	0	0	0	1	0	0	0	1	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0
27	2	7	3	4	0	2	1	1	1	2	3	4	2	1	12	10	17	1	0	0	3	2	1	0	0	0	0	0	1	8
31	3	3	3	15	1	0	0	4	7	1	2	0	0	1	0	1	0	0	2	0	2	0	4	2	7	2	0	3	0	0
33	2	4	3	1	1	4	1	2	3	0	5	2	3	1	1	2	0	2	3	2	1	3	3	1	2	1	1	5	4	0
34	17	9	1	0	1	2	5	1	2	0	18	1	5	0	1	2	0	1	0	3	0	0	1	3	0	0	0	1	0	2
42	6	0	4	3	0	0	0	6	4	3	4	5	1	3	1	2	6	2	0	0	6	2	1	0	0	0	0	0	0	0
45	5	8	4	3	0	0	0	3	0	1	0	0	1	0	0	1	4	0	0	2	0	11	0	1	0	0	0	1	2	0
68	2	1	2	3	1	2	0	1	1	0	0	0	0	0	0	0	3	0	0	0	0	0	1	0	0	0	0	0	0	0
72	2	3	1	1	0	4	1	0	0	3	1	3	2	2	1	0	1	5	9	13	5	0	4	1	3	2	0	0	1	0
79	6	0	0	1	1	0	1	0	0	0	1	0	0	0	0	5	0	0	0	1	0	4	0	1	0	0	1	3	1	0
82	4	2	2	3	1	0	0	0	2	6	4	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	4	2	0
83	0	1	0	1	0	0	0	0	0	1	0	0	0	2	0	1	1	0	1	1	0	0	1	0	0	0	0	1	0	0
90	5	2	4	15	6	4	6	1	6	6	4	7	0	5	1	3	3	1	0	3	7	10	8	1	5	7	8	8	6	2
AAB	**4.93**	**3.33**	**2.33**	**2.73**	**2.00**	**1.40**	**1.73**	**2.33**	**1.67**	**2.47**	**2.87**	**3.60**	**3.53**	**2.40**	**2.80**	**5.33**	**4.87**	**3.67**	**2.07**	**2.33**	**2.27**	**2.53**	**3.47**	**1.40**	**2.07**	**1.20**	**1.73**	**1.47**	**1.80**	**0.93**
4	3	2	2	4	0	0	0	0	0	0	7	0	0	0	1	3	1	5	1	1	5	4	0	3	1	1	1	1	2	0
8	1	1	0	1	1	0	0	0	0	0	0	1	0	5	0	0	1	2	7	8	2	1	6	1	2	1	0	0	0	1
25	8	3	6	2	10	5	8	2	4	7	10	1	0	2	1	8	8	2	0	0	2	0	2	0	3	2	3	5	10	1
26	20	5	2	11	3	0	1	5	0	5	1	5	9	5	14	0	4	7	9	11	2	1	1	0	1	6	0	0	5	2
28	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	0	1	0	0	0	0	0	0	0	0	1
29	7	12	6	3	4	4	0	4	1	0	2	22	22	13	18	22	12	2	1	0	0	3	0	0	11	1	0	0	2	2
35	7	5	2	2	2	1	2	2	2	2	1	6	4	1	1	1	6	3	1	2	0	2	1	0	1	0	2	2	0	1
41	5	1	0	0	0	0	0	0	5	0	1	5	1	3	2	7	0	0	0	0	0	1	1	0	0	3	0	0	0	0
44	9	9	3	5	5	2	3	11	4	8	9	9	5	0	0	2	15	7	1	2	0	19	37	8	7	2	15	2	1	0
47	1	1	1	1	0	1	0	0	0	0	0	0	1	2	1	2	0	0	0	0	0	0	0	0	1	0	0	0	1	0
77	6	0	0	0	0	0	8	0	0	0	0	2	0	1	1	17	11	5	0	0	0	0	1	5	0	0	1	1	0	0
80	1	1	0	0	0	0	1	2	0	0	2	0	1	0	0	1	0	0	0	0	12	1	0	2	0	1	0	0	0	0
81	1	7	12	4	1	2	2	4	0	2	4	0	7	4	3	9	0	0	1	3	4	4	0	0	3	0	4	2	2	2
85	3	0	0	4	2	4	1	2	1	4	6	3	1	0	0	4	7	6	4	3	1	0	0	0	0	0	0	0	0	0
86	2	0	0	4	2	2	0	3	8	9	0	0	2	0	0	2	8	16	5	5	5	2	3	2	1	1	0	9	4	4
ABA	**1.60**	**1.87**	**1.73**	**1.27**	**2.00**	**1.20**	**1.13**	**0.87**	**1.27**	**0.87**	**1.13**	**1.40**	**1.67**	**0.53**	**0.53**	**0.87**	**1.47**	**1.07**	**1.20**	**0.07**	**0.67**	**0.47**	**0.40**	**0.67**	**0.80**	**1.20**	**1.13**	**2.13**	**0.60**	**0.60**
2	1	0	0	1	1	0	0	0	0	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
16	2	2	2	0	2	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	2	0	2	1	0	0	0	1	0	0
24	1	0	0	0	1	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
36	4	3	1	1	3	2	4	3	3	1	2	3	2	0	2	4	4	3	6	0	2	1	0	1	0	2	1	1	1	1
37	1	5	5	4	1	1	9	3	0	4	2	1	18	4	0	0	1	0	2	1	0	0	0	1	4	15	8	18	5	1
38	7	3	5	4	4	4	1	2	4	3	1	9	2	1	0	6	0	3	3	0	0	0	0	3	5	1	0	9	3	5
39	2	4	4	0	2	1	1	1	2	1	6	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0
43	0	1	0	0	1	1	0	0	0	0	0	2	0	0	1	0	2	0	0	0	0	0	0	0	0	0	1	0	0	0
46	0	2	0	1	2	1	0	0	0	1	0	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0	5	0	0	0
49	3	4	3	0	12	2	2	3	0	2	1	3	3	1	0	0	12	6	1	0	0	3	1	2	0	0	0	2	0	0
67	1	2	3	7	0	4	0	1	6	1	0	0	0	0	1	0	2	0	2	0	4	0	0	1	3	0	2	1	0	0
78	1	1	3	0	0	2	0	0	1	0	0	0	0	0	3	1	0	1	0	0	1	1	2	0	0	0	0	0	0	0
84	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	3	0	0	1	0	0	0	0	0	0	0	0
88	0	1	0	1	0	0	0	0	0	0	5	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
ABB	**3.40**	**2.20**	**1.93**	**2.53**	**2.87**	**1.13**	**1.87**	**1.40**	**1.27**	**1.67**	**2.27**	**1.20**	**1.73**	**2.87**	**2.47**	**0.80**	**2.87**	**1.73**	**1.80**	**0.73**	**2.20**	**0.73**	**0.67**	**1.47**	**1.67**	**0.80**	**1.07**	**1.00**	**0.93**	**0.47**
1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	3	0	1	2	0	2	0	0	2	0	2	1	2	0	1	0	3	1	1	0	1	1	2	0	0	1	2	0	0	0
15	0	0	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
21	12	2	5	5	8	4	6	3	1	3	2	5	0	2	12	4	12	1	6	0	0	0	4	2	1	2	1	1	1	3
22	12	3	1	11	14	0	2	1	0	2	14	1	13	5	0	0	10	2	2	0	3	0	0	11	0	0	2	6	2	1
30	3	5	4	3	2	2	6	5	2	0	3	1	1	0	4	0	1	3	7	1	3	0	0	0	1	2	2	1	0	2
32	4	8	6	2	1	0	4	2	1	5	1	1	0	0	0	0	0	3	2	1	1	1	0	0	1	2	3	1	0	0
40	1	3	2	0	1	1	3	2	2	1	2	2	0	1	1	2	1	0	1	1	0	0	0	2	5	2	1	0	1	0
48	4	1	0	4	1	0	2	1	1	3	0	0	1	1	0	0	0	0	1	0	0	0	1	1	15	3	1	0	2	0
50	3	2	2	3	1	0	0	2	0	0	0	2	0	0	0	0	2	0	1	0	1	0	3	0	0	0	0	0	0	0
69	2	1	4	1	0	3	1	0	1	0	0	4	3	1	2	4	4	2	2	2	2	3	0	2	0	0	4	2	2	0
70	2	3	0	0	2	3	1	1	0	4	1	0	1	0	6	2	9	10	0	3	5	0	0	4	1	0	0	0	0	0
71	1	0	0	1	0	0	0	3	8	0	2	1	1	32	11	0	1	0	0	0	0	0	0	0	0	0	0	1	6	1
87	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
89	4	5	3	6	11	2	3	1	1	7	7	0	2	0	0	0	0	4	4	3	17	5	0	0	0	0	0	3	0	0
Grand Total	**3.50**	**2.60**	**2.03**	**2.62**	**1.95**	**1.25**	**1.43**	**1.47**	**1.50**	**1.67**	**2.37**	**1.98**	**2.02**	**1.72**	**1.82**	**2.25**	**2.88**	**1.82**	**1.55**	**1.32**	**2.22**	**2.18**	**1.53**	**1.05**	**1.47**	**1.00**	**1.20**	**1.60**	**1.13**	**0.70**

Average of RL																													
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
3.27	**1.80**	**1.27**	**1.27**	**1.27**	**0.93**	**1.73**	**2.20**	**2.20**	**1.00**	**0.87**	**0.73**	**0.80**	**2.47**	**0.80**	**1.07**	**0.87**	**2.07**	**2.33**	**0.80**	**1.13**	**0.33**	**0.93**	**0.73**	**0.80**	**0.47**	**0.73**	**0.07**	**1.07**	**0.87**
1	0	1	1	0	0	0	2	0	0	0	0	3	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	2	0	4	1	0	0	0	0	0	0	2	0	0	0	0	1	0	2	0	3	0	0	0	3	0	0	0	0	0
13	0	2	1	0	1	0	0	7	0	0	0	0	4	1	1	0	1	0	0	6	0	2	0	0	0	1	0	0	0
6	5	5	9	4	6	5	0	1	0	1	4	4	24	8	2	1	5	3	7	1	1	8	6	0	0	0	0	7	9
7	6	1	0	0	0	7	5	0	6	5	1	0	0	0	0	1	0	0	0	0	0	2	0	6	1	7	0	0	0
0	1	1	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0
3	0	1	1	1	1	3	0	3	0	0	2	2	0	0	1	1	4	0	0	1	2	0	0	0	0	0	0	1	0
0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
3	3	3	1	4	1	5	0	0	3	1	0	1	2	0	2	1	3	2	0	3	0	1	0	1	0	1	0	3	0
2	6	1	0	2	0	0	0	0	3	1	0	0	1	0	5	1	0	1	0	3	0	0	4	0	0	0	0	0	0
0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	3	0	3	1	5	26	17	0	2	0	0	5	0	0	6	18	25	4	0	0	0	0	1	5	2	0	2	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	2	1	1	1	1	0	0	5	1	1	2	1	1	0	2	0	0	2	1	0	1	0	1	0	0	0	0	0	4
2	1	0	0	2	3	0	0	0	1	1	0	0	0	2	1	0	0	0	0	0	0	1	0	0	1	0	0	3	0
1.93	**1.13**	**0.80**	**0.87**	**0.67**	**0.80**	**1.20**	**0.47**	**0.33**	**0.33**	**1.07**	**0.27**	**0.47**	**0.20**	**0.27**	**1.27**	**0.40**	**0.20**	**0.73**	**1.67**	**1.40**	**0.40**	**0.47**	**0.13**	**0.27**	**0.20**	**0.07**	**0.27**	**1.07**	**0.6**
1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0
1	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	2	1	0	0	0	0	0	0	1	0	0	0
1	1	3	0	1	5	0	0	3	1	0	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
2	2	1	4	0	0	3	0	0	1	0	0	0	0	0	1	2	0	2	0	0	0	1	0	0	0	0	3	2	1
9	3	1	2	0	0	4	2	0	0	1	3	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1
1	1	3	0	5	0	6	4	0	1	1	0	1	0	0	3	1	0	4	15	0	0	1	0	1	0	0	0	0	0
5	6	2	1	1	5	1	1	1	0	10	0	0	2	0	6	0	0	0	1	0	2	1	0	0	0	0	0	3	7
2	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	7	1	2	0	0	0	0	0	0	0	0	0	1	9	0
2	3	0	2	1	1	0	0	0	0	0	0	2	0	2	0	0	0	0	0	3	2	2	0	0	0	0	0	0	0
2	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0
3	0	0	2	0	0	3	0	0	0	3	0	2	1	1	1	0	0	0	6	16	1	0	0	2	1	0	0	1	0
0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
3.33	**1.53**	**2.20**	**1.67**	**2.80**	**1.60**	**1.20**	**0.93**	**1.27**	**1.20**	**1.67**	**2.67**	**1.40**	**0.47**	**1.40**	**0.53**	**1.73**	**2.13**	**1.00**	**1.40**	**0.47**	**1.00**	**0.47**	**0.60**	**0.87**	**0.53**	**0.93**	**0.20**	**0.93**	**0.53**
1	0	5	3	2	7	1	1	1	0	0	2	2	0	2	2	0	3	4	2	2	0	1	0	4	1	3	1	0	4
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	4	3	0	3	0	0	0	0	1	2	3	0	2	1	0	0	0	0	0	0	6	4	1	2	3	0	0	2	0
3	3	4	1	3	2	1	0	3	0	0	1	0	0	1	2	0	1	1	0	0	1	1	0	1	0	1	0	0	0
10	2	5	1	9	2	3	1	3	6	5	3	2	0	3	2	6	5	5	0	0	0	0	0	0	0	2	1	3	0
1	1	1	0	2	0	1	0	0	0	0	0	0	2	4	0	4	0	0	0	0	0	0	0	0	0	0	0	2	0
0	0	0	0	0	1	0	0	0	0	5	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
7	2	2	12	6	2	1	6	2	0	2	23	13	0	0	0	0	2	0	0	0	0	0	0	0	3	1	0	0	3
1	6	2	4	4	5	6	0	0	1	1	3	0	0	1	0	0	0	1	0	1	0	0	0	1	1	1	1	4	0
8	2	0	0	8	2	2	4	0	3	5	0	0	0	8	0	5	12	1	16	0	4	1	0	2	0	0	0	0	0
2	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	9	6	1	0	0	0	0	0	0	0	0	0	0	0
2	1	2	1	0	2	0	0	7	3	1	1	1	1	1	0	0	1	1	2	0	0	0	4	2	0	2	0	0	0
4	0	4	2	0	1	0	0	2	2	0	0	0	2	0	2	1	0	0	0	3	2	0	3	0	0	4	0	0	0
2	1	3	1	2	0	1	2	1	0	1	1	2	0	0	0	1	2	1	1	1	2	0	1	1	0	0	0	1	1
7	0	2	0	2	0	2	0	0	1	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.20	**1.40**	**1.13**	**0.73**	**0.60**	**0.67**	**0.87**	**0.47**	**1.27**	**0.80**	**0.67**	**0.33**	**1.07**	**0.27**	**0.40**	**0.13**	**0.33**	**1.00**	**1.40**	**0.73**	**0.53**	**0.40**	**0.20**	**0.33**	**0.33**	**0.80**	**0.73**	**0.20**	**0.33**	**0.27**
0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	1	1	3	0	0	3	0	2	0	0	2	0	0	0	4	0	0	0	2	0	0	0	0	0	2	1	0
1	5	3	0	1	4	0	0	1	2	0	1	1	0	0	0	1	4	0	0	2	0	0	2	3	0	1	0	2	0
1	1	0	3	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	1	2	0	1	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0
3	2	1	2	1	0	3	0	2	5	2	0	3	0	0	0	0	0	0	2	0	0	0	0	0	6	2	0	0	1
0	4	2	1	3	0	4	1	1	1	3	2	2	0	1	1	0	0	1	1	1	2	1	2	1	4	3	0	2	3
2	0	3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	1	0	0	0	0
2	2	2	2	0	2	1	0	0	2	2	1	0	2	3	1	0	0	5	0	3	0	1	0	0	0	0	0	0	0
2	0	1	0	0	1	1	0	0	0	0	0	2	0	0	0	1	1	0	2	0	1	0	0	0	0	1	0	0	0
1	1	1	2	1	0	3	3	5	1	1	0	3	0	0	0	2	4	0	0	1	0	1	1	0	0	3	1	0	0
0	0	0	0	0	0	0	0	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	1	2	0	0	0	1	0	3	0	0	1	0	0	0	0	0	0	3	1	0	0	0	0	0	0	0	0	0	0
1	3	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	2	12	3	0	1	0	0	0	0	0	0	0	0
2.43	**1.47**	**1.35**	**1.13**	**1.33**	**1.00**	**1.25**	**1.02**	**1.27**	**0.83**	**1.07**	**1.00**	**0.93**	**0.85**	**0.72**	**0.75**	**0.83**	**1.35**	**1.37**	**1.15**	**0.88**	**0.53**	**0.52**	**0.45**	**0.57**	**0.50**	**0.62**	**0.18**	**0.85**	**0.57**

Output

Tests of Within-Subjects Effects							
Measure: MEASURE_1							
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	
Minute	Sphericity Assumed	370.609	29	12.78	3.862	0	* Min effect of minute
	Greenhouse-Geisser	370.609	11.996	30.894	3.862	0	
	Huynh-Feldt	370.609	16.311	22.721	3.862	0	
	Lower-bound	370.609	1	370.609	3.862	0.054	
Minute * Grou	Sphericity Assumed	257.329	87	2.958	0.894	0.746	* No group x minute interaction
	Greenhouse-Geisser	257.329	35.988	7.15	0.894	0.649	
	Huynh-Feldt	257.329	48.934	5.259	0.894	0.68	
	Lower-bound	257.329	3	85.776	0.894	0.45	
Error(Minute)	Sphericity Assumed	5374.12	1624	3.309			
	Greenhouse-Geisser	5374.12	671.774	8			
	Huynh-Feldt	5374.12	913.426	5.883			
	Lower-bound	5374.12	56	95.966			

Tests of Between-Subjects Effects						
Measure: MEASURE_1						
Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	
Intercept	3410.003	1	3410.003	164.61	0	
Group	78.108	3	26.036	1.257	0.298	* No group main effect
Error	1160.08	56	20.716			

Extinction Across Days

Output

Tests of Within-Subjects Effects							
Measure: MEASURE_1							
Source		Type III Sum of Squares	df	Mean Square	F	Sig.	
Day	Sphericity Assumed	158.7	1	158.7	100.276	0	* Main effect of Day
	Greenhouse-Geisser	158.7	1	158.7	100.276	0	
	Huynh-Feldt	158.7	1	158.7	100.276	0	
	Lower-bound	158.7	1	158.7	100.276	0	
Day * Gro	Sphericity Assumed	2.381	3	0.794	0.501	0.683	* No day x group interaction
	Greenhouse-Geisser	2.381	3	0.794	0.501	0.683	
	Huynh-Feldt	2.381	3	0.794	0.501	0.683	
	Lower-bound	2.381	3	0.794	0.501	0.683	
Error(Day	Sphericity Assumed	88.627	56	1.583			
	Greenhouse-Geisser	88.627	56	1.583			
	Huynh-Feldt	88.627	56	1.583			
	Lower-bound	88.627	56	1.583			

Tests of Between-Subjects Effects						
Measure: MEASURE_1						
Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	
Intercept	765.917	1	765.917	183.041	0	
Group	14.498	3	4.833	1.155	0.335	* No main effect of group
Error	234.326	56	4.184			

Experiment 2

Renewal

Input

Row Lab	Average of LL First 3 min 1	2	3	Average of RL First 3 min 1	2	3
AAA	**1.73**	**1.40**	**3.40**	**1.27**	**1.33**	**1.80**
3	0	1	0	0	1	0
7	1	0	6	0	1	1
23	0	0	0	6	1	0
27	0	0	8	3	9	8
31	3	3	1	1	4	3
33	3	5	2	0	0	1
34	5	0	4	0	1	2
42	4	4	6	0	0	0
45	2	2	5	5	0	4
68	1	0	4	1	0	3
72	1	0	5	1	0	2
79	0	0	2	1	1	1
82	3	1	3	0	0	0
83	1	0	0	1	1	0
90	2	5	5	0	1	2
AAB	**2.13**	**2.00**	**2.47**	**0.93**	**0.67**	**0.93**
4	2	0	4	1	1	2
8	0	0	0	1	0	0
25	4	5	3	2	0	2
26	6	2	10	0	0	1
28	0	0	1	1	0	4
29	1	1	5	2	2	2
35	1	2	1	1	3	0
41	0	4	2	1	1	1
44	7	0	0	0	0	0
47	3	1	0	0	2	1
77	1	2	1	0	0	1
80	1	1	3	4	1	0
81	5	8	5	1	0	0
85	1	4	1	0	0	0
86	0	0	1	0	0	0
ABA	**2.27**	**2.33**	**4.67**	**2.00**	**2.27**	**2.73**
2	0	0	0	0	3	3
6	1	0	0	0	0	0
16	1	0	2	1	3	2
24	0	0	0	3	0	1
36	3	7	5	7	1	6
37	5	1	12	1	1	4
38	6	5	8	1	1	0
39	2	0	12	5	6	5
43	0	2	2	2	1	2
46	0	2	3	3	6	4
49	13	13	16	1	2	1
67	1	1	1	0	4	2
78	0	3	6	3	5	4
84	0	1	0	2	1	0
88	2	0	3	1	0	7
ABB	**2.20**	**2.53**	**4.33**	**1.53**	**1.33**	**1.53**
1	0	0	0	0	0	1
5	1	0	0	1	0	0
15	0	0	0	0	0	2
21	6	6	0	2	0	0
22	3	4	1	2	1	1
30	4	5	3	4	3	3
32	2	1	0	4	3	2
40	1	1	4	0	4	3
48	2	4	1	1	2	0
50	2	2	2	2	1	1
69	4	2	4	3	3	4
70	1	1	3	0	1	5
71	6	11	44	1	0	1
87	0	0	0	2	0	0
89	1	1	3	1	2	0
Grand Tot	**2.08**	**2.07**	**3.72**	**1.43**	**1.40**	**1.75**

Output

Number of Groups: 4
Number of Measurements: 1

Number of subjects in...
Group 1: 15
Group 2: 14
Group 3: 15
Group 4: 15

Between contrast coefficients

Contrast	Group... 1	2	3	4
B1	1	1	0	-2
B2	1	1	-2	0
B3	1	-1	0	0

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	9.372	1	9.372	4.949	* significant ABA renewal effect: ABA vs. controls, p = .03
B2	0.453	1	0.453	0.239	* No AAB renewal effect, F < 1
B3	0.204	1	0.204	0.108	* No difference between controls, AAA vs. ABB, F < 1.
Error	104.158	55	1.894		

ABA vs. Rest

Number of Groups: 4
Number of Measurements: 1

Number of subjects in...
Group 1: 15
Group 2: 14
Group 3: 15
Group 4: 15

Between contrast coefficients

Contrast	Group... 1	2	3	4
B1	1	1	1	-3
B2	1	1	-2	0
B3	1	-1	0	0

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	12.218	1	12.218	6.452	ABA renewal. p = .016
B2	0.453	1	0.453	0.239	No AAB renewal, F < 1
B3	0.204	1	0.204	0.108	No diff AAA vs. ABB, F < 1.
Error	104.158	55	1.894		

Experiment 2

Reinstatement

Input

Row Labels	Average of Pre-Reinst	Average of Pre-NonReinst	Average of Reinst	Average of NonReinst	Pre
AAA	**7.90**	**9.03**	**22.40**	**7.10**	
3	10	4	8	4	7.00
7	3	8	20	1	5.50
23	1	0	27	3	0.50
27	17	19	42	13	18.00
31	15	23	36	17	19.00
33	12	14	26	7	13.00
34	5	7	82	4	6.00
42	2.5	6	8	3.5	4.25
45	10	6	19.5	22	8.00
68	7.5	5.5	12	7.5	6.50
72	1.5	3	2.5	2	2.25
79	4	2	27	4.5	3.00
82	1	5	7	3	3.00
83	4	3	5	7	3.50
90	25	30	14	8	27.50
AAB	**11.37**	**12.63**	**19.77**	**7.63**	
4	13	9	24	12	11.00
8	2	3	2	0	2.50
25	38	48	40	24	43.00
26	6	47	51	5	26.50
28	3	7	4	5	5.00
29	39	7	68	1	23.00
35	26	16	23	17	21.00
41	3.5	6	6	2.5	4.75
44	3	2	4.5	5.5	2.50
47	2	1.5	6.5	6.5	1.75
77	3	3.5	5.5	6.5	3.25
80	4	1.5	6	2.5	2.75
81	15	17	32	14	16.00
85	7	9	14	7	8.00
86	6	12	10	6	9.00
ABA	**13.03**	**12.07**	**22.97**	**12.43**	
2	0	7	25	20	3.50
6	0	0	0	0	0.00
16	9	11	17	4	10.00
24	6	4	16	5	5.00
36	46	42	46	36	44.00
37	28	19	30	24	23.50
38	24	27	43	20	25.50
39	41	18	28	47	29.50
43	3.5	2	6	1	2.75
46	9	6.5	12	2	7.75
49	5	20	38	4	12.50
67	9.5	6	33.5	3.5	7.75
78	8.5	8.5	9	3	8.50
84	2	3	8	0	2.50
88	4	7	33	17	5.50
ABB	**7.67**	**10.07**	**17.80**	**5.03**	
1	2	2	4	1	2.00
5	6	5	9	3	5.50
15	4	3	20	0	3.50
21	15	17	48	8	16.00
22	0	4	11	0	2.00
30	18	17	29	6	17.50
32	5	13	23	2	9.00
40	17	16	9	15	16.50
48	2	4.5	5.5	1.5	3.25
50	2.5	4	6	2.5	3.25
69	8	6	10	4.5	7.00
70	11.5	11	33	15.5	11.25
71	9	38.5	23.5	10.5	23.75
87	0	0	7	1	0.00
89	15	10	29	5	12.50
Grand Total	**9.99**	**10.95**	**20.73**	**8.05**	

Output

Number of Groups:	4			
Number of Measurements:	3			
Number of subjects in...				
Group 1:	15			
Group 2:	15			
Group 3:	15			
Group 4:	15			
Between contrast coefficients				
Contrast	Group...			
	1	2	3	4
AAA/ABB vs. B1	1	1	-1	-1
AAA vs. ABB B2	1	-1	0	0
AAB vs. ABA B3	0	0	1	-1
Within contrast coefficients				
Contrast	Measurement...			
	1	2	3	
Pre vs. Post W1	2	-1	-1	
Reinst vs. N W2	0	1	-1	

Analysis of Variance Summary Table					
Source	SS	df	MS	F	
Between					
AAA/ABB vs. B1	390.875	1	390.875	1.298	* No group main effects, largest F = 1.518, p = .223 (Control groups vs. Renewal groups, or AAA/ABB vs. AAB/ABA)
AAA vs. ABB B2	98.178	1	98.178	0.326	
AAB vs. ABA B3	182.756	1	182.756	0.607	
Error	16865.586	56	301.171		
Within					
Pre vs. Post W1	614.917	1	614.917	15.989	* Main effect of post-outcome delivery responding, i.e. more responding post-outcome delivery than pre-outcome delivery on test, p = .00
B1W1	9.834	1	9.834	0.256	* No interactions, largest p = .184
B2W1	69.689	1	69.689	1.812	
B3W1	59.513	1	59.513	1.547	
Error	2153.672	56	38.458		
Reinst vs. N W2	4826.008	1	4826.008	35.944	* Main effect of Reinstatement, p = .00
B1W2	54.675	1	54.675	0.407	* No interactions, all Fs < 1
B2W2	24.067	1	24.067	0.179	
B3W2	9.600	1	9.600	0.071	
Error	7518.900	56	134.266		

Simple effects

Number of Groups: 4

Number of Measurements: 3

Number of subjects in...

Group 1: 15

Group 2: 15

Group 3: 15

Group 4: 15

Between contrast coefficients

Contrast	Group...			
	1	2	3	4
AAA simple	B1	1	0	0	0
ABB simple	B2	0	1	0	0
AAB simple	B3	0	0	1	0
ABA simple	B4	0	0	0	1

*** Caution ***

B1 coefficients do not sum to zero

B2 coefficients do not sum to zero

B3 coefficients do not sum to zero

B4 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
Reinst vs. N W1	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
AAA simple B1	7207.339	1	7207.339	23.931	* Dummy
ABB simple B2	5024.450	1	5024.450	16.683	* Dummy
AAB simple B3	7761.800	1	7761.800	25.772	* Dummy
ABA simple B4	11496.013	1	11496.013	38.171	* Dummy
Error	16865.586	56	301.171		
Within					
Reinst vs. N W1	4826.008	1	4826.008	35.944	* Main effect reinstatment
B1W1	1755.675	1	1755.675	13.076	* All simple effects significant. Group AAA, p = .001, Group ABB, p = .004, Group AAB, p = .006, Group ABA, p = .016
B2W1	1222.408	1	1222.408	9.104	
B3W1	1104.133	1	1104.133	8.223	
B4W1	832.133	1	832.133	6.198	
Error	7518.900	56	134.266		

Experiment 2

Number of c-Fos in mOFC/lOFC/pDMS/DH CA1

mOFC

AAA	AAB	ABA	ABB
238.7000	217.8000	203.7000	265.9000
234.8000	163.3000	203.3000	195.7000
261.9000	284.9000	289.8000	268.0000
245.4000	257.7000	308.8000	249.9000
267.9000	268.9000	256.3000	243.0000
277.6000	253.1000	247.4000	261.2000
295.2000	253.5000	199.3000	275.3000
267.8000	283.6000	217.3000	244.6000
274.8000	247.4000	278.0000	284.0000
276.9000	251.0000	267.3000	271.5000
269.5000	305.0000	218.0000	295.3000
270.6000	273.8000	265.1000	264.5000
256.8000	221.7000	263.4000	275.7000
273.3000	226.2000	280.3000	228.1000
254.7000	238.4000	239.7000	241.0000

lOFC

AAA	AAB	ABA	ABB
127.8000	118.0000	130.3000	163.4000
112.7000	104.7000	108.4000	139.7000
136.9000	100.6000	144.5000	101.5000
127.8000	127.5000	130.2000	109.1000
116.3000	124.9000	126.8000	131.2000
127.0000	129.7000	116.8000	116.3000
110.4000	119.3000	106.2000	104.5000
145.0000	155.0000	135.7000	112.6000
105.8000	113.6000	106.2000	130.0000
123.5000	115.0000	96.2500	129.8000
110.2000	167.8000	133.0000	144.7000
111.3000	123.5000	110.4000	142.0000
133.4000	115.5000	129.6000	132.2000
145.5000	128.6000	149.0000	126.6000
145.3000	118.0000	122.1000	91.6000

pDMS

AAA	AAB	ABA	ABB
100.7500	124.1000	98.1300	117.9000
129.2000	57.2200	96.2500	126.8000
97.3300	151.1000	142.9000	89.0000
117.3000	147.2000	88.0900	116.3000
218.7000	172.0000	202.3000	165.9000
178.2000	113.2000	181.9000	152.5000
214.8000	175.0000	171.9000	179.6000
204.0000	204.9000	108.4000	160.4000
212.4000	213.5000	212.2000	236.1000
132.8000	217.6000	169.5000	141.0000
139.1000	215.4000	188.8000	176.5000
160.0000	164.8000	179.8000	189.6000
141.9000	57.0000	192.1000	188.1000
140.0000	138.2000	131.6000	137.7000
134.5000	132.2000	124.5000	106.4000

DH CA1

AAA	AAB	ABA	ABB
28.1700	58.6300	48.7500	25.6300
42.0000	12.5000	21.5000	28.8600
43.5000	61.0000	62.2500	35.1300
27.8600	27.7000	67.5000	24.9100
38.7500	32.4200	46.1300	32.7500
56.0000	25.0000	41.0000	40.8000
73.3300	43.5000	29.6700	39.0000
33.1400	49.6000	31.6300	29.7500
45.6700	32.0000	36.0000	26.9100
21.0000	33.6400	46.1700	46.8300
39.0000	40.7300	44.0000	36.2000
53.3300	44.7000	23.1700	56.0000
37.2500	54.5000	49.0000	65.0000
46.6700	41.7000	48.6000	33.1700
45.2700	42.0000	43.8900	36.3800

APPENDIX B

Experiment 3 (Gordons Specialty Feed)

Pavlovian Conditioning, 8 sessions

Input

Row Labels	Column Labels Average of PreCS 1	2	3	4	5	6	7	8
LPS	**4.11328125**	**5**	**5.875**	**6.3046875**	**6.4375**	**5.56640625**	**4.91796875**	**5.4140625**
62	1.875	3	2.8125	6.25	3.625	4.4375	3.125	4.9375
63	5.0625	3.4375	7.75	4.4375	9.25	4.9375	8.625	5.25
64	5	8	6.5	4.5	5	2.125	2.3125	1.875
66	3.625	7.5	6.625	6.4375	8.875	7.125	7	8.375
67	3.9375	4.8125	6.4375	5.8125	4.3125	7.75	3.0625	3.125
72	5	5.875	10.25	11.75	13.8125	9.625	5.125	12.0625
73	3.1875	5.1875	7.8125	9.4375	8.75	6.625	4.125	4.75
74	4.4375	6	9.8125	8.8125	8.5	10.6875	11.9375	9.375
77	5.0625	4.8125	2.75	4.8125	7.5	5.625	2.125	4
79	4.0625	4.1875	1.5625	4	1.9375	2.4375	3.75	2.625
83	4.875	1.9375	5	3.9375	3.125	2.875	2.4375	5.4375
84	2.5	3.5	2.75	4.5	6.3125	5.0625	9.625	4.6875
87	2.8125	7.8125	7.25	8.125	4.5625	6.75	2.4375	3.75
88	5.6875	5.9375	6.25	8.125	6.375	2.8125	3.625	6.25
89	3.8125	5.4375	7.3125	4.625	7.4375	7.875	6.5	7.1875
90	4.875	2.5625	3.125	5.3125	3.625	2.3125	2.875	2.9375
SAL	**4.142857143**	**4.834821429**	**5.647321429**	**6.321428571**	**6.138392857**	**6.754464286**	**4.941964286**	**4.683035714**
61	4.625	8.75	10.6875	5.6875	6.3125	4.3125	7.6875	1.8125
62	7.5	5.375	12	10.9375	9.8125	11.625	10	8.875
63	1.75	5.5	5.875	9.375	10.25	10.375	5.5625	9.3125
64	3.25	4.25	5.875	7.5	10.3125	10.875	8.6875	6.1875
69	3.5	3.375	3.75	7.0625	4.3125	5.5625	3.375	3.0625
70	6.25	3.3125	2.6875	2.125	3.9375	6.3125	3.625	3.25
71	3.0625	2.4375	3.5	5.4375	4.9375	7.9375	3.125	4.0625
75	3	7.4375	8.6875	6.125	6.5625	4.8125	3	3.3125
76	5.5625	2.25	1.5	3.4375	3.5	4.125	2.375	2.1875
80	2.375	3.0625	2.3125	5.9375	6.125	5.6875	7.875	3
81	2.875	5	5.8125	8	7.375	5.3125	1.625	4.1875
82	5.6875	7.0625	5.5	8.5	4.0625	7.6875	4.0625	4.5
85	3.875	4.625	5.125	2.4375	4.75	6.0625	6.1875	5.5625
86	4.6875	5.25	5.75	5.9375	3.6875	3.875	2	6.25
Grand Total	**4.127083333**	**4.922916667**	**5.76875**	**6.3125**	**6.297916667**	**6.120833333**	**4.929166667**	**5.072916667**

Row Labels	Column Labels Average of CS 1	2	3	4	5	6	7	8
LPS	**5.05859375**	**9.35546875**	**13.3984375**	**14.62109375**	**16.234375**	**15.76953125**	**15.5078125**	**16.83984375**
62	3.8125	8.5	17.875	14.8125	16.75	15.25	15.75	16.4375
63	4.8125	8.1875	12.25	13	18.875	11.6875	14.4375	15.625
64	5.1875	10.625	14.9375	10.375	9.4375	8.125	9.25	10.4375
66	5	10.1875	14.0625	11.9375	16.375	15.4375	15.25	15.5
67	3.8125	10.5625	14.9375	14.6875	15.3125	19.6875	18.875	25.8125
72	5.5625	11.5	16.6875	18.8125	21.125	23.5625	20.75	23.8125
73	6.8125	9.75	15.75	18.3125	20.5625	20.5	20.5625	18.6875
74	7.3125	11.875	16.9375	19.3125	24.125	31.6875	30.4375	40.125
77	3.625	7.25	11.625	15.375	15.75	13.3125	11.4375	10.875
79	2.5	4.6875	7.5625	10.5625	9.1875	12.5625	10.375	8.875
83	3.25	7.8125	10.9375	10.4375	11.8125	12.4375	8.9375	7.75
84	5.25	7.5	9.0625	15.125	16.375	16.125	17.3125	21.4375
87	6.375	13.75	19.5	22.5625	18.3125	13.75	14	13.3125
88	6.8125	9.75	12.75	14.125	16.3125	10.625	12.25	11.375
89	5.75	10.4375	8.9375	11.9375	14.875	17.4375	17.375	16.1875
90	5.0625	7.3125	10.5625	12.5625	14.5625	10.125	11.125	13.1875
SAL	**5.196428571**	**9.102678571**	**11.99553571**	**13.98660714**	**16.45982143**	**17.12946429**	**15.25892857**	**14.09821429**
61	7.3125	13.875	17.625	14.125	23.875	19.4375	22.375	17.4375
62	8.5	9.1875	19.5	14.5	19.6875	16.875	16.3125	14.5625
63	3.75	6.8125	10.625	19.1875	18.25	26.4375	21.3125	21.75
64	5.6875	10.5	9.25	16.375	20.3125	24.4375	20.75	11.25
69	5.125	7.25	13.6875	17.3125	14.6875	14.125	12.0625	12.5
70	5.125	9	12.0625	11.4375	14.5625	15.375	15.9375	12.6875
71	3.3125	8	12.6875	11.9375	12.375	15.125	10.625	6.3125
75	4.9375	9.9375	12.8125	12.0625	15.4375	12	10.25	14.6875
76	5.8125	7.8125	5.4375	12.0625	10.8125	8.625	5.1875	7.1875
80	1.875	7.875	12.125	13.125	18.6875	17.9375	22.8125	18.25
81	4.6875	7.4375	14	19.125	20.8125	17.5	15.8125	17.1875
82	6.1875	11.8125	11.125	18.8125	15.8125	24.125	13.75	13.4375
85	3.8125	7.625	6.1875	7.0625	12.5625	15.5	16.25	18.4375
86	6.625	10.3125	10.8125	8.6875	12.5625	12.3125	10.1875	11.6875
Grand Total	**5.122916667**	**9.2375**	**12.74375**	**14.325**	**16.33958333**	**16.40416667**	**15.39166667**	**15.56041667**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CS	Sphericity Assumed	7050.978	1	7050.978	364.980	<.001
	Greenhouse-Geisser	7050.978	1.000	7050.978	364.980	<.001
	Huynh-Feldt	7050.978	1.000	7050.978	364.980	<.001
	Lower-bound	7050.978	1.000	7050.978	364.980	<.001
CS * group	Sphericity Assumed	5.372	1	5.372	.278	.602
	Greenhouse-Geisser	5.372	1.000	5.372	.278	.602
	Huynh-Feldt	5.372	1.000	5.372	.278	.602
	Lower-bound	5.372	1.000	5.372	.278	.602
Error(CS)	Sphericity Assumed	540.927	28	19.319		
	Greenhouse-Geisser	540.927	28.000	19.319		
	Huynh-Feldt	540.927	28.000	19.319		
	Lower-bound	540.927	28.000	19.319		
session	Sphericity Assumed	2243.079	7	320.440	32.398	<.001
	Greenhouse-Geisser	2243.079	3.172	707.254	32.398	<.001
	Huynh-Feldt	2243.079	3.752	597.903	32.398	<.001
	Lower-bound	2243.079	1.000	2243.079	32.398	<.001
session * group	Sphericity Assumed	75.111	7	10.730	1.085	.374
	Greenhouse-Geisser	75.111	3.172	23.683	1.085	.362
	Huynh-Feldt	75.111	3.752	20.021	1.085	.366
	Lower-bound	75.111	1.000	75.111	1.085	.307
Error(session)	Sphericity Assumed	1938.553	196	9.891		
	Greenhouse-Geisser	1938.553	88.803	21.830		
	Huynh-Feldt	1938.553	105.044	18.455		
	Lower-bound	1938.553	28.000	69.234		
CS * session	Sphericity Assumed	1258.812	7	179.830	46.896	<.001
	Greenhouse-Geisser	1258.812	2.955	425.925	46.896	<.001
	Huynh-Feldt	1258.812	3.460	363.775	46.896	<.001
	Lower-bound	1258.812	1.000	1258.812	46.896	<.001
CS * session * group	Sphericity Assumed	17.948	7	2.564	.669	.698
	Greenhouse-Geisser	17.948	2.955	6.073	.669	.572
	Huynh-Feldt	17.948	3.460	5.187	.669	.594
	Lower-bound	17.948	1.000	17.948	.669	.420
Error(CS*session)	Sphericity Assumed	751.599	196	3.835		
	Greenhouse-Geisser	751.599	82.753	9.082		
	Huynh-Feldt	751.599	96.892	7.757		
	Lower-bound	751.599	28.000	26.843		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	41193.596	1	41193.596	482.839	<.001
group	6.465	1	6.465	.076	.785
Error	2388.832	28	85.315		

Experiment 3 (Gordons Specialty Feed)

Instrumental Training, 8 sessions

Input

Average of Ave Column Labels / Row Labels	1	2	3	4	5	6	7	8
LPS	**2.19253255**	**4.96292776**	**6.71045524**	**7.96050136**	**8.8097316**	**9.55978**	**10.5434564**	**10.9109854**
62	4.164606536	7.15245624	10.3884616	10.8706512	14.0718074	18.8929	19.2263692	16.1014053
63	2.014652015	3.98807246	4.67721315	6.79309385	8.02863512	5.83053	8.19297329	9.0084296
64	1.981757358	7.08492976	12.8634271	12.1918735	11.4212381	15.2818	19.7032032	20.8246532
66	3.523506447	6.03164716	6.10528365	7.24585315	7.29873758	6.62515	9.88780191	10.4446947
67	0.934219198	5.87542524	9.5342407	8.56723138	13.7197388	16.1767	18.8438438	13.867373
72	2.945326279	5.86302077	4.91949153	9.1999519	9.80645832	10.912	12.5324811	15.4938583
73	1.632159005	1.31356682	4.40914943	8.37148709	10.7425894	10.0433	15.0770963	17.5756308
74	2.780350509	5.14020938	9.88778413	11.5978929	7.24425131	10.6341	9.46019071	9.20282866
77	2.646673873	5.02162611	5.22113022	4.87221946	4.47522523	3.70015	5.83060561	4.39142896
79	1.354139431	5.27636299	6.0349742	7.5452572	6.21111703	6.6002	7.13810034	9.25040425
83	0.4254004	1.18134963	5.75365365	7.06562719	7.22844652	8.45845	10.6497551	14.2190259
84	2.307128841	5.23886304	6.74177403	7.81488888	8.51549345	5.12553	5.07995495	6.70653153
87	1.42038264	3.7502398	8.39125813	9.47493381	9.59033221	11.1937	9.95861244	11.0138558
88	1.707027956	4.02616959	3.60277778	3.87522523	4.29986549	4.304	3.25302803	3.12502503
89	2.582872176	4.67090313	2.57747748	4.85243295	5.5504145	4.4792	4.82927928	5.975
90	2.66031813	7.7920021	6.25918714	7.02940211	12.7513551	14.6987	9.03200701	7.37562172
SAL	**1.892430858**	**4.25631404**	**6.63467038**	**8.5664763**	**8.6978461**	**9.28584**	**10.4193259**	**10.2224707**
61	4.061754519	6.98719424	9.77035859	11.3347231	11.4762963	10.6319	11.6827575	11.2098428
62	3.0965063	4.93729023	8.1891477	9.46942599	10.5993617	7.99208	12.839752	14.9873139
63	2.776383721	5.26326782	8.39979747	10.665555	7.95726179	11.0017	16.8569746	18.3274051
64	0.32525025	0.40025025	2.43280786	4.74622121	4.54842322	4.80125	5.67972973	9.20708208
69	3.533041238	6.52617615	9.06107936	9.8599651	8.41504701	10.1681	9.16053359	14.0834175
70	2.598919818	5.45199449	8.41076074	8.77058312	8.71771438	12.2556	16.4129633	11.4442473
71	0.125	1.41628075	5.1033033	7.01267622	8.01324578	8.125	6.03093093	6.50648148
75	3.365542814	8.63123131	8.93988926	14.2737841	12.4089955	13.9946	12.8710653	6.59986132
76	0.525225225	2.10771431	6.99641873	9.51603653	9.66301868	8.70208	10.6992304	9.45870871
80	1.382049994	4.95815762	5.00883603	9.25500354	10.2388394	8.57726	10.6350346	12.1962872
81	2.196482113	6.18786772	3.82795295	3.97677678	4.72617618	4.80048	5.70452953	4.97972973
82	0.200025025	0.75025025	3.31130541	5.79408755	5.62682683	7.25128	8.93248248	7.35663163
85	2.18280095	5.39517082	9.38602603	11.4552544	14.0140435	15.6195	13.3849736	13.0325815
86	0.12505005	0.57555055	4.04770188	3.80057558	5.36459517	6.08088	4.9796046	3.725
Grand Total	**2.052485094**	**4.63317469**	**6.67508897**	**8.24328967**	**8.75751836**	**9.43194**	**10.4855288**	**10.5896786**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
session	Sphericity Assumed	1878.209	7	268.316	53.276	<.001
	Greenhouse-Geisser	1878.209	2.712	692.573	53.276	<.001
	Huynh-Feldt	1878.209	3.138	598.508	53.276	<.001
	Lower-bound	1878.209	1.000	1878.209	53.276	<.001
session * group	Sphericity Assumed	8.875	7	1.268	.252	.971
	Greenhouse-Geisser	8.875	2.712	3.273	.252	.841
	Huynh-Feldt	8.875	3.138	2.828	.252	.868
	Lower-bound	8.875	1.000	8.875	.252	.620
Error(session)	Sphericity Assumed	987.118	196	5.036		
	Greenhouse-Geisser	987.118	75.934	13.000		
	Huynh-Feldt	987.118	87.868	11.234		
	Lower-bound	987.118	28.000	35.254		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	13806.633	1	13806.633	250.224	<.001
group	2.619	1	2.619	.047	.829
Error	1544.961	28	55.177		

APPENDIX B

Experiment 3 (Gordons Specialty Feed)

Pavlovian Instrumental Transfer

Input

Row Labels	Average of Pre	Average of Same	Average of Different
LPS	**4.5703125**	**8.65625**	**4.171875**
62	3.25	1.5	4.75
63	1.6875	13.75	2.375
64	9.5625	0.75	3.625
66	3.1875	12	5.25
67	4.0625	9	0.75
72	6	14.75	3.875
73	14.6875	10.875	10.125
74	4.9375	17.125	5.125
77	3.3125	2.5	5.375
79	4.125	9.875	9.75
83	4.1875	11.875	1.875
84	3.3125	3	1.375
87	5.125	12.375	3.875
88	2.0625	2.875	3.75
89	2.25	8.25	3.75
90	1.375	8	1.125
SAL	**3.75**	**6.017857143**	**5.455357143**
61	2.625	4.375	2.375
62	5.5	4.5	11.5
63	2.5	9.5	6
64	5.4375	6.375	3
69	6.125	9.625	7.125
70	3.375	2.5	5.25
71	2.6875	4.625	4.625
75	3.5625	9.75	8.625
76	3.0625	6.875	7.5
80	1.3125	6.125	3.25
81	4.625	8	6.125
82	3.125	6.25	6
85	5.3125	4.25	1.75
86	3.25	1.5	3.25
Grand Total	**4.1875**	**7.425**	**4.770833333**

Output

Number of Groups: 2
Number of Measurements: 3

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group... 1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	11.776	1	11.776	0.811	* No main effect of group, p = .375
B2	1081.483	1	1081.483	74.464	* Dummy
B3	1614.430	1	1614.430	111.159	* Dummy
Error	406.660	28	14.524		
Within					
W1	73.032	1	73.032	10.818	* Main effect of post-baseline responding
B1W1	0.102	1	0.102	0.015	* No interaction with group
B2W1	36.835	1	36.835	5.456	* Both simple effects significant
B3W1	36.260	1	36.260	5.371	
Error	189.027	28	6.751		
W2	95.092	1	95.092	9.455	* Main effect of PIT (Same > Different), p = .005
B1W2	57.423	1	57.423	5.710	* Interaction, p = .024
B2W2	2.215	1	2.215	0.220	* No simple effect for sham animals
B3W2	160.877	1	160.877	15.996	* Simple effect for LPS animals
Error	281.604	28	10.057		

Experiment 3 (Gordons Specialty Feed)

Outcome Devaluation

Input

Row Labels	Average of Devalued	Average of Valued
LPS	**0.953125**	**2.36875**
62	0.2	2.45
63	1.05	2.05
64	0.75	2.45
66	1.3	1.3
67	0.55	3.15
72	1.6	4.1
73	4.55	4.85
74	0.8	4.55
77	0.45	0.85
79	1.25	1.6
83	0.35	1.2
84	0.1	2.25
87	0.3	0.5
88	0.75	0.85
89	0.65	3
90	0.6	2.75
SAL	**0.685714286**	**1.357142857**
61	0.65	1.1
62	0.6	1.3
63	1.75	1.95
64	1	1.7
69	0.7	1.1
70	0.2	0.55
71	0.45	0.9
75	0.8	1.6
76	0.6	0.4
80	0.45	1.1
81	1.15	2.15
82	0.85	3
85	0.05	0.6
86	0.35	1.55
Grand Total	**0.828333333**	**1.896666667**

Output

Number of Groups: 2
Number of Measurements: 2

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group... 1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2
W1	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	6.107	1	6.107	4.303	* Main effect of group, p = .047
B2	29.213	1	29.213	20.583	* Dummy
B3	88.279	1	88.279	62.200	* Dummy
Error	39.740	28	1.419		
Within					
W1	16.262	1	16.262	38.364	* Main effect (Valued > Devalued)
B1W1	2.068	1	2.068	4.878	* Interaction, p = .035
B2W1	3.156	1	3.156	7.445	* Simple effect for sham animals, p = .011
B3W1	16.032	1	16.032	37.822	* Simple effect for LPS animals
Error	11.869	28	0.424		

Experiment 3 (Gordons Specialty Feed)

Outcome-selective reinstatement

Input

Row Labels	Average of Pre-Reinst	Average of Pre-NonReinst	Average of Reinst	Average of NonReinst	Pre
LPS	**17.125**	**14.6875**	**45.25**	**5.75**	
62	79	7	118	1	43.00
63	4	40	48	5	22.00
64	5	11	36	6	8.00
66	43	31	43	1	37.00
67	0	16	66	0	8.00
72	24	0	25	0	12.00
73	31	8	54	20	19.50
74	7	7	44	9	7.00
77	4	1	32	0	2.50
79	2	5	24	2	3.50
83	20	43	31	2	31.50
84	1	1	1	4	1.00
87	1	1	49	6	1.00
88	11	26	16	8	18.50
89	3	18	45	20	10.50
90	39	20	92	8	29.50
SAL	**6.642857143**	**15.07142857**	**40.42857143**	**4.5**	
61	1	1	57	3	1.00
62	10	4	24	8	7.00
63	4	3	37	0	3.50
64	13	23	18	0	18.00
69	4	9	36	3	6.50
70	3	26	41	4	14.50
71	8	30	29	8	19.00
75	5	7	76	2	6.00
76	16	5	64	9	10.50
80	0	5	71	4	2.50
81	6	4	33	14	5.00
82	15	12	32	7	13.50
85	1	66	33	0	33.50
86	7	16	15	1	11.50
Grand Total	**12.23333333**	**14.86666667**	**43**	**5.166666667**	

Output

Number of Groups: 2
Number of Measurements: 3

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group...	
	1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	307.792	1	307.792	0.987	* No main effect of group
B2	14522.881	1	14522.881	46.574	* Dummy
B3	23874.380	1	23874.380	76.564	* Dummy
Error	8730.989	28	311.821		
Within					
W1	2237.401	1	2237.401	15.877	* Main effect of post-baseline responding
B1W1	20.179	1	20.179	0.143	* No interaction with group
B2W1	1257.440	1	1257.440	8.923	* Both simple effects significant
B3W1	981.760	1	981.760	6.967	
Error	3945.799	28	140.921		
W2	21240.686	1	21240.686	67.951	* Main effect (Reinstated > Nonrreinstated)
B1W2	47.619	1	47.619	0.152	* No Interaction
B2W2	9036.036	1	9036.036	28.907	* Simple effect for sham animals
B3W2	12482.000	1	12482.000	39.931	* Simple effect for LPS animals
Error	8752.464	28	312.588		

Experiment 3 (Irradiated Specialty Feed)

Pavlovian Conditioning, 4 sessions

Input

Row Labels	Average of PreCS 1	2	3	4	Average of CS 1	2	3	4
LPS	**6.71875**	**5.62109375**	**7.2890625**	**7.734375**	**18.37109375**	**18.1640625**	**18.6132813**	**20.1015625**
62	4.4375	4.0625	5.125	5.0625	11.125	10.875	10.0625	14.3125
63	4.375	1.9375	9.1875	5.9375	23.5	20.875	24.4375	27
64	9.375	7.625	9.75	7.875	19	15.9375	19.5625	17.1875
66	10.0625	12.5	10.6875	11.625	12.75	19.75	18.8125	19.875
67	10.625	7.5625	16.375	22.8125	26.6875	18.75	28.5	30.8125
72	6.8125	5.8125	10.5625	16.875	24.5625	31.3125	29.25	27.625
73	7.1875	5.8125	4.0625	5.8125	23.1875	15.875	18.25	22.8125
74	7.25	3.6875	5.5	2.3125	30.9375	35.9375	32.4375	35.4375
77	6.75	5.625	8.1875	9.4375	13.125	15.375	12.4375	17.125
79	2	3	3.1875	3	6.375	7.5	7.8125	7
83	7.4375	7.8125	11.6875	12.1875	11.625	13.6875	12.5625	15.0625
84	5.6875	4.375	4.75	3.5625	18.875	17.75	20.1875	17.75
87	6.4375	4.375	6.5625	6.9375	23.375	18.75	18.875	23.5
88	4.875	7.3125	4.5	5	13.6875	12.9375	13.875	15.5
89	9.3125	4.1875	3.125	2.625	21.375	19.6875	20.0625	18.9375
90	4.875	4.25	3.375	2.6875	13.75	15.625	10.6875	11.6875
SAL	**7.142857143**	**6.37053571**	**5.86607143**	**6.83482143**	**20.01785714**	**17.9151786**	**19.65625**	**19.6205357**
61	4	1.6875	3.4375	2.75	21.0625	15.3125	16.75	16.625
62	10.5	9.375	8.4375	12.125	20.9375	18.375	23.625	21.4375
63	8.0625	8.4375	7.1875	7.125	26.375	28.625	29.125	30.5625
64	10.875	12.0625	11.9375	15.5	23.5625	21.6875	26.5	19.125
69	8.875	6.125	5.8125	4.8125	20	14.1875	13.75	10.75
70	10.1875	6.75	9	7.375	26.25	24.125	22.9375	29.125
71	11.4375	11.625	8.3125	8.375	18.6875	18.1875	16.3125	13.75
75	3	2.4375	1.5625	0.875	11.25	11.3125	9.8125	6.6875
76	6.5625	6.4375	5.5	5.625	10.625	9.0625	8.6875	8.4375
80	4.1875	5.6875	4.5	6.9375	20.5625	19.25	21.125	27.0625
81	6.8125	6.5625	2.6875	4.375	23	21.0625	20.5	26.8125
82	8.3125	6.5625	7	10.125	28.0625	22.1875	30.125	29.875
85	2.1875	1.625	3.0625	3.25	17.75	17.125	18.125	15.9375
86	5	3.8125	3.6875	6.4375	12.125	10.3125	17.8125	18.5
Grand Total	**6.916666667**	**5.97083333**	**6.625**	**7.31458333**	**19.13958333**	**18.0479167**	**19.1**	**19.8770833**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CS	Sphericity Assumed	9125.854	1	9125.854	126.575	<.001
	Greenhouse-Geisser	9125.854	1.000	9125.854	126.575	<.001
	Huynh-Feldt	9125.854	1.000	9125.854	126.575	<.001
	Lower-bound	9125.854	1.000	9125.854	126.575	<.001
CS * group	Sphericity Assumed	9.020	1	9.020	.125	.726
	Greenhouse-Geisser	9.020	1.000	9.020	.125	.726
	Huynh-Feldt	9.020	1.000	9.020	.125	.726
	Lower-bound	9.020	1.000	9.020	.125	.726
Error(CS)	Sphericity Assumed	2018.759	28	72.099		
	Greenhouse-Geisser	2018.759	28.000	72.099		
	Huynh-Feldt	2018.759	28.000	72.099		
	Lower-bound	2018.759	28.000	72.099		
session	Sphericity Assumed	75.111	3	25.037	3.443	.020
	Greenhouse-Geisser	75.111	2.065	36.374	3.443	.037
	Huynh-Feldt	75.111	2.311	32.494	3.443	.032
	Lower-bound	75.111	1.000	75.111	3.443	.074
session * group	Sphericity Assumed	23.987	3	7.996	1.100	.354
	Greenhouse-Geisser	23.987	2.065	11.616	1.100	.341
	Huynh-Feldt	23.987	2.311	10.377	1.100	.346
	Lower-bound	23.987	1.000	23.987	1.100	.303
Error(session)	Sphericity Assumed	610.783	84	7.271		
	Greenhouse-Geisser	610.783	57.819	10.564		
	Huynh-Feldt	610.783	64.722	9.437		
	Lower-bound	610.783	28.000	21.814		
CS * session	Sphericity Assumed	2.912	3	.971	.264	.851
	Greenhouse-Geisser	2.912	2.565	1.135	.264	.821
	Huynh-Feldt	2.912	2.947	.988	.264	.847
	Lower-bound	2.912	1.000	2.912	.264	.611
CS * session * group	Sphericity Assumed	23.638	3	7.879	2.147	.100
	Greenhouse-Geisser	23.638	2.565	9.215	2.147	.111
	Huynh-Feldt	23.638	2.947	8.021	2.147	.102
	Lower-bound	23.638	1.000	23.638	2.147	.154
Error(CS*session)	Sphericity Assumed	308.301	84	3.670		
	Greenhouse-Geisser	308.301	71.821	4.293		
	Huynh-Feldt	308.301	82.510	3.737		
	Lower-bound	308.301	28.000	11.011		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	39621.312	1	39621.312	294.025	<.001
group	.614	1	.614	.005	.947
Error	3773.140	28	134.755		

Experiment 3 (Irradiated Specialty Feed)

Instrumental Training, 4 sessions

Input

Average of Averaged over lever Column Labels				
Row Labels	**1**	**2**	**3**	**4**
LPS	**12.55887921**	**14.1416206**	**18.7021887**	**17.6736734**
62	15.07457816	20.0151985	22.6340258	21.3433661
63	10.02227171	8.3759566	10.0225397	11.75
64	17.87952174	21.9489365	27.4257713	31.1428571
66	13.6744034	13.7304067	14.0577287	12.9207221
67	17.31554612	23.1000662	22.0275108	26.218175
72	13.74065599	8.81136364	19.9255365	14.865059
73	14.02070914	16.5062678	30.6880013	26.4697458
74	14.82415993	17.7678723	26.2979035	20.807242
77	7.564212172	9.99225541	11.5925183	11.7174393
79	7.243574659	12.1035952	15.6423061	12.0082699
83	17.09045341	14.4990437	24.5615616	22.3921583
84	11.50275918	11.2127753	22.6670788	17.7723721
87	10.20467827	13.8894751	17.8100037	11.0540822
88	4.311438749	4.17882883	4.97875375	7.86053432
89	11.13108859	12.7857946	16.9169169	17.223127
90	15.34201616	17.3480928	11.9868633	17.2336246
SAL	**13.03820904**	**12.9298814**	**16.0155723**	**15.6671735**
61	14.58506266	13.8833834	16.7733673	20.036869
62	15.11781139	15.4442678	16.427312	29.8986695
63	13.76842105	13.0148221	17.2797582	12.8002629
64	8.636914868	14.7532694	18.454591	16.5502357
69	15.97153802	13.7018379	23.9597771	19.2032221
70	12.14996308	11.0826862	13.9873793	16.3325387
71	14.87375294	13.3395666	20.4124568	15.5057856
75	18.1862427	7.69996527	19.3433986	11.2288667
76	14.51791635	13.2136484	11.4710815	12.6223284
80	15.8566058	13.3394726	20.6946484	18.9492326
81	6.524146293	9.54568831	10.0107584	11.5841385
82	9.734200366	12.9648619	12.3179107	13.3637974
85	14.02426521	14.1589572	13.2469839	11.8268713
86	8.588085801	14.8759123	9.83858859	9.43761016
Grand Total	**12.78256646**	**13.5761423**	**17.4484344**	**16.7373068**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	457.319	3	152.440	15.867	<.001
	Greenhouse-Geisser	457.319	2.685	170.327	15.867	<.001
	Huynh-Feldt	457.319	3.000	152.440	15.867	<.001
	Lower-bound	457.319	1.000	457.319	15.867	<.001
sessions * group	Sphericity Assumed	41.686	3	13.895	1.446	.235
	Greenhouse-Geisser	41.686	2.685	15.526	1.446	.238
	Huynh-Feldt	41.686	3.000	13.895	1.446	.235
	Lower-bound	41.686	1.000	41.686	1.446	.239
Error(sessions)	Sphericity Assumed	807.003	84	9.607		
	Greenhouse-Geisser	807.003	75.178	10.735		
	Huynh-Feldt	807.003	84.000	9.607		
	Lower-bound	807.003	28.000	28.822		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	27206.772	1	27206.772	374.255	<.001
group	54.948	1	54.948	.756	.392
Error	2035.484	28	72.696		

Experiment 3 (Irradiated Specialty Feed)

Pavlovian Instrumental Transfer

Input

Row Labels	Average of Pre	Average of Same	Average of Different
LPS	**2.421875**	**7.1953125**	**2.8046875**
62	1.25	4.125	0
63	0.9375	5.875	1.375
64	1.125	3.875	1.625
66	2.8125	12.25	1.5
67	4.8125	6.75	1.875
72	1.25	6.25	5.5
73	1.6875	15.625	7.125
74	0.75	6.25	4
77	2.75	0.5	7
79	1.75	9.375	2.375
83	0.8125	5.125	2.5
84	2.3125	8.875	0.75
87	0.75	8.375	0.625
88	4.75	7	4.625
89	3.875	9.75	2.125
90	7.125	5.125	1.875
SAL	**2.183035714**	**5.633928571**	**2.580357143**
61	0.3125	0.25	0.125
62	0.5	1.625	0.375
63	0.0625	0.5	2.25
64	6.1875	11.625	4.375
69	3.625	5.125	1.5
70	3.375	3.25	0.25
71	3.5625	14.25	5
75	1.375	7.25	2.75
76	2.75	1.875	1.875
80	2.5	2.875	0.125
81	0.5	4.75	3.75
82	1.4375	13.375	6
85	2.75	6.625	5.375
86	1.625	5.5	2.375
Grand Total	**2.310416667**	**6.466666667**	**2.7**

Output

Number of Groups: 2
Number of Measurements: 3

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group... 1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	10.202	1	10.202	0.844	*No main effect of group, p = 0.366
B2	504.487	1	504.487	41.755	* Dummy
B3	822.949	1	822.949	68.113	* Dummy
Error	338.297	28	12.082		
Within					
W1	100.900	1	100.900	18.666	* Main effect of post-baseline responding
B1W1	2.129	1	2.129	0.394	* No interaction with group
B2W1	34.554	1	34.554	6.392	* Both simple effects significant
B3W1	70.898	1	70.898	13.116	
Error	151.358	28	5.406		
W2	206.887	1	206.887	30.605	* Main effect of PIT (Same > Different)
B1W2	6.674	1	6.674	0.987	* No Interaction, p = .329
B2W2	65.270	1	65.270	9.656	* Simple effect for sham animals, p = .004
B3W2	154.221	1	154.221	22.814	* Simple effect for LPS animals
Error	189.275	28	6.760		

Experiment 3 (Irradiated Specialty Feed)

Outcome devaluation

Input

Row Labels	Average of Devalued	Average of Valued
LPS	**0.6125**	**1.328125**
62	0.2	2.1
63	0.55	0.3
64	0.6	1.05
66	0.9	5.05
67	0.45	2.5
72	0.4	0.8
73	0.8	1.75
74	0.75	1.5
77	0.5	0.85
79	0.6	0.9
83	0.5	0.6
84	0.25	0.55
87	0.45	0.3
88	1.95	1.15
89	0.25	0.25
90	0.65	1.6
SAL	**0.45**	**1.271428571**
61	0.1	0.55
62	0.65	4.5
63	0.4	1.2
64	0.8	0.9
69	1.25	1.1
70	0.3	0.9
71	0.55	0.4
75	0.3	0.95
76	0.45	1.45
80	0.15	0.95
81	0	0.15
82	0.55	3.8
85	0.2	0.3
86	0.6	0.65
Grand Total	**0.536666667**	**1.301666667**

Output

Number of Groups: 2
Number of Measurements: 2

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group... 1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2
W1	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	0.179	1	0.179	0.190	* No main effect of group, p = .666
B2	20.743	1	20.743	21.955	* Dummy
B3	30.128	1	30.128	31.888	* Dummy
Error	26.455	28	0.945		
Within					
W1	8.820	1	8.820	12.378	* Main effect (Valued > Devalued)
B1W1	0.042	1	0.042	0.059	* No Interaction, p = .810
B2W1	4.723	1	4.723	6.629	* Simple effect for sham animals, p = .015
B3W1	4.097	1	4.097	5.750	* Simple effect for LPS animals, p = .023
Error	19.951	28	0.713		

Experiment 3 (Irradiated Specialty Feed)

Outcome-selective reinstatement

Input

Row Labels	Average of Pre-Reinst	Average of Pre-NonReinst	Average of Reinst	Average of NonReinst	Pre
LPS	10.0625	13.75	49.1875	3.75	
62	2	0	0	0	1.00
63	0	0	28	1	0.00
64	1	45	91	5	23.00
66	16	60	92	9	38.00
67	18	14	4	3	16.00
72	1	3	63	0	2.00
73	9	4	122	5	6.50
74	46	2	35	2	24.00
77	2	3	25	1	2.50
79	26	13	71	13	19.50
83	0	2	15	5	1.00
84	0	0	63	4	0.00
87	9	11	85	0	10.00
88	23	19	17	8	21.00
89	8	43	30	0	25.50
90	0	1	46	4	0.50
SAL	14.78571429	4.571428571	51.21428571	3.928571429	
61	0	0	49	0	0.00
62	0	0	6	2	0.00
63	0	4	7	1	2.00
64	83	5	93	15	44.00
69	38	3	109	2	20.50
70	2	3	49	1	2.50
71	42	0	60	0	21.00
75	1	0	8	2	0.50
76	11	5	22	3	8.00
80	0	0	47	1	0.00
81	0	4	68	8	2.00
82	15	14	91	14	14.50
85	9	3	77	3	6.00
86	6	23	31	3	14.50
Grand Total	12.26666667	9.466666667	50.13333333	3.833333333	

Output

Number of Groups: 2
Number of Measurements: 3

Number of subjects in...
Group 1: 14
Group 2: 16

Between contrast coefficients

Contrast	Group... 1	2
B1	1	-1
B2	1	0
B3	0	1

*** Caution ***
B2 coefficients do not sum to zero
B3 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	0.001	1	0.001	1.94193e-6	* No main effect of group
B2	19608.482	1	19608.482	30.706	* Dummy
B3	22425.130	1	22425.130	35.117	* Dummy
Error	17880.221	28	638.579		
Within					
W1	5243.343	1	5243.343	27.077	* Main effect of post-baseline responding
B1W1	55.210	1	55.210	0.285	* No interaction with group
B2W1	2988.107	1	2988.107	15.431	* Both simple effects significant
B3W1	2262.042	1	2262.042	11.681	
Error	5422.018	28	193.643		
W2	32097.686	1	32097.686	57.780	* Main effect (Reinstated > Nonrreinstated)
B1W2	12.753	1	12.753	0.023	* No Interaction
B2W2	15651.571	1	15651.571	28.175	* Simple effect for sham animals
B3W2	16516.531	1	16516.531	29.732	* Simple effect for LPS animals
Error	15554.397	28	555.514		

Experiment 3

Number of Astrocytes

Row Labels	Average of AVERAGE
LPS	1058.9375
62	1119
63	1120
64	1196
66	1050.5
67	1103
72	971
73	1052.5
74	1081.5
77	988
79	1129.5
83	944.5
84	1089
87	994.5
88	1106
89	1083.5
90	914.5
SAL	873.8214286
61	911.5
62	997
63	817
64	759.5
69	963.5
70	891.5
71	1059
75	859
76	770
80	839.5
81	837.5
82	871
85	858.5
86	799
Grand Total	972.55

Unpaired t test
Tabular results

1	Table Analyzed	GFAP Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=6.255, df=28
13		
14	**How big is the difference?**	
15	Mean of column A	873.8
16	Mean of column B	1059
17	Difference between means (B - A) ± SEM	185.1 ± 29.60
18	95% confidence interval	124.5 to 245.7
19	R squared (eta squared)	0.5828
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.240, 13, 15
23	P value	0.6831
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 3

Number of Microglia

Row Labels	Average of AVERAGE
LPS	685.90625
62	733.5
63	571.5
64	674
66	781
67	741
72	715
73	660.5
74	684.5
77	496
79	705
83	603.5
84	682
87	658.5
88	760.5
89	854
90	654
SAL	426.2857143
61	551
62	465.5
63	483.5
64	390.5
69	331
70	367.5
71	513
75	354
76	430.5
80	329
81	385.5
82	361
85	537.5
86	468.5
Grand Total	564.75

Unpaired t test
Tabular results

1	Table Analyzed	IBA1 Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=8.742, df=28
13		
14	**How big is the difference?**	
15	Mean of column A	426.3
16	Mean of column B	685.9
17	Difference between means (B - A) ± SEM	259.6 ± 29.70
18	95% confidence interval	198.8 to 320.5
19	R squared (eta squared)	0.7319
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.223, 15, 13
23	P value	0.7231
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 3

Number of Neurons

Row Labels	Average of AVERAGE
LPS	1117.375
62	1212
63	1030
64	995
66	1137
67	1076
72	1049.5
73	1224.5
74	1150.5
77	1059
79	1176
83	1140
84	1174.5
87	1116
88	1059.5
89	1103.5
90	1175
SAL	1172.821429
61	1070.5
62	1282.5
63	1259
64	1318.5
69	1086
70	1026
71	1194
75	1151
76	1048
80	1231
81	1184.5
82	1263.5
85	1174.5
86	1130.5
Grand Total	1143.25

	Unpaired t test Tabular results	
1	Table Analyzed	NeuN Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	0.0682
9	P value summary	ns
10	Significantly different (P < 0.05)?	No
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=1.897, df=28
13		
14	**How big is the difference?**	
15	Mean of column A	1173
16	Mean of column B	1117
17	Difference between means (B - A) ± SEM	-55.45 ± 29.23
18	95% confidence interval	-115.3 to 4.426
19	R squared (eta squared)	0.1139
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.862, 13, 15
23	P value	0.2492
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 3

Number of c-Fos

Row Labels	Average of AVERAGE
LPS	161.90625
62	188.5
63	129.5
64	186.5
66	158.5
67	207.5
72	118.5
73	168.5
74	175
77	126.5
79	155
83	131.5
84	174
87	127
88	216.5
89	175
90	152.5
SAL	93.57142857
61	89
62	158
63	71.5
64	67
69	103.5
70	74.5
71	180.5
75	128.5
76	69.5
80	50
81	91.5
82	64
85	95.5
86	67
Grand Total	130.0166667

Unpaired t test
Tabular results

1	Table Analyzed	cfos Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=5.519, df=28
13		
14	**How big is the difference?**	
15	Mean of column A	93.57
16	Mean of column B	161.9
17	Difference between means (B - A) ± SEM	68.33 ± 12.38
18	95% confidence interval	42.97 to 93.70
19	R squared (eta squared)	0.5210
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.610, 13, 15
23	P value	0.3754
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 3

c-Fos-NeuN Intensity

Row Labels	Average of AVERAGED
LPS	22.0841875
62	20.629
63	17.522
64	20.721
66	27.803
67	25.137
72	18.76
73	20.367
74	28.357
77	16.894
79	23.937
83	22.089
84	28.573
87	19.706
88	24.516
89	19.592
90	18.744
SAL	14.58521429
61	13.997
62	22.376
63	11.716
64	9.868
69	17.051
70	10.556
71	22.042
75	17.407
76	10.552
80	15.43
81	15.117
82	16.123
85	11.672
86	10.286
Grand Total	18.58466667

Unpaired t test
Tabular results

1	Table Analyzed	cfos-NeuN Intensity
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=5.137, df=28
13		
14	**How big is the difference?**	
15	Mean of column A	14.59
16	Mean of column B	22.08
17	Difference between means (B - A) ± SEM	7.499 ± 1.460
18	95% confidence interval	4.509 to 10.49
19	R squared (eta squared)	0.4852
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.167, 13, 15
23	P value	0.7676
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 3 (Gordons Specialty Feed)

GFAP correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	GFAP	PIT SCORE
62	1119	0.0364
63	817	0.0217
64	759.5	0.0026
66	1050.5	0.0210
67	1103	0.1491
69	963.5	0.0546
70	891.5	-0.0039
71	1059	0.1242
72	971	0.1646
73	1052.5	0.0097
74	1081.5	0.1488
75	859	0.0678
76	770	0.0572
77	988	0.0447
79	1129.5	0.0325
80	839.5	-0.1101
81	837.5	0.0072
82	871	0.0013
83	944.5	0.0880
84	1089	0.0230
61	911.5	-0.0422
62	997	-0.0282
63	1120	0.0383
64	1196	0.0516
85	858.5	0.0437
86	799	-0.1052
87	994.5	0.0342
88	1106	-0.0077
89	1083.5	0.0199
90	914.5	-0.0426

GFAP	DEVAL SCORE
1119	0.05752315
817	-0.0393111
759.5	-0.1737746
1050.5	0.08374562
1103	0.10782189
963.5	0.06913164
891.5	0.03091403
1059	0.52443609
971	-0.007515
1052.5	0.0170345
1081.5	-0.082627
859	0.01481918
770	-0.0421553
988	-0.3950223
1129.5	0.02146857
839.5	-0.2695717
837.5	0.05672044
871	-0.0023567
944.5	-0.0099143
1089	0.11643213
911.5	0.36413645
997	0.41710144
1120	0.09221817
1196	0.07706912
858.5	0.02019241
799	-0.3182978
994.5	0.00785064
1106	0.3380988
1083.5	0.06562652
914.5	0.07031285

GFAP	REINST SCORE
1119	0.398761972
817	0.772222222
759.5	0.367346939
1050.5	0.303030303
1103	1
963.5	0.273684211
891.5	0.352888655
1059	0.265480896
971	0.337837838
1052.5	0.025661376
1081.5	0.004220697
859	0.653881615
770	0.053140097
988	0.470588235
1129.5	0.443452381
839.5	0.192307692
837.5	0.345833333
871	0.135832522
944.5	0.335495589
1089	-0.11111111
911.5	0.095575221
997	0.013793103
1120	0.38
1196	0.123672818
858.5	0.492537313
799	0.34984985
994.5	0.033411033
1106	0.181616833
1083.5	0.139043382
914.5	0.447513676

Correlation Tabular results	A GFAP Counts vs. PIT Score
Pearson r	
r	0.3788
95% confidence interval	0.02141 to 0.6503
R squared	0.1435
P value	
P (two-tailed)	0.0390
P value summary	*
Significant? (alpha = 0.05)	Yes
Number of XY Pairs	30

Correlation Tabular results	A GFAP Counts vs. Devaluation Score
Pearson r	
r	0.3957
95% confidence interval	0.04132 to 0.6616
R squared	0.1566
P value	
P (two-tailed)	0.0304
P value summary	*
Significant? (alpha = 0.05)	Yes
Number of XY Pairs	30

Correlation Tabular results	A GFAP Counts vs. Reinstatement Score
Pearson r	
r	-0.1550
95% confidence interval	-0.4880 to 0.2174
R squared	0.02402
P value	
P (two-tailed)	0.4135
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Experiment 3 (Gordons Specialty Feed)

IBA1 correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	IBA1	PIT SCORE
62	733.5	0.0364
63	483.5	0.0217
64	390.5	0.0026
66	781	0.0210
67	741	0.1491
69	331	0.0546
70	367.5	-0.0039
71	513	0.1242
72	715	0.1646
73	660.5	0.0097
74	684.5	0.1488
75	354	0.0678
76	430.5	0.0572
77	496	0.0447
79	705	0.0325
80	329	-0.1101
81	385.5	0.0072
82	361	0.0013
83	603.5	0.0880
84	682	0.0230
61	551	-0.0422
62	465.5	-0.0282
63	571.5	0.0383
64	674	0.0516
85	537.5	0.0437
86	468.5	-0.1052
87	658.5	0.0342
88	760.5	-0.0077
89	854	0.0199
90	654	-0.0426

IBA1	DEVAL SCORE
733.5	0.05752315
483.5	-0.03931111
390.5	-0.17377461
781	0.08374562
741	0.10782189
331	0.06913164
367.5	0.03091403
513	0.52443609
715	-0.00751505
660.5	0.0170345
684.5	-0.08262696
354	0.01481918
430.5	-0.0421553
496	-0.39502231
705	0.02146857
329	-0.26957168
385.5	0.05672044
361	-0.00235673
603.5	-0.00991433
682	0.11643213
551	0.36413645
465.5	0.41710144
571.5	0.09221817
674	0.07706912
537.5	0.02019241
468.5	-0.31829779
658.5	0.00785064
760.5	0.3380988
854	0.06562652
654	0.07031285

IBA1	REINST SCORE
733.5	0.398761972
483.5	0.772222222
390.5	0.367346939
781	0.303030303
741	1
331	0.273684211
367.5	0.352888655
513	0.265480896
715	0.337837838
660.5	0.025661376
684.5	0.004220697
354	0.653881615
430.5	0.053140097
496	0.470588235
705	0.443452381
329	0.192307692
385.5	0.345833333
361	0.135832522
603.5	0.335495589
682	-0.11111111
551	0.095575221
465.5	0.013793103
571.5	0.38
674	0.123672818
537.5	0.492537313
468.5	0.34984985
658.5	0.033411033
760.5	0.181616833
854	0.139043382
654	0.447513676

Correlation Tabular results	A IBA1 Counts vs. PIT Score
Pearson r	
r	0.3197
95% confidence interval	-0.04580 to 0.6098
R squared	0.1022
P value	
P (two-tailed)	0.0850
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Correlation Tabular results	A IBA1 Counts vs. Devaluation Score
Pearson r	
r	0.2385
95% confidence interval	-0.1332 to 0.5514
R squared	0.05690
P value	
P (two-tailed)	0.2043
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Correlation Tabular results	A IBA1 Counts vs. Reinstatement Score
Pearson r	
r	-0.07104
95% confidence interval	-0.4205 to 0.2968
R squared	0.005047
P value	
P (two-tailed)	0.7091
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Experiment 3 (Gordons Specialty Feed)

c-Fos-NeuN colocalization correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	cfos-NeuN	PIT SCORE
62	20.629	0.0364
63	11.716	0.0217
64	9.868	0.0026
66	27.803	0.0210
67	25.137	0.1491
69	17.051	0.0546
70	10.556	-0.0039
71	22.042	0.1242
72	18.76	0.1646
73	20.367	0.0097
74	28.357	0.1488
75	17.407	0.0678
76	10.552	0.0572
77	16.894	0.0447
79	23.937	0.0325
80	15.43	-0.1101
81	15.117	0.0072
82	16.123	0.0013
83	22.089	0.0880
84	28.573	0.0230
61	13.997	-0.0422
62	22.376	-0.0282
63	17.522	0.0383
64	20.721	0.0516
85	11.672	0.0437
86	10.286	-0.1052
87	19.706	0.0342
88	24.516	-0.0077
89	19.592	0.0199
90	18.744	-0.0426

cfos-NeuN	DEVAL SCORE
20.629	0.0575231
11.716	-0.0393111
9.868	-0.1737746
27.803	0.0837456
25.137	0.1078219
17.051	0.0691316
10.556	0.030914
22.042	0.5244361
18.76	-0.007515
20.367	0.0170345
28.357	-0.082627
17.407	0.0148192
10.552	-0.0421553
16.894	-0.3950223
23.937	0.0214686
15.43	-0.2695717
15.117	0.0567204
16.123	-0.0023567
22.089	-0.0099143
28.573	0.1164321
13.997	0.3641365
22.376	0.4171014
17.522	0.0922182
20.721	0.0770691
11.672	0.0201924
10.286	-0.3182978
19.706	0.0078506
24.516	0.3380988
19.592	0.0656265
18.744	0.0703129

cfos-NeuN	REINST SCORE
20.629	0.398762
11.716	0.7722222
9.868	0.3673469
27.803	0.3030303
25.137	1
17.051	0.2736842
10.556	0.3528887
22.042	0.2654809
18.76	0.3378378
20.367	0.0256614
28.357	0.0042207
17.407	0.6538816
10.552	0.0531401
16.894	0.4705882
23.937	0.4434524
15.43	0.1923077
15.117	0.3458333
16.123	0.1358325
22.089	0.3354956
28.573	-0.1111111
13.997	0.0955752
22.376	0.0137931
17.522	0.38
20.721	0.1236728
11.672	0.4925373
10.286	0.3498498
19.706	0.033411
24.516	0.1816168
19.592	0.1390434
18.744	0.4475137

	Correlation Tabular results	A c-fos-NeuN Intensity vs. PIT Score
1	**Pearson r**	
2	r	0.4030
3	95% confidence interval	0.04999 to 0.6665
4	R squared	0.1624
5		
6	**P value**	
7	P (two-tailed)	0.0272
8	P value summary	*
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Devaluation Score
1	**Pearson r**	
2	r	0.3757
3	95% confidence interval	0.01785 to 0.6482
4	R squared	0.1412
5		
6	**P value**	
7	P (two-tailed)	0.0408
8	P value summary	*
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Reinstatement Score
1	**Pearson r**	
2	r	-0.2031
3	95% confidence interval	-0.5250 to 0.1696
4	R squared	0.04125
5		
6	**P value**	
7	P (two-tailed)	0.2817
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

Experiment 3 (Gordons Specialty Feed)

NeuN correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	NeuN	PIT SCORE
62	1212	0.0364
63	1259	0.0217
64	1318.5	0.0026
66	1137	0.0210
67	1076	0.1491
69	1086	0.0546
70	1026	-0.0039
71	1194	0.1242
72	1049.5	0.1646
73	1224.5	0.0097
74	1150.5	0.1488
75	1151	0.0678
76	1048	0.0572
77	1059	0.0447
79	1176	0.0325
80	1231	-0.1101
81	1184.5	0.0072
82	1263.5	0.0013
83	1140	0.0880
84	1174.5	0.0230
61	1070.5	-0.0422
62	1282.5	-0.0282
63	1030	0.0383
64	995	0.0516
85	1174.5	0.0437
86	1130.5	-0.1052
87	1116	0.0342
88	1059.5	-0.0077
89	1103.5	0.0199
90	1175	-0.0426

NeuN	DEVAL SCORE
1212	0.05752315
1259	-0.03931111
1318.5	-0.17377461
1137	0.08374562
1076	0.10782189
1086	0.06913164
1026	0.03091403
1194	0.52443609
1049.5	-0.00751505
1224.5	0.0170345
1150.5	-0.08262696
1151	0.01481918
1048	-0.0421553
1059	-0.39502231
1176	0.02146857
1231	-0.26957168
1184.5	0.05672044
1263.5	-0.00235673
1140	-0.00991433
1174.5	0.11643213
1070.5	0.36413645
1282.5	0.41710144
1030	0.09221817
995	0.07706912
1174.5	0.02019241
1130.5	-0.31829779
1116	0.00785064
1059.5	0.3380988
1103.5	0.06562652
1175	0.07031285

NeuN	REINST SCORE
1212	0.398761972
1259	0.772222222
1318.5	0.367346939
1137	0.303030303
1076	1
1086	0.273684211
1026	0.352888655
1194	0.265480896
1049.5	0.337837838
1224.5	0.025661376
1150.5	0.004220697
1151	0.653881615
1048	0.053140097
1059	0.470588235
1176	0.443452381
1231	0.192307692
1184.5	0.345833333
1263.5	0.135832522
1140	0.335495589
1174.5	-0.11111111
1070.5	0.095575221
1282.5	0.013793103
1030	0.38
995	0.123672818
1174.5	0.492537313
1130.5	0.34984985
1116	0.033411033
1059.5	0.181616833
1103.5	0.139043382
1175	0.447513676

	Correlation Tabular results	A NeuN Counts vs. PIT Score
1	**Pearson r**	
2	r	-0.2807
3	95% confidence interval	-0.5821 to 0.08849
4	R squared	0.07881
5		
6	**P value**	
7	P (two-tailed)	0.1329
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A NeuN Counts vs. Devaluation Score
1	**Pearson r**	
2	r	-0.02694
3	95% confidence interval	-0.3835 to 0.3366
4	R squared	0.0007257
5		
6	**P value**	
7	P (two-tailed)	0.8876
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A NeuN Counts vs. Reinstatement Score
1	**Pearson r**	
2	r	-0.01069
3	95% confidence interval	-0.3695 to 0.3509
4	R squared	0.0001142
5		
6	**P value**	
7	P (two-tailed)	0.9553
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	30

Experiment 3 (Gordons Specialty Feed)

c-Fos correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	cfos	PIT SCORE
62	188.5	0.0364
63	71.5	0.0217
64	67	0.0026
66	158.5	0.0210
67	207.5	0.1491
69	103.5	0.0546
70	74.5	-0.0039
71	180.5	0.1242
72	118.5	0.1646
73	168.5	0.0097
74	175	0.1488
75	128.5	0.0678
76	69.5	0.0572
77	126.5	0.0447
79	155	0.0325
80	50	-0.1101
81	91.5	0.0072
82	64	0.0013
83	131.5	0.0880
84	174	0.0230
61	89	-0.0422
62	158	-0.0282
63	129.5	0.0383
64	186.5	0.0516
85	95.5	0.0437
86	67	-0.1052
87	127	0.0342
88	216.5	-0.0077
89	175	0.0199
90	152.5	-0.0426

cfos	DEVAL SCORE
188.5	0.05752315
71.5	-0.03931111
67	-0.17377461
158.5	0.08374562
207.5	0.10782189
103.5	0.06913164
74.5	0.03091403
180.5	0.52443609
118.5	-0.00751505
168.5	0.0170345
175	-0.08262696
128.5	0.01481918
69.5	-0.0421553
126.5	-0.39502231
155	0.02146857
50	-0.26957168
91.5	0.05672044
64	-0.00235673
131.5	-0.00991433
174	0.11643213
89	0.36413645
158	0.41710144
129.5	0.09221817
186.5	0.07706912
95.5	0.02019241
67	-0.31829779
127	0.00785064
216.5	0.3380988
175	0.06562652
152.5	0.07031285

cfos	REINST SCORE
188.5	0.398761972
71.5	0.772222222
67	0.367346939
158.5	0.303030303
207.5	1
103.5	0.273684211
74.5	0.352888655
180.5	0.265480896
118.5	0.337837838
168.5	0.025661376
175	0.004220697
128.5	0.653881615
69.5	0.053140097
126.5	0.470588235
155	0.443452381
50	0.192307692
91.5	0.345833333
64	0.135832522
131.5	0.335495589
174	-0.111111111
89	0.095575221
158	0.013793103
129.5	0.38
186.5	0.123672818
95.5	0.492537313
67	0.34984985
127	0.033411033
216.5	0.181616833
175	0.139043382
152.5	0.447513676

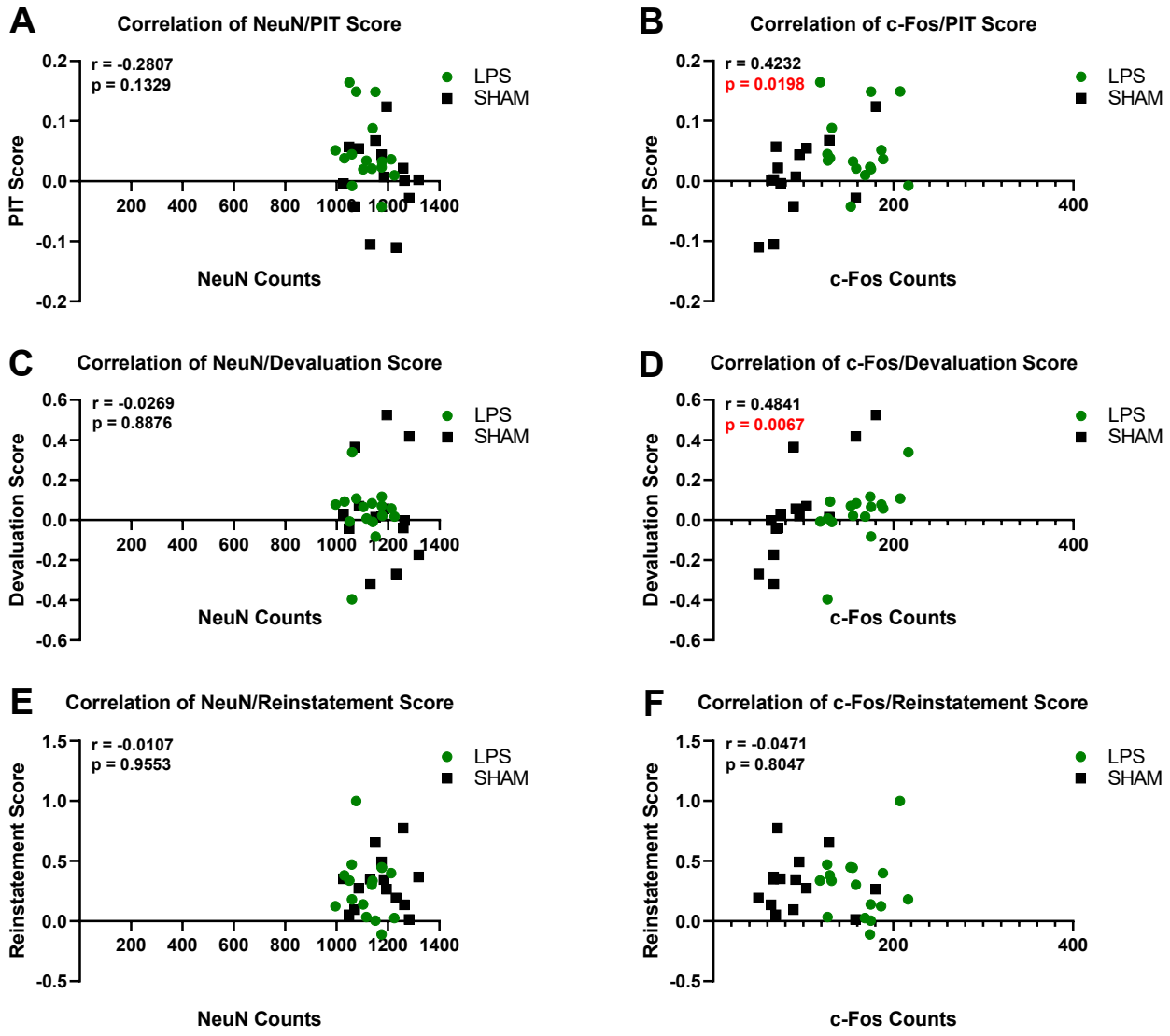
	Correlation Tabular results	A c-fos Counts vs. PIT Score
1	**Pearson r**	
2	r	0.4232
3	95% confidence interval	0.07428 to 0.6798
4	R squared	0.1791
5		
6	**P value**	
7	P (two-tailed)	0.0198
8	P value summary	*
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos Counts vs. Devaluation Score
1	**Pearson r**	
2	r	0.4841
3	95% confidence interval	0.1499 to 0.7190
4	R squared	0.2343
5		
6	**P value**	
7	P (two-tailed)	0.0067
8	P value summary	**
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos Counts vs. Reinstatement Score
1	**Pearson r**	
2	r	-0.04712
3	95% confidence interval	-0.4006 to 0.3186
4	R squared	0.002220
5		
6	**P value**	
7	P (two-tailed)	0.8047
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

Experiment 3

Correlation between NeuN and c-Fos expressions, and behavioural performances using Gordons Specialty Feed Chow



Experiment 3 (Irradiated Specialty Feed)

GFAP correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	GFAP	PIT SCORE
62	1119	0.11301
63	817	0
64	759.5	-0.01181
66	1050.5	0.04904
67	1103	0.07048
69	963.5	0.0461
70	891.5	0.08914
71	1059	0.13748
72	971	0.09733
73	1052.5	0.035
74	1081.5	0.00431
75	859	0.0514
76	770	0.06577
77	988	0.00832
79	1129.5	0.09928
80	839.5	0.06091
81	837.5	0.00408
82	871	0.0193
83	944.5	0.05435
84	1089	0.04748
61	911.5	0.05833
62	997	0.04389
63	1120	0.03347
64	1196	-0.01851
85	858.5	0.0376
86	799	0.06032
87	994.5	0.10161
88	1106	0.03218
89	1083.5	0.04768
90	914.5	0.02268

GFAP	DEVAL SCORE
1119	0.06971438
817	-0.05513953
759.5	-0.11168485
1050.5	0.16432356
1103	0.04747216
963.5	-0.00607202
891.5	-0.22529866
1059	-0.20144429
971	-0.10588371
1052.5	0.02895098
1081.5	0.03210703
859	0.03701671
770	-0.17936824
988	-0.03739185
1129.5	0.01599517
839.5	-0.26298631
837.5	0.00585767
871	0.06318923
944.5	-0.03730904
1089	-0.09044375
911.5	0.01392201
997	0.12574952
1120	0.00884348
1196	-0.07587517
858.5	0.02326429
799	0.06042036
994.5	0.00048172
1106	-0.01317296
1083.5	0.00285319
914.5	0.04692912

GFAP	REINST SCORE
1119	0
817	0.333333333
759.5	-0.08284652
1050.5	0.614277763
1103	0.003846154
963.5	0.306191033
891.5	0.29
1059	0.410566868
971	0.496062992
1052.5	0.522119816
1081.5	-0.0316092
859	-0.52941176
770	0.127272727
988	0.280769231
1129.5	0.203063725
839.5	0
837.5	-0.05555556
871	0.317657966
944.5	0.35
1089	0
911.5	1
997	-0.5
1120	0
1196	0.684091355
858.5	0.398191519
799	0.587538829
994.5	0.805383023
1106	0.069674185
1083.5	0.441176471
914.5	0.2

	Correlation Tabular results	A GFAP Counts vs. PIT Score
1	**Pearson r**	
2	r	0.1745
3	95% confidence interval	-0.1982 to 0.5031
4	R squared	0.03046
5		
6	**P value**	
7	P (two-tailed)	0.3563
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A GFAP Counts vs. Devaluation Score
1	**Pearson r**	
2	r	0.2542
3	95% confidence interval	-0.1168 to 0.5629
4	R squared	0.06462
5		
6	**P value**	
7	P (two-tailed)	0.1752
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A GFAP Counts vs. Reinstatement Score
1	**Pearson r**	
2	r	0.07685
3	95% confidence interval	-0.2915 to 0.4253
4	R squared	0.005906
5		
6	**P value**	
7	P (two-tailed)	0.6865
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

Experiment 3 (Irradiated Specialty Feed)

IBA1 correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	IBA1	PIT SCORE
62	733.5	0.113014
63	483.5	0
64	390.5	-0.011814
66	781	0.049038
67	741	0.070476
69	331	0.046104
70	367.5	0.089144
71	513	0.137483
72	715	0.097334
73	660.5	0.034996
74	684.5	0.004306
75	354	0.051397
76	430.5	0.065767
77	496	0.008317
79	705	0.099275
80	329	0.060908
81	385.5	0.004083
82	361	0.019295
83	603.5	0.054351
84	682	0.047476
61	551	0.058333
62	465.5	0.043887
63	571.5	0.033474
64	674	-0.018506
85	537.5	0.037596
86	468.5	0.060317
87	658.5	0.101605
88	760.5	0.032182
89	854	0.047683
90	654	0.022676

IBA1	DEVAL SCORE
733.5	0.0697144
483.5	-0.0551395
390.5	-0.1116849
781	0.1643236
741	0.0474722
331	-0.006072
367.5	-0.2252987
513	-0.2014443
715	-0.1058837
660.5	0.028951
684.5	0.032107
354	0.0370167
430.5	-0.1793682
496	-0.0373918
705	0.0159952
329	-0.2629863
385.5	0.0058577
361	0.0631892
603.5	-0.037309
682	-0.0904438
551	0.013922
465.5	0.1257495
571.5	0.0088435
674	-0.0758752
537.5	0.0232643
468.5	0.0604204
658.5	0.0004817
760.5	-0.013173
854	0.0028532
654	0.0469291

IBA1	REINST SCORE
733.5	0
483.5	0.333333333
390.5	-0.08284652
781	0.614277763
741	0.003846154
331	0.306191033
367.5	0.29
513	0.410566868
715	0.496062992
660.5	0.522119816
684.5	-0.0316092
354	-0.52941176
430.5	0.127272727
496	0.280769231
705	0.203063725
329	0
385.5	-0.05555556
361	0.317657966
603.5	0.35
682	0
551	1
465.5	-0.5
571.5	0
674	0.684091355
537.5	0.398191519
468.5	0.587538829
658.5	0.805383023
760.5	0.069674185
854	0.441176471
654	0.2

	Correlation Tabular results	A IBA1 Counts vs. PIT Score
1	**Pearson r**	
2	r	0.1628
3	95% confidence interval	-0.2098 to 0.4941
4	R squared	0.02651
5		
6	**P value**	
7	P (two-tailed)	0.3900
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A IBA1 Counts vs. Devaluation Score
1	**Pearson r**	
2	r	0.3581
3	95% confidence interval	-0.002509 to 0.6363
4	R squared	0.1282
5		
6	**P value**	
7	P (two-tailed)	0.0520
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A IBA1 Counts vs. Reinstatement Score
1	**Pearson r**	
2	r	0.2839
3	95% confidence interval	-0.08512 to 0.5844
4	R squared	0.08057
5		
6	**P value**	
7	P (two-tailed)	0.1285
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

Experiment 3 (Irradiated Specialty Feed)

c-Fos-NeuN colocalization correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	cfos-NeuN	PIT SCORE
62	20.629	0.1130137
63	11.716	0
64	9.868	-0.0118138
66	27.803	0.0490385
67	25.137	0.0704763
69	17.051	0.0461039
70	10.556	0.0891436
71	22.042	0.1374825
72	18.76	0.0973336
73	20.367	0.0349955
74	28.357	0.0043061
75	17.407	0.0513965
76	10.552	0.0657671
77	16.894	0.0083169
79	23.937	0.0992754
80	15.43	0.0609081
81	15.117	0.0040835
82	16.123	0.0192951
83	22.089	0.0543515
84	28.573	0.0474764
61	13.997	0.0583333
62	22.376	0.0438871
63	17.522	0.0334738
64	20.721	-0.0185065
85	11.672	0.0375958
86	10.286	0.0603175
87	19.706	0.1016053
88	24.516	0.0321817
89	19.592	0.0476825
90	18.744	0.0226759

cfos-NeuN	DEVAL SCORE
20.629	0.0697144
11.716	-0.0551395
9.868	-0.1116849
27.803	0.1643236
25.137	0.0474722
17.051	-0.006072
10.556	-0.2252987
22.042	-0.2014443
18.76	-0.1058837
20.367	0.028951
28.357	0.032107
17.407	0.0370167
10.552	-0.1793682
16.894	-0.0373918
23.937	0.0159952
15.43	-0.2629863
15.117	0.0058577
16.123	0.0631892
22.089	-0.037309
28.573	-0.0904438
13.997	0.013922
22.376	0.1257495
17.522	0.0088435
20.721	-0.0758752
11.672	0.0232643
10.286	0.0604204
19.706	0.0004817
24.516	-0.013173
19.592	0.0028532
18.744	0.0469291

cfos-NeuN	REINST SCORE
20.629	0
11.716	0.3333333
9.868	-0.0828465
27.803	0.6142778
25.137	0.0038462
17.051	0.306191
10.556	0.29
22.042	0.4105669
18.76	0.496063
20.367	0.5221198
28.357	-0.0316092
17.407	-0.5294118
10.552	0.1272727
16.894	0.2807692
23.937	0.2030637
15.43	0
15.117	-0.0555556
16.123	0.317658
22.089	0.35
28.573	0
13.997	1
22.376	-0.5
17.522	0
20.721	0.6840914
11.672	0.3981915
10.286	0.5875388
19.706	0.805383
24.516	0.0696742
19.592	0.4411765
18.744	0.2

	Correlation Tabular results	A c-fos-NeuN Intensity vs. PIT Score
1	**Pearson r**	
2	r	0.1371
3	95% confidence interval	-0.2348 to 0.4739
4	R squared	0.01878
5		
6	**P value**	
7	P (two-tailed)	0.4702
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Devaluation Score
1	**Pearson r**	
2	r	0.3474
3	95% confidence interval	-0.01474 to 0.6289
4	R squared	0.1207
5		
6	**P value**	
7	P (two-tailed)	0.0600
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Reinstatement Score
1	**Pearson r**	
2	r	-0.1215
3	95% confidence interval	-0.4615 to 0.2497
4	R squared	0.01476
5		
6	**P value**	
7	P (two-tailed)	0.5225
8	P value summary	ns
9	Significant? (alpha = 0.05	No
10		
11	**Number of XY Pairs**	30

Experiment 3 (Irradiated Specialty Feed)

NeuN correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	NeuN	PIT SCORE
62	1212	0.113014
63	1259	0
64	1318.5	-0.011814
66	1137	0.049038
67	1076	0.070476
69	1086	0.046104
70	1026	0.089144
71	1194	0.137483
72	1049.5	0.097334
73	1224.5	0.034996
74	1150.5	0.004306
75	1151	0.051397
76	1048	0.065767
77	1059	0.008317
79	1176	0.099275
80	1231	0.060908
81	1184.5	0.004083
82	1263.5	0.019295
83	1140	0.054351
84	1174.5	0.047476
61	1070.5	0.058333
62	1282.5	0.043887
63	1030	0.033474
64	995	-0.018506
85	1174.5	0.037596
86	1130.5	0.060317
87	1116	0.101605
88	1059.5	0.032182
89	1103.5	0.047683
90	1175	0.022676

NeuN	DEVAL SCORE
1212	0.06971438
1259	-0.05513953
1318.5	-0.11168485
1137	0.16432356
1076	0.04747216
1086	-0.00607202
1026	-0.22529866
1194	-0.20144429
1049.5	-0.10588371
1224.5	0.02895098
1150.5	0.03210703
1151	0.03701671
1048	-0.17936824
1059	-0.03739185
1176	0.01599517
1231	-0.26298631
1184.5	0.00585767
1263.5	0.06318923
1140	-0.03730904
1174.5	-0.09044375
1070.5	0.01392201
1282.5	0.12574952
1030	0.00884348
995	-0.07587517
1174.5	0.02326429
1130.5	0.06042036
1116	0.00048172
1059.5	-0.01317296
1103.5	0.00285319
1175	0.04692912

NeuN	REINST SCORE
1212	0
1259	0.33333333
1318.5	-0.08284652
1137	0.61427776
1076	0.00384615
1086	0.30619103
1026	0.29
1194	0.41056687
1049.5	0.49606299
1224.5	0.52211982
1150.5	-0.0316092
1151	-0.52941176
1048	0.12727273
1059	0.28076923
1176	0.20306373
1231	0
1184.5	-0.05555556
1263.5	0.31765797
1140	0.35
1174.5	0
1070.5	1
1282.5	-0.5
1030	0
995	0.68409136
1174.5	0.39819152
1130.5	0.58753883
1116	0.80538302
1059.5	0.06967419
1103.5	0.44117647
1175	0.2

Correlation Tabular results	A NeuN Counts vs. PIT Score
Pearson r	
r	-0.1242
95% confidence interval	-0.4637 to 0.2472
R squared	0.01542
P value	
P (two-tailed)	0.5133
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Correlation Tabular results	A NeuN Counts vs. Devaluation Score
Pearson r	
r	0.1497
95% confidence interval	-0.2226 to 0.4838
R squared	0.02240
P value	
P (two-tailed)	0.4299
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Correlation Tabular results	A NeuN Counts vs. Reinstatement Score
Pearson r	
r	-0.3537
95% confidence interval	-0.6332 to 0.007582
R squared	0.1251
P value	
P (two-tailed)	0.0552
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	30

Experiment 3

Experiment 3 (Irradiated Specialty Feed)

c-Fos correlated with sPIT, Outcome Devaluation, and Outcome-selective Reinstatement

Rat	cfos	PIT SCORE
62	188.5	0.11301
63	71.5	0
64	67	-0.0118
66	158.5	0.04904
67	207.5	0.07048
69	103.5	0.0461
70	74.5	0.08914
71	180.5	0.13748
72	118.5	0.09733
73	168.5	0.035
74	175	0.00431
75	128.5	0.0514
76	69.5	0.06577
77	126.5	0.00832
79	155	0.09928
80	50	0.06091
81	91.5	0.00408
82	64	0.0193
83	131.5	0.05435
84	174	0.04748
61	89	0.05833
62	158	0.04389
63	129.5	0.03347
64	186.5	-0.0185
85	95.5	0.0376
86	67	0.06032
87	127	0.10161
88	216.5	0.03218
89	175	0.04768
90	152.5	0.02268

cfos	DEVAL SCORE
188.5	0.06971438
71.5	-0.0551395
67	-0.1116849
158.5	0.16432356
207.5	0.04747216
103.5	-0.006072
74.5	-0.2252987
180.5	-0.2014443
118.5	-0.1058837
168.5	0.02895098
175	0.03210703
128.5	0.03701671
69.5	-0.1793682
126.5	-0.0373918
155	0.01599517
50	-0.2629863
91.5	0.00585767
64	0.06318923
131.5	-0.037309
174	-0.0904438
89	0.01392201
158	0.12574952
129.5	0.00884348
186.5	-0.0758752
95.5	0.02326429
67	0.06042036
127	0.00048172
216.5	-0.013173
175	0.00285319
152.5	0.04692912

cfos	REINST SCORE
188.5	0
71.5	0.333333333
67	-0.082846522
158.5	0.614277763
207.5	0.003846154
103.5	0.306191033
74.5	0.29
180.5	0.410566868
118.5	0.496062992
168.5	0.522119816
175	-0.031609195
128.5	-0.529411765
69.5	0.127272727
126.5	0.280769231
155	0.203063725
50	0
91.5	-0.055555556
64	0.317657966
131.5	0.35
174	0
89	1
158	-0.5
129.5	0
186.5	0.684091355
95.5	0.398191519
67	0.587538829
127	0.805383023
216.5	0.069674185
175	0.441176471
152.5	0.2

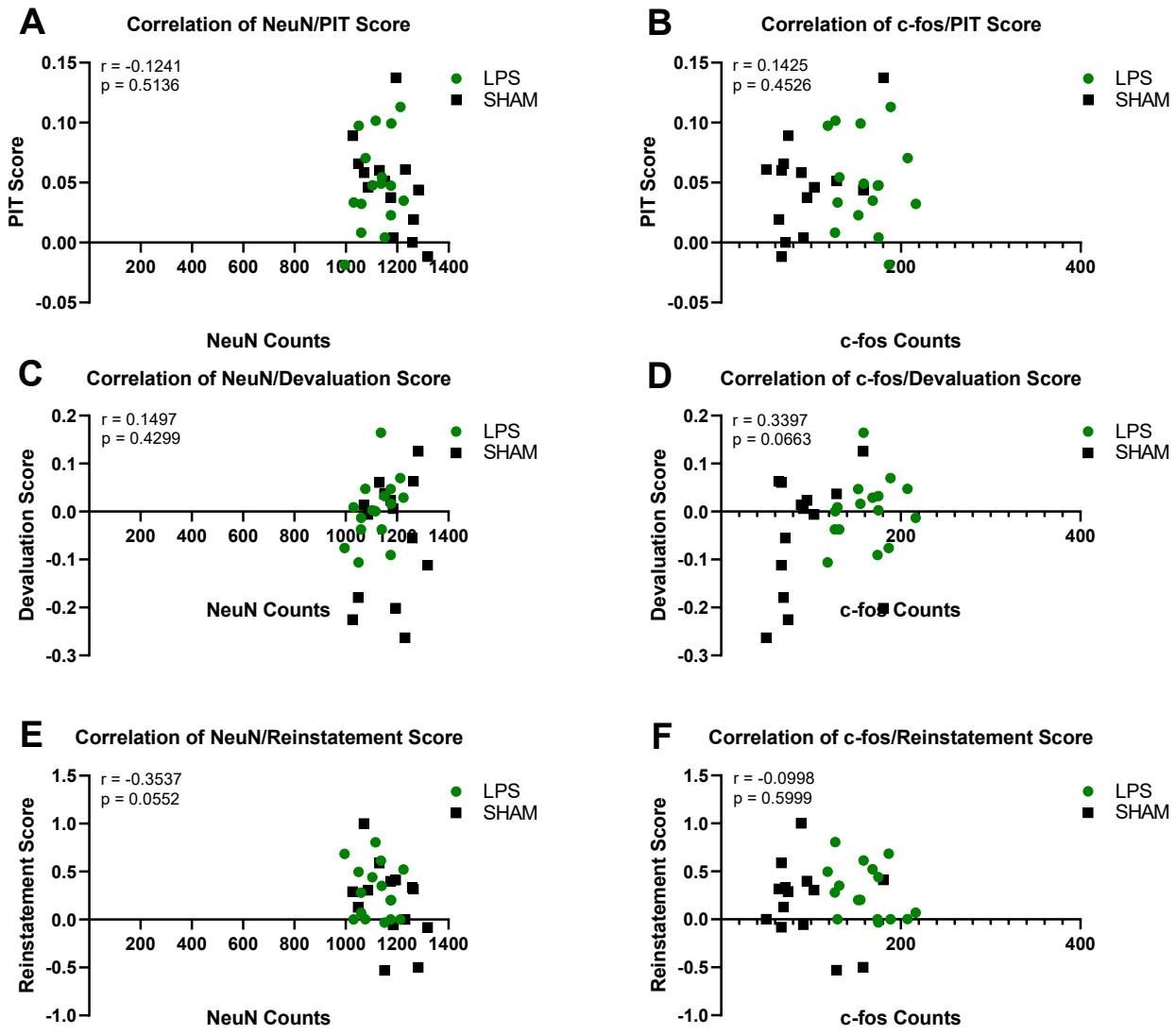
Correlation Tabular results	A c-fos Counts vs. PIT Score
Pearson r	
r	0.1423
95% confidence interval	-0.2297 to 0.4781
R squared	0.02025
P value	
P (two-tailed)	0.4532
P value summary	ns
Significant? (alpha = 0.05	No
Number of XY Pairs	30

Correlation Tabular results	A c-fos Counts vs. Devaluation Score
Pearson r	
r	0.3397
95% confidence interval	-0.02343 to 0.6237
R squared	0.1154
P value	
P (two-tailed)	0.0663
P value summary	ns
Significant? (alpha = 0.05	No
Number of XY Pairs	30

Correlation Tabular results	A c-fos Counts vs. Reinstatement Score
Pearson r	
r	-0.09976
95% confidence interval	-0.4441 to 0.2702
R squared	0.009952
P value	
P (two-tailed)	0.5999
P value summary	ns
Significant? (alpha = 0.05	No
Number of XY Pairs	30

Experiment 3

Correlation between NeuN and c-Fos expressions, and behavioural performances using Irradiated Specialty Feed Chow



Experiment 4 (Irradiated Specialty Feed)

Instrumental Training, 15 sessions

Input

Average of RATE PRESS	Column														
Row Labels	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
LPS	0.395652	1.293913	2.165217	2.924348	3.653043	4.092174	4.865217	6.2195652	6.622174	6.7778261	7.466522	7.6986957	8.665217	8.1543478	9.3778261
14	0.61	1.52	2.7	2.87	4.04	3.38	4.66	5.28	6.13	6	7.09	5.59	7.43	6.84	5.68
16	0.13	1.07	2.02	3.66	4.9	4.24	6.95	9.31	8.48	11.92	10.95	6.04	7.6	8.19	6.65
21	0.54	1.95	3.96	2.99	2.61	4.88	5.25	6.2	8.92	8.37	9.99	7.28	5.87	8.78	7.93
31	1.29	2.98	4.07	4.98	6.3	7.64	6.99	8.35	10.16	9.43	9.64	9.06	10.1	13.55	12.39
32	0.85	3.43	3.12	3.81	7.1	6.52	9.49	11.87	14.66	11.93	11.74	10.88	12.83	16.18	18.09
34	0.03	0.07	0.22	1.29	2.21	2.81	4.17	5.98	5.59	4.3	5.45	4.38	3.6	4.76	8.46
35	0.12	1.01	2.95	4.37	3.67	3.41	4.44	6.99	8.85	7.85	9.26	7.31	9.19	7.37	10.8
36	0.12	1.9	3.52	4.27	4.79	5.57	4.54	9.51	14.61	16.93	14.21	11.16	15.98	20.67	26.71
44	0.02	0.07	0.69	1.3	1.75	1.75	1.32	1.67	2.91	2.66	2.98	3.98	7.11	4.53	6.6
46	0.15	0.5	0.77	2.13	3.26	4.12	6.2	6.92	6.74	5.27	5.56	5.74	7.73	7.19	4.44
47	0.56	1.69	2.48	2.99	4.99	5.52	6.55	7.38	6.51	5.26	6.68	9.51	8.04	6.81	6.32
49	0.79	1.75	2.04	4.12	2.91	0.89	4.18	5.37	4.53	5.5	7.47	17.65	13.39	14.68	14.28
50	0.84	1.6	4.36	4.59	6.4	8.35	6.69	9.6	6.8	7.76	6.95	5.83	6.66	4.92	5.87
51	0.23	0.87	2.8	5.01	3.71	5.8	4.25	6.68	5.03	6.05	5.99	5.77	5.16	6.48	6.78
52	0.02	0.07	0.13	0.13	0.75	2.92	5.13	4.83	5.16	5.46	7.03	7.52	10.01	6.06	6.91
53	0.47	2	2.92	4.49	4.33	2.43	2.72	4.72	5.57	4	5.61	6.78	8.14	7.73	5.36
60	0.66	1.41	1.57	3.59	4.74	5.13	6.8	6.5	6.67	8.36	7.3	7.45	8.13	5.72	7.1
61	0.1	1.56	2.09	2.19	4.86	1.89	4.4	5.13	6.79	5.34	9.5	8.17	8.5	7.07	10.12
62	0.05	0.18	0.15	0.08	0.02	0.05	0.03	0.03	0.03	0.43	1.87	3.3	9.25	7.52	12.54
63	0.3	0.37	0.13	0.12	0.05	0.82	2.53	4.23	1.13	4.22	7.32	7.58	7.62	5.48	8.57
67	0.43	1.48	3.07	2.94	3.16	5.45	4.52	4.95	5.85	6.59	5.96	11.74	13.31	8.68	12.01
69	0.05	0.25	0.75	1.46	1.58	2.34	2.5	3.57	4	3.64	4.07	5.93	6.84	2.97	5.86
70	0.74	2.03	3.29	3.88	5.89	8.21	7.59	7.98	7.19	8.62	9.11	8.42	6.81	5.37	6.22
SAL	0.423889	1.0877778	1.601667	2.348889	2.667222	3.395556	3.967222	4.8616667	5.337222	6.1272222	6.625	6.4222222	6.684444	6.125	6.8127778
12	0.25	1.66	1.37	1.77	1.86	4.24	4.04	3.63	2.4	5.28	4.44	3.41	3.46	3.39	3.24
17	0.05	0.03	0.51	0.78	1.79	3.56	4.18	3.57	5.04	4.94	6.07	3.67	2.47	2.22	5.98
19	0.8	0.8	2.6	3.8	1.51	2.59	3.51	3.39	3.72	4.43	5.85	3.13	5.87	6.4	5.46
25	1.53	2.5	3.69	4.42	6.22	7.93	6.84	12.12	15.94	13.48	12.81	12.62	7.67	8.72	8.43
26	0.07	0.02	0.81	2.59	1.83	3.08	5.57	5.07	6.22	6.13	7.57	4.36	5.53	3.4	3.35
28	0.57	2.05	2.09	3.09	3.39	3.56	5.23	8.75	6.78	6.6	8.26	6.07	5.66	6.7	7.8
40	0.7	0.82	2.15	3.33	2.2	1.44	3.73	4.64	3.55	7.72	6.94	8.03	6.69	6	4.9
41	0.02	0.05	0.1	0.05	0.03	0.2	2.48	3.69	3.51	3.69	4.64	4.54	5.49	5.85	6.88
42	1.15	3	3	3.6	3.94	4.72	3.9	5.75	7	6.45	6.82	7.09	7.55	5.27	7.03
48	0.12	1.61	2.19	4.44	4.16	6.63	4.37	4.37	4.21	6.3	6.93	8.68	6.67	6.12	5.47
55	0.3	0.32	0.17	0.05	0.12	0.07	0.07	0.5	6.35	6.63	7.48	6.68	6.65	6.52	5.63
56	0.54	0.89	3.02	2.25	4.54	5.66	8.5	8.69	8.05	9.35	8.8	8.1	8.51	9.77	8.69
57	0.52	2.13	2.16	3.83	4.34	5.45	4.44	7.97	8.75	9.16	9.78	12.44	14.56	10.1	14.1
58	0.05	0.54	1.07	1.71	4.12	4.38	3.97	3.38	4.07	2.67	3.8	6.48	8.21	5.81	7.21
59	0.03	0.12	0.08	0.12	0.07	0.05	0.07	0.32	1.01	1.79	2.74	4.14	4.92	6	6.25
66	0.32	1.29	2.04	2.02	2.9	2.28	2.71	3.46	3.56	4.68	4.62	4.05	5.05	4.42	5.8
71	0.51	1.13	0.97	2.13	1.69	2.52	3.2	4.01	1.9	4.89	4.53	4.73	6.57	6.69	6.7
73	0.1	0.62	0.81	2.3	3.3	2.76	4.6	4.2	4.01	6.1	7.17	7.38	8.79	6.87	9.71
Grand Total	0.408049	1.2034146	1.917805	2.671707	3.220244	3.786341	4.470976	5.6234146	6.058049	6.4921951	7.097073	7.1382927	7.79561	7.2634146	8.2517073

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
session	Sphericity Assumed	3588.596	14	256.328	72.653	<.001
	Greenhouse-Geisser	3588.596	3.583	1001.619	72.653	<.001
	Huynh-Feldt	3588.596	4.091	877.176	72.653	<.001
	Lower-bound	3588.596	1.000	3588.596	72.653	<.001
session * group	Sphericity Assumed	70.810	14	5.058	1.434	.133
	Greenhouse-Geisser	70.810	3.583	19.764	1.434	.230
	Huynh-Feldt	70.810	4.091	17.308	1.434	.224
	Lower-bound	70.810	1.000	70.810	1.434	.238
Error(session)	Sphericity Assumed	1926.361	546	3.528		
	Greenhouse-Geisser	1926.361	139.729	13.786		
	Huynh-Feldt	1926.361	159.552	12.074		
	Lower-bound	1926.361	39.000	49.394		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	14126.003	1	14126.003	279.449	<.001
group	169.841	1	169.841	3.360	.074
Error	1971.430	39	50.549		

Action-outcome Pairings, 15 sessions

Input

Average of RNFS	Column														
Row Labels	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
LPS	17.04348	23.913043	25.69565	26.30435	26.73913	28	27.95652	27.869565	27.82609	28.913043	29	29.043478	29.17391	29.086957	29.086957
14	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
16	8	29	30	29	30	29	29	29	29	29	29	29	29	29	30
21	29	29	29	29	29	30	29	29	30	29	29	29	29	30	29
31	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
32	29	29	29	30	30	29	29	29	29	29	29	29	29	29	29
34	2	4	13	29	29	29	29	29	29	29	29	29	29	29	29
35	7	29	29	29	29	29	29	29	29	29	29	29	29	29	29
36	6	29	29	30	29	29	30	29	29	30	29	29	29	29	29
44	1	4	29	29	29	29	29	30	30	29	29	29	30	29	29
46	9	26	29	30	29	29	29	29	29	29	29	29	29	29	29
47	29	29	30	29	29	29	29	29	29	29	29	29	29	29	29
49	29	29	29	29	29	29	29	29	30	29	29	29	29	29	29
50	29	29	29	29	29	29	29	29	29	29	29	30	29	29	29
51	14	29	29	30	29	29	29	29	29	29	29	29	29	29	29
52	1	4	8	8	29	29	29	29	29	29	29	29	29	29	30
53	28	29	29	29	29	29	29	29	29	30	29	29	30	30	29
60	30	29	29	29	29	30	29	29	30	29	29	29	30	29	29
61	6	29	29	30	29	29	29	29	30	29	29	29	29	29	29
62	3	11	9	5	1	3	2	2	2	25	29	29	29	29	29
63	16	22	7	7	3	29	29	29	24	29	29	29	29	29	29
67	26	29	29	29	29	30	30	29	29	29	29	29	29	29	29
69	3	15	29	29	29	29	29	29	29	29	29	29	30	29	29
70	29	29	30	29	29	29	30	29	29	29	29	29	29	29	29
SAL	17.05556	22.666667	25.61111	25.11111	25	25.33333	26.44444	28.555556	29.16667	29.166667	29.11111	29.166667	29.22222	29.111111	29.166667
12	15	29	29	29	29	29	29	29	29	29	29	29	29	29	29
17	3	2	30	29	29	29	29	29	29	29	29	29	30	29	29
19	29	29	30	29	29	29	29	29	29	30	29	29	29	29	29
25	29	29	29	29	29	29	30	29	29	29	30	30	29	29	30
26	4	1	30	29	29	29	30	29	29	29	30	29	29	29	29
28	29	29	29	29	29	29	29	29	29	30	29	29	29	29	29
40	29	29	30	30	30	29	29	29	29	29	29	30	29	29	29
41	1	3	6	3	2	12	29	30	29	29	29	29	30	29	29
42	29	29	29	30	29	29	29	29	29	29	29	29	30	29	29
48	7	29	29	30	29	29	29	29	29	29	29	29	29	29	29
55	16	18	10	3	7	4	4	29	29	29	29	29	29	29	30
56	29	29	29	30	29	29	29	29	29	29	29	30	29	30	29
57	29	29	29	29	29	30	30	29	30	29	29	29	29	29	29
58	3	29	29	29	29	29	29	30	30	29	29	29	29	29	29
59	2	7	5	7	4	3	4	19	29	30	29	29	29	29	29
66	18	29	29	29	29	29	30	29	30	29	29	29	29	29	30
71	29	29	30	29	30	30	29	29	29	29	29	29	29	29	29
73	6	29	29	29	29	29	29	29	29	29	29	29	30	30	29
Grand Total	17.04878	23.365854	25.65854	25.78049	25.97561	26.82927	27.29268	28.170732	28.41463	29.02439	29.04878	29.097561	29.19512	29.097561	29.121951

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	5963.471	14	425.962	15.073	<.001
	Greenhouse-Geisser	5963.471	3.207	1859.645	15.073	<.001
	Huynh-Feldt	5963.471	3.617	1648.558	15.073	<.001
	Lower-bound	5963.471	1.000	5963.471	15.073	<.001
sessions * group	Sphericity Assumed	157.129	14	11.224	.397	.976
	Greenhouse-Geisser	157.129	3.207	48.999	.397	.768
	Huynh-Feldt	157.129	3.617	43.437	.397	.792
	Lower-bound	157.129	1.000	157.129	.397	.532
Error(sessions)	Sphericity Assumed	15430.321	546	28.261		
	Greenhouse-Geisser	15430.321	125.064	123.379		
	Huynh-Feldt	15430.321	141.078	109.374		
	Lower-bound	15430.321	39.000	395.649		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	436818.067	1	436818.067	2159.779	<.001
group	22.360	1	22.360	.111	.741
Error	7887.800	39	202.251		

Magazine Entries, 15 sessions

Input

Average of Mag	Column														
Row Labels	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
LPS	331.4348	188.78261	152.2174	173.0435	149.1304	148.9565	137.2609	194.17391	214.4783	211	197.0435	336.78261	337.5217	316	347.78261
14	389	218	134	165	124	176	127	191	179	203	154	477	464	305	474
16	426	275	134	217	158	165	165	160	254	196	201	330	266	374	360
21	489	176	82	168	133	106	130	143	216	125	128	238	234	249	246
31	254	111	70	162	123	109	86	111	126	145	217	192	208	465	278
32	380	93	86	152	165	121	99	205	276	299	277	543	320	419	450
34	175	167	284	177	197	193	139	189	235	221	230	487	461	261	414
35	451	287	105	126	107	135	169	257	225	165	207	282	304	267	297
36	420	190	91	167	170	141	137	180	180	255	199	447	390	356	404
44	170	163	296	188	166	150	215	208	189	174	174	251	290	244	366
46	297	198	282	181	144	142	155	191	234	218	169	423	280	334	342
47	259	121	86	159	141	137	146	354	183	110	180	321	296	244	236
49	316	182	182	178	210	241	139	187	240	234	224	169	312	197	243
50	308	119	74	176	138	118	89	158	143	199	145	361	519	407	423
51	535	341	103	150	116	123	186	236	290	215	266	445	348	358	331
52	331	197	328	295	286	81	144	231	292	260	257	355	325	255	366
53	371	135	117	155	128	243	188	263	257	359	336	369	420	352	306
60	349	148	75	146	118	117	100	147	145	130	135	287	321	322	275
61	232	181	144	143	136	209	127	246	244	186	158	262	348	309	321
62	233	214	183	123	61	50	82	53	148	336	141	81	94	195	453
63	335	83	73	171	102	185	87	108	122	177	164	293	443	254	268
67	501	225	105	174	165	184	145	271	244	191	202	456	383	396	453
69	138	423	396	254	221	176	190	237	306	249	180	291	317	358	385
70	264	95	71	153	121	124	112	140	205	206	188	386	420	347	308
SAL	287.8889	167.5	155.8333	165	156.9444	179.4444	138.7222	226.44444	218.5	195.77778	211.5556	339.88889	343.1111	321.83333	333.66667
12	517	137	136	193	200	124	129	259	253	182	256	395	397	407	330
17	262	143	258	273	173	127	133	155	205	192	212	325	286	488	281
19	303	258	82	168	258	175	151	239	199	205	225	335	201	265	304
25	217	112	58	93	118	155	106	215	239	190	144	398	327	280	439
26	338	227	258	78	176	149	93	201	203	219	249	351	349	373	352
28	306	90	85	110	123	121	96	177	157	151	164	264	280	293	281
40	393	249	119	149	182	230	182	193	175	169	171	202	520	359	310
41	139	268	332	313	125	403	122	127	252	126	263	284	347	307	409
42	259	83	87	147	123	121	144	230	150	249	136	512	325	339	378
48	240	181	97	158	156	145	100	157	259	224	219	357	384	287	281
55	241	63	243	28	156	348	161	400	126	102	179	319	322	225	294
56	439	131	98	206	116	123	113	177	155	140	273	376	374	269	403
57	436	157	138	162	204	135	150	216	278	292	218	391	416	319	354
58	39	249	178	222	145	112	183	277	228	268	239	280	327	269	187
59	213	113	146	157	109	216	141	336	267	152	154	121	217	286	336
66	249	183	86	170	149	243	184	309	228	274	246	358	361	408	365
71	445	203	261	193	200	136	175	205	286	162	194	530	343	246	268
73	146	168	143	150	112	167	134	203	273	227	266	320	400	373	434
Grand Total	312.3171	179.43902	153.8049	169.5122	152.561	162.3415	137.9024	208.34146	216.2439	204.31707	203.4146	338.14634	339.9756	318.56098	341.58537

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	3362379.793	14	240169.985	51.272	<.001
	Greenhouse-Geisser	3362379.793	6.832	492170.577	51.272	<.001
	Huynh-Feldt	3362379.793	8.645	388930.061	51.272	<.001
	Lower-bound	3362379.793	1.000	3362379.793	51.272	<.001
sessions * group	Sphericity Assumed	52415.546	14	3743.968	.799	.670
	Greenhouse-Geisser	52415.546	6.832	7672.360	.799	.586
	Huynh-Feldt	52415.546	8.645	6062.962	.799	.613
	Lower-bound	52415.546	1.000	52415.546	.799	.377
Error(sessions)	Sphericity Assumed	2557590.383	546	4684.231		
	Greenhouse-Geisser	2557590.383	266.438	9599.205		
	Huynh-Feldt	2557590.383	337.163	7585.621		
	Lower-bound	2557590.383	39.000	65579.241		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	31843015.142	1	31843015.142	2452.598	<.001
group	28.463	1	28.463	.002	.963
Error	506351.950	39	12983.383		

Breakpoint, 3 sessions

Input

Row Labels	Average of DAY 1	Average of DAY 2	Average of DAY 3
LPS	**67.60869565**	**50**	**44.56521739**
14	65	45	40
16	45	45	55
21	65	50	30
31	80	40	25
32	105	50	55
34	65	55	25
35	50	35	30
36	110	75	45
44	50	60	70
46	80	65	65
47	50	25	50
49	75	45	40
50	55	50	65
51	70	55	50
52	65	55	65
53	40	25	30
60	60	50	25
61	70	40	30
62	75	50	50
63	70	65	35
67	85	60	55
69	60	60	50
70	65	50	40
SAL	**50.27777778**	**37.5**	**32.22222222**
12	35	35	10
17	5	15	5
19	50	30	20
25	40	45	40
26	40	25	30
28	70	30	25
40	30	35	35
41	40	35	45
42	50	30	30
48	30	35	50
55	80	45	30
56	45	40	45
57	90	70	45
58	55	35	10
59	60	45	40
66	65	45	35
71	60	40	35
73	60	40	50
Grand Total	**60**	**44.51219512**	**39.14634146**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	9179.448	2	4589.724	32.776	<.001
	Greenhouse-Geisser	9179.448	1.473	6230.204	32.776	<.001
	Huynh-Feldt	9179.448	1.556	5897.662	32.776	<.001
	Lower-bound	9179.448	1.000	9179.448	32.776	<.001
sessions * group	Sphericity Assumed	162.375	2	81.187	.580	.562
	Greenhouse-Geisser	162.375	1.473	110.206	.580	.513
	Huynh-Feldt	162.375	1.556	104.323	.580	.522
	Lower-bound	162.375	1.000	162.375	.580	.451
Error(sessions)	Sphericity Assumed	10922.585	78	140.033		
	Greenhouse-Geisser	10922.585	57.462	190.084		
	Huynh-Feldt	10922.585	60.702	179.939		
	Lower-bound	10922.585	39.000	280.066		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	267996.394	1	267996.394	678.086	<.001
group	5986.638	1	5986.638	15.147	<.001
Error	15413.768	39	395.225		

Percentage baseline responding, 3 sessions

Input

Row Labels	Average of DAY 1 PR	Average of DAY 2 PR	Average of DAY 3 PR
LPS	**56.08088943**	**35.39786985**	**30.50534526**
14	67.60636909	35.63038371	28.19107283
16	30.19662921	28.08988764	45.17790262
21	53.91828533	33.48961822	15.0703282
31	49.44567627	15.96452328	7.243163341
32	72.26629872	17.87972864	20.81177418
34	76.10062893	59.59119497	15.72327044
35	31.05470628	15.28699164	12.11421979
36	58.10520666	29.29862229	11.98783324
44	48.30483048	66.00660066	80.2580258
46	91.76626826	65.60424967	63.6122178
47	33.57235984	9.995654063	32.59452412
49	36.44444444	14	10.94444444
50	51.26002291	43.52806415	69.1580756
51	80.33622709	51.94984153	42.57957834
52	56.72131148	38.68852459	54.75409836
53	26.18112579	11.66250149	13.8045936
60	47.88732394	37.08920188	9.624413146
61	57.59007679	19.59047057	12.89623942
62	66.95287744	31.78983952	32.70980272
63	66.43874644	58.91737892	19.71509972
67	60.99693922	31.91954526	28.27576155
69	68.67283951	61.2654321	47.5308642
70	58.04126274	36.91275168	26.84563758
SAL	**43.99028888**	**25.07246981**	**20.65851068**
12	41.2345679	37.77777778	5.925925926
17	2.092050209	8.833100883	3.021850302
19	45.38191115	20.45381911	11.82486417
25	16.73789174	22.88105413	17.27207977
26	42.66826923	17.82852564	25.44070513
28	70.02160376	16.26636167	12.96225696
40	17.17408275	20.68696331	22.898777
41	32.22026948	24.75102519	38.66432337
42	39.71789161	15.7139322	15.4664687
48	17.07498144	19.30215293	40.33655036
55	94.58398744	31.78963893	16.61433804
56	24.04714381	19.57988784	23.85704781
57	59.5703125	36.26302083	17.05729167
58	40.8997955	21.29195236	3.127631421
59	64.75832942	41.29516659	33.00484905
66	80.22774327	46.75638371	29.33057281
71	57.9181855	27.13649251	22.68124747
73	45.49618321	22.69720102	32.36641221
Grand Total	**50.7728209**	**30.86476739**	**26.18234471**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	13620.813	2	6810.406	35.363	<.001
	Greenhouse-Geisser	13620.813	1.459	9336.414	35.363	<.001
	Huynh-Feldt	13620.813	1.540	8844.494	35.363	<.001
	Lower-bound	13620.813	1.000	13620.813	35.363	<.001
sessions * group	Sphericity Assumed	28.204	2	14.102	.073	.929
	Greenhouse-Geisser	28.204	1.459	19.332	.073	.874
	Huynh-Feldt	28.204	1.540	18.314	.073	.885
	Lower-bound	28.204	1.000	28.204	.073	.788
Error(sessions)	Sphericity Assumed	15021.825	78	192.588		
	Greenhouse-Geisser	15021.825	56.897	264.019		
	Huynh-Feldt	15021.825	60.061	250.108		
	Lower-bound	15021.825	39.000	385.175		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	150854.752	1	150854.752	268.832	<.001
group	3503.485	1	3503.485	6.243	.017
Error	21884.827	39	561.149		

Sucrose consumed, 3 sessions

Input

Average of Sucrose	Column Labels		
Row Labels	1	2	3
LiCl	**18.75**	**8.95**	**5.2**
LPS	**18.3**	**8.4**	**5.2**
21	13	5	4
32	23	13	7
35	18	6	4
46	18	7	4
47	14	6	4
52	16	7	5
53	14	5	3
61	24	14	7
63	23	14	9
70	20	7	5
SAL	**19.2**	**9.5**	**5.2**
17	14	7	5
28	18	15	7
40	16	7	4
42	21	6	3
48	16	6	4
56	16	6	2
57	25	12	8
58	23	14	9
59	22	13	6
73	21	9	4
SAL	**18.57142857**	**18.3333**	**18.2857**
LPS	**18**	**18.2308**	**18.6154**
14	14	16	17
16	13	16	17
31	22	25	26
34	22	25	23
36	19	19	27
44	13	16	14
49	19	17	18
50	19	19	20
51	15	18	16
60	20	12	14
62	19	16	15
67	20	22	18
69	19	16	17
SAL	**19.5**	**18.5**	**17.75**
12	15	14	11
19	16	11	13
25	34	26	22
26	22	22	21
41	15	20	19
55	16	15	16
66	24	21	22
71	14	19	18
Grand Total	**18.65853659**	**13.7561**	**11.9024**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
session	Sphericity Assumed	1056.557	2	528.278	106.707	<.001
	Greenhouse-Geisser	1056.557	1.646	641.874	106.707	<.001
	Huynh-Feldt	1056.557	1.852	570.385	106.707	<.001
	Lower-bound	1056.557	1.000	1056.557	106.707	<.001
session * treatment	Sphericity Assumed	13.866	2	6.933	1.400	.253
	Greenhouse-Geisser	13.866	1.646	8.424	1.400	.253
	Huynh-Feldt	13.866	1.852	7.485	1.400	.253
	Lower-bound	13.866	1.000	13.866	1.400	.244
session * devaluation	Sphericity Assumed	895.446	2	447.723	90.436	<.001
	Greenhouse-Geisser	895.446	1.646	543.997	90.436	<.001
	Huynh-Feldt	895.446	1.852	483.410	90.436	<.001
	Lower-bound	895.446	1.000	895.446	90.436	<.001
session * treatment * devaluation	Sphericity Assumed	3.480	2	1.740	.351	.705
	Greenhouse-Geisser	3.480	1.646	2.114	.351	.663
	Huynh-Feldt	3.480	1.852	1.878	.351	.689
	Lower-bound	3.480	1.000	3.480	.351	.557
Error(session)	Sphericity Assumed	366.354	74	4.951		
	Greenhouse-Geisser	366.354	60.904	6.015		
	Huynh-Feldt	366.354	68.537	5.345		
	Lower-bound	366.354	37.000	9.901		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	25805.604	1	25805.604	706.046	<.001
treatment	6.993	1	6.993	.191	.664
devaluation	1664.245	1	1664.245	45.534	<.001
treatment * devaluation	.997	1	.997	.027	.870
Error	1352.331	37	36.549		

Outcome Devaluation (Habit Test)

Input

Row Labels	Average of RATE PRESS
LPS	**6.109782609**
LiCl	**3.259**
21	4.485
32	5.48
35	2.595
46	2.29
47	4.385
52	4.19
53	2.49
61	1.79
63	1.395
70	3.49
Sal	**8.302692308**
14	8.97
16	8.175
31	13.055
34	9.37
36	15.745
44	3.89
49	9.165
50	9.865
51	5.68
60	5.085
62	3.59
67	8.77
69	6.575
SAL	**4.856111111**
LiCl	**4.1865**
17	2.09
28	9.265
40	1.795
42	3.19
48	5.485
56	6.98
57	7.775
58	0.9
59	1.895
73	2.49
Sal	**5.693125**
12	3.49
19	4.29
25	8.37
26	8.075
41	3.985
55	4.78
66	6.275
71	6.28
Grand Total	**5.559390244**

Output

Number of Groups: 4
Number of Measurements: 1

Number of subjects in...
Group 1: 10
Group 2: 8
Group 3: 10
Group 4: 13

Between contrast coefficients

Contrast	Group... 1	2	3	4	
B1	1	1	-1	-1	Sham vs. LPS
B2	1	-1	1	-1	Deval.
B3	1	-1	-1	1	Int, LPS x D
B4	1	-1	0	0	Sham Dev
B5	0	0	1	-1	LPS Dev

Analysis of Variance Summary Table

Source		SS	df	MS	F	
Between						
Sham vs. LPS	B1	7.040	1	7.040	0.989	* No main effect of Sham vs. LPS, F < 1.
Deval.	B2	106.753	1	106.753	14.996	* Main effect of deval, p = .00
Int, LPS x D	B3	31.127	1	31.127	4.373	* Interaction, p = .043
Sham Dev	B4	10.089	1	10.089	1.417	* No deval effect for Shams, p = .241
LPS Dev	B5	143.785	1	143.785	20.198	* Deval effect for group LPS, p = .00
Error		263.394	37	7.119		

Experiment 4

Number of Astrocytes

Row Labels	Average
LPS	**1017.2**
14	1062.5
16	1080
21	957.5
31	1268.5
32	969
34	1134.5
35	883
36	972
44	960.5
46	895
47	1029.5
49	1088
50	1015.5
51	1073
52	928
53	996
60	1048.5
61	901
62	1031.5
63	1029.5
67	1034
69	975
70	1063.5
SAL	**875.944**
12	848
17	776.5
19	978.5
25	1024
26	924
28	800.5
40	870.5
41	856
42	850
48	766.5
55	850.5
56	865
57	892.5
58	864.5
59	871.5
66	1071.5
71	810.5
73	846.5
Grand Total	**955.183**

Unpaired t test
Tabular results

1	Table Analyzed	GFAP Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=5.380, df=39
13		
14	**How big is the difference?**	
15	Mean of column A	875.9
16	Mean of column B	1017
17	Difference between means (B - A) ± SEM	141.3 ± 26.26
18	95% confidence interval	88.14 to 194.4
19	R squared (eta squared)	0.4260
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.156, 22, 17
23	P value	0.7698
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 4

Number of Microglia

Row Labels	Average
LPS	**685.587**
14	739
16	814
21	693.5
31	722
32	749
34	682
35	652
36	707
44	590
46	685.5
47	648
49	670.5
50	633
51	697
52	637
53	703
60	571
61	665
62	718.5
63	649.5
67	707
69	699.5
70	735.5
SAL	**485.833**
12	385
17	395
19	423.5
25	424.5
26	420
28	574
40	581
41	473
42	452
48	437.5
55	631
56	522.5
57	498.5
58	478.5
59	477
66	518
71	595
73	459
Grand Total	**597.89**

Unpaired t test
Tabular results

1	Table Analyzed	IBA1 Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=10.27, df=39
13		
14	**How big is the difference?**	
15	Mean of column A	485.8
16	Mean of column B	685.6
17	Difference between means (B - A) ± SEM	199.8 ± 19.45
18	95% confidence interval	160.4 to 239.1
19	R squared (eta squared)	0.7300
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.828, 17, 22
23	P value	0.1833
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

Experiment 4

c-Fos-NeuN Intensity

Row Labels	Average
LPS	22.0631
14	24.944
16	23.768
21	18.712
31	27.041
32	20.134
34	23.393
35	13.847
36	25.769
44	17.673
46	18.741
47	22.619
49	23.054
50	25.091
51	26.58
52	23.947
53	19.031
60	24.834
61	19.675
62	24.718
63	17.897
67	23.24
69	15.955
70	26.788
SAL	15.0748
12	18.604
17	14.456
19	20.192
25	22.073
26	14.612
28	11.465
40	12.699
41	18.468
42	14.02
48	13.863
55	14.696
56	14.923
57	15.938
58	10.481
59	13.505
66	15.798
71	11.915
73	13.639
Grand Total	18.9951

Unpaired t test
Tabular results

1	Table Analyzed	cfos-NeuN Intensity
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	<0.0001
9	P value summary	****
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=6.433, df=39
13		
14	**How big is the difference?**	
15	Mean of column A	15.07
16	Mean of column B	22.06
17	Difference between means (B - A) ± SEM	6.988 ± 1.086
18	95% confidence interval	4.791 to 9.185
19	R squared (eta squared)	0.5148
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.499, 22, 17
23	P value	0.3977
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

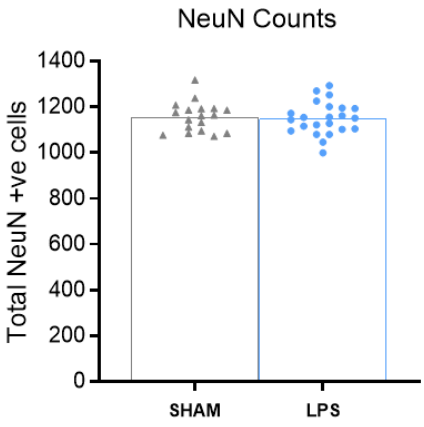
Experiment 4

Number of Neurons

Row Labels	Average
LPS	1149.7
14	1293.5
16	1143.5
21	999.5
31	1161.5
32	1156
34	1151.5
35	1080
36	1128
44	1171.5
46	1252
47	1193
49	1155
50	1225
51	1104.5
52	1270
53	1102.5
60	1116.5
61	1195.5
62	1079.5
63	1122
67	1046.5
69	1201.5
70	1094.5
SAL	1156.9
12	1318
17	1072
19	1095
25	1084.5
26	1144
28	1113
40	1238.5
41	1165.5
42	1085
48	1161
55	1175.5
56	1192.5
57	1185.5
58	1076.5
59	1191.5
66	1132
71	1185.5
73	1208
Grand Total	1152.8

Unpaired t test
Tabular results

1	Table Analyzed	NeuN Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	0.7405
9	P value summary	ns
10	Significantly different (P < 0.05)?	No
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=0.3336, df=39
13		
14	**How big is the difference?**	
15	Mean of column A	1157
16	Mean of column B	1150
17	Difference between means (B - A) ± SEM	-7.165 ± 21.48
18	95% confidence interval	-50.61 to 36.28
19	R squared (eta squared)	0.002845
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.222, 22, 17
23	P value	0.6806
24	P value summary	ns
25	Significantly different (P < 0.05)?	No

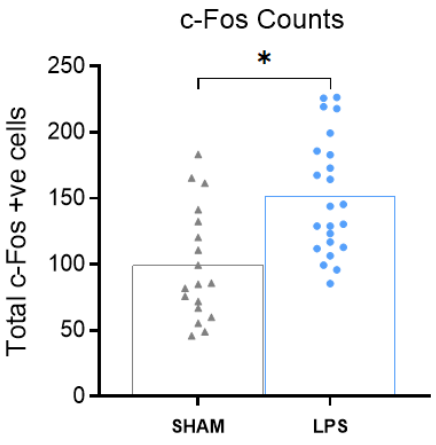


Experiment 4

Number of c-Fos

Row Labels	Average
LPS	151.935
14	173
16	186
21	129
31	226
32	129
34	183
35	96
36	219.5
44	145.5
46	130.5
47	167.5
49	117
50	199.5
51	164.5
52	226.5
53	99.5
60	123.5
61	85.5
62	112
63	106.5
67	218
69	144
70	113
SAL	99.6667
12	86
17	49
19	67
25	111
26	46
28	132.5
40	60
41	161.5
42	76
48	99.5
55	165.5
56	120.5
57	85
58	55.5
59	72
66	141.5
71	183.5
73	82
Grand Total	128.988

	Unpaired t test Tabular results	
1	Table Analyzed	cfos Cell Count
2		
3	Column B	LPS
4	vs.	vs.
5	Column A	SAL
6		
7	**Unpaired t test**	
8	P value	0.0005
9	P value summary	***
10	Significantly different (P < 0.05)?	Yes
11	One- or two-tailed P value?	Two-tailed
12	t, df	t=3.788, df=39
13		
14	**How big is the difference?**	
15	Mean of column A	99.67
16	Mean of column B	151.9
17	Difference between means (B - A) ± SEM	52.27 ± 13.80
18	95% confidence interval	24.36 to 80.18
19	R squared (eta squared)	0.2690
20		
21	**F test to compare variances**	
22	F, DFn, Dfd	1.117, 22, 17
23	P value	0.8264
24	P value summary	ns
25	Significantly different (P < 0.05)?	No



Experiment 4

GFAP correlated with Breakpoint and Habit Test

Rat	GFAP	AVERAGED BREAKPOINT
57	892.5000	68.33333333
58	864.5000	33.33333333
59	871.5000	48.33333333
66	1071.5000	48.33333333
60	1048.5000	45
61	901.0000	46.66666667
62	1031.5000	58.33333333
63	1029.5000	56.66666667
67	1034.0000	66.66666667
69	975.0000	56.66666667
70	1063.5000	51.66666667
71	810.5000	45
73	846.5000	50
40	870.5000	33.33333333
41	856.0000	40
42	850.0000	36.66666667
48	766.5000	38.33333333
44	960.5000	60
46	895.0000	70
47	1029.5000	41.66666667
52	928.0000	61.66666667
53	996.0000	31.66666667
49	1088.0000	53.33333333
50	1015.5000	56.66666667
51	1073.0000	58.33333333
55	850.5000	51.66666667
56	865.0000	43.33333333
25	1024.0000	41.66666667
26	924.0000	31.66666667
28	800.5000	41.66666667
31	1268.5000	48.33333333
32	969.0000	70
34	1134.5000	48.33333333
35	883.0000	38.33333333
36	972.0000	76.66666667
12	848.0000	26.66666667
14	1062.5000	50
16	1080.0000	48.33333333
17	776.5000	8.333333333
19	978.5000	33.33333333
21	957.5000	48.33333333

GFAP	HABIT TEST
892.50	0.4158
864.50	0.1765
871.50	0.2948
1071.50	0.5303
1048.50	0.5079
901.00	0.1784
1031.50	0.2489
1029.50	0.2462
1034.00	0.6376
975.00	0.4933
1063.50	0.3793
810.50	0.5804
846.50	0.2435
870.50	0.2961
856.00	0.5187
850.00	0.3041
766.50	0.3654
960.50	0.3396
895.00	0.2296
1029.50	0.4102
928.00	0.5061
996.00	0.3126
1088.00	0.4441
1015.50	0.5630
1073.00	0.4445
850.50	0.4501
865.00	0.4566
1024.00	0.5160
924.00	0.5341
800.50	0.5818
1268.50	0.6346
969.00	0.3765
1134.50	0.5541
883.00	0.3025
972.00	0.5725
848.00	0.4835
1062.50	0.6026
1080.00	0.5085
776.50	0.3824
978.50	0.4803
957.50	0.4057

	Correlation Tabular results	A GFAP Counts vs. Breakpoint
1	**Pearson r**	
2	r	0.3496
3	95% confidence interval	0.04701 to 0.5934
4	R squared	0.1222
5		
6	**P value**	
7	P (two-tailed)	0.0251
8	P value summary	*
9	Significant? (alpha = 0.05)	Yes
10		
11	**Number of XY Pairs**	41

	Correlation Tabular results	A GFAP Counts vs. Habit Test
1	**Pearson r**	
2	r	0.3566
3	95% confidence interval	0.05495 to 0.5986
4	R squared	0.1271
5		
6	**P value**	
7	P (two-tailed)	0.0221
8	P value summary	*
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	41

Experiment 4

IBA1 correlated with Breakpoint and Habit Test

Rat	IBA1	AVERAGED BREAKPOINT
57	498.5000	68.33333333
58	478.5000	33.33333333
59	477.0000	48.33333333
66	518.0000	48.33333333
60	571.0000	45
61	665.0000	46.66666667
62	718.5000	58.33333333
63	649.5000	56.66666667
67	707.0000	66.66666667
69	699.5000	56.66666667
70	735.5000	51.66666667
71	595.0000	45
73	459.0000	50
40	581.0000	33.33333333
41	473.0000	40
42	452.0000	36.66666667
48	437.5000	38.33333333
44	590.0000	60
46	685.5000	70
47	648.0000	41.66666667
52	637.0000	61.66666667
53	703.0000	31.66666667
49	670.5000	53.33333333
50	633.0000	56.66666667
51	697.0000	58.33333333
55	631.0000	51.66666667
56	522.5000	43.33333333
25	424.5000	41.66666667
26	420.0000	31.66666667
28	574.0000	41.66666667
31	722.0000	48.33333333
32	749.0000	70
34	682.0000	48.33333333
35	652.0000	38.33333333
36	707.0000	76.66666667
12	385.0000	26.66666667
14	739.0000	50
16	814.0000	48.33333333
17	395.0000	8.333333333
19	423.5000	33.33333333
21	693.5000	48.33333333

IBA1	HABIT TEST
498.50	0.4158
478.50	0.1765
477.00	0.2948
518.00	0.5303
571.00	0.5079
665.00	0.1784
718.50	0.2489
649.50	0.2462
707.00	0.6376
699.50	0.4933
735.50	0.3793
595.00	0.5804
459.00	0.2435
581.00	0.2961
473.00	0.5187
452.00	0.3041
437.50	0.3654
590.00	0.3396
685.50	0.2296
648.00	0.4102
637.00	0.5061
703.00	0.3126
670.50	0.4441
633.00	0.5630
697.00	0.4445
631.00	0.4501
522.50	0.4566
424.50	0.5160
420.00	0.5341
574.00	0.5818
722.00	0.6346
749.00	0.3765
682.00	0.5541
652.00	0.3025
707.00	0.5725
385.00	0.4835
739.00	0.6026
814.00	0.5085
395.00	0.3824
423.50	0.4803
693.50	0.4057

	Correlation Tabular results	A IBA1 Counts vs. Breakpoint
1	**Pearson r**	
2	r	0.5922
3	95% confidence interval	0.3480 to 0.7612
4	R squared	0.3507
5		
6	**P value**	
7	P (two-tailed)	<0.0001
8	P value summary	****
9	Significant? (alpha = 0.05)	Yes
10		
11	**Number of XY Pairs**	41

	Correlation Tabular results	A IBA1 Counts vs. Habit Test
1	**Pearson r**	
2	r	0.1061
3	95% confidence interval	-0.2083 to 0.4007
4	R squared	0.01126
5		
6	**P value**	
7	P (two-tailed)	0.5090
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	41

Experiment 4

c-Fos-NeuN colocalization correlated with Breakpoint and Habit Test

Rat	cfos-NeuN	AVERAGED BREAKPOINT
57	15.938	68.33333333
58	10.481	33.33333333
59	13.505	48.33333333
66	15.798	48.33333333
60	24.834	45
61	19.675	46.66666667
62	24.718	58.33333333
63	17.897	56.66666667
67	23.24	66.66666667
69	15.955	56.66666667
70	26.788	51.66666667
71	11.915	45
73	13.639	50
40	12.699	33.33333333
41	18.468	40
42	14.02	36.66666667
48	13.863	38.33333333
44	17.673	60
46	18.741	70
47	22.619	41.66666667
52	23.947	61.66666667
53	19.031	31.66666667
49	23.054	53.33333333
50	25.091	56.66666667
51	26.58	58.33333333
55	14.696	51.66666667
56	14.923	43.33333333
25	22.073	41.66666667
26	14.612	31.66666667
28	11.465	41.66666667
31	27.041	48.33333333
32	20.134	70
34	23.393	48.33333333
35	13.847	38.33333333
36	25.769	76.66666667
12	18.604	26.66666667
14	24.944	50
16	23.768	48.33333333
17	14.456	8.333333333
19	20.192	33.33333333
21	18.712	48.33333333

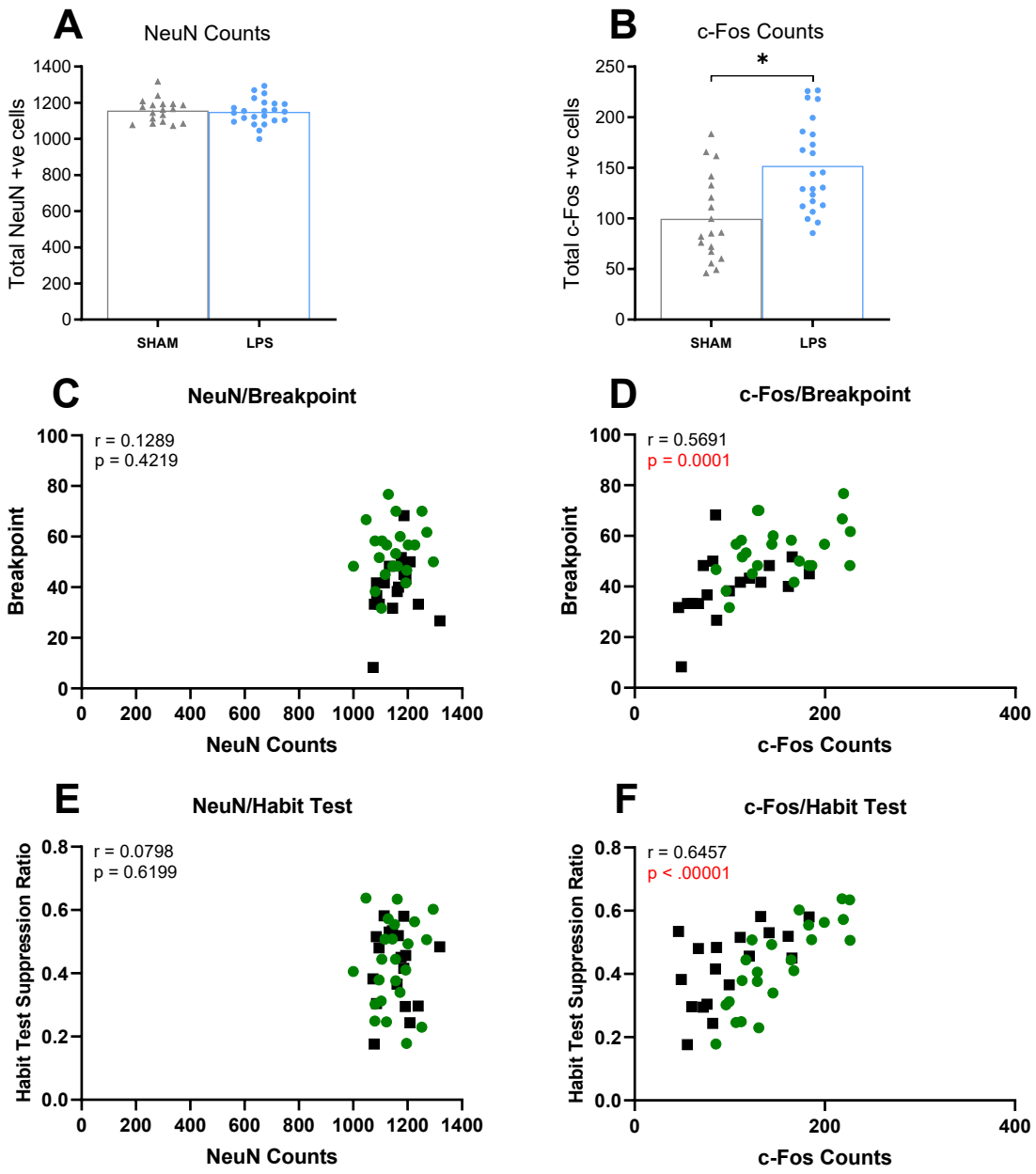
cfos-NeuN	HABIT TEST
15.938	0.4158
10.481	0.1765
13.505	0.2948
15.798	0.5303
24.834	0.5079
19.675	0.1784
24.718	0.2489
17.897	0.2462
23.24	0.6376
15.955	0.4933
26.788	0.3793
11.915	0.5804
13.639	0.2435
12.699	0.2961
18.468	0.5187
14.02	0.3041
13.863	0.3654
17.673	0.3396
18.741	0.2296
22.619	0.4102
23.947	0.5061
19.031	0.3126
23.054	0.4441
25.091	0.5630
26.58	0.4445
14.696	0.4501
14.923	0.4566
22.073	0.5160
14.612	0.5341
11.465	0.5818
27.041	0.6346
20.134	0.3765
23.393	0.5541
13.847	0.3025
25.769	0.5725
18.604	0.4835
24.944	0.6026
23.768	0.5085
14.456	0.3824
20.192	0.4803
18.712	0.4057

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Breakpoint
1	**Pearson r**	
2	r	0.4291
3	95% confidence interval	0.1399 to 0.6508
4	R squared	0.1841
5		
6	**P value**	
7	P (two-tailed)	0.0051
8	P value summary	**
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	41

	Correlation Tabular results	A c-fos-NeuN Intensity vs. Habit Test
1	**Pearson r**	
2	r	0.3761
3	95% confidence interval	0.07738 to 0.6128
4	R squared	0.1414
5		
6	**P value**	
7	P (two-tailed)	0.0154
8	P value summary	*
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	41

Experiment 4

Correlation between NeuN and c-Fos expressions, and behavioural performances



Experiment 4

NeuN correlated with Breakpoint and Habit Test

Rat	NeuN	AVERAGED BREAKPOINT
57	1185.50	68.33333333
58	1076.50	33.33333333
59	1191.50	48.33333333
66	1132.00	48.33333333
60	1116.50	45
61	1195.50	46.66666667
62	1079.50	58.33333333
63	1122.00	56.66666667
67	1046.50	66.66666667
69	1201.50	56.66666667
70	1094.50	51.66666667
71	1185.50	45
73	1208.00	50
40	1238.50	33.33333333
41	1165.50	40
42	1085.00	36.66666667
48	1161.00	38.33333333
44	1171.50	60
46	1252.00	70
47	1193.00	41.66666667
52	1270.00	61.66666667
53	1102.50	31.66666667
49	1155.00	53.33333333
50	1225.00	56.66666667
51	1104.50	58.33333333
55	1175.50	51.66666667
56	1192.50	43.33333333
25	1084.50	41.66666667
26	1144.00	31.66666667
28	1113.00	41.66666667
31	1161.50	48.33333333
32	1156.00	70
34	1151.50	48.33333333
35	1080.00	38.33333333
36	1128.00	76.66666667
12	1318.00	26.66666667
14	1293.50	50
16	1143.50	48.33333333
17	1072.00	8.333333333
19	1095.00	33.33333333
21	999.50	48.33333333

NeuN	HABIT TEST
1185.50	0.4158
1076.50	0.1765
1191.50	0.2948
1132.00	0.5303
1116.50	0.5079
1195.50	0.1784
1079.50	0.2489
1122.00	0.2462
1046.50	0.6376
1201.50	0.4933
1094.50	0.3793
1185.50	0.5804
1208.00	0.2435
1238.50	0.2961
1165.50	0.5187
1085.00	0.3041
1161.00	0.3654
1171.50	0.3396
1252.00	0.2296
1193.00	0.4102
1270.00	0.5061
1102.50	0.3126
1155.00	0.4441
1225.00	0.5630
1104.50	0.4445
1175.50	0.4501
1192.50	0.4566
1084.50	0.5160
1144.00	0.5341
1113.00	0.5818
1161.50	0.6346
1156.00	0.3765
1151.50	0.5541
1080.00	0.3025
1128.00	0.5725
1318.00	0.4835
1293.50	0.6026
1143.50	0.5085
1072.00	0.3824
1095.00	0.4803
999.50	0.4057

	Correlation Tabular results	A NeuN Counts vs. Breakpoint
1	**Pearson r**	
2	r	0.1289
3	95% confidence interval	-0.1862 to 0.4199
4	R squared	0.01661
5		
6	**P value**	
7	P (two-tailed)	0.4220
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	41

	Correlation Tabular results	A NeuN Counts vs. Habit Test
1	**Pearson r**	
2	r	0.07986
3	95% confidence interval	-0.2335 to 0.3782
4	R squared	0.006377
5		
6	**P value**	
7	P (two-tailed)	0.6197
8	P value summary	ns
9	Significant? (alpha = 0.05)	No
10		
11	**Number of XY Pairs**	41

Experiment 4

c-Fos correlated with Breakpoint and Habit Test

Rat	cfos	AVERAGED BREAKPOINT
57	85.00	68.33333333
58	55.50	33.33333333
59	72.00	48.33333333
66	141.50	48.33333333
60	123.50	45
61	85.50	46.66666667
62	112.00	58.33333333
63	106.50	56.66666667
67	218.00	66.66666667
69	144.00	56.66666667
70	113.00	51.66666667
71	183.50	45
73	82.00	50
40	60.00	33.33333333
41	161.50	40
42	76.00	36.66666667
48	99.50	38.33333333
44	145.50	60
46	130.50	70
47	167.50	41.66666667
52	226.50	61.66666667
53	99.50	31.66666667
49	117.00	53.33333333
50	199.50	56.66666667
51	164.50	58.33333333
55	165.50	51.66666667
56	120.50	43.33333333
25	111.00	41.66666667
26	46.00	31.66666667
28	132.50	41.66666667
31	226.00	48.33333333
32	129.00	70
34	183.00	48.33333333
35	96.00	38.33333333
36	219.50	76.66666667
12	86.00	26.66666667
14	173.00	50
16	186.00	48.33333333
17	49.00	8.333333333
19	67.00	33.33333333
21	129.00	48.33333333

cfos	HABIT TEST
85.00	0.4158
55.50	0.1765
72.00	0.2948
141.50	0.5303
123.50	0.5079
85.50	0.1784
112.00	0.2489
106.50	0.2462
218.00	0.6376
144.00	0.4933
113.00	0.3793
183.50	0.5804
82.00	0.2435
60.00	0.2961
161.50	0.5187
76.00	0.3041
99.50	0.3654
145.50	0.3396
130.50	0.2296
167.50	0.4102
226.50	0.5061
99.50	0.3126
117.00	0.4441
199.50	0.5630
164.50	0.4445
165.50	0.4501
120.50	0.4566
111.00	0.5160
46.00	0.5341
132.50	0.5818
226.00	0.6346
129.00	0.3765
183.00	0.5541
96.00	0.3025
219.50	0.5725
86.00	0.4835
173.00	0.6026
186.00	0.5085
49.00	0.3824
67.00	0.4803
129.00	0.4057

	Correlation Tabular results	A c-fos Counts vs. Breakpoint
1	**Pearson r**	
2	r	0.5691
3	95% confidence interval	0.3169 to 0.7461
4	R squared	0.3238
5		
6	**P value**	
7	P (two-tailed)	0.0001
8	P value summary	***
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	41

	Correlation Tabular results	A c-fos Counts vs. Habit Test
1	**Pearson r**	
2	r	0.6458
3	95% confidence interval	0.4219 to 0.7954
4	R squared	0.4170
5		
6	**P value**	
7	P (two-tailed)	<0.0001
8	P value summary	****
9	Significant? (alpha = 0.05	Yes
10		
11	**Number of XY Pairs**	41

Experiment 5 (Gordons Specialty Feed)

Pavlovian Conditioning, 8 sessions

Input

Average of PreCS average	Column Labels							
Row Labels	1	2	3	4	5	6	7	8
M4 GFAP	**3.283088235**	**5.051470588**	**5.801470588**	**4.988970588**	**4.893382353**	**4.900735294**	**3.841911765**	**4.783088235**
DCZ	**3.276041667**	**5.239583333**	**5.598958333**	**4.833333333**	**4.484375**	**4.489583333**	**4.1875**	**4.796875**
7	1.625	4.0625	3.5	2.375	3.0625	2.25	2.625	1.9375
13	2.625	5.375	6.5	3.1875	5.1875	3.25	3.75	3.875
18	3.8125	5.3125	3.125	3.5	4	5.625	3.9375	3.9375
20	4	4.75	7.0625	5.3125	3.875	6.6875	3.8125	6.5625
21	3.6875	7.25	5.1875	3.75	4.625	2.5625	3.625	5.375
25	3.875	5.3125	5.875	5.875	4.75	4.125	4	4.375
26	3.625	3.8125	4.75	5.5	3	5.25	6.875	8.125
27	3.4375	4	2.8125	2.75	4	3.9375	2.9375	1.9375
28	2.8125	6.5	6.8125	7.875	6.9375	5.375	4.25	6.625
34	2.1875	4.1875	6.0625	4.4375	5.375	6.9375	5.75	4.5
35	4.0625	6.75	6.8125	4.1875	3.6875	2.625	3.25	4.375
39	3.5625	5.5625	8.6875	9.25	5.3125	5.25	5.4375	5.9375
VEH	**3.3**	**4.6**	**6.2875**	**5.3625**	**5.875**	**5.8875**	**3.0125**	**4.75**
6	1.3125	2.375	6.5	4.125	2.5625	5.5	1.5	2.625
10	2.5625	5	3.8125	5.625	5.4375	6.75	4.25	4.625
17	3.375	3.6875	6.375	4.25	6.375	3.1875	2	3.3125
31	2.75	3.5	4.625	2.8125	5.625	5	3.625	6
40	6.5	8.4375	10.125	10	9.375	9	3.6875	7.1875
mcherry	**3.633928571**	**5.910714286**	**6.272321429**	**5.473214286**	**4.986607143**	**4.196428571**	**4.709821429**	**3.915178571**
DCZ	**3.647727273**	**5.829545455**	**6.414772727**	**5.255681818**	**4.8125**	**3.954545455**	**4.227272727**	**3.903409091**
1	2.625	3.9375	6.125	3.75	2.6875	1.875	3.1875	3.4375
2	3.25	4.25	5.9375	4.25	5.25	6.1875	6.3125	5.9375
5	4.875	3.3125	7.875	4.5625	5.1875	5.875	5	4.625
23	1.3125	4.375	6.1875	7.0625	4.3125	3.3125	1.1875	3.25
24	3.125	8.5625	7.375	6.4375	8.75	5.25	5.25	4.375
29	2.5	6	4.625	5.1875	2.625	2.375	5.1875	3.4375
30	2.875	2.5	5.6875	4.125	5.9375	3.125	4.8125	4.0625
36	7.1875	12.6875	14.5	10	7.75	4.3125	4.6875	4.5
38	4.9375	5.3125	4.4375	7.1875	5.125	4.8125	2.375	3.6875
41	3.5	6.25	2.8125	1	2.1875	2.9375	5.0625	3.1875
42	3.9375	6.9375	5	4.25	3.125	3.4375	3.4375	2.4375
VEH	**3.583333333**	**6.208333333**	**5.75**	**6.270833333**	**5.625**	**5.083333333**	**6.479166667**	**3.958333333**
9	2.9375	4.5	3.6875	4.3125	3.5625	4.125	4.625	6.0625
33	3.75	7.4375	8.1875	7.75	9.1875	7.125	8.1875	3.4375
37	4.0625	6.6875	5.375	6.75	4.125	4	6.625	2.375
Grand Total	**3.441532258**	**5.439516129**	**6.014112903**	**5.20766129**	**4.935483871**	**4.58266129**	**4.233870968**	**4.391129032**

Average of CS average	Column Labels							
Row Labels	1	2	3	4	5	6	7	8
M4 GFAP	**5.705882353**	**10.67279412**	**12.03676471**	**13.77573529**	**14.34191176**	**14.66176471**	**14.42647059**	**14.90808824**
DCZ	**5.765625**	**11.1875**	**12.16666667**	**13.67708333**	**13.74479167**	**14.52604167**	**14.08333333**	**14.86979167**
7	3.0625	8	10.5625	11.9375	14	12.375	12.5625	14
13	7.875	10.9375	10.3125	7.375	6.9375	11.375	7.5	12.1875
18	2.625	10.0625	8	10.5625	9.8125	23.5625	9.125	11.5625
20	6	10	9.3125	12.3125	12.6875	12.125	14.5625	13.25
21	6.0625	12.875	9.3125	8.8125	12	11.9375	12.3125	12.9375
25	9.125	11.6875	16.9375	18.6875	17.1875	17.25	15.0625	14.1875
26	6.75	11.5625	13.5	13.0625	14.3125	14.625	22.25	20.5
27	6	10.8125	11.0625	16.1875	14.25	14.125	12.5625	12
28	2.75	11.4375	16.0625	16.9375	14.375	16.125	14.625	16.5625
34	4.1875	8.375	8.875	14.1875	12.1875	12.875	16.625	17.1875
35	7.5625	16.5625	16	15.75	15.75	15.25	12.0625	15.4375
39	7.1875	11.9375	16.0625	18.3125	21.4375	12.6875	19.75	18.625
VEH	**5.5625**	**9.4375**	**11.725**	**14.0125**	**15.775**	**14.9875**	**15.25**	**15**
6	3.0625	7.0625	10	14.25	12.5625	12.9375	12.625	12.5
10	5.6875	8	8.3125	12	11.875	12.75	17	15.9375
17	6.3125	7.875	13.0625	15.8125	17.0625	17.6875	17.25	18.5
31	5.375	8	10.75	10.9375	16.125	12.4375	15.0625	14.875
40	7.375	16.25	16.5	17.0625	21.25	19.125	14.3125	13.1875
mcherry	**5.883928571**	**11.56696429**	**12.74553571**	**14.51785714**	**14.79464286**	**16.01339286**	**14.69642857**	**15.48214286**
DCZ	**5.897727273**	**11.42045455**	**12.98863636**	**14.70454545**	**15.22159091**	**15.9375**	**14.53977273**	**15.0625**
1	6.25	10.6875	12.8125	9.6875	8.9375	11.5625	9.6875	14.75
2	5.25	10.9375	13.9375	15.1875	19	20.9375	21.625	20.3125
5	3.875	7.125	12.5	13.25	12.5	20.5	22.5625	17.1875
23	4.125	7.125	12.4375	16.875	14.0625	16.625	12.4375	16.375
24	8	14.875	14.5625	18.0625	20.8125	19.875	16.4375	15
29	4.3125	8.1875	12.1875	11.875	14.625	12.0625	14.5625	11.375
30	4.8125	7.4375	11.5625	12.5	16.75	12.8125	10.125	11.5625
36	7.0625	18.25	27.0625	27.1875	26.375	21.625	18.125	16.75
38	8	11.1875	8.25	13.5625	13.0625	16.0625	9.25	14.3125
41	5.9375	11.9375	6.3125	7.8125	10.1875	12.4375	15.4375	16.625
42	7.25	17.875	11.25	15.75	11.125	10.8125	9.6875	11.4375
VEH	**5.833333333**	**12.10416667**	**11.85416667**	**13.83333333**	**13.22916667**	**16.29166667**	**15.27083333**	**17.02083333**
9	5.4375	8.0625	9.8125	12.6875	10.375	10.875	12.375	16.1875
33	6	13.4375	12.9375	14.0625	17.3125	21.8125	16.8125	14.0625
37	6.0625	14.8125	12.8125	14.75	12	16.1875	16.625	20.8125
Grand Total	**5.786290323**	**11.0766129**	**12.35685484**	**14.1108871**	**14.54637097**	**15.27217742**	**14.5483871**	**15.16733871**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CS	Sphericity Assumed	7815.644	1	7815.644	742.205	<.001
	Greenhouse-Geisser	7815.644	1.000	7815.644	742.205	<.001
	Huynh-Feldt	7815.644	1.000	7815.644	742.205	<.001
	Lower-bound	7815.644	1.000	7815.644	742.205	<.001
CS * group	Sphericity Assumed	10.375	2	5.187	.493	.616
	Greenhouse-Geisser	10.375	2.000	5.187	.493	.616
	Huynh-Feldt	10.375	2.000	5.187	.493	.616
	Lower-bound	10.375	2.000	5.187	.493	.616
Error(CS)	Sphericity Assumed	294.849	28	10.530		
	Greenhouse-Geisser	294.849	28.000	10.530		
	Huynh-Feldt	294.849	28.000	10.530		
	Lower-bound	294.849	28.000	10.530		
session	Sphericity Assumed	1363.858	7	194.837	27.685	<.001
	Greenhouse-Geisser	1363.858	4.086	333.801	27.685	<.001
	Huynh-Feldt	1363.858	5.213	261.633	27.685	<.001
	Lower-bound	1363.858	1.000	1363.858	27.685	<.001
session * group	Sphericity Assumed	35.172	14	2.512	.357	.985
	Greenhouse-Geisser	35.172	8.172	4.304	.357	.943
	Huynh-Feldt	35.172	10.426	3.374	.357	.966
	Lower-bound	35.172	2.000	17.586	.357	.703
Error(session)	Sphericity Assumed	1379.358	196	7.038		
	Greenhouse-Geisser	1379.358	114.404	12.057		
	Huynh-Feldt	1379.358	145.960	9.450		
	Lower-bound	1379.358	28.000	49.263		
CS * session	Sphericity Assumed	974.139	7	139.163	48.789	<.001
	Greenhouse-Geisser	974.139	4.780	203.795	48.789	<.001
	Huynh-Feldt	974.139	6.295	154.738	48.789	<.001
	Lower-bound	974.139	1.000	974.139	48.789	<.001
CS * session * group	Sphericity Assumed	24.189	14	1.728	.606	.859
	Greenhouse-Geisser	24.189	9.560	2.530	.606	.800
	Huynh-Feldt	24.189	12.591	1.921	.606	.843
	Lower-bound	24.189	2.000	12.095	.606	.553
Error(CS*session)	Sphericity Assumed	559.062	196	2.852		
	Greenhouse-Geisser	559.062	133.840	4.177		
	Huynh-Feldt	559.062	176.272	3.172		
	Lower-bound	559.062	28.000	19.966		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	37620.685	1	37620.685	740.813	<.001
group	21.427	2	10.713	.211	.811
Error	1421.923	28	50.783		

Experiment 5 (Gordons Specialty Feed)

Instrumental Training, 8 sessions

Input

Average of Averaged over levers	Column Labels							
Row Labels	1	2	3	4	5	6	7	8
M4 GFAP	**1.168190023**	**4.08886**	**5.37714**	**7.50326**	**10.4622**	**11.3367**	**12.0273**	**14.3248**
DCZ	**1.013200092**	**3.67378**	**5.02656**	**7.14112**	**9.28248**	**9.93612**	**10.4228**	**12.9206**
7	0.025	0.05005	1.432022	3.826051	9.056321	6.578704	10.95806	13.90886
13	1.063663814	4.876459	1.226126	1.87505	2.8752	3.203103	2.602528	3.5
18	1.3139722	4.447649	7.408384	13.02221	19.28478	17.09186	14.46895	15.05676
20	0.025	4.563005	4.778303	7.231208	9.17229	9.704267	13.16099	16.0206
21	1.448138161	5.993255	7.481915	10.503	10.15505	15.80231	19.96764	21.68116
25	0.5003003	1.864489	5.128253	5.729323	7.689276	9.253932	9.020502	10.17366
26	0.774482175	1.584074	6.704939	8.844543	9.63403	10.79465	11.69271	12.76588
27	4.289449975	10.14267	8.116747	13.54886	14.14253	11.80665	16.9806	30.53566
28	1.792768859	6.091627	6.178804	9.569121	13.38611	14.29358	7.706757	10.60355
34	0.550475475	2.130511	3.350676	2.251001	3.751602	4.502302	4.276426	3.001902
35	0.32515015	1.586774	4.552928	2.625576	4.148818	3.528203	3.152903	3.97505
39	0.05	0.754748	3.959599	6.667515	8.093798	12.67388	11.08575	13.76356
VEH	**1.540165858**	**5.08508**	**6.21852**	**8.37241**	**13.2935**	**14.6981**	**15.8781**	**17.695**
6	1.932303885	8.112195	6.509819	7.656642	16.05669	19.13057	16.85418	19.44401
10	1.560039133	6.714054	11.85909	17.63305	18.18692	20.05926	25.61976	23.82638
17	1.565500936	4.446754	3.302653	3.800025	11.7414	9.881957	9.808909	9.549061
31	0	0.07505	1.996145	2.10035	5.10493	6.58033	6.906406	9.417608
40	2.642985335	6.077336	7.4249	10.67198	15.37736	17.83856	20.20103	26.23787
mcherry	**1.122619269**	**3.63821**	**5.2681**	**7.00074**	**11.1598**	**12.0693**	**11.96**	**12.2513**
DCZ	**0.982054338**	**3.68486**	**4.85867**	**6.44415**	**10.2048**	**11.0397**	**11.436**	**11.3687**
1	2.239203276	6.135668	8.692925	9.996678	20.67253	12.23581	21.74824	22.15712
2	0.075	0.150025	0.17505	0.225025	1.406771	4.922072	3.739122	5.252452
5	0.075	2.657295	5.378103	4.883153	10.60267	10.28156	13.50951	14.06853
23	1.12800918	4.81686	4.657586	5.800876	8.873186	8.406832	6.571901	8.046796
24	1.739978319	6.617684	5.879654	10.87688	12.09518	13.19658	10.75586	12.46164
29	0	0.55993	3.215495	7.750262	12.14111	12.57468	15.39039	13.95278
30	0.375375375	1.125131	4.637476	5.318716	6.787587	8.256131	9.756882	12.19558
36	1.593804275	7.659834	5.24046	6.127728	11.62162	13.08141	8.156081	10.7367
38	2.875526593	5.688896	5.557069	7.735013	7.608627	11.21704	11.72024	9.150976
41	0.225225225	2.103947	3.176827	4.200651	7.461139	11.22752	12.68714	7.200325
42	0.475475475	3.018193	6.834685	7.970635	12.98199	16.03731	11.76009	9.832264
VEH	**1.638024017**	**3.46715**	**6.76935**	**9.04159**	**14.6615**	**15.8442**	**13.8814**	**15.4879**
9	0.050025025	0.35035	8.090047	14.73265	24.88361	31.37038	22.32984	18.43096
33	1.092208672	2.430365	3.626777	4.026426	4.551151	7.305831	7.905831	7.851251
37	3.771838355	7.620743	8.591235	8.365678	14.54976	8.856481	11.40847	20.18151
Grand Total	**1.147609683**	**3.88534**	**5.32789**	**7.27632**	**10.7772**	**11.6675**	**11.9969**	**13.3884**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
sessions	Sphericity Assumed	4385.335	7	626.476	67.262	<.001
	Greenhouse-Geisser	4385.335	2.832	1548.385	67.262	<.001
	Huynh-Feldt	4385.335	3.409	1286.382	67.262	<.001
	Lower-bound	4385.335	1.000	4385.335	67.262	<.001
sessions * group	Sphericity Assumed	167.011	14	11.929	1.281	.222
	Greenhouse-Geisser	167.011	5.664	29.484	1.281	.277
	Huynh-Feldt	167.011	6.818	24.495	1.281	.269
	Lower-bound	167.011	2.000	83.506	1.281	.294
Error(sessions)	Sphericity Assumed	1825.532	196	9.314		
	Greenhouse-Geisser	1825.532	79.302	23.020		
	Huynh-Feldt	1825.532	95.453	19.125		
	Lower-bound	1825.532	28.000	65.198		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	37620.685	1	37620.685	740.813	<.001
group	21.427	2	10.713	.211	.811
Error	1421.923	28	50.783		

Experiment 5 (Gordons Specialty Feed)

Pavlovian Instrumental Transfer

Input

Row Labels	Average of Pre	Average of Same	Average of Different
M4 GFAP	**2.455882353**	**2.073529412**	**1.294117647**
DCZ	**2.765625**	**1.71875**	**1.458333333**
7	2.5625	3.25	0.625
13	1.875	1.125	0.125
18	2.5	2.125	0.625
20	8.9375	0.75	5.875
21	0.3125	1.875	3.75
25	1.0625	0.625	0
26	0.9375	0	0.75
27	4.75	0.125	3.25
28	2.9375	4.5	0.75
34	0.4375	0.5	0.5
35	0.1875	2	0.375
39	6.6875	3.75	0.875
VEH	**1.7125**	**2.925**	**0.9**
6	0.4375	2.75	0
10	0.625	1.875	1.125
17	2.5625	6.25	1.625
31	2.6875	2	0.125
40	2.25	1.75	1.625
mcherry	**1.861607143**	**4.589285714**	**2.258928571**
DCZ	**1.755681818**	**4.113636364**	**2.204545455**
1	1.0625	4.25	0.625
2	2.5	6.125	2
5	2.5	2.375	0.375
23	1.5625	5	1.125
24	0.5625	1.5	4.625
29	3.25	2.125	2.25
30	2.1875	1.125	3.25
36	0.5	7.875	2.125
38	0.375	6.5	2
41	1.5	2.625	4.125
42	3.3125	5.75	1.75
VEH	**2.25**	**6.333333333**	**2.458333333**
9	0.125	5.875	0
33	6.5625	11.625	6.75
37	0.0625	1.5	0.625
Grand Total	**2.1875**	**3.209677419**	**1.72983871**

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group... 1	2	3	
B1	1	1	-2	M4+DCZ vs. R
B2	1	-1	0	Controls
B3	1	0	0	mCherry+DCZ
B4	0	1	0	M4+Veh
B5	0	0	1	M4+DCZ

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	8.718	1	8.718	1.157	* No between main effects, M4+DCZ vs. Rest is .291
B2	0.344	1	0.344	0.046	* F < 1 controls main effect
B3	239.020	1	239.020	31.724	* Dummy
B4	154.090	1	154.090	20.452	* Dummy
B5	141.263	1	141.263	18.749	* Dummy
Error	210.959	28	7.534		
Within					
W1	2.977	1	2.977	1.215	* No main effect of pre vs. Post, p = .28
B1W1	26.668	1	26.668	10.885	* Interaction with M4+DCZ x rest, p = .003.
B2W1	0.693	1	0.693	0.283	* No interaction with controls, F < 1
B3W1	14.443	1	14.443	5.896	* Simple effect mCherry, p = .022
B4W1	4.610	1	4.610	1.882	* No simple effect vehicle group, p = .181
B5W1	11.084	1	11.084	4.524	* Simple effect M4+DCZ, p = .042
Error	68.597	28	2.450		
W2	39.926	1	39.926	11.031	* Main effect of specific PIT (Same > Different), p = .003
B1W2	15.355	1	15.355	4.242	* Interaction with M4+DCZ vs. Rest, p = .049
B2W2	1.518	1	1.518	0.419	* No interaction with controls, F < 1
B3W2	20.045	1	20.045	5.538	* Simple effect mCherry+DCZ, p = .026
B4W2	29.566	1	29.566	8.168	* Simple effect vehicles, p = .008
B5W2	0.407	1	0.407	0.112	* No simple effect M4+DCZ, F < 1.
Error	101.348	28	3.620		

Experiment 5 (Gordons Specialty Feed)

Outcome Devaluation

Input

Row Labels	Average of Mag Entries	Average of Devalued	Average of Valued
M4 GFAP	**1.723529412**	**0.958823529**	**1.391176471**
DCZ	**1.529166667**	**0.9875**	**1.004166667**
7	1.25	0.75	2.05
13	0.65	0.1	0.5
18	0.95	0.15	1.7
20	5.9	2.65	1.8
21	0.85	0.4	0.6
25	0.75	0	0.35
26	1.55	3.2	0.75
27	1.5	1.3	0.95
28	0.65	0.45	1
34	1.55	0.1	0.15
35	0.8	0.3	0.95
39	1.95	2.45	1.25
VEH	**2.19**	**0.89**	**2.32**
6	4.9	0.25	0.2
10	1.25	0.55	3.95
17	1.95	1.25	2.1
31	1.1	1.75	2
40	1.75	0.65	3.35
mcherry	**1.485714286**	**0.7**	**1.482142857**
DCZ	**1.490909091**	**0.709090909**	**1.313636364**
1	2.75	1.35	1.3
2	1.15	0.3	0.45
5	0.85	0.75	1
23	1.85	1.2	2.9
24	1.8	0.5	0.85
29	0.4	0.2	0.2
30	1.2	0.25	1.3
36	3.55	1.8	4.05
38	1.65	1.05	0.7
41	0.45	0.15	1.25
42	0.75	0.25	0.45
VEH	**1.466666667**	**0.666666667**	**2.1**
9	0.25	0.15	0.25
33	3.15	1.5	2.9
37	1	0.35	3.15
Grand Total	**1.616129032**	**0.841935484**	**1.432258065**

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group... 1	2	3	
B1	1	1	-2	M4+DCZ vs. C
B2	1	-1	0	Controls
B3	1	0	0	
B4	0	1	0	
B5	0	0	1	

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3	
W1	1	0	0	Mag
W2	0	1	-1	Deval

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	1.249	1	1.249	0.630	* No main effect M4+DCZ vs rest, F < 1
B2	3.241	1	3.241	1.634	* No control main effect, p = .212
B3	45.267	1	45.267	22.822	* Dummy
B4	65.670	1	65.670	33.108	* Dummy
B5	49.585	1	49.585	24.998	* Dummy
Error	55.539	28	1.984		
Within					
W1	81.513	1	81.513	48.018	* Dummy
B1W1	0.225	1	0.225	0.132	* No difference in mag entries between any groups, all Fs < 1
B2W1	0.848	1	0.848	0.499	
B3W1	24.451	1	24.451	14.404	* Dummy
B4W1	29.453	1	29.453	17.350	* Dummy
B5W1	28.060	1	28.060	16.530	* Dummy
Error	47.531	28	1.698		
W2	7.039	1	7.039	11.907	* Main effect of Deval, p = .002
B1W2	3.650	1	3.650	6.175	* Deval x M4+DCZ vs. Rest interaction p = .019
B2W2	1.583	1	1.583	2.677	* No Deval x control interaction, p = .113
B3W2	2.010	1	2.010	3.400	* Almost simple effect for mCherry group, p = .076
B4W2	8.194	1	8.194	13.861	* Simple effect for veh group, p = .001
B5W2	0.002	1	0.002	0.003	* No simple effect for M4+DCZ, F < 1
Error	16.552	28	0.591		

Experiment 5 (Gordons Specialty Feed)

Outcome-selective reinstatement

Input

Row Labels	Average of Pre-Reinst	Average of Pre-NonReinst	Average of Reinst	Average of NonReinst	PRE
M4 GFAP	**3.764705882**	**2.058823529**	**58.94117647**	**3.529411765**	
DCZ	**2.666666667**	**1.75**	**52.5**	**2**	
7	3	1	44	0	2.00
13	1	0	22	2	0.50
18	1	0	27	5	0.50
20	0	0	71	0	0.00
21	7	3	52	2	5.00
25	4	3	33	2	3.50
26	4	0	43	0	2.00
27	0	0	84	8	0.00
28	1	0	40	3	0.50
34	8	3	47	1	5.50
35	3	11	74	1	7.00
39	0	0	93	0	0.00
VEH	**6.4**	**2.8**	**74.4**	**7.2**	
6	0	1	89	3	0.50
10	4	3	79	3	3.50
17	0	1	80	2	0.50
31	6	8	69	28	7.00
40	22	1	55	0	11.50
mcherry	**6**	**5.357142857**	**51.07142857**	**8.357142857**	
DCZ	**5.636363636**	**3.727272727**	**49.27272727**	**5.636363636**	
1	0	0	38	0	0.00
2	3	5	26	3	4.00
5	2	1	58	5	1.50
23	4	0	58	2	2.00
24	5	14	26	2	9.50
29	0	0	51	17	0.00
30	0	0	89	0	0.00
36	15	4	73	0	9.50
38	3	0	25	9	1.50
41	11	1	17	1	6.00
42	19	16	81	23	17.50
VEH	**7.333333333**	**11.33333333**	**57.66666667**	**18.33333333**	
9	0	0	43	1	0.00
33	12	31	50	13	21.50
37	10	3	80	41	6.50
Grand Total	**4.774193548**	**3.548387097**	**55.38709677**	**5.709677419**	

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group...		
	1	2	3
B1	1	1	-2
B2	1	-1	0
B3	1	0	0
B4	0	1	0
B5	0	0	1

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	623.376	1	623.376	2.773	* No between main effects, M4+DCZ vs. Rest
B2	1066.581	1	1066.581	4.745	* F < 1 controls main effect
B3	13020.614	1	13020.614	57.925	* Dummy
B4	19665.375	1	19665.375	87.485	* Dummy
B5	12863.340	1	12863.340	57.225	* Dummy
Error	6294.004	28	224.786		
Within					
W1	14685.346	1	14685.346	122.883	* Main effect of pre vs. Post
B1W1	44.640	1	44.640	0.374	* No interaction with M4+DCZ x rest
B2W1	347.085	1	347.085	2.904	* No interaction with controls, F < 1
B3W1	3803.045	1	3803.045	31.823	* Simple effect mCherry
B4W1	5940.750	1	5940.750	49.711	* Simple effect vehicle group
B5W1	5016.681	1	5016.681	41.978	* Simple effect M4+DCZ
Error	3346.191	28	119.507		
W2	38040.553	1	38040.553	147.026	* Main effect (Reinstated > Nonrreinstated)
B1W2	0.343	1	0.343	0.001	* No interaction with M4+DCZ vs. Rest
B2W2	398.240	1	398.240	1.539	* No interaction with controls, F < 1
B3W2	10472.727	1	10472.727	40.477	* Simple effect mCherry+DCZ
B4W2	12882.250	1	12882.250	49.790	* Simple effect vehicles
B5W2	15301.500	1	15301.500	59.140	* Simple effect M4+DCZ
Error	7244.523	28	258.733		

Experiment 5 (Irradiated Specialty Feed)

Pavlovian Conditioning, 4 sessions

Input

Row Labels	Average of PreCS average 1	2	3	4	Average of CS average 1	2	3	4
M4 GFAP	**5.3125**	**4.23529412**	**3.23529412**	**3.64338235**	**16.94485294**	**15.1764706**	**14.4264706**	**14.5441176**
DCZ	**5.682291667**	**4.20833333**	**3.21354167**	**3.5**	**16.00520833**	**14.5520833**	**13.59375**	**13.46875**
7	5.4375	5.875	2.0625	1.1875	12.5	14.375	12.0625	9.8125
13	3.625	4.1875	2.8125	2.9375	11.9375	11.875	14.375	13.625
18	6.5625	4.125	4.125	4.1875	13.875	12.0625	10.4375	12.1875
20	10.3125	6.5625	5.0625	7.6875	23.6875	17.125	15.3125	16.25
21	5.625	3.5	4	3	9.5	10.75	8.5625	8.3125
25	5.625	5.375	3.875	4.375	15.1875	13.75	10.25	9.5625
26	5.0625	3.625	1.625	3.125	19.6875	18.125	15.125	16.8125
27	3	1.375	1.0625	2.5	17.375	15.75	17.0625	13.9375
28	5.5	3.625	2.6875	2.4375	11.125	10.6875	8.75	8.9375
34	6.0625	3.8125	1.9375	1.375	18.1875	18.375	17.125	17.1875
35	6.25	3.8125	3.125	3.1875	20.1875	15.625	16.75	13.75
39	5.125	4.625	6.1875	6	18.8125	16.125	17.3125	21.25
VEH	**4.425**	**4.3**	**3.2875**	**3.9875**	**19.2**	**16.675**	**16.425**	**17.125**
6	4.25	4.5625	3.75	4.4375	27.625	18.75	21.75	27.0625
10	5.0625	3.25	2	5.0625	18.9375	14.125	11.1875	13.4375
17	2.1875	2.375	1.125	1.9375	14.3125	12.375	11.9375	11.9375
31	4.375	3.8125	3.8125	6.8125	16.9375	20	21.375	19.875
40	6.25	7.5	5.75	1.6875	18.1875	18.125	15.875	13.3125
mcherry	**5.147321429**	**4.26339286**	**3.41071429**	**3.46875**	**16.84821429**	**17.9821429**	**16.3973214**	**16.1294643**
DCZ	**5.727272727**	**4.61363636**	**3.80681818**	**3.75**	**17.125**	**18.7556818**	**16.4943182**	**16.3863636**
1	6	5.4375	4.125	4.4375	14.0625	18.3125	22.75	22.375
2	9.125	8.75	7.6875	4.6875	28.375	28.875	23.125	20.8125
5	4.125	2.4375	2.25	1.5	12.875	12.125	8.9375	7.125
23	9.6875	5.3125	5.3125	4.8125	20.5	23.8125	19.5	18.75
24	3.75	4	2.375	5.4375	14.75	20.125	20.0625	23.9375
29	6.0625	2.875	2.9375	3.625	14.9375	12.75	9.625	11.875
30	6.6875	8.6875	2.875	7.3125	17.1875	19.5625	15.625	15.3125
36	4.875	4.1875	6.9375	3.875	21.5625	27.25	26.875	31.25
38	4.5625	3.3125	3.75	0.6875	12.8125	12.5625	9.6875	6.375
41	3.5	3.8125	2.875	2.3125	20.25	20.1875	16.75	16.5
42	4.625	1.9375	0.75	2.5625	11.0625	10.75	8.5	5.9375
VEH	**3.020833333**	**2.97916667**	**1.95833333**	**2.4375**	**15.83333333**	**15.1458333**	**16.0416667**	**15.1875**
9	2.75	1.9375	0.75	1.6875	17.625	17.625	15.4375	15.6875
33	3.8125	3.5625	2.75	3.0625	16.4375	14.875	18	17.75
37	2.5	3.4375	2.375	2.5625	13.4375	12.9375	14.6875	12.125
Grand Total	**5.237903226**	**4.24798387**	**3.31451613**	**3.56451613**	**16.90120968**	**16.4435484**	**15.3165323**	**15.2600806**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CS	Sphericity Assumed	8746.239	1	8746.239	282.571	<.001
	Greenhouse-Geisser	8746.239	1.000	8746.239	282.571	<.001
	Huynh-Feldt	8746.239	1.000	8746.239	282.571	<.001
	Lower-bound	8746.239	1.000	8746.239	282.571	<.001
CS * group	Sphericity Assumed	106.921	2	53.460	1.727	.196
	Greenhouse-Geisser	106.921	2.000	53.460	1.727	.196
	Huynh-Feldt	106.921	2.000	53.460	1.727	.196
	Lower-bound	106.921	2.000	53.460	1.727	.196
Error(CS)	Sphericity Assumed	866.667	28	30.952		
	Greenhouse-Geisser	866.667	28.000	30.952		
	Huynh-Feldt	866.667	28.000	30.952		
	Lower-bound	866.667	28.000	30.952		
session	Sphericity Assumed	114.261	3	38.087	8.018	<.001
	Greenhouse-Geisser	114.261	1.986	57.527	8.018	<.001
	Huynh-Feldt	114.261	2.290	49.894	8.018	<.001
	Lower-bound	114.261	1.000	114.261	8.018	.008
session * group	Sphericity Assumed	27.629	6	4.605	.969	.451
	Greenhouse-Geisser	27.629	3.972	6.955	.969	.431
	Huynh-Feldt	27.629	4.580	6.032	.969	.438
	Lower-bound	27.629	2.000	13.815	.969	.392
Error(session)	Sphericity Assumed	399.004	84	4.750		
	Greenhouse-Geisser	399.004	55.614	7.174		
	Huynh-Feldt	399.004	64.122	6.223		
	Lower-bound	399.004	28.000	14.250		
CS * session	Sphericity Assumed	1.710	3	.570	.230	.875
	Greenhouse-Geisser	1.710	2.358	.725	.230	.830
	Huynh-Feldt	1.710	2.773	.617	.230	.861
	Lower-bound	1.710	1.000	1.710	.230	.635
CS * session * group	Sphericity Assumed	25.011	6	4.169	1.680	.136
	Greenhouse-Geisser	25.011	4.716	5.304	1.680	.155
	Huynh-Feldt	25.011	5.545	4.511	1.680	.142
	Lower-bound	25.011	2.000	12.506	1.680	.205
Error(CS*session)	Sphericity Assumed	208.430	84	2.481		
	Greenhouse-Geisser	208.430	66.020	3.157		
	Huynh-Feldt	208.430	77.631	2.685		
	Lower-bound	208.430	28.000	7.444		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	24362.507	1	24362.507	403.147	<.001
group	111.080	2	55.540	.919	.411
Error	1692.063	28	60.431		

Experiment 5 (Irradiated Specialty Feed)

Instrumental Training, 4 sessions

Input

Average of Averaged over levers	Column Labels			
Row Labels	1	2	3	4
M4 GFAP	**17.38688836**	**18.6862207**	**22.2198513**	**22.8394139**
DCZ	**15.63913065**	**16.465257**	**20.4152464**	**19.0390623**
7	24.56736787	24.0139767	30.5483431	34.2769157
13	5.637254902	3.85	8.87323944	6.91188359
18	29.13540934	34.383174	33.9648747	42.6205167
20	20.08250945	16.4229121	22.0064757	25.839599
21	14.35065425	17.8274956	13.300086	15.6162109
25	13.60989811	15.076661	17.5596143	2.6001001
26	15.26974215	15.3191803	21.1135387	2.74185464
27	18.65490628	29.6401745	38.8900673	36.4514406
28	21.39007663	22.8796249	24.1119124	29.5734857
34	5.753378378	5.48451106	11.2530531	8.85570692
35	10.79972814	6.68954099	11.0094194	9.05692443
39	8.418642262	5.99583311	12.3523329	13.9241088
VEH	**21.58150687**	**24.0165336**	**26.5509029**	**31.9602579**
6	24.67305195	25.6296852	22.8904167	35.8005209
10	19.06385461	20.7942934	29.7989996	30.7189671
17	15.50619657	16.9466688	21.9748792	21.2005109
31	18.90366568	20.6217154	20.3620127	23.9933913
40	29.76076555	36.0903051	37.7282065	48.0878994
mcherry	**16.95361477**	**18.3774393**	**22.3465811**	**23.0372943**
DCZ	**17.03424484**	**17.8978435**	**21.6509044**	**21.1613373**
1	26.24533309	31.1152989	49.406495	31.5878378
2	9.46030436	11.3708904	15.6965691	15.0637648
5	13.27465723	16.0748414	13.5629641	11.7518286
23	20.69498617	21.4996892	24.7854376	23.3160771
24	14.71566012	19.5024453	14.1175065	25.0960735
29	14.72372047	12.8958137	17.5534772	17.7524456
30	13.54844792	17.8315624	17.5646857	19.7609408
36	21.30539499	13.6334232	20.368092	21.9365642
38	17.96344309	18.4417003	16.7330478	22.8784728
41	18.4689572	14.1768396	24.5247828	21.7515541
42	16.97578862	20.3337741	23.8468904	21.879151
VEH	**16.65797117**	**20.1359571**	**24.8973957**	**29.9158032**
9	11.73858341	20.7368009	31.9334822	33.2928789
33	10.1808478	8.31811026	9.3986519	17.9676348
37	28.05448231	31.3529601	33.3600529	38.4868957
Grand Total	**17.19121642**	**18.546771**	**22.2770841**	**22.9287792**

Output

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
session	Sphericity Assumed	808.165	3	269.388	15.652	<.001
	Greenhouse-Geisser	808.165	2.470	327.192	15.652	<.001
	Huynh-Feldt	808.165	2.921	276.686	15.652	<.001
	Lower-bound	808.165	1.000	808.165	15.652	<.001
session * group	Sphericity Assumed	206.398	6	34.400	1.999	.075
	Greenhouse-Geisser	206.398	4.940	41.781	1.999	.090
	Huynh-Feldt	206.398	5.842	35.332	1.999	.077
	Lower-bound	206.398	2.000	103.199	1.999	.154
Error(session)	Sphericity Assumed	1445.760	84	17.211		
	Greenhouse-Geisser	1445.760	69.160	20.905		
	Huynh-Feldt	1445.760	81.785	17.678		
	Lower-bound	1445.760	28.000	51.634		

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	51683.517	1	51683.517	194.746	<.001
group	975.199	2	487.600	1.837	.178
Error	7430.917	28	265.390		

Experiment 5 (Irradiated Specialty Feed)

Pavlovian Instrumental Transfer

Input

Row Labels	Average of Pre	Average of Same	Average of Different
M4 GFAP	**1.242647059**	**2.316176471**	**0.963235294**
DCZ	**0.9375**	**1.53125**	**1.135416667**
7	3.125	1.5	0.75
13	1	1.625	3.25
18	0.0625	3.125	0.5
20	0.125	0.375	0.5
21	1.5625	2.5	3.625
25	0.0625	0.375	0.375
26	0.1875	1.875	0.5
27	0	0.125	0.125
28	2.1875	1.625	0.5
34	2.5625	2.125	2.25
35	0.375	2.375	0.625
39	0	0.75	0.625
VEH	**1.975**	**4.2**	**0.55**
6	5.5625	0.5	0.75
10	0.1875	0.625	0.625
17	0.0625	2.625	0.25
31	1.625	6.75	0.875
40	2.4375	10.5	0.25
mcherry	**1.151785714**	**3.473214286**	**1.428571429**
DCZ	**0.994318182**	**3.386363636**	**1.443181818**
1	0.125	4.125	0.25
2	1.5625	7.875	2.75
5	0.8125	3.25	4.5
23	1	2.125	0
24	1	3.5	0.125
29	1.6875	1.5	0.25
30	0.375	0.875	4.125
36	2.625	2.5	0.75
38	0.1875	3.625	0.75
41	0.5625	4.375	0.375
42	1	3.5	2
VEH	**1.729166667**	**3.791666667**	**1.375**
9	0	0	0.75
33	4.6875	9.75	2.375
37	0.5	1.625	1
Grand Total	**1.201612903**	**2.838709677**	**1.173387097**

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group... 1	2	3	
B1	1	1	-2	M4+DCZ vs. C
B2	1	-1	0	Controls
B3	1	0	0	
B4	0	1	0	
B5	0	0	1	

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3	
W1	2	-1	-1	Pre vs. Post
W2	0	1	-1	sPIT

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	17.727	1	17.727	3.960	* No main effects, although control vs. M4+DCZ, p = .056
B2	1.438	1	1.438	0.321	
B3	124.364	1	124.364	27.781	
B4	122.910	1	122.910	27.456	
B5	51.960	1	51.960	11.607	
Error	125.344	28	4.477		
Within					
W1	12.690	1	12.690	6.966	* Main effect pre vs. Post, no interactions
B1W1	1.745	1	1.745	0.958	
B2W1	2.232	1	2.232	1.225	
B3W1	14.796	1	14.796	8.123	* Only simple effect is for mCherry group though.
B4W1	1.735	1	1.735	0.952	
B5W1	1.253	1	1.253	0.688	
Error	51.004	28	1.822		
W2	51.033	1	51.033	14.731	* Main effect sPIT, p = .001
B1W2	17.139	1	17.139	4.947	* Interaction, p = .034
B2W2	3.586	1	3.586	1.035	* No control x sPIT interaction, p = .318
B3W2	20.768	1	20.768	5.995	* Simple effect only for each control again though, p = .021
B4W2	40.641	1	40.641	11.731	* p = .002
B5W2	0.940	1	0.940	0.271	* No simple effect M4+DCZ, F < 1
Error	97.003	28	3.464		

Experiment 5 (Irradiated Specialty Feed)

Outcome Devaluation

Input

Row Labels	Average of Mag Entries	Average of Devalued	Average of Valued
M4 GFAP	**1.482352941**	**0.647058824**	**0.882352941**
DCZ	**1.525**	**0.6125**	**0.6875**
7	1.5	0.85	1.65
13	0.65	0.1	0.25
18	1	0.65	0.65
20	2.8	0.3	0.3
21	3	0.8	1.15
25	0.95	0.15	0.2
26	2.7	0.4	0.4
27	0.7	0.35	0.5
28	1.65	0.9	0.5
34	0.8	1.9	1.05
35	1.4	0.4	1.3
39	1.15	0.55	0.3
VEH	**1.38**	**0.73**	**1.35**
6	0.6	0.2	0.3
10	1	0.5	0.2
17	1.25	0.3	1.9
31	2.6	1.3	0.8
40	1.45	1.35	3.55
mcherry	**1.628571429**	**0.489285714**	**1.3**
DCZ	**1.768181818**	**0.527272727**	**1.45**
1	1.15	0.1	0.3
2	2.3	0.6	0.75
5	1.55	0.2	0.55
23	2.85	0.4	1.4
24	2.3	1.15	3.6
29	0.95	0.1	0.25
30	1.85	0.7	2.9
36	3.3	0.95	1.6
38	1.9	0.75	1.9
41	0.65	0.35	2
42	0.65	0.5	0.7
VEH	**1.116666667**	**0.35**	**0.75**
9	0.45	0.2	0.6
33	1.75	0.35	1.15
37	1.15	0.5	0.5
Grand Total	**1.548387097**	**0.575806452**	**1.070967742**

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group... 1	2	3
B1	1	1	-2
B2	1	-1	0
B3	1	0	0
B4	0	1	0
B5	0	0	1

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement... 1	2	3
W1	1	0	0
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	0.720	1	0.720	0.794	* No main effect M4+DCZ vs rest, F < 1
B2	0.872	1	0.872	0.963	* No control main effect, p = .212
B3	51.438	1	51.438	56.754	* Dummy
B4	23.900	1	23.900	26.370	* Dummy
B5	31.923	1	31.923	35.222	* Dummy
Error	25.377	28	0.906		
Within					
W1	69.928	1	69.928	103.715	* Dummy
B1W1	5.87774e-7	1	5.87774e-7	8.71766e-7	* No difference in mag entries between any groups, all Fs < 1
B2W1	1.098	1	1.098	1.629	
B3W1	34.391	1	34.391	51.008	* Dummy
B4W1	13.133	1	13.133	19.478	* Dummy
B5W1	27.908	1	27.908	41.391	* Dummy
Error	18.879	28	0.674		
W2	3.938	1	3.938	13.846	* Main effect of Deval, p = .001
B1W2	1.563	1	1.563	5.494	* Deval x M4+DCZ vs. Rest interaction p = .026
B2W2	0.344	1	0.344	1.208	* No Deval x control interaction
B3W2	4.683	1	4.683	16.464	* Simple effect for mCherry group, p = .000
B4W2	1.156	1	1.156	4.063	* Almost simple effect for veh group, p = .053
B5W2	0.034	1	0.034	0.119	* No simple effect for M4+DCZ, F < 1
Error	7.964	28	0.284		

Experiment 5 (Irradiated Specialty Feed)

Outcome-selective reinstatement

Input

Row Labels	Average of Pre-Reinst	Average of Pre-NonReinst	Average of Reinst	Average of NonReinst	PRE
M4 GFAP	**15.35294118**	**7.058823529**	**73.29411765**	**8.705882353**	
DCZ	**11**	**7.833333333**	**71.91666667**	**10.08333333**	
7	1	1	77	2	1.00
13	0	0	31	22	0.00
18	6	9	68	8	7.50
20	23	13	128	33	18.00
21	4	5	58	14	4.50
25	14	14	151	12	14.00
26	9	6	69	13	7.50
27	3	0	82	4	1.50
28	27	33	90	2	30.00
34	23	13	41	1	18.00
35	22	0	46	1	11.00
39	0	0	22	9	0.00
VEH	**25.8**	**5.2**	**76.6**	**5.4**	
6	2	0	23	2	1.00
10	1	0	30	5	0.50
17	11	0	34	7	5.50
31	44	21	153	13	32.50
40	71	5	143	0	38.00
mcherry	**7.142857143**	**3.285714286**	**61.92857143**	**3.5**	
DCZ	**9**	**4**	**54.18181818**	**4**	
1	5	6	28	1	5.50
2	0	3	27	4	1.50
5	2	3	57	1	2.50
23	0	3	87	1	1.50
24	2	1	45	0	1.50
29	30	0	48	1	15.00
30	5	11	31	17	8.00
36	0	5	28	1	2.50
38	1	5	123	1	3.00
41	0	0	42	8	0.00
42	54	7	80	9	30.50
VEH	**0.333333333**	**0.666666667**	**90.33333333**	**1.666666667**	
9	0	0	38	0	0.00
33	1	2	69	5	1.50
37	0	0	164	0	0.00
Grand Total	**11.64516129**	**5.35483871**	**68.16129032**	**6.35483871**	

Output

Number of Groups: 3
Number of Measurements: 3

Number of subjects in...
Group 1: 11
Group 2: 8
Group 3: 12

Between contrast coefficients

Contrast	Group...		
	1	2	3
B1	1	1	-2
B2	1	-1	0
B3	1	0	0
B4	0	1	0
B5	0	0	1

*** Caution ***
B3 coefficients do not sum to zero
B4 coefficients do not sum to zero
B5 coefficients do not sum to zero

Within contrast coefficients

Contrast	Measurement...		
	1	2	3
W1	2	-1	-1
W2	0	1	-1

Analysis of Variance Summary Table

Source	SS	df	MS	F	
Between					
B1	307.966	1	307.966	0.360	* No between main effects, M4+DCZ vs. Rest
B2	1478.216	1	1478.216	1.726	* F < 1 controls main effect
B3	15340.371	1	15340.371	17.913	* Dummy
B4	24384.375	1	24384.375	28.474	* Dummy
B5	33428.028	1	33428.028	39.034	* Dummy
Error	23978.476	28	856.374		
Within					
W1	16930.194	1	16930.194	67.965	* Main effect of pre vs. Post
B1W1	69.662	1	69.662	0.280	* No interaction with M4+DCZ x rest
B2W1	334.552	1	334.552	1.343	* No interaction with controls, F < 1
B3W1	3742.561	1	3742.561	15.024	* Simple effect mCherry
B4W1	5808.000	1	5808.000	23.316	* Simple effect vehicle group
B5W1	7980.056	1	7980.056	32.035	* Simple effect M4+DCZ
Error	6974.884	28	249.103		
W2	60169.966	1	60169.966	66.441	* Main effect (Reinstated > Nonrreinstated)
B1W2	16.561	1	16.561	0.018	* No interaction with M4+DCZ vs. Rest
B2W2	1760.011	1	1760.011	1.943	* No interaction with controls, F < 1
B3W2	13850.182	1	13850.182	15.294	* Simple effect mCherry+DCZ
B4W2	24180.250	1	24180.250	26.700	* Simple effect vehicles
B5W2	22940.167	1	22940.167	25.331	* Simple effect M4+DCZ
Error	25357.402	28	905.621		