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REVIEW ARTICLE

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Cortical neurophysiology of primary isolated dystonia and non-dystonic adults: A meta-analysis

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive method to assess neurophysiology of the primary motor cortex in humans. Dystonia is a poorly understood neurological movement disorder, often presenting in an idiopathic, isolated form across different parts of the body. The neurophysiological profile of isolated dystonia compared to healthy adults remains unclear. We conducted a systematic review with meta-analysis of neurophysiologic TMS measures in people with isolated dystonia to provide a synthesized understanding of cortical neurophysiology associated with isolated dystonia. We performed a systematic database search and data were extracted independently by the two authors. Separate meta-analyses were performed for TMS measures of: motor threshold, corticomotor excitability, short interval intracortical inhibition, cortical silent period, intracortical facilitation and afferent-induced inhibition. Standardized mean differences were calculated using a random effects model to determine overall effect sizes and confidence intervals. Heterogeneity was explored using dystonia type subgroup analysis. The search resulted in 78 studies meeting inclusion criteria, of these 57 studies reported data in participants with focal hand dystonia, cervical dystonia, blepharospasm or spasmodic dysphonia, and were included in at least one meta-analysis. The cortical silent period, short-interval intracortical inhibition and afferent-induced inhibition was found to be reduced in isolated dystonia compared to controls. Reduced GABAergic-mediated inhibition in the primary motor cortex in idiopathic isolated dystonia's suggest interventions targeted to aberrant cortical disinhibition could provide a novel treatment. Future meta-analyses require neurophysiology studies to use homogeneous cohorts of isolated dystonia participants, publish raw data values, and record electromyographic responses from dystonic musculature where possible.

KEYWORDS

blepharospasm, dystonia, spasmodic dysphonia, torticollis, transcranial magnetic stimulation

Abbreviations: AMT, active motor threshold; APB, abductor pollicis brevis; BLP, blepharospasm; CD, cervical dystonia; CI, confidence interval; CME, corticomotor excitability; CSP, cortical silent period; EMG, electromyography; FDI, first dorsal interosseous; FHD, focal hand dystonia; GABA, gamma-aminobutyric acid; ICF, intracortical facilitation; ISI, Interstimulus interval; LAI, long-interval inhibition; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; OO, orbicularis oculi; RMT, resting motor thershold; SAI, short-afferent inhibition; SD, spasmodic dysphonia; SICI, short-interval intracortical inhibition; SMD, standardized mean difference; S-R, stimulus-response curve; TMS, transcranial magnetic stimulation.

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1 | INTRODUCTION

Dystonia is a neurological movement disorder characterized by intermittent or sustained muscle contractions that result in abnormal postures and repetitive movements (Albanese et al., 2013). Idiopathic, isolated dystonia describes a dystonic phenotype of unknown cause and physical impairment focal to a particular body part, for example the hand (focal hand dystonia, FHD, including writer's cramp and musician's dystonia), neck (cervical dystonia, CD), eyelids (blepharospasm, BLP) or larynx (spasmodic dysphonia, SD). Although the exact pathophysiology is not completely known, there is increasing evidence that dystonia arises from an aberrant functional neural network, involving the sensorimotor cortex, basal ganglia, brainstem and cerebellum (Bradnam & Barry, 2013; Corp et al., 2019; Prudente et al., 2014; Shakkottai et al., 2017). The lack of understanding of the pathophysiology of dystonia has limited development of new and effective treatments for this recalcitrant movement disorder. Further research into the neurophysiology of the different forms of isolated dystonia may help guide future neurorehabilitation interventions and ultimately improve patient treatment outcomes.

The corticomotor neurophysiology of idiopathic, isolated dystonia has been explored non-invasively in humans using transcranial magnetic stimulation (TMS). TMS is applied over the primary motor cortex (M1) to probe excitability of the corticomotor pathway and intracortical neural circuits (Barker et al., 1985; Chen, 2000). There are several measures that can be assessed with TMS, reflecting different aspects of cortical neurophysiology. For example, the TMS motor threshold is defined as the lowest single-pulse TMS intensity needed to evoke a response of a given size at rest (resting motor threshold, RMT) or during voluntary muscle contraction (active motor threshold, AMT). Motor threshold is routinely assessed in TMS studies, and reflects the total intrinsic membrane excitability from the stimulated M1, spinal cord, neuromuscular junction and muscle (Ziemann et al., 1996a). Corticomotor excitability (CME) can be inferred by measuring the amplitude of the motor-evoked potential (MEP) evoked by suprathreshold single-pulse TMS (Chen, 2000). Studies investigating CME may use a single TMS intensity or a stimulus-response (S-R) curve measuring the amplitude of MEP responses across a range of TMS intensities (Devanne et al., 1997). There are several TMS measures used to infer gamma-aminobutyric acid (GABA) receptor-mediated cortical inhibition within M1. The cortical silent period (CSP) is evoked when single-pulse TMS is delivered over the contralateral M1 during voluntary activation of the target muscle. Duration of the CSP measured from the active electromyography (EMG) provides a measure of $GABA_B$ receptor mediated inhibition (Wasserman et al., 2008). Paired pulse TMS delivers two stimuli from one coil at inter-stimulus intervals (ISI) and can be used to infer intracortical inhibition or facilitation within a hemisphere. At short intervals (termed short interval intracortical inhibition, SICI) MEP suppression is mediated by $GABA_A$ synaptic activity (Kujirai et al., 1993), while at long intervals (termed long interval intracortical inhibition, LICI) $GABA_B$ mediated receptor activity is thought to be responsible for the MEP suppression (Ziemann et al., 1996a, 1996b). Paired pulse TMS can also be used to assess intracortical facilitation (ICF), of which the underlying mechanisms are thought to involve NMDA receptor activity on excitatory glutamatergic interneurons (Ziemann et al., 1998). Finally, afferent-mediated inhibition pairs electrical stimulation of a mixed peripheral nerve or digital nerve with TMS over the contralateral M1 to provide a measure of sensory-motor integration occurring within the cortical motor strip (Turco, El-Sayes, Savoie, et al., 2018). Short-latency afferent inhibition (SAI) uses intervals of ~20 ms and produces an inhibitory modulation of the M1 either via thalamocortical projections or directly from the somatosensory cortex (Tokimura et al., 2000), mediated by cholinergic (Di Lazzaro et al., 2000) and $GABA_A$ pathways (Di Lazzaro et al., 2007; Turco, El-Sayes, Locke, et al., 2018). Long latency afferent inhibition (LAI) requires ISIs of ~100–200 ms and reflects activity in cortico-cortical pathways involving M1 and the primary and secondary somatosensory areas (Chen et al., 1999) and is mediated by $GABA_A$ activity (Turco, El-Sayes, Locke, et al., 2018). Other TMS paradigms also exist, but the measures cited above are the most common.

Many TMS studies with small sample sizes have compared cortical neurophysiology in people living with idiopathic isolated dystonia and healthy controls. The findings of these studies have been used to build our understanding of the neural mechanisms contributing to dystonia. However, considering the low statistical power interpretations should be made with caution, such as reported for the phenomenon of "surround inhibition" where a retrospective analysis found most studies were statistically underpowered for between-group effects (Kassavetis et al., 2018). A meta-analysis is a quantitative study design that can statistically combine data of individual studies, including those with small sample sizes, to provide a more robust understanding of a research question (Borenstein et al., 2009). The results of meta-analysis provide a synthesized view of the evidence base, and a more precise estimate of the effect of disease or treatment on an outcome measure compared to an individual study alone (Haidich, 2010). A meta-analysis of TMS studies may provide a higher level of understanding of the aberrant cortical neurophysiology present in isolated dystonia by comparing their responses to TMS to that of control adults.

The aim of this study was to conduct the first meta-analysis of TMS outcome measures comparing cortical neurophysiology of people with idiopathic, isolated dystonia to healthy control participants. A synthesized view of the normal and

abnormal corticomotor mechanisms measured using TMS may contribute to understanding the dystonia phenotype and potentially provide neural targets for therapeutic interventions to improve treatment outcomes.

2 | METHODS

The study was registered on PROSPERO (CRD42018115853) in November 2018. A systematic search of the literature was performed using the databases Scopus, PubMed, PEDro, Medline and CINAHL using the following terms "dystonia" OR "writer's cramp" OR "musician's cramp" OR "torticollis" OR "blepharospasm" OR "dysphonia" AND "Transcranial Magnetic Stimulation" OR "TMS" published between January 1990 and June 2019. Citations were downloaded and duplicate titles removed. Titles and abstracts were screened independently by each author, and those meeting inclusion criteria were downloaded for full text screening. Reference lists and citations for identified studies meeting the inclusion criteria were hand-searched to identify relevant studies. The TMS measures included in our analysis were; RMT, AMT, CME (MEP or S-R curves), CSP, SICI, LICI, ICF and afferent-induced inhibition (SAI, LAI). To be included, articles had to report a comparison between adults with an isolated form of dystonia and a control group using one or more of the aforementioned TMS measures. Intervention studies were included if pre-intervention data were reported. Studies investigating non-isolated, secondary or functional dystonia were excluded, as were studies with a mix of isolated dystonia types together with secondary or functional dystonia types. Case studies, review articles, TMS mapping studies, and studies using deep brain stimulation were also excluded. Each TMS protocol was separately scrutinized by two authors, both of whom are experienced neuroscientists. TMS protocols that did not use acceptable data collection and analysis methodology were excluded. Any discrepancies during screening were discussed to obtain mutual consensus. No methodological quality or risk of bias assessment was performed, and ethical review was not required for this study.

Data extraction was performed independently by both authors. Corresponding authors for studies published after 2011 were contacted by email to request access to their datasets, and studies that did not report actual data (means and variance) were excluded. We extracted; author name, dystonia type, number of participants, TMS measure, details of TMS protocol, muscle(s) from which EMG was recorded, task (if relevant), the mean and standard deviation of each TMS outcome for each group, and the statistical finding from the between group analysis for each TMS measure. Comprehensive Meta-analysis software (Comprehensive Meta-Analysis Version 3, Biostat) was used to analyse each TMS measure. A random effects model was used to account for differences in TMS methodology, study design and participant populations, as we included all isolated dystonia phenotypes (Borenstein et al., 2010). Results were reported as standardized mean differences (SMD) with 95% confidence intervals (CI). Interpretation of the magnitude of SMD was >0.8 large effect, 0.5–0.79 moderate effect and 0.2–0.49 weak effect (Cohen, 1998). Data were combined in the meta-analysis when more than one muscle located in the same body part (e.g. forearm and hand) was tested, when homologous muscles were tested bilaterally, when the same data were analysed in two different ways (e.g. SR curve slope and area under the curve), and for afferent-induced inhibition, when a range of ISIs were used in a single study. This was done as measurements from multiple muscles in the same anatomical location, multiple measures from the same muscles and different ISIs assessing a common mechanism cannot be considered independent measures, and so combining is an appropriate methodological approach (Borenstein et al., 2009). When measures were made from two muscles innervated differently (e.g. cortico-bulbar vs. corticospinal pathways) data were not combined as the authors considered these as independent measures. Finally, as we could not know if the muscle under study was dystonic, even if EMG recordings were made from a dystonic region (e.g. hand muscles in FHD), we referred to muscles as "local" or "remote" to the dystonic body part. Labelling a muscle as local only indicates it is located close to the dystonic region, not that it is necessarily affected by the dystonia. Heterogeneity was assessed for each meta-analysis using the I^2 statistic, where <25% indicates low, 25%–75% indicate moderate and >75% indicates substantial heterogeneity (Higgins et al., 2003). When heterogeneity was high, a priori subgroup analysis of dystonia type was conducted to explore if combining different phenotypes was a source of heterogeneity (Haidich, 2010). The *N*-fail safe method determined the number of published studies required to negate the resulting effect size. A low fail-safe *N* number indicates the findings of the meta-analysis may be susceptible to publication bias (Table 1).

3 | RESULTS

The literature search found 78 published studies meeting the inclusion criteria. Of these, 57 papers reported the mean ± *SD* for at least one TMS measure and were included in one or more meta-analyses (Figure 1). Study characteristics ordered by TMS measure are provided in Table 1. The types of isolated dystonia included in the meta-analyses were FHD including musician's dystonia and writer's cramp in 41 studies, CD in 14 studies, BLP in 2 studies and SD in 3 studies. The results of the CSP, SICI and afferent-inhibition meta-analyses revealed differences between dystonia and controls and are detailed below. The results of the ICF, CME,

TABLE 1 Studies included in the meta-analyses

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Amadio et al. (2000)	CD 13 dystonia 20 controls	SCM, UT Bilateral	No difference between groups for RMT
Amadio et al. (2014)	CD 8 dystonia 8 controls	FDI Hand not performing the geste	No difference between groups for RMT
Baumer et al., (2007)	FHD 7 dystonia 8 controls	FDI Affected side	No difference between groups for RMT and AMT
Beck et al., (2008)	FHD 16 dystonia 20 controls	APB Affected side	No difference between groups for RMT
Beck, Houdayer, et al. (2009)	FHD 10 dystonia 10 controls	APB Affected side	No difference between groups for RMT and AMT
Beck, Schubert, et al. (2009b)	FHD 16 dystonia 20 controls	APB Affected side	No difference between groups for RMT
Beck, Shamim, et al., (2009b)	FHD 13 dystonia 12 controls	FDI, APB Bilateral	No difference between groups for RMT
Belvisi, Suppa, et al. (2013)	FHD 14 dystonia 14 controls	FDI Affected side	No difference between groups for RMT and AMT
Bologna, Paparella, et al. (2016)	CD and FHD 13 CD 13 FHD 13 controls	FDI Affected side in FHD, CD unknown	No difference between groups for RMT and AMT
Boyadjian et al. (2011)	FHD 10 dystonia 10 controls	ECR, FDI Right	No difference between groups for AMT
Brighina, Romano et al. (2009)	FHD 8 dystonia 8 controls	ECR, FDI Bilateral	No difference between groups for RMT
Butefisch, Boroojerdi et al. (2005)	FHD 7 dystonia 7 controls	APB, 4th DI Affected side	No difference between groups for RMT
Chen, Wassermann et al. 1997)	FHD 8 dystonia 18 controls	ECR Bilateral	No difference between groups for RMT
Erro, Rocchi, et al. (2018)	CD 12 dystonia 12 controls	FDI Right	No difference between groups for RMT or AMT
Furuya, Ueharam, et al. (2018)	FHD 20 FHD 20 musicians without FHD 20 controls	FDS Affected side	No difference between groups for RMT and AMT
Ganos, Ferre, et al. (2017)	CD 17 dystonia 19 controls	FDI Dominant hand	No difference between groups for RMT and AMT

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Gilio et al. (2003)	FHD 10 dystonia 8 controls	Forearm extensor Affected side	No difference between groups for RMT and AMT
Hanajima, Okabe, et al. ((2008))	FHD 7 dystonia 11 controls	FDI Affected side	No difference between groups for AMT
Hubsch et al. (2013)	FHD 21 dystonia 25 controls	APB, ADM Right	No difference between groups for RMT and AMT
Koch et al. (2014)	CD 20 dystonia 10 controls	FDI, APB Right	No difference between groups for RMT and AMT
MacKinnon, Velickovic, et al. (2004)	FHD 9 dystonia 9 controls	FCR Affected side	No difference between groups for RMT
Niehaus, von Alt-Stutterheim, et al. (2001)	FHD 25 dystonia 25 control	FDI Bilateral	No difference between groups for RMT
Pirio Richardson et al. (2009)	FHD 14 dystonia 17 controls	ADM Dominant	Trend for lowered RMT in dystonia group compared to controls
Pirio Richardson (2015)	CD 9 dystonia 9 controls	FDI Right	No difference between groups for RMT A trend for reduced AMT in the dystonia group compared to controls
Porcacchia, Palomar et al. (2014)	CD 14 dystonia 14 controls	FDI Left	No difference between groups for RMT
Porcacchia, Alvarez de Toledo et al., (2019)	CD 12 dystonia 13 controls	FDI Left	No difference between groups for RMT and AMT
Quartarone, Bagnato, et al. (2005)	FHD 10 dystonia 10 controls	FDI, APB, ADM, ECR, BB Bilateral	No difference between groups in RMT for any muscle tested
Quartarone et al. (2003)	FHD 10 dystonia 10 control	APB, FDI Right	No difference between groups for RMT or AMT
Richardson et al. (2008)	FHD 13 dystonia 17 controls	ADM Affected side	RMT reduced in dystonia group compared to controls
Ridding et al. (1995)	FHD 15 dystonia 8 controls	FDI Right/Bilateral ($n = 10$)	No difference between groups for RMT and AMT
Rosenkranz, Altenmuller, et al. (2000)	FHD 5 MD 5 healthy musicians 5 controls	FCR, ECR Affected side	No difference between groups for RMT

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Rosenkranz, Butler, et al. (2009)	FHD 8 MD 8 healthy musicians 6 controls	APB Affected side	No difference between groups for AMT
Rosenkranz, Williamon, et al. (2005)	FHD 7 MD 6 WC 8 healthy musicians 8 controls	FDI Not reported	No difference between groups for AMT
Samargia et al. (2016)	SD 10 SD 8 MTD patient controls 10 controls	FDI, mass Dominant hand	No difference between groups for FDI RMT or masseter AMT
Schwenkreis et al. (1999)	CD 20 dystonia 21 controls	FDI Bilateral	No difference between groups for RMT
Siggelkow et al. (2002)	CD 11 dystonia 11 controls	ECR and FCR Right	No difference between groups for RMT
Sohn and Hallett (2004)	FHD 7 dystonia 7 controls	ADM Affected side	No difference between groups for RMT
Sommer, Ruge et al. (2002)	FHD and BLP 15 WC and MD 16 BLP 23 controls	ADM Affected side	No difference between groups for RMT and AMT
Stinear and Byblow (2004)a	FHD 7 dystonia 8 controls	FDI Affected side	A reduction in AMT in dystonia compared to controls
Stinear and Byblow (2004)b	FHD 7 dystonia 8 controls	APB, FDI Affected side	No difference between groups for RMT and AMT
Stinear and Byblow (2004)c	FHD 5 dystonia (7 hands) 7 controls	FDI Affected side	No difference between groups for RMT and AMT
Stinear and Byblow (2005)	FHD 8 dystonia 8 controls	FDI Affected side	No difference between groups for AMT
Suppa et al. (2015)	SD 10 dystonia 10 controls	FDI Bilateral	No difference between groups for RMT
Tinazzi, Zarattini, et al. (2006)	FHD 10 dystonia 14 controls	FCR, ECR Affected side	No difference between groups for RMT
Veugen, Hoffland, et al. (2013)	FHD 15 dystonia 10 controls	FDI, ADM Affected side	No difference between groups for RMT

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Zittel et al., (2015)	CD 12 dystonia 8 controls	FDI Right	No difference between groups for RMT
Corticomotor excitability			
Amadio et al. (2000)	CD 13 dystonia 20 controls	SCM, UT Bilateral TMS intensity maximum output Task: Rest, active (approx. 20% MVC)	No difference between groups at rest Increased in both muscles when active in dystonia compared to controls
Amadio et al. (2014)	CD 8 dystonia 8 controls	FDI Hand not performing the geste TMS intensity 120% RMT Task: Rest	No difference between groups
Beck et al. (2008)	FHD 16 dystonia 20 controls	FDI Affected side TMS intensity 140% MT Task: Rest, premotor, phasic, tonic	No difference between groups
Beck, Houdayer, et al. (2009)	FHD 10 dystonia 10 controls	APB Affected TMS intensity 140% MT Task: Rest	No difference between groups
Beck, Schubert, et al. (2009a)	FHD 16 dystonia 20 controls	APB Affected side TMS intensity 140% MT Task: Rest, 10% MVC, 20% MVC	No difference between groups
Belvisi, Suppa, et al. (2013)	FHD 14 dystonia 14 controls	FDI Affected side TMS intensity MEP_{1mV} Task: Rest	No difference between groups
Bradnam et al. (2015)	FHD 8 dystonia 8 controls	FDI Affected side TMS intensity 120% RMT and MEP_{S50} Task: Rest	No difference between groups
Butefisch, Boroojerdi, et al. (2005)	FHD 7 dystonia 7 controls	APB, 4th DI Affected side TMS intensity MEP_{1mV} Task: Rest	No difference between groups
Chen, Wassermann, et al. (1997)	FHD 8 dystonia 18 controls	ECR Bilateral TMS intensity 110% RMT Task: rest, 20% MVC	No difference between groups
Erro, Rocchi, et al. (2018)	CD 12 dystonia 12 controls	ABP, ADM, FDI Right side TMS intensity MEP_{1mv} for APB Task: Rest	No difference between groups for MEP_{1mv} Larger MEPs in ADM and FDI in dystonia No difference between groups for ABP MEP
Furuya, Uehara, et al. (2018)	FHD 20 MD 20 musicians without dystonia 20 controls	FDS, EDC Right/affected side TMS intensity $MEP_{0.2–0.4\ mV}$ Task: Rest	No difference between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Ganos, Ferre, et al. (2017)	CD 17 dystonia 19 controls	FDI, ADM Dominant hand TMS intensity MEP_{1mv} Task: Rest, onset of movement	No difference between groups
Gilio et al. (2003)	FHD 10 dystonia 8 controls	Forearm extensor Affected side TMS intensity 120% RMT Task: Rest, 4 bins prior to movement, voluntary contraction	No difference between groups
Hanajima, Okabe, et al. (2008)	FHD 7 dystonia 11 controls	FDI More affected side TMS intensity MEP_{1mv} Task: Rest, 10% MVC	No difference between groups
Hubsch et al. (2013)	FHD 21 dystonia 25 controls	APB, ADM Right TMS intensity 130% RMT Task: Rest	No difference between groups
Koch et al. (2014)	CD 20 dystonia 10 controls	FDI, APB Right TMS intensity MEP_{1mv} Task: Rest	No difference between groups
Nelson, Hoque, et al. (2010)	FHD 7 dystonia 7 controls	FDI Bilateral TMS intensity MEP_{1mV} Task: Rest, pen hold	No difference between groups
Niehaus, von Alt-Stutterheim, et al. (2010)	FHD 25 dystonia 25 control	FDI Bilateral TMS intensity 80% MSO Task: Active	No difference between groups
Pirio Richardson et al., (2009)	FHD 14 dystonia 17 controls	ADM Affected/Dominant TMS intensity 140%RMT Task: Rest, pre-movement	No difference between groups
Pirio Richardson (2015)	CD 9 dystonia 9 controls	FDI Right TMS intensity: 120%RMT Task: Rest	No difference between groups
Porcacchia, Palomar, et al. (2014)	CD 14 dystonia 14 controls	FDI Left TMS intensity: MEP_{1mV} Task:Rest	No difference between groups
Porcacchia, Alvarez de Toledo, et al. (2019)	CD 12 dystonia 13 controls	FDI Right TMS intensity: MEP_{1mV} Task: Rest	No difference between groups
Quartarone et al. (2003)	FHD 10 dystonia 10 control	APB, FDI Right TMS intensity 130% RMT Task: Rest	No difference between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Richardson et al. (2008)	FHD 13 dystonia 17 controls	ADM, FDI Affected TMS intensity 140% RMT Task: Rest, movement	No difference between groups
Rosenkranz, Altenmuller, et al. (2000)	FHD 5 MD 5 healthy musicians 5 controls	FCR, ECR Affected TMS intensity 120% RMT Task: Rest	No difference between groups
Rosenkranz, Williamon, et al. (2005)	FHD - 7 MD dystonia 6 WC dystonia 8 musicians 8 controls	FDI Not reported TMS intensity MEP_{1mV} Task: Rest, vibration	No difference between groups
Rosenkranz, Butler, et al. (2009)	FHD 8 MD 8 healthy musicians 6 controls	APB, FDI, ADM Affected TMS intensity MEP_{1mV} Task: Rest	No difference between groups
Samargia et al. (2016)	SD 10 SD dystonia 10 controls	FDI, Masseter Right/dominant TMS intensity FDI MEP_{1mV} Masseter $MEP_{0.3mV}$ S-R curve (slope, AUC) Task: FDI rest, Masseter active	No difference between groups
Siggelkow et al. (2002)	CD 11 dystonia 11 controls	ECR and FCR Right TMS intensity 120% MT Task: Rest	No difference between groups
Stinear and Byblow (2004a)	FHD 7 dystonia 8 controls	FDI Affected/Bilateral TMS intensity 150%AMT Task: Rest	No difference between groups
Stinear and Byblow (2004b)	FHD 7 dystonia 8 controls	APB, FDI Affected/Bilateral TMS intensity 120% RMT Task: Rest, ON/OFF key press	No difference between groups
Stinear and Byblow (2004c)	FHD 5 dystonia (7 hands) 7 controls	FDI Affected/Bilateral TMS intensity 160% AMT Task: Rest	No difference between groups
Suppa et al. (2015)	SD 10 dystonia 10 controls	FDI Bilateral TMS intensity $MEP_{0.8–1mV}$ Task: Linguistic, non-linguistic	MEP amplitude increased in dominant hemisphere in dystonia compared to controls No difference in non-dominant hemisphere
Tinazzi, Zarattini, et al. (2006)	FHD 10 dystonia 14 controls	FCR, ECR Affected TMS intensity RMT + 30% MSO Task: Rest	MEP amplitude decreased in ECR and normal in FCR in dystonia compared to controls
Zittel et al., (2015)	CD 12 dystonia 8 controls	FDI Right TMS intensity 120% RMT Task: Rest	No difference between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Cortical Silent Period			
Allam et al. (2005)	BLP 10 dystonia 8 controls	OO Affected TMS intensity: Highest tolerable Task: 100% MVC CSP duration defined as end of MEP to the latency when EMG activity returned to mean pre-stimulus level	CSP shorter in dystonia compared to controls
Amadio et al. (2000)	CD 13 dystonia 20 controls	SCM, UT Bilateral TMS intensity 100% MSO Task: Rest, 20% MVC CSP duration calculated as difference between end of SP and latency of muscle response	CSP shorter in both muscles in dystonia compared to controls
Boyadjian et al. (2011)	FHD 10 dystonia 10 controls	ECR, FDI Right TMS intensity 110%–190% AMT Task: ECR + FDI co-contraction, ECR + FDI + MD co-contraction CSP defined as time between beginning of MEP and resumption of EMG activity	CSP shortened in dystonia compared to controls
Kimberley et al. (2009)	FHD 6 dystonia 9 controls	FDI Affected TMS intensity 120%RMT Task: 25%MVC CSP defined as length of time between first peak of FDI activation until recurrence of at least 50% of mean of pre-stimulus background EMG	CSP shortened in dystonia compared to controls
Koch et al. (2014)	CD 20 dystonia 10 controls	FDI, APB Right TMS intensity 130% RMT Task:50% MVC CSP defined as duration between onset of MEP and visible return of EMG	No difference between groups
Niehaus, von Alt-Stutterheim et al. (2001)	FHD 25 dystonia 25 control	FDI Bilateral TMS intensity 80% MSO Task: Active CSP defined as interval between onset of EMG response and end of EMG activity inhibition	CSP shortened in dystonia compared to controls No difference between sides in dystonia group
Pirio Richardson (2015)	CD 9 dystonia 9 controls	FDI Right TMS intensity 120% RMT Task:10% MVC CSP determined from onset of TMS test pulse artefact to resumption of EMG activity	CSP shortened in dystonia compared to controls

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Quartarone et al. (2003)	FHD 10 dystonia 10 control	APB, FDI Dominant TMS intensity 130% RMT Task:15% MVC CSP defined as interval between MEP onset and recovery of continuous EMG activity after EMG suppression	CSP shorter in dystonia compared to controls but did not reach statistical significance.
Samargia et al. (2014)	FHD and SD 11 FHD 8 SD 9 controls	FDI Affected/Dominant TMS intensity 120% RMT Task: 25% MVC CSP defined as duration between TMS-induced MEP and return of 50% of prestimulus FDI activity	CSP shortened in both dystonia groups compared to controls
Samargia et al. (2016)	SD 10 SD 10 controls	FDI, Masseter Dominant TMS intensity 120%RMT Task: 25% MVC CSP onset defined as TMS-induced MEP, and offset was point at which muscle contraction returned to 50% of prestimulus average	Masseter CSP shortened in SD compared to controls
Schwenkreis et al. (1999)	CD 20 dystonia 21 controls	FDI Bilateral TMS intensity 20%–30% MVC Task: 150% RMT CSP duration was measured from end of MEP (onset of EMG suppression) until re-occurrence of EMG activity	No difference between groups
Stinear & Byblow (2004c)	FHD 5 dystonia (7 hands) 7 controls	FDI TMS intensity 160%AMT Task: 5%–20% MVC pinch grip CSP duration measurement not stated	No difference between groups
Suppa et al. (2015)	SD 10 dystonia 10 controls	FDI Dominant TMS intensity MEP_{1mv} Task: 50% MVC Task: linguistic, non-linguistic Onset and end-latency of the CSP measured in accordance with their previous studies	CSP shortened in dystonia compared to controls
Short (and long) intracortical inhibition			
Amadio et al. (2014)	CD 8 dystonia 8 controls	FDI Hand not performing the geste ISI: 1, 3 ms CS: RMT – 10% MSO TS: RMT + 20% MSO Task: Rest and during sensory trick	No difference in SICI between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Beck et al. (2008)	FHD 16 dystonia 20 controls	APB Affected ISI: 2.5 ms CS: adjusted to 30% inhibition at rest TS: MEP_{1mV} FDI task: Rest, premotor, phasic, tonic	SICI reduced in the premotor and phasic phase in dystonia compared to controls No difference between groups for SICI at rest and during tonic muscle contraction
Beck, Schubert, et al. (2009b)	FHD 16 dystonia 20 controls	APB Affected ISI: 2.5 ms CS: adjusted to 40% inhibition at rest TS: MEP_{1mV} Task: 10% MVC, 20% MVC	SICI absent during 10% MVC in dystonia but maintained in controls No difference in SICI between groups during 20% MVC
Gilio et al. (2003)	FHD 10 dystonia 8 controls	Forearm extensor Right/affected side SICI ISI: 3 ms CS: 80% RMT TS: 120% RMT Task: Rest, tonic wrist extension	SICI reduced in dystonia group compared to controls
Hubsch et al. (2013)	FHD 21 dystonia 25 controls	APB, ADM Right *SICI* ISI: 2.5 ms CS: 70% RMT TS: 130% RMT *LICI* ISI: 100 ms CS: 120% RMT TS: 130% RMT Task: Rest	No difference between groups for SICI or LICI
Kagi et al. (2017)	CD 21 dystonia 8 controls	FDI dominant hand ISI: 2 & 3 ms CS: 80% AMT TS: MEP_{1mV} SICI S-R Curve ISI: 2 ms CS: 70%, 80%, 90% Test pulse intensity Task: Rest	No difference between groups for SICI or SICI S-R curve
Kanovsky et al. (2003)	CD 21 dystonia 16 controls	FDI Bilateral ISI: 3, 5, 7 ms CS: 80% RMT TS: 125% RMT Task: Rest	SICI reduced in hemisphere contralateral to head turn (3 ms, 5 ms ISI) and no different in hemisphere ipsilateral to head turn in dystonia group compared to controls
Meunier et al. (2012)	FHD 13 dystonia 13 controls	FPB, ADM More affected side ISI: 90 ms CS: 110% RMT TS: 120% RMT Task: Rest	No difference in LICI between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Quartarone et al. (2003)	FHD 10 dystonia 10 control	APB, FDI Dominant ISI: 2 ms CS: 90% AMT TS: MEP_{1mV} Task: Rest	SICI reduced in dystonia compared to controls
Ridding et al. (1995)	FHD 15 dystonia 8 controls	FDI Right/Bilateral ($n = 10$) ISI: 1, 2, 3, 4, 5, 6 ms CS: AMT—5% MSO TS: MEP_{1mV} Task: Rest	SICI reduced both sides in dystonia compared to controls
Samargia et al. (2016)	SD 10 SD dystonia 10 controls	FDI, Mass Dominant ISI: 3 ms CS: 80% RMT TS: MEP_{1mV} Task: FDI rest, Masseter active	No difference in SICI between groups
Siggelkow et al. (*2002)	CD 11 dystonia 11 controls	ECR and FCR Right ISI: 3 ms CS: 70% MT TS: 120% MT Task: Rest	No difference in SICI between groups
Simonetta-Moreau et al. (2006)	FHD 13 dystonia 10 controls	ECR, FDI Affected ISI: 2 ms CS: 80% AMT TS: $MEP_{0.5–1.5\ mV}$ Task: Rest, 10%–15% MVC	No difference in SICI between groups No difference if dystonic posture is in wrist flexion or extension in dystonia group
Stinear & Byblow (2004a)	FHD 7 dystonia 8 controls	FDI Affected/Bilateral ISI: 2,3 ms, optimal ~2.5−6 ms CS: 80% RMT or 50%–90% AMT TS: 150% AMT Task: Rest	No difference in SICI between groups at optimal ISI SICI threshold higher in dystonia compared to controls
Stinear & Byblow (2004)b	FHD 7 dystonia 8 controls	APB*, FDI Dominant ISI: Optimal 2.3–2.8 ms CS: 80% RMT, 90% AMT TS: 120% RMT Task: Rest, ON/OFF key press *predetermined 30% inhibition at rest	No difference in SICI between groups
Stinear and Byblow (2004c)	FHD 5 dystonia (7 hands) 7 controls	FDI Dominant ISI: 2.5 ms CS: 50% inhibition TS: 160% AMT Task: Rest	No difference in SICI between groups
Intracortical facilitation			

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Amadio et al. (2014)	CD 8 dystonia 8 controls	FDI Hand not performing the geste ISI: 15, 20 ms CS: RMT – 10% MSO TS: RMT + 20% MSO Task: Rest and during sensory trick	ICF increased in dystonia group compared to controls
Hubsch et al. (2013)	FHD 21 dystonia 25 controls	APB, ADM Right ISI: 15 ms CS: 70% RMT TS: 130% RMT Task: Rest	No difference in ICF between groups
Kagi et al. (2017)	CD 21 dystonia 8 controls	FDI Dominant hand ISI: 10, 12, 15 ms CS: 80% AMT TS: MEP_{1mV} Task: Rest	No difference in ICF between groups
Kanovsky et al. (2003)	CD 21 dystonia 16 controls	FDI Bilateral ISI: 10, 15, 20 ms CS: 80% RMT TS: 125% RMT Task: Rest	ICF in ipsilateral (all ISIs) & contralateral (10, 20 ms ISIs) hemisphere (in relation to head turn) increased in dystonia compared to controls Greater facilitation in contralateral versus ipsilateral hemisphere in dystonia group (15, 20 ms ISIs)
Ridding et al. (1995)	FHD 15 dystonia 8 controls	FDI Right/Bilateral ($n = 10$) ISI: 7−15 ms CS: AMT – 5% MSO TS: MEP_{1mV} Task: Rest	No difference in ICF between groups
Samargia et al. (2016)	SD 10 SD dystonia 10 controls	FDI, Masseter Dominant ISI: 10 ms CS: 80% RMT TS: MEP_{1mV} Task: FDI rest, Masseter active	No difference in ICF between groups
Siggelkow et al. (2002)	CD 11 dystonia 11 controls	ECR and FCR Right ISI:13 ms CS: 70% MT TS: 120% MT Task: Rest	No difference in ICF between groups
Afferent-induced inhibition			
Baumer et al. (2007)	FHD 7 dystonia 8 controls	FDI Affected side ISI: 25, 30, 40 ms TS: MEP_{1mV} D2 conditioning Task: Rest	No difference in SAI between groups

(Continues)

TABLE 1 (Continued)

Study	Patient sample	Protocol details for dystonia patients	Main finding(s)
Hubsch et al. (2013)	FHD 21 dystonia 25 controls	APB, ADM Right ISI: 20 and 200 ms TS: 130%RMT Median nerve conditioning Task: Rest	No difference in SAI between groups in both muscles LAI reduced in APB in dystonia compared to controls No difference in LAI between groups in ADM
Meunier et al. (2012)	FHD 12 dystonia 13 controls	FPB, ADM More affected side ISI: 150 ms TS: 120% RMT Median nerve conditioning Task: Rest	LAI reduced in FPB (affected muscle) and a trend for reduction in the ADM (non-involved muscle) in dystonia group compared to controls
Pirio Richardson et al. (2009)	FHD 14 dystonia 17 controls	ADM, FDI Dominant ISI: 180 ms TS: 140% RMT D2 and D5 conditioning Task: rest, movement	Trend for reduced LAI in both muscles at rest in dystonia group compared to controls No difference between groups for LAI during movement
Richardson et al. (2008)	FHD 13 dystonia 17 controls	ADM Affected ISI: 23 ms TS: 140% RMT D2 and D5 conditioning Task: Rest, move	No difference between dystonia group and controls for SAI at rest SAI during movement increased in the ADM in dystonia group & decreased in controls
Simonetta-Moreau et al. (2006)	FHD 13 dystonia 10 controls	ECR, FDI Affected ISI: 40 ms CS: 0.9 PT TS: $MEP_{0.5–1.5\ mV}$ Task: Rest, 10%–15%MVC	A strong trend for reduced SAI in dystonia group compared to controls
Zittel et al. (2015)	CD 12 dystonia 8 controls	FDI Right ISI: 25, 30, 40 ms TS: 120% RMT D2 conditioning Task: Rest	SAI reduced in dystonia group compared to controls

Abbreviations: %MSO, percent maximum stimulator output; 4th DI, fourth dorsal interosseous; ADM, abductor digiti minimi; AMT, active motor threshold; APB, abductor pollicis brevis; AUC, area under the curve; BB, biceps brachii; BLP, blepharospasm; CD, Cervical dystonia; CS, conditioning stimulus; CSP, cortical silent period; D, digit; ECR, extensor carpi radialis; ECR, extensor carpi radialis; EDC, extensor digitorum communis; FCR, flexor carpi radialis; FDI, first dorsal interosseous; FDS, flexor digitorum superficialis; FHD, focal hand dystonia; FPB, flexor pollicis brevis; ICF, intracortical facilitation; ISI, interstimulus interval; LAI, long afferent inhibition; LICI, long interval intracortical inhibition; Mass, masseter; MEP, motor-evoked potential; ms, milliseconds; MSO, maximal stimulator output; mV, millivolt; MVC, maximal voluntary contraction; RMT, rest motor threshold; SAI, short afferent inhibition; SCM, sternocleidomastoid; SD, Spasmodic dysphonia; SICI, short interval intracortical inhibition; TMS, transcranial magnetic stimulation; TS, test stimulus; UT, upper trapezius.

RMT and AMT meta-analyses did not reveal differences between dystonia and controls and are detailed in Supporting Information 2. A meta-analysis of LICI was not performed due to only two studies meeting inclusion criteria.

3.1 | Cortical Silent Period

There were 18 studies investigating the duration of the CSP in an isolated dystonia. From these, 13 studies reported the mean ± *SD* and were included in the CSP meta-analysis. Across the 13 studies, there were 157 isolated dystonia patients (FHD, 6 studies; CD, 4 studies; SD, 3 studies; BLP, 1 study) and 168 healthy controls. The sample size ranged from 5 to 25 participants per study. EMG recordings were taken from local hand and/or forearm muscles in all 6 studies of FHD (Boyadjian et al., 2011; Kimberley et al., 2009; Niehaus et al., 2001; Quartarone et al., 2003; Samargia et al., 2014; Stinear & Byblow, 2004c). In CD, one study recorded EMG from local neck muscles

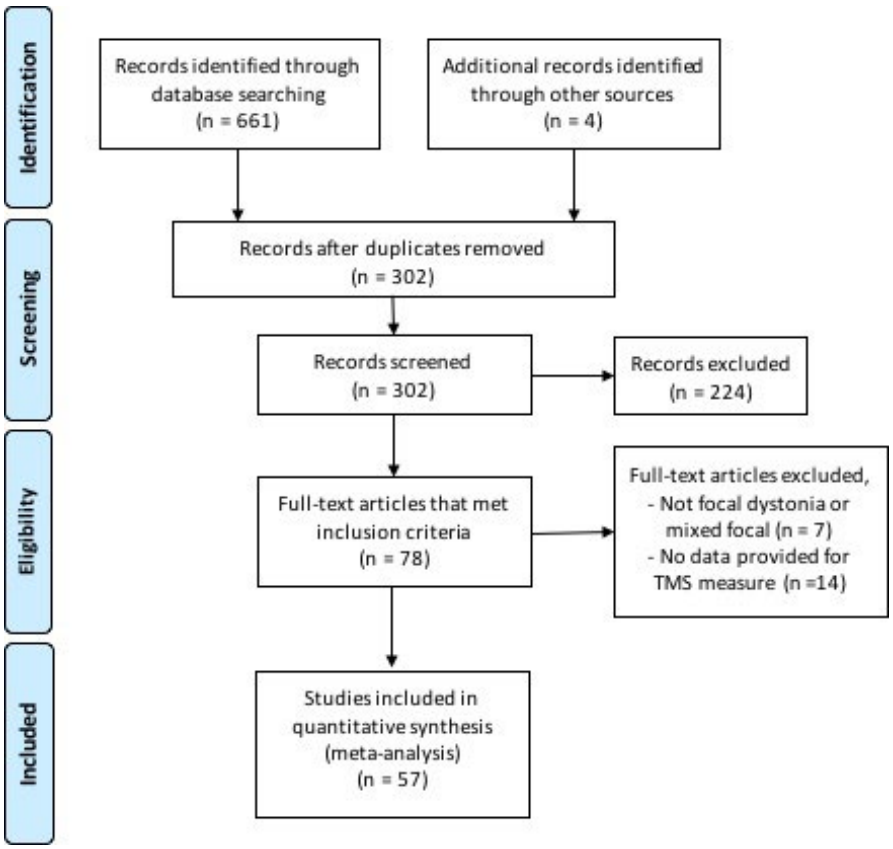


FIGURE 1 PRISMA diagram for the systematic selection of studies

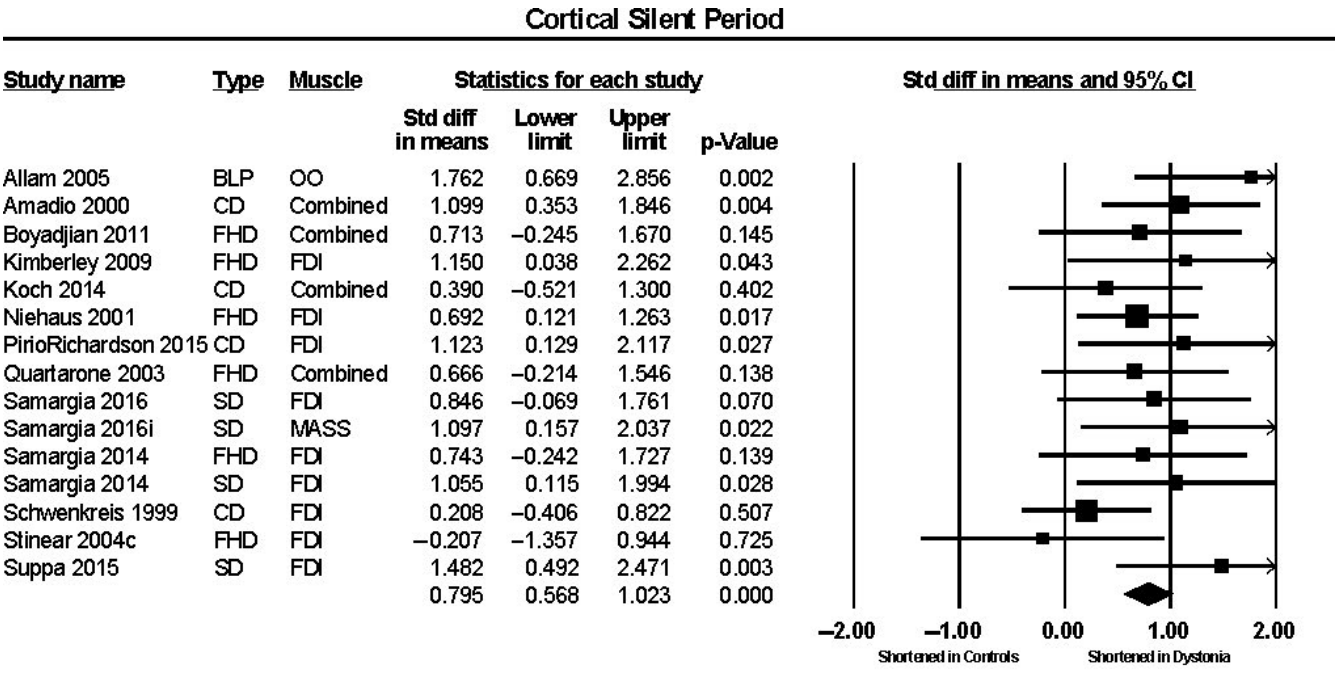


FIGURE 2 Forest plot for cortical silent period (CSP) duration in isolated dystonia compared to controls. FHD, focal hand dystonia; CD, cervical dystonia; BLP, blepharospasm; SD, spasmodic dysphonia; OO, orbicularis oculi; FDI, first dorsal interosseous; Combined, multiple muscles from the same body part were combined. The overall effect of dystonia on CSP duration revealed a high effect favouring shorter CSP in dystonia than controls. Squares represent point estimates of treatment effect (larger squares indicate larger samples), horizontal lines are 95% confidence intervals and the diamond represents the pooled difference (summary) effect and 95% confidence interval

(Amadio et al., 2000), and three from remote hand muscles (Koch et al., 2014; Pirio Richardson, 2015; Schwenkreis et al., 1999). In SD, one study recorded EMG from the local masseter muscle (Samargia et al., 2016) and three studies recorded EMG from remote hand muscles (Samargia et al., 2014, 2016; Suppa et al., 2015). In BLP the EMG was recorded from the local Orbicularis Oculi (OO) muscle (Allam et al., 2005). The SMD between groups was 0.8, 95% CI (0.57–1.02), $p < .0001$, a high effect size indicating shorter CSP duration in isolated dystonia compared to controls (Figure 2). Heterogeneity was low ($I^2 = 3.03$). The *N*-failsafe value was 182 non-significant unpublished studies. The findings indicate a reduction in $GABA_B$ mediated inhibition as assessed by the CSP duration in idiopathic, isolated dystonia.

3.2 | Short-interval intracortical inhibition

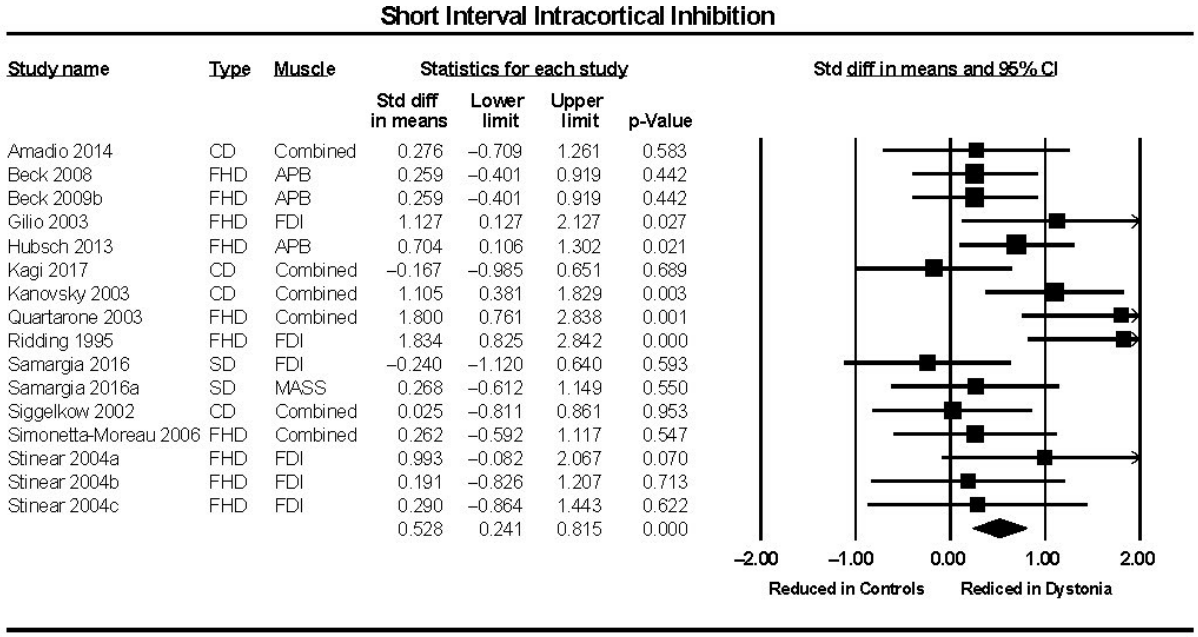
There were 26 studies found that used paired-pulse TMS to measure short-interval intracortical inhibition (SICI). Of these, 15 studies (205 isolated dystonia and 188 controls) reported data and were included in the meta-analysis. Dystonia types were FHD (10 studies), CD (4 studies) and SD (1 study). There were no studies in BLP. Sample sizes ranged from 5 to 25 participants. The EMG recordings were taken from local hand or forearm muscles in all ten studies in FHD (Beck et al., 2008; Beck, Schubert, et al., 2009; Gilio et al., 2003; Hubsch et al., 2013; Quartarone et al., 2003; Ridding et al., 1995; Simonetta-Moreau et al., 2006; Stinear & Byblow, 2004a, 2004b, 2004c). EMG recordings were taken from remote hand muscles in all four CD studies (Amadio et al., 2014; Kagi et al., 2017; Kanovsky et al., 2003; Siggelkow et al., 2002). In the one study in SD, EMG recordings were made from both the local masseter and remote first dorsal interosseous (FDI; Samargia et al., 2016). All SICI recordings were taken with the target muscle at rest, apart from in two studies (Beck, Schubert, et al., 2009; Samargia et al., 2016), where the muscle was preactivated (Masseter only in Samargia et al., 2016). The SMD between groups was 0.53, 95% CI (0.24–0.82), $p < .0001$, a moderate effect size indicating reduced SICI in isolated dystonia compared to controls (Figure 3a). Heterogeneity was medium ($I^2 = 44.3$) and was explored by dystonia type subgroup analysis as outlined a priori (Figure 3b). For FHD, the SMD between groups was 0.71, 95% CI (0.35–1.08), $p < .0001$, a moderate effect size indicating reduced SICI in FHD compared to controls. For CD participants the SMD between groups was 0.34, 95% CI (−0.27 to 0.94), $p = .28$, a weak effect size indicating little difference in SICI between CD and controls. The one study in SD found an SMD between groups of 0.1, 95% CI (−0.61 to 0.64), $p = .97$. The *N*-fail safe value was 84 non-significant unpublished studies. The findings indicate reduction in $GABA_A$ mediated inhibition, as measured by SICI, in local hand muscle cortical representations in FHD, but not when assessed in remote hand muscle representations in CD. Observation of the Forest plot for SD subtype (Figure 3b) suggests SICI may be reduced in the local masseter (corticobulbar innervation), but not in the remote FDI (corticospinal innervation) cortical muscle representations.

3.3 | Afferent-induced inhibition

There were 11 studies identified that measured afferent-induced inhibition, utilizing a range of ISIs ranging from 20 to 200 ms. Of these, seven studies (6 FHD, 1 CD) reported data and were included in the meta-analysis, including 88 people with dystonia and 94 controls. Study sample size ranged from 7 to 25 participants. There were six studies in FHD and one study in CD. All EMG recordings were from local hand or forearm muscles in the FHD studies (Baumer et al., 2007; Hubsch et al., 2013; Meunier et al., 2012; Pirio Richardson et al., 2009; Richardson et al., 2008; Simonetta-Moreau et al., 2006) and from a remote hand muscle in CD (Zittel et al., 2015). The SMD between groups was 0.50, 95% CI (0.20–0.80), $p = .001$, a moderate effect size indicating reduced afferent-induced inhibition in dystonia compared to controls (Figure 4). Heterogeneity risk was low ($I^2 = 0$). The *N*-fail safe value was 13 non-significant unpublished studies. The moderate effect size indicated reduced afferent-induced inhibition in local and remote hand/forearm muscle cortical representations in idiopathic isolated dystonia compared to controls.

4 | DISCUSSION

As shown using TMS, people with idiopathic isolated dystonia have reduced M1 GABA-mediated cortical inhibition relative to healthy controls. Reduced $GABA_B$-mediated inhibition was evidenced by shorter CSP duration, and reduced $GABA_A$-mediated inhibition from lower values of afferent-inhibition. Shorter CSPs were seen in all types of isolated dystonia, regardless of whether local or remote muscle representations were tested. In contrast, $GABA_A$-mediated inhibition measured using SICI was reduced in people with FHD only and was not reduced in CD or SD sub-types. TMS measures of glutamatergic facilitation, net CME and intrinsic membrane excitability, were not different between dystonia and control groups suggesting these neurophysiological processes are normal in the dystonic brain. Overall, the findings of this review provide a more robust view of the TMS literature investigating the neurophysiology of idiopathic isolated dystonia and have implications regarding our understanding of the pathophysiology of dystonia.



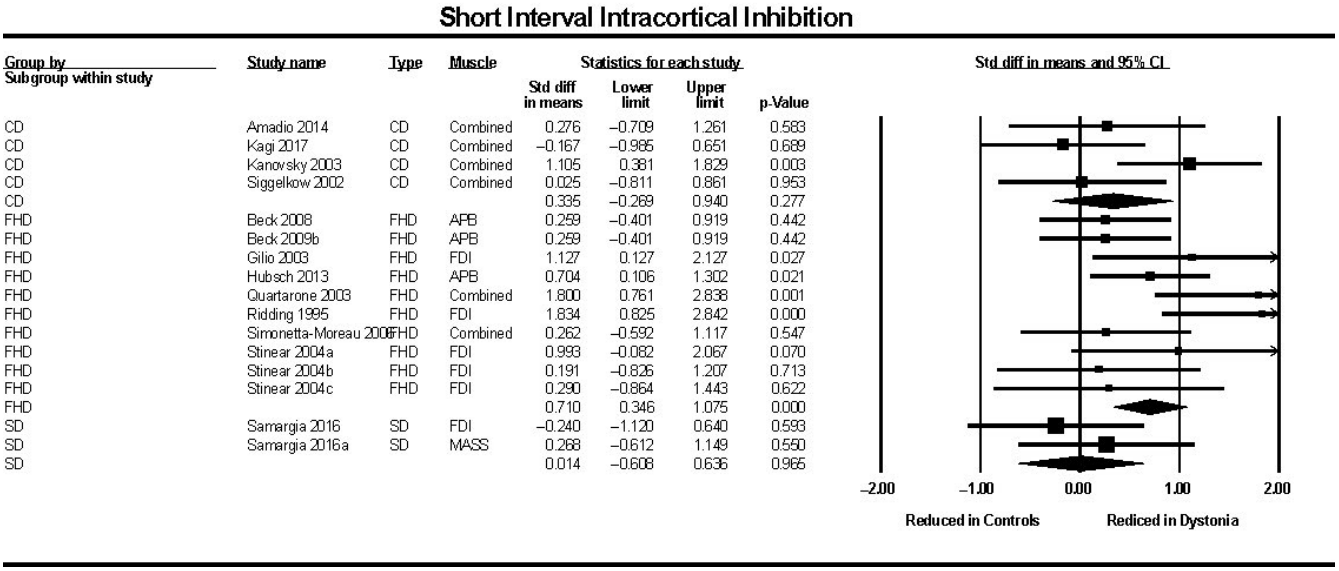


FIGURE 3 A. Forest plot for short interval intracortical inhibition (SICI) in isolated dystonia compared to controls. FHD, focal hand dystonia; CD, cervical dystonia; SD, spasmodic dysphonia; FDI, first dorsal interosseous; APB, abductor pollicis brevis; MASS, masseter, Combined = multiple muscles from the same body part were combined. The overall effect of dystonia on SICI revealed a moderate effect favouring less SICI in dystonia than controls. Note: Samargia et al. (2016) appears twice as the MASS and FDI were analysed as separate measures. B. Forest plot for SICI in isolated dystonia compared to controls for the subgroup analysis. Abbreviations as for Figure 3a. The overall effect of dystonia on SICI revealed a moderate effect favouring less SICI in FHD than controls, a weak effect favouring less SICI in CD than controls and less than weak effect favouring less SICI IN SD than controls. Squares represent point estimates of treatment effect (larger squares indicate larger samples), horizontal lines are 95% confidence intervals and the diamond represents the pooled difference (summary) effect and 95% confidence interval

4.1 | Intracortical inhibition

Gamma-aminobutyric acid is a key neurotransmitter that regulates the balance of excitation and inhibition in the brain. The CSP duration is a measure of $GABA_B$-mediated inhibition of corticomotor cells through activity of inhibitory interneurons located within superficial layers of M1 (Wasserman et al., 2008). Synthesis of data on CSP duration revealed shorter CSPs in people with isolated dystonia compared to healthy controls, that was not different between the dystonia subtypes investigated (CD, FHD, SD, BLP). This finding is consistent with narrative summaries of the literature (Udupa & Chen, 2019), as most individual studies (though often with small sample sizes) have reported that people with dystonia

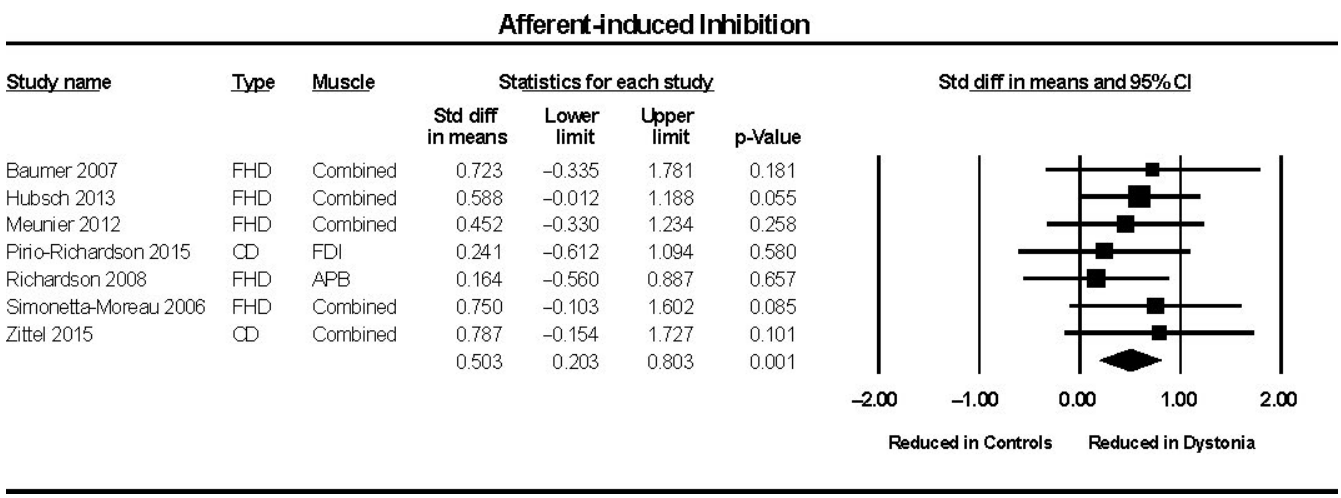


FIGURE 4 Forest plot for afferent-induced inhibition in isolated dystonia compared with controls. FHD, focal hand dystonia; CD, cervical dystonia; FDI, first dorsal interosseous; APB, abductor pollicis brevis; Combined, multiple muscles from the same body part were combined. The overall effect of dystonia on afferent-induced inhibition revealed a moderate effect favouring reduced inhibition in dystonia than controls. Squares represent point estimates of treatment effect (larger squares indicate larger samples), horizontal lines are 95% confidence intervals and the diamond represents the pooled difference (summary) effect and 95% confidence interval

have shorter CSP duration and therefore reduced $GABA_B$-mediated inhibition in M1 relative to controls. Although there was variation in the TMS methods used to evoke and measure the CSP, these did not appear to cause heterogeneity in the findings. As CSP duration was shorter when tested in local or distant muscle cortical representations relative to the dystonic musculature (e.g. in the hand or neck region of people with CD) this may indicate $GABA_B$ inhibitory interneurons are broadly dysfunctional in the M1 and that aberrant inhibition is not specific to cortical representations that control the affected dystonic musculature. Alternatively, it may suggest aberrant $GABA_B$-mediated inhibition detected in the M1 is a consequence of dysfunction occurring in other cortical or subcortical areas that have projections that terminate on M1 $GABA_B$ inhibitory interneurons. Therefore, reduced $GABA_B$-mediated inhibition within M1 may be the result of widespread neural network dysregulation that consequently affects the balance of excitation and inhibition in M1.

Another TMS method to assess $GABA_B$-mediated inhibition is LICI, however only two studies using LICI met our selection criteria. Both studies concluded there was no difference in LICI between FHD and controls (Hubsch et al., 2013; Meunier et al., 2012). As CSP and LICI are thought to be mediated by $GABA_B$ transmission, the different effects of dystonia on these measures may be explained by differences in delivering TMS during voluntary activation which is required to measure the CSP versus rest conditions used to assess LICI, that LICI studies were underpowered, or that LICI and CSP probe different neurophysiological mechanisms in M1, or for other reasons. Overall, the current literature suggests that $GABA_B$-mediated inhibition in the M1 appears to be reduced in all sub-types of dystonia as evidenced by the CSP duration, further research using LICI as an outcome is required.

Short interval intracortical inhibition, a measure of $GABA_A$-mediated inhibition, was found in the meta-analysis to be reduced in isolated dystonia compared to controls, an important finding considering many small studies have reported inconsistent results. Although caution is advised when interpreting this result, as a moderate heterogeneity risk was found, with dystonia subtype a potential source of variability. Subgroup analyses revealed SICI was reduced in FHD, but not in CD or SD, when compared to healthy controls. While these findings suggest $GABA_A$-mediated inhibition is different between the sub-types of dystonia, it may also reflect methodological differences between the target muscle and the affected body region. Often studies will utilize the hand as a target region to measure TMS responses. In people with FHD the hand region is representative of the local or affected musculature, but in people with CD or SD this is a region distant to the abnormal dystonic musculature. In our initial search, we located one study ($n = 10$) in CD that investigated SICI in the sternocleidomastoid (SCM) muscle (Hanajima et al., 1998). The study found SICI in the presumably dystonic and contracted SCM was reduced in CD compared to controls, but SICI was normal when measured from resting hand muscles. Similarly, a study in SD ($n = 10$) found reduced SICI in the activated masseter muscle and normal SICI in the resting hand muscle representations of the same patients (Samargia et al., 2016). Together, these studies indicate deficits in $GABA_A$-mediated inhibition revealed by reduced SICI may only exist in cortical representations of muscles in the analogous dystonic body region. However, an alternative explanation could be that for TMS protocols using the SCM and masseter, SICI was measured during muscle contraction, which is known to reduce SICI, therefore, differences could be explained by voluntary

activation. Furthermore, heterogeneity due to methodological variability of the SICI protocol may also explain current findings. The protocol for SICI requires researchers to select the conditioning stimulus intensity, interstimulus interval, test stimulus intensity, as well as the target muscle of interest, and there are many variations of acceptable SICI protocols (Chipchase et al., 2012). A contemporary SICI technique to explore cortical excitation and inhibition in neurological populations is that of 'threshold tracking' (Vucic et al., 2006). Yet to our knowledge threshold tracking paired-pulse TMS has not been used in dystonia. Further studies are needed comparing SICI in local and remote cortical representations from multiple dystonia subtypes as the relationship between reduced SICI and clinical expression of dystonia in subtypes other than FHD is unclear.

4.2 | Afferent-induced inhibition

Afferent-induced inhibition, a measure of sensorimotor integration mediated by $GABA_A$ transmission (Di Lazzaro et al., 2000, 2007; Turco, El-Sayes, Locke, et al., 2018), was found to be reduced in isolated dystonia compared to controls. All included studies found a reduction in afferent-induced inhibition, including the CD studies where EMG was recorded from remote hand muscles. There was also low heterogeneity despite methodological variation between the type of afferent stimulation (cutaneous digital or peripheral nerve). As all studies were in FHD or CD patients, additional studies in BLP, SD, and CD are recommended to be confident in the findings for these subtypes. In Parkinson's disease, afferent inhibition has also been shown to be reduced or absent relative to controls and is affected by medication status (Sailer et al., 2003). Reduced afferent-induced inhibition indicates abnormal sensorimotor integration within M1, which is unsurprising as cortical processing of sensory information is known to be abnormal in dystonia (Avanzino et al., 2015; Murase et al., 2006). Abnormal sensorimotor control may be responsible for several impairments, such as impaired sensation, proprioception, spatial and temporal perception, oculomotor control, among others experienced in dystonia (Desrochers et al., 2019). The presence of a sensory geste also suggests abnormal reliance on sensorimotor networks, and a potential mechanism for alleviating the dystonic contraction (Desrochers et al., 2019). Understanding the mechanisms leading to reduced afferent-induced inhibition in isolated dystonia may provide novel therapeutic targets which could be explored in future research for alleviating sensorimotor symptoms.

4.3 | Intracortical facilitation

Glutamatergic facilitation within M1, measured by ICF, revealed no differences between dystonia and controls. One study of FHD found a small effect in favour of greater ICF in controls (Hubsch et al., 2013), and the other a medium size effect in favour of greater ICF in dystonia (Ridding et al., 1995). All CD studies recorded EMG from distant (non-dystonic) muscles, with contrasting findings (Amadio et al., 2014; Kanovsky et al., 2003). Methodological variability in TMS measures may be a reason for inconsistent individual study results, as ISIs ranged between 7 and 20 ms, with a range of intensities used for conditioning and test TMS stimulation. It is important that consensus on best-practice TMS protocols for probing ICF is achieved to reduce variability in the literature. The current synthesis of the literature indicates ICF is normal in isolated dystonia, however the unexplained heterogeneity suggests this should be interpreted conservatively.

4.4 | Corticomotor and intrinsic membrane excitability

Many studies investigated CME and motor threshold in dystonia. While most CME studies reported no difference between groups, there were some disparate findings as represented by the wide standardized mean difference confidence interval. The meta-analyses conclusively demonstrated that net CME or intrinsic membrane excitability, measured using CME or MT's appears to be normal in isolated dystonia.

4.5 | Study limitations

The main limitation of the review was that risk of bias was unable to be assessed from the included studies, as is usual when performing a systematic review. To collate the most data possible, we opted to include multiple study designs (i.e. experimental cohort studies, randomized controlled trials) and studies that were designed for different research questions from our own. Therefore, no risk of bias tool was deemed a fair assessment of methodological study quality for the purposes of our research question. The authors instead carefully scrutinized the TMS methodology using their combined technical experience, and only included studies where TMS methods conformed to accepted procedures of data collection and reduction. While we acknowledge this as a limitation, we do not believe this decision to affect the overall findings of the meta-analysis or study conclusions. Furthermore, due to insufficient reporting of data in original studies, many studies were not able to be included in our review. Insufficient reporting of data in TMS studies was highlighted recently, and a TMS reporting checklist developed for this purpose (Chipchase et al., 2012). The implication of excluding data from these studies is unknown and could potentially strengthen or weaken the conclusions of the current review.

4.6 | Future directions

Future TMS studies must make use of the TMS reporting checklist (Chipchase et al., 2012) to ensure consistent and minimum reporting guidelines are met. Adequate reporting will facilitate future synthesis of the evidence base, which is particularly useful for clinical populations like dystonia that often suffer from small sample studies. Future research in CD, SD and BLP should attempt to assess cortical neurophysiology in local (dystonic) muscle representations, even if technically challenging, as it appears some measures may be dependent on the muscle cortical representation tested. In addition, assessing task-dependant impacts on cortical neurophysiology may also be important given the dystonic contraction can often be worsened by voluntary movement. As such, our current conclusions are only relevant for TMS measures of CME recorded from muscles at rest, but future meta-analyses could summarize task-related differences in CME and other TMS measures between isolated dystonia and control participants. Future studies should also adopt the most recent dystonia classification system (Albanese et al., 2013) to ensure consistent comparisons can be made in the literature. Finally, there are other TMS protocols not included in this review, such as surround inhibition (Kassavetis et al., 2018), interhemispheric inhibition (Beck, Shamim, et al., 2009; Niehaus et al., 2001; Summers et al., 2020), cerebellar-brain inhibition (Bradnam et al., 2015; Koch et al., 2014) and premotor cortex to M1 dual-coil TMS (Pirio Richardson, 2015; Pirio Richardson et al., 2014). Future meta-analyses of these more complex measures could be the focus of future reviews.

4.7 | Conclusions

Reduced GABAergic mediated inhibition in M1 of people with idiopathic isolated dystonia relative to controls was identified using several TMS measures (CSP, SICI, SAI) in this review. While ICF was normal in dystonia, the significant heterogeneity between studies suggests the evidence for glutamatergic-mediated neural function in dystonia is still somewhat inconclusive. Meta-analyses of small sample individual patient studies should be encouraged in rare disorders to help overcome the limitations of interpreting data from underpowered studies. Given there are no curative treatments for idiopathic isolated dystonia, a synthesized view of the evidence base may help researchers identify neural mechanisms that could be targeted with novel therapeutic interventions or assessed as an outcome measure of a therapeutic trial. Important considerations in the design and reporting of future TMS studies to allow for data to be synthesized are encouraged. Knowledge gained from this review suggests future interventions could target deficient GABA-mediated inhibitory cortical circuits within M1 and investigate if positive behavioural or clinical changes occur as a result.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

LB conceived the study and performed the meta-analysis. AM performed the search. LB, AM screened the articles, extracted the data, and wrote the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in figshare at [doi 10.6084/m9.figshare.13078019], reference number.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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