VIEWPOINT

A Reflection on Plasticity Research in Writing Dystonia

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ABSTRACT: Much attention has focused on the hypothesis that there is enhanced plasticity of sensorimotor circuits in patients with dystonia. A common experimental method to assess plasticity in dystonia research is paired associative stimulation (PAS). Excessive, nonfocal effects of PAS were observed in early studies of dystonia; however, these large effects have not been uniformly replicated. In this viewpoint, data from 15 patients with writing dystonia are presented. We suggest that, as in healthy individuals, the effects of PAS are highly variable. A review of previous studies examining PAS in writing dystonia highlights the range of results that have been observed. We conclude that current experimental evidence cannot be fully explained by the notion that PAS responses in writing dystonia are consistently excessive or nonspecific. The variability of PAS responses is such that enhanced plasticity should not be considered a dystonic fingerprint, because the direction of response can vary, and there is overlap between patient and healthy data. We also discuss evidence questioning the assumption that PAS responses are a clear correlate to levels of synaptic plasticity; we need to define more specifically what PAS responses signify in the dystonic brain. Our conclusions are limited to PAS in writing dystonia; however, much variation exists with other plasticity protocols. Large multicenter studies of both focal and generalized forms of dystonia, probing variability of individual neurophysiological profiles, are encouraged. This will reveal the true role of plasticity in the pathophysiology of dystonia and may expose subject-specific therapeutic interventions that are currently concealed.

Key Words: writing dystonia; writers' cramp; dystonia; paired associative stimulation; plasticity

In recent years, attention has centered around the hypothesis of abnormal regulation of plasticity within sensorimotor circuits in primary dystonia.[1] In theory, this hypothesis is very attractive. Increased plasticity in dystonia could result in an excessively responsive neuronal machinery with an increased tendency to form sensorimotor associations. The resulting excessive neuronal plastic changes and 'noise' could slowly degrade motor control and lead to the clinical symptoms of dystonia. Genetic mutations that confer risk for dystonia could influence mechanisms that govern plasticity, and environmental risk factors, such as intensive practice in musicians' dystonia, can be eloquently explained by abnormal plasticity.[2] Initial studies that shaped the plasticity hypothesis in dystonia used a version of paired associative stimulation (PAS).[3-7] This method repeatedly pairs electrical stimulation of a peripheral nerve with transcranial magnetic stimulation (TMS) of the motor cortex.[8] The inter-stimulus interval is adjusted to ensure that inputs to the motor cortex initiated by nerve stimulation occur simultaneously with magnetic stimulation. It is widely accepted as a noninvasive manner in which to examine brain plasticity in humans.[9]

In healthy controls, however, the response to plasticity paradigms such as PAS are highly variable between subjects. Some of the factors underlying this variability

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are beginning to be elucidated.[9-12] In fact, a large body of evidence has emerged since PAS was first described, such as the timing specificity and spatial focality, that has led to reinterpretation of many of the key features of PAS.[13] In the dystonia literature, a similar pattern of increasing complexity has emerged. Early studies clearly described large facilitatory and inhibitory effects of different PAS protocols in focal hand dystonia.[3,7] However, more recently, some studies failed to find any effect of PAS protocols in patients with focal dystonia,[14] or no difference between the response of healthy subjects and those with dystonia.[15] In addition, several papers now emphasize that the abnormality in dystonia may be subtler than a simple increase in plasticity in the target muscle group (often abductor pollicis brevis [APB], a median nerve innervated muscle). Instead, patients may have a greater spread of the effect to nontarget muscles, such as abductor digiti minimi (ADM) (heterotopic spread), or a lack of homeostatic interaction between the response to PAS and other plasticity-inducing protocols on the motor cortex.[5,14]

In this work, we illustrate some of the features of PAS responses in dystonia by presenting data from 15 subjects with writing dystonia. We suggest that the variation in PAS response is large, in keeping with that observed in neurophysiological studies of PAS in healthy subjects. We also review the existing literature examining PAS in writing dystonia.

Lack of a Dystonic Fingerprint in 15 Patients With Writing Dystonia

As already noted, early studies examining plasticity responses in dystonia found excessive responses to plasticity protocols in both magnitude and spread to nontarget muscles. Plasticity response is typically assessed by looking for increases in the mean amplitude of motor evoked potentials (MEPs), after PAS has been performed, as a surrogate marker of corticospinal excitability.

With this aim, we looked at the mean of 30 MEPs to target (APB) and nontarget (first dorsal interosseous [FDI], ADM) muscles. The resting motor threshold (RMT), active motor threshold, and recruitment curves (RC), before (baseline) and after (at 0 minutes and 30 minutes [T0 and T30]) PAS, also were recorded. We used the archetypal variety of PAS in which the median nerve is stimulated 25 ms before the TMS pulse to the motor cortex (PAS25).[16] Full experimental details and clinical characteristics of patients (both simple and complex writing dystonia) are given in the Supplemental Data.

Table 1 gives an overview of the main results. If we first look at the 30MEP data, no net change is seen in the mean amplitude (mV) of the motor evoked potential in any of the intrinsic hand muscles tested. Thus, no net plasticity response was observed in APB, FDI, or ADM, and 30MEP was remarkably stable at T0 and T30 in each muscle. In addition, baseline markers of corticospinal excitability, RMT, and active motor threshold remained unchanged (given as % stimulus intensity). Furthermore, we looked in detail at the recruitment curves of each patient. The gradually increasing stimulus intensity used to elicit the RC should be sensitive to subtle shifts in corticospinal excitability outside the range of the '1 mV' 30MEP stimulus intensity. We analyzed the curves by fitting a linear regression to the RC (*r*RC) for *each* individual subjects for *each* muscle tested. No evidence was seen for any change in motor cortex excitability as assessed by the slope of the *r*RC. In summary, plasticity was not excessive in magnitude or spread; in fact, at a group level, very little PAS response was observed.

TABLE 1. Minimal PAS25 response in 15 patients with writing dystonia[a]

	Muscle	Baseline	T0	T30
RMT (%SI)	APB	44 ± 2.4	44 ± 2.5	44 ± 2.3
AMT (%SI)	APB	36 ± 2.2	36 ± 2.1	36 ± 2.1
30MEP (mV)	APB	1.1 ± 0.12	1.1 ± 0.12	1.1 ± 0.18
	FDI	2.1 ± 0.39	1.9 ± 0.29	2.1 ± 0.41
	ADM	1.2 ± 0.29	1.1 ± 0.27	1.4 ± 0.27
rRC (mV/%SI)	APB	1.2 ± 0.34	1.1 ± 0.30	1.2 ± 0.32
	FDI	1.6 ± 0.28	1.4 ± 0.26	1.5 ± 0.28
	ADM	1.1 ± 0.19	0.87 ± 0.17	1.2 ± 0.21

[a]Time points before (baseline) and after paired associative stimulation (PAS25) (T0, T30). All data given as mean ± SEM, to 2 s.f. or nearest integer. Muscles examined were abductor pollicis brevis (APB), first dorsal interosseous (FDI) and abductor digiti minimi (ADM). Resting motor threshold (RMT) (F [2, 28] = 0.84, $p = 0.44$) and active motor threshold (AMT) (F [2, 28] = 1.1, $p = 0.36$) did not change over time. A significant effect of 'MUSCLE' on 30 motor evoked potentials (30MEP) was found (F [2,28] = 5.2, $p = 0.012$) but no change in 30MEP over 'TIME' (F [2,28] = 0.68, $p = 0.52$) or any significant interaction between 'MUSCLE*TIME' was seen (F [4,56] = 0.78, $p = 0.54$). There was no significant effect on recruitment curve regression values (rRC) on 'MUSCLE' (F [2, 28] = 1.90, $p = 0.16$), 'TIME' (F [2, 28] = 1.34, $p = 0.278$) or 'MUSCLE*TIME' (F [2, 28] = 0.94, $p = 0.447$).

Variability of PAS Response

In healthy subjects, large inter-subject variability of the response to PAS occurs. For example, in a sample of 27 people using a variety of PAS, only 14 showed the expected increase in corticospinal excitability, whereas the other 13 exhibited a decrease.[10,17] Furthermore interindividual variability of PAS response is indirectly acknowledged in studies that select PAS "responders" (e.g., defining them as people who facilitate by at least 120%), and exclude those with no response or inhibition as "non-responders."[18] In addition, individual day-to-day variation in the PAS response may be seen.[10,19]

Our own data suggest that intersubject variability to PAS is also likely to be an inherent feature of dystonia. Figure 1 demonstrates the individual variability of

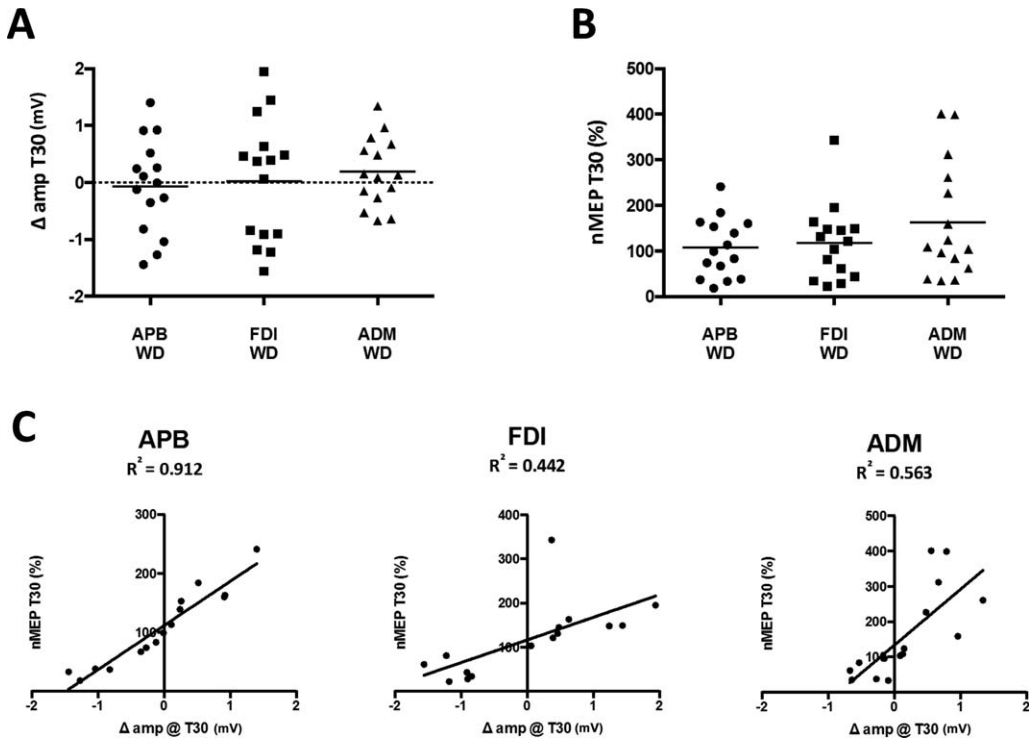

FIG. 1. Variability of paired associative stimulation (PAS25) response in writing dystonia. Each point is data from 1 subject. Muscles examined were abductor pollicis brevis (APB), first dorsal interosseous (FDI) and abductor digiti minimi (ADM). (**A**) Change in amplitude of 30 motor evoked potentials (30MEP) at 30 minutes (Δ amp T30) for the 3 hand muscles in writing dystonia demonstrating both inhibitors and facilitators to PAS25. (**B**) The same data as (**A**) shown as normalized MEP or % change to baseline (nMEP T30). This has been displayed to facilitate comparison with previous studies. (**C**) Correlation of nMEP and Δ MEP amp at T30. For APB (the motor hotspot), the shared variance is high (91.2%); however, for FDI and ADM, the shared variance is much lower (44.2% and 56.3%, respectively). Both of these measures are used interchangeably currently in research articles.

responses to PAS25 in APB, FDI, and ADM. Both change in MEP amplitude at 30 minutes after PAS25 (Fig. 1A) and percentage change of MEP at 30 minutes after PAS25 (Fig. 1B) are shown. Some patients facilitate to PAS25 (amplitude of 30MEP larger at T30 compared to baseline or % change >100) and some patients inhibit to PAS25 (amplitude of 30MEP smaller at T30 compared with baseline or percent change <100). This pattern was seen in all three muscles. Because an approximately equal number of inhibitors and facilitators were found, with a similar range of magnitude for each muscle, little net change in excitability was seen at the group level after PAS25. In our analysis of 15 patients, a similar standard error of the mean of 30MEP was found as in the early papers that demonstrated a clear exaggeration of the PAS response,[3] and thus variability is likely an important and consistent feature in this patient group, as it is in healthy individuals.

What Underlies Variability of PAS Response?

Genetic factors, cortical anatomy, age, sex, time of day, attention to paradigm, recent motor learning, lifelong motor training, parallel motor activity, RMT, priming, and pharmacological influences have all been shown to influence the magnitude of PAS response.[17,20-25] Routine experimental design is unlikely to completely control for all of these and other yet to be identified factors. Subtle differences in the way the PAS protocol is delivered (such as stimulus intensity, the number of pairs of stimulations, and the rate of repetitions) also may affect outcomes.

The increased number of variables in a patient group, such as dystonia, or variability in phenotype and medications, are likely to complicate things further. We examined key clinical and electrophysiological parameters for their statistical power to predict PAS25 response in each muscle and did not find a clear relationship to the magnitude of PAS25 response (Table 2).

Such variability makes the interpretation of the pathophysiological significance of studies of PAS in dystonia rather difficult until the factors that can reliably predict PAS response are better understood. This variability also could explain the wide range of results observed in studies that attempt to replicate previous work (particularly if small numbers of subjects are used).

Review of PAS and Writing Dystonia

We performed a review of all studies that allowed data to be extracted for direct comparison, and these

TABLE 2. Individual PAS25 responses for *each* muscle and their relation to clinical and electrophysiological parameters[a]

		Clinical Descriptors						Electrophysiological Variables						
		Age (yrs)	Sex (M/F)	Previous Botox (Y/N)	Duration of Dystonia (yrs)	Overflow to Other Tasks	Presence of Tremor (Y/N)	Baseline MEP	Δ RMT	Δ AMT	Δ APB	Δ FDI	Δ ADM	Δ rRC
Statistical comparator		Corr	*t* test	*t* test	Corr	ANOVA	*t* test	Corr	Corr	Corr	Corr	Corr	Corr	Corr
PAS25 response	APB	0.23	0.98	0.47	0.97	0.029	0.65	0.053	43	0.16	-	0.17	0.34	0.72
	FDI	0.35	0.87	0.48	0.47	0.36	0.64	0.32	-	-	0.17	-	0.27	0.09
	ADM	0.87	0.28	0.29	0.41	0.44	0.21	0.14	-	-	0.34	0.27	-	0.027

[a]No clinical descriptors such as overflow of dystonia to other tasks or the presence of tremor demonstrated a clear relationship to paired associative stimulation (PAS25) responses. No patients were taking medication known to influence PAS25 response. Individual electrophysiological variables also did not demonstrate potential to predict PAS25 response. For categorical clinical characteristics, the *p* statistic is given from the independent *t* test (binary categorical variable) or one-way ANOVA (nominal categorical variable). For continuous variables the *p* statistic (two-tailed) is given from Pearson's correlation. Muscle specific analysis was undertaken for baseline MEP and the change in *r*RC (i.e., change in the slope of the RC of ADM muscle from baseline to T30 was correlated with the change of amplitude of the MEP of ADM muscle from baseline to T30).
MEP, motor evoked potential; RMT, resting motor threshold; AMT, active motor threshold; APB, abductor pollicis brevis; FDI, first dorsal interosseous; ADM, abductor digiti minimi; *r*RC, linear regression of recruitment curves.

are summarized in Figure 2 and Table 3. The overall impression is that the initial results have not been uniformly replicated in later work.

The first study on 10 patients found an exaggerated response in the target muscle (APB: >300% facilitation) as well as facilitation of responses in nontarget ("heterotopic") muscles that were normally unaffected by the median nerve PAS protocols (in this study FDI, although more commonly ADM is tested).[3] Studies by Weise et al.[7] and Belvisi et al.[26] found a more modest exaggeration of the PAS response in writing dystonia, as well as excessive spread of the effect to heterotopic muscles. However, Meunier and colleagues[15] found *a smaller* response to PAS in patients with focal hand dystonia compared with healthy controls, using a PAS protocol with a lower stimulus intensity (that evoked MEPs of 0.5 mV at baseline) than in the "standard" protocol. When they increased the TMS intensity to evoke MEPs of 1 mV in APB at baseline, they did find facilitation in both APB and ADM (Fig. 2A), but responses did not significantly differ in magnitude from controls.[15] Interestingly, the fractional increase in the APB and ADM responses after PAS were greater than in some other studies[7,26] that *did* find a difference in PAS response between writing dystonia and controls. This highlights the problem in defining abnormality with regard to a control group when variability is so high. A study by Hubsch et al. found a PAS25 response comparable to controls until a comparison at 30 minutes after PAS, when the plasticity response was still present in patients with dystonia but not in controls (in both APB and ADM muscles).[27] In the correlations of individual PAS responses detailed in this study, one also can identify a significant proportion of patients with inhibition to PAS (as in our study). Finally, the present study and that of Kang et al.[14] demonstrated no overall effect of PAS.

Based on evidence from these studies, whether the response in the target muscle, and indeed the nontarget or heterotopic muscles, is consistently enhanced remains unclear.

Methodological Observations

A methodological issue that can influence interpretation of the PAS response is the use of normalized MEPs (nMEPs). The nMEP is calculated by dividing the mean MEP post PAS by the mean baseline MEP. This gives a fractional change in magnitude and facilitates comparison between studies as it attempts to "normalize" for variance in baseline MEP. One interesting repercussion of this calculation is that it may bias results in FDI and ADM. The variability of the baseline MEPs in FDI and ADM is probably greater than in APB, because the motor "hotspot" is usually focused over the position that best elicits a reliable amplitude of MEP in APB. Thus, if, as is often the case, the amplitude of MEPs recorded from ADM at baseline is very small, then a small increase in the magnitude of MEPs after PAS will lead to a large percentage increase in facilitation (change in magnitude/small number $\times 100 =$ large percentage change). This is demonstrated graphically with our dataset in Figure 1: A weaker correlation is found between the effect of PAS calculated as nMEP and change in absolute MEP amplitude for FDI and ADM than in APB. Also, a larger range of percentage change values are found in FDI and ADM than in APB, despite very similar changes in the absolute amplitude across the three muscles.

A further point regarding the nMEP is that by performing analysis in this way, inhibitors to PAS can only have an nMEP range between 0 and 100% whereas facilitators can have a range from 100% to infinity (the highest % change in nMEP in the current study was 401%). Taking an average of nMEP when

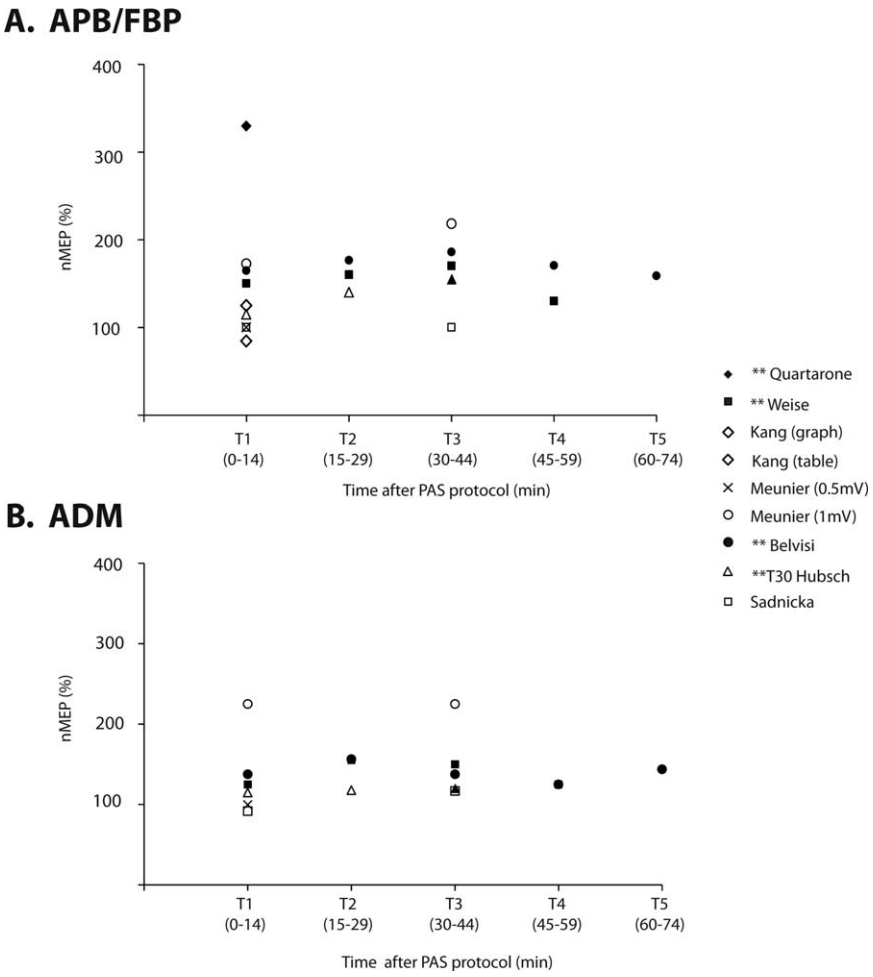

FIG. 2. Graphical comparison of previous studies examining paired associative stimulation (PAS) in writing dystonia. Mean normalized motor evoked potential (nMEP) for abductor or flexor pollicus brevis (APB/FPB) and abductor digitii minimi (ADM) are displayed. Studies are grouped into 5 time epochs (T1-T5) as detailed below the axis. The group mean is displayed as confidence intervals/standard errors were not available all studies. Where a discrepancy between tabulated and graphical data was found, both values are displayed. Table 3 accompanies this figure and gives the clinical details of patients and electrophysiological protocols used in each study. Studies that found a statistical difference between dystonic and control data are marked by a solid black symbol (Quartarone, Weise, Belvisi, Hubsch at T30). The Meunier study (1 mV) failed to find a significant difference between dystonia and control PAS responses yet had PAS responses greater than other studies that *did* find a difference between the 2 groups. This highlights the problem in defining abnormality with regard to a control group when variability is so high.

there are both inhibitors and facilitators is therefore not valid mathematically, because the range for facilitation is greater and thus mean data will tend to over-represent facilitation.

PAS in Perspective

In health, as already emphasized, considerable inter-individual and day-to-day variability occurs in the response to PAS protocols. In addition, considerable complexity is present in the PAS effect itself.[13] For example, some evidence suggests that multiple pathways may contribute to the PAS response rather than the most direct pathway, as is often assumed.[16] Furthermore, PAS is no longer considered to be specific to the target muscle.[13] In several reported instances, changes in the excitability of corticospinal projections have been more pronounced in muscles innervated by a different nerve.[28] What mechanisms of neuroplastic adaptation are engaged by PAS is largely unknown. Assumptions framing PAS as a method that evokes spike timing–dependent plasticity at the synaptic level have been questioned, and possibly a range of cellular mechanisms are involved, perhaps even at different levels of the motor system.[13]

Finally, abnormalities in PAS response have been demonstrated in a multitude of central nervous system disorders (for example: Alzheimer's disease,[29] autism,[30] cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy,[31] migraine,[32] multiple sclerosis,[33] Parkinson's disease[34]). Defining disease-specific profiles of PAS response remains a research challenge.

Reflections on PAS and Writing Dystonia

This viewpoint highlights the observation that some experimental evidence cannot be simply explained by

TABLE 3. Methodological details of previous studies examining PAS in writing dystonia[a]

First author	Year	Patients (n)	Mean age	Muscles recorded	Sensory stim to median n.	TMS M1 site	TMS SI %	Freq of pairs	No of pairs	ISI	Dur (min)	Conclusion
Quartarone	2003	Simple WD (10)	45	APB, FDI	100 μs, 300%pT	APB	1mV	0.05Hz	90	25ms	30	Enhanced facilitation of APB and FDI muscles compared to controls.
Weise	2006	Simple and dystonic WD (10)	39	APB, ADM	200 μs, 300%pT	APB	1mV	0.1Hz	180	21.5ms	30	LTP-like as well as LTD-like plasticity is abnormal with respect to magnitude, temporal properties and spatial organisation.
Kang	2011	Simple and dystonic WD (10)	47	APB	1ms, M-wave	APB	1mV	0.25Hz	225	25ms	15	No change in motor evoked potential (MEP) amplitude seen after PAS25 in APB muscle.
Meunier (Exp 1) (Exp 3)	2012	WD and MD (13) (7)	51	FPB, ADM	250%pT	FPB	 0.5 mV 1-1.5 mV	0.2 Hz	240	25ms	20	No difference in PAS25 response between patients and controls in either target FPB or non-target ADM in Exp 1 and 3.
Belvisi	2013	Simple and dystonia WD (10)	43	ABP, ADM	200 μs 300%pT	APB	0.5-1mV	0.25Hz	200	25ms	13.3	Enhanced facilitation of APB and ADM muscles compared to controls
Hubsch	2013	Simple WD (21)	43	APB, ADM	250%pT	APB	90%AMT	5Hz	600	25ms	2	Comparable responses in APB and ADM in controls and dystonia until T30. At T30 facilitation only in dystonia group.
Sadnicka	-	Simple and dystonic WD (15)	54	APB, ADM	200 μs, 300%pT	APB	1mV	0.2Hz	180	25ms	15	Group data reveals no PAS25 response in APB or ADM. Inter-subject variability highlighted.

[a]The first author and year the article was published index each study. 'Simple' WD describes patients in which dystonic features were present only when writing. 'Dystonic' WD is when dystonia also occurred with other manual activities. The number of patients (*n*) is bracketed. Muscles recorded included abductor pollicis brevis (APB), flexor pollicis brevis (FPB), first dorsal intersseous (FDI) and abductor digiti minimi (ADM). Flexor pollicis brevis (FPB). Duration and intensity (as a percentage of the perceptual threshold (pT) of the sensory stimulation to the median nerve (median n.) are given. The TMS hotspot (motor cortex [M1] site), and stimulus intensity (SI%) are described and the frequency and number of pairings, the interstimulus interval (ISI), and the total duration (Dur) of the paired associative stimulation (PAS) paradigm are detailed. No study has used the same PAS paradigm, and the range of stimulation parameters is evident when studies are tabulated in this manner.

the notion of consistently *exaggerated* responses to PAS25 in patients with writing dystonia. Although such a hypothesis remains valid, the variability of PAS is such that studies have been underpowered to answer this question. Irrespective of whether patients with dystonia show enhanced PAS25 responses, such an effect cannot be regarded as a "dystonic fingerprint" (at least for patients with writing dystonia), because the direction of response can vary, and there is overlap between patient and healthy data. Furthermore, in healthy individuals PAS is no longer considered to be specific to the target muscle; arguments that dystonia has a greater spread of response must also account for this finding in healthy subjects.

Perhaps abnormal plasticity is not the primary driver of the clinical presentation. Clinically, one is struck by the highly conserved stereotypical abnormalities that are exhibited by each patient. Although writing dystonia can spread to the other hand, it is typified by its stability over time and task specificity, which would not be clearly predicted from simple "runaway" plasticity. Similarly, loss of topographic specificity is not clearly supported by clinical cases, because sometimes only an individual digit assumes the abnormal posture.

More generally, there are perhaps more questions than answers as to what PAS responses represent at the neuronal or synaptic level. Much work suggests that it cannot be assumed that PAS responses are a clear correlate to levels of synaptic plasticity, and future research should try and define in a more specific manner what PAS responses signify in the dystonic brain.

Whilst seemingly disappointing, the conclusions drawn here may have important implications for the planning and outcome of future studies in this field. For example, it becomes difficult to use magnitude of PAS response at a group level as a marker of potential therapeutic effect of a novel intervention, because it hides this individual variability and complexity. If individual plasticity profiles are given more weight within studies, then subject-specific interventions may have greater potential. Otherwise, at the group level a study that aims to "reduce plasticity" may have its beneficial effects on excessive PAS responders hidden by a negative effect on those that have minimal response to PAS.

Scope of This Work

Our conclusions are limited to the use of PAS25 protocols in writing dystonia. We did not extend our review to other forms of noninvasive brain stimulation examining plasticity or those that assess the expression of homeostatic plasticity. These other protocols have been used in the same group of patients, and some[5,6,35] but not all[26] have reported increased responses in dystonia. However, the same caveats may exist with these data. The numbers of patients examined with each protocol has been small. Given that the variation in response to theta burst protocols[11,36,37] and 1 Hz rTMS[38] is at least as large as that to PAS, likely these effects also may fail to be replicated in some future studies.

Finally, we do not know whether these conclusions are valid for other forms of dystonia. Other focal and generalized dystonias also have been reported to have increased responses to a variety of plasticity-inducing protocols.[1,4,39-44] Large multicenter studies are needed to fully explore the variability of plasticity responses in these subtypes of dystonia and to better assess for potential cliniconeurophysiological correlations.

A limitation of this current work is that we have compared studies that have used slightly different PAS methods. As variations on methods have proliferated, deviations in results have become more numerous, and these methodological variations are often held accountable. Methodological variation is not, however, the only explanation for the range of results observed in different studies using PAS paradigms. Indeed, scientific evaluation of individual variability, which has its foundation in the physiology of each patient, may hold the key to defining the role of plasticity in the pathophysiology of dystonia.

Conclusion

Our work and that of others demonstrate unrecognized complexities regarding experimental methodology and pathophysiological assumptions in patients with writing dystonia. Better understanding of these factors is needed to advance the plasticity hypothesis in dystonia and to facilitate the search for novel treatments for this disabling condition.

Supplementary Table Clinical characteristics of patients

Key to abbreviations: Hand Handedness assessed by Edinburgh Handedness Inventory; R right; L left; Overflow '-' no overflow to tasks other than writing; '+' one other task; '++' multiple other tasks; Last botox last botulinum toxin injection given in either m months or y years; '-' has never received botulinum toxin injections. ■

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Supporting Data

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