Feedforward somatosensory inhibition is normal in cervical dystonia

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Abstract:

Background: Insufficient cortical inhibition is a key pathophysiological finding in dystonia. Subliminal sensory stimuli were reported to transiently inhibit somatosensory processing. Here we investigated whether such subliminal feedforward inhibition is reduced in patients with cervical dystonia.

Methods: Sixteen cervical dystonia patients and 16 matched healthy controls performed a somatosensory detection task. We measured the drop in sensitivity to detect a threshold-level digital nerve shock when it was preceded by a subliminal conditioning shock, compared to when it was not.

Results: Subliminal conditioning shocks reduced sensitivity to threshold stimuli to a similar extent in both patients and controls, suggesting that somatosensory feedforward inhibition is normal in cervical dystonia.

Conclusion: Somatosensory feedforward inhibition was normal in this group of cervical dystonia patients. Our results qualify previous concepts of a general dystonic deficit in sensorimotor inhibitory processing.

Main Text

Dystonia is a movement disorder characterized by sustained muscle contractions that lead to twisting movements, or abnormal posture [1]. One key pathophysiological finding in primary (or according to the new classification, isolated [1]) dystonia is insufficient cortical inhibition [2]. Somatosensory abnormalities have been described in patients with primary dystonia, including impaired spatial acuity and abnormal tactile temporal discrimination [3]. The spatial spread and time constant of local inhibitory cortical networks could explain both [2].

These networks regulate cortical excitability and also selectivity [4]. Double-pulse motor and sensory paradigms have been used to study their noise-suppression and response-regulation properties. A low-intensity stimulus causes a brief transient suppression of cortical excitability, which is typically measured as a decreased cortical response to a second stimulus[4, 5]. This paired-stimulus suppression is thought to reflect feedforward inhibition within a single intra-cortical, or possibly thalamocortical, circuit.

Even subliminal stimuli can trigger such feedforward somatosensory inhibition. Subliminal shocks may impair perception of a subsequent threshold shock [4]. Neuroimaging revealed somatosensory deactivations caused by such subliminal stimulation [4]. The subliminal stimuli are thought to trigger an inhibitory cortical gating mechanism to avoid excessive vulnerability to noise. Studies in in animal models suggested inhibitory interneurons in somatosensory cortex [6] as the possible mechanism for this effect. The activity of these interneurons was precisely timed with respect to spikes in thalamocortical afferent fibres, and their fast-spiking behavior was consistent with known properties of GABAergic cortical neurons. The suspected inhibitory interneurons were found to be highly sensitive to minimal

thalamic inputs, consistent with a possible role in preventing excessive responses to noise. Importantly, these interneurons were shown to underlie a brief window of inhibition within layer IV of a single cortical barrel. Their inhibitory effect on cortical field potentials was maximal at a latency of around 30 ms, suggesting this time window for the feedforward inhibitory mechanism. A similar mechanism was also hypothesized to underlie subliminal feedforward inhibition in humans [4]. High-frequency EEG oscillations superimposed on the N20 somatosensory evoked potential have been proposed as a direct readout of the effects of inhibitory circuits within the primary somatosensory cortex [7], though we are unaware of direct pharmacological evidence for a GABAergic mechanism underlying this measure. Interestingly, the HFO amplitude was reported to be reduced in CD [7].

Based on these pathophysiological considerations, we investigated whether this subliminal-induced feedforward inhibition is reduced in patients affected by dystonia. Given that dystonia is widely associated with insufficient somatosensory and motor cortical inhibition, reduced subliminal inhibition was predicted. Patients and volunteers detected threshold shocks on the index finger. A subliminal conditioning shock was presented immediately before a random subset of threshold shocks. Inhibition was quantified using signal detection theory, as the drop in sensitivity to detect the threshold shock when the conditioning shock was present, compared to when it was absent.

Subjects and Methods

Participants

Sixteen patients affected by cervical dystonia (CD) (7 male, 1 left-handed, mean age ± SD: 56.2 ± 8.8 years) and 16 healthy controls matched for age, sex and hand dominance were included in the study. Patients were recruited from the Botulinum Toxin clinics of the National Hospital of Neurology and Neurosurgery of one of the authors (KPB). Testing was performed at a minimum interval of 12 weeks following Botulinum Toxin injections for cervical dystonic symptoms. Written informed consent was obtained from all participants. The study was approved by the research ethics committee of University College London and adhered to the ethical standards of the Declaration of Helsinki.

Experimental procedure

Verbal and written instructions about the task were given to participants at the beginning of the session. The participant's left hand was placed comfortably on a table, and a pair of ring electrodes was placed over the distal phalanx of the index finger with the cathode 1 cm proximal to the anode. Stimulation was delivered with a neurophysiological stimulator (Stanmore stimulator, Medical Physics Department, UCL), whose current level and pulse duration were controlled by a computer. Within the range used here, shock intensity depends only on the total charge transferred from the electrode, which is the product of the amplitude and duration of the current pulse. Therefore, we obtained estimates of somatosensory perception by holding pulse amplitude at 10 mA and varying pulse duration [8]. To identify individual somatosensory thresholds, the method of limits was used to estimate the lowest shock intensity at which a tactile stimulus could be reliably detected. Pulses of increasing width were applied until participants reported a sensation. The pulse width obtained with this procedure was successively tested in a detection block and adjusted until

exactly 5 of 10 pulses were detected. This level was considered as a working estimate of each subject's tactile threshold. Subliminal stimulation was delivered at below threshold intensity (15% less then threshold intensity [4]). An additional sensory detection block with 10 subliminal pulses and 10 catch trials in which no stimulus was present was recorded to confirm that the subliminal stimuli were not detectable.

Participants performed a somatosensory detection task consisting of four trial types: 30 trials with shock intensity at threshold delivered on the left index finger, 30 trials in which a subliminal shock was delivered 30 ms before the threshold test pulse on the left index finger, 30 trials in which only the subliminal shock was presented on the left index finger, without a threshold test pulse and 30 catch trials in which neither subliminal shock nor threshold test pulse were present. Trial order was randomised. Participants were blindfolded throughout the task. The beginning of each trial was signaled by an auditory cue. The shock, if present, was delivered after a variable interval of time between 800 ms and 850 ms thereafter, and a second auditory cue 800 ms later indicated the end of the trial (Figure 1A). Participants were required to indicate whether or not they felt the shock, making unspeeded verbal responses. Data for each trial were recorded and analysed later.

[PLEASE INSERT FIGURE 1]

Data analysis

Somatosensory detection results were analysed using signal detection analysis [9]. Accordingly to the experimental design, we considered two experimental conditions: near-threshold shocks that were preceded by a subliminal conditioning pulse and near-threshold shocks that were not. Then, we computed the number of hits (trials in

which the threshold shock was present and participants said 'yes'), false alarms (number of stimulus-absent catch trials in which participants said 'yes'), misses (number of stimulus-present trials in which participants said 'no') and correct rejections (number of stimulus-absent catch trials in which participants said 'no') for each experimental condition. Hit rates [the proportion of stimulus-present trials to which subject responded 'yes'] and false alarm rates [the proportion of stimulus-absent trials in which the subject responded 'yes'] were calculated [9]. These were used to obtain the perceptual sensitivity index (d'), a measure of discriminability in detecting the signal against background noise [9]. The tendency to report stimuli as present irrespective of their actual occurrence (C, response bias) was also obtained.

Separate measures of sensitivity and response bias were calculated for near-threshold shocks that were preceded by subliminal conditioning, and for those that were not. The difference between these values represents an index of the strength of subliminal inhibition.

A 2x2 ANOVA with 'Condition' as within factor (two levels: 'threshold pulse and 'subliminal pulse + threshold pulse') and 'Group' (CD, control) as between factor was performed on sensitivity and response bias data.

Results

Detailed clinical patient characteristics are presented in Table 1.

[PLEASE INSERT TABLE 1]

Direct statistical comparison does not reveal difference in somatosensory threshold level between the groups ($t(30)=0.871$, $p=0.391$, CD patients: mean pulse duration

(microseconds) = 68.75; SD = 21.07; mean pulse duration (microseconds) = 63.56; SD = 11.12; see also Table 2 for individual somatosensory threshold data).

[PLEASE INSERT TABLE 1]

Sensitivity data showed a significant main effect of Condition ($F(1,30)=25.643$; $p<0.001$). No significant effect of Group was found ($F(1,30)=1.788$; $p=0.191$), and the interaction between Condition and Group was not significant ($F(1,30)=0.449$; $p=0.508$). Thus, subliminal conditioning pulses significantly reduced sensitivity to threshold shocks in both CD patients and controls (respectively, $t(15) = 4.226$, $p = 0.001$; $t(15) =2.991$, $p = 0.009$) (Figure 1B).

Response bias data revealed a significant main effect of Condition ($F(1,30)=35.446$; $p<0.001$), no significant effect of Group ($F(1,30)=0.340$; $p=0.564$) and no significant interaction ($F(1,30)=1.231$; $p=0.276$). A more liberal bias was present in both groups (CD patients: $t(15) = 5.373$, $p < 0.001$; healthy controls: $t(15) =3.214$, $p = 0.006$), when the subliminal pulse was present than when it was absent (Figure 1C).

Discussion

Reduced cortical inhibitory processing has been a central finding in primary dystonia, and an important clue to the underlying pathophysiology [2]. The concept of a general deficit in cortical inhibitory processing was suggested by previous reports of a dystonic deficit in a wide range of tasks and measures thought to reflect inhibitory processing [2]. In the motor system, some studies reported deficits of temporally-specific inhibition in dystonia, including CD [10, 11], writer's cramp [12, 13] and generalized dystonia [14]. Surround inhibition, a form of action-related spatial lateral

inhibition between finger muscles, was deficient in focal hand dystonia [15]. Within the somatosensory system, tactile spatial acuity, as measured by the grating orientation test [16] is thought to depend on the lateral inhibition between adjacent cortical tactile receptive fields [17]. Accordingly, tactile acuity was reported to be impaired in focal forms of primary dystonia, such as CD, focal hand dystonia and blepharospasm [18-21]. Additionally, several studies have reported dystonic deficits in "tactile discrimination time" – the minimum delay between two cutaneous stimuli at which an asynchrony can reliably be detected [19, 22-24]. Thus, this literature might suggest a general deficit in all corticalinhibitory processing in dystonia, perhaps reflecting a single underlying pathophysiology of cortical circuits.

However, the tasks described above can also be viewed according to a taxonomy of inhibitory processing, with two independent axes. The first factor distinguishes spatial from temporal inhibitory mechanisms, while the second distinguishes somatosensory from motor inhibitory functions. Dystonic deficits have been reported for different combinations of the spatial-temporal and somatosensory-motor factors. However, few studies have compared the severity of deficits across multiple tasks, and it remains unknown whether the deficit is more prominent for spatial vs. temporal measures, or for somatosensory vs. motor functions. Moreover, some studies have reported normal levels of inhibition in primary dystonia [19, 20, 25-29].

Here we investigated behavioural correlates of feedforward subliminal inhibition, a temporal form of inhibition within the somatosensory system, for the first time in a group of 16 CD patients and healthy controls. We found no evidence for any dystonic deficit, suggesting that sensory gating triggered by weak stimuli is intact in CD. Thus,

our results are not consistent with previous reports of a general deficit in cortical inhibitory processing.

We consider three possible reasons for this discrepancy. First, previous accounts of a *general* deficit in cortical inhibitory processing could be overemphasized. For example, *cognitive* inhibitory function is accepted to be normal in dystonia [30]. Some previous studies reported normal sensory [19, 20, 26] and motor [25, 27-29, 31] inhibition. Feedforward subliminal somatosensory inhibition is thought to depend on cortico-cortical and thalamocortical projections, based on neuroimaging evidence and behavioural studies of spatial spread [4, 32]. Thus, there is a convincing link to a specific inhibitory circuit, yet no deficit was found. This specific form of somatosensory inhibition may therefore be preserved in dystonia.

Second, our result could reflect the somatotopic character of dystonia. Our patients were recruited on the basis of diagnosed *cervical* dystonia, but our measures of somatosensory inhibition were taken by stimulating the fingers. An inhibitory processing deficit might therefore exist only for those somatotopic regions where dystonic movements are expressed. For example, our patients might potentially exhibit a somatosensory inhibition deficit if stimulated in the neck region, but not the hand. However, the clinical literature contains clear examples of deficient inhibition without any dystonic movements, either somatotopically-localised or otherwise. For example, temporal discrimination for *manual* stimuli was impaired in *cervical* dystonia [22], and also in non-manifesting DYT1 gene carriers [14].

Third, subliminal inhibition might not, in fact, depend on intracortical interneuronal circuits. While neuroimaging studies have suggested that somatosensory inhibition is responsible for this perceptual effect [4, 32], the involvement of cortical inhibitory

interneurons has not been conclusively established, either by animal recordings or by pharmacological interventions with GABA antagonists [33].

We also acknowledge several limitations in our study. First, we have examined the clinical population of CD, so we cannot generalise to all primary dystonias. Second, our investigation used only the 'classic' subliminal somatosensory inhibition parameters. Inhibition of adjacent fingers [32] or with different conditioning-test latencies, might reveal a dystonic inhibitory deficit. We proposed above that 'cortical inhibition' may not be a unitary construct. Measures of 'inhibition' in dystonia may be distinguished according to whether they involve spatial or temporal processing, and according to whether they involve somatosensory or motor function. We believe this is the first test of feedforward subliminal inhibition in any dystonic population. Our results suggest that this form of inhibition, at least, is unaffected in cervical dystonia. Further research is required to investigate this form of inhibition in other body parts of patients with CD, and in other forms of dystonia.

Author Contributions

A: Drafting/revising the manuscript for content, including medical writing for content. B: Acquisition of data. C: Study supervision or coordination.

CG, EF, KPB, PH: A,B,C

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Table captions

Table 1. Patient's clinical characteristics.

^ = all patients have been receiving Botulinum toxin injections (last injection performed at a minumum of 12 weeks prior to study participation). * = for migraine. ^ = for restless-legs syndrome.

Table 2. Somatosensory threshold for CD patients and healthy controls.

Individual somatosensory threshold values for both CD patient group and healthy control group. Threshold values are expressed as pulse duration (microseconds). Pulse amplitude was set at 10mA.

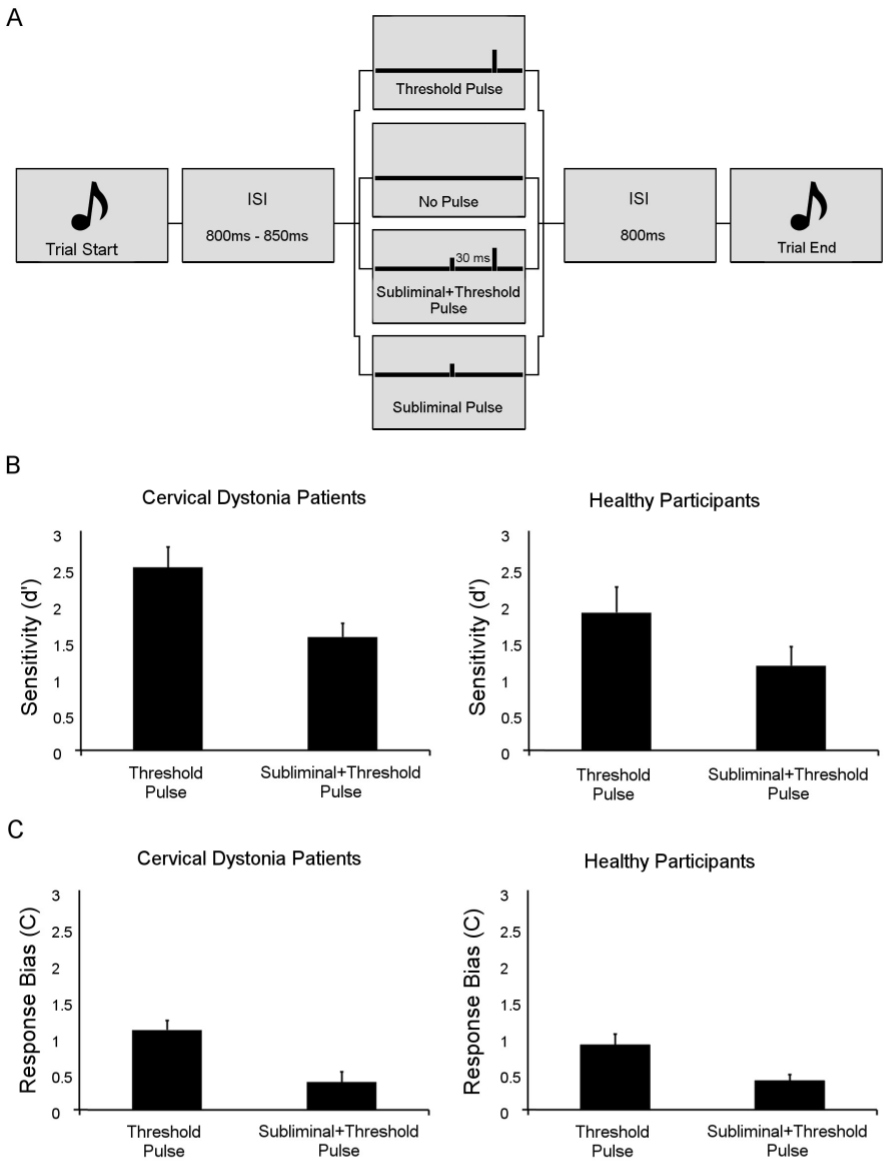
Figure caption

Figure 1. Experimental paradigm and results.

A: Timeline of each experimental trial. Participants received one of four conditions at random (i) a pulse with intensity at threshold, (ii) a catch trial in which no stimuli were present, (iii) a subliminal shock delivered 30 ms before the threshold test pulse and (iv) only the subliminal shock. At the end of the trial, participants verbally reported whether or not they felt the threshold shock.

B: Sensitivity results. A preceding subliminal stimulus reduces sensitivity to a subsequent threshold stimulus in both CD patients and healthy volunteer participants.

C: Response bias results: A conditioning subliminal stimulus increases liberal bias (probability of responding 'shock present' irrespective of condition).


A
Threshold Pulse
No Pulse
30 ms
Subliminal+Threshold Pulse
Subliminal Pulse
Trial Start
ISI
800ms - 850ms
ISI
800ms
Trial End
B
Cervical Dystonia Patients
Healthy Participants
Sensitivity (d')
Threshold Pulse
Subliminal+Threshold Pulse
C
Cervical Dystonia Patients
Healthy Participants
Response Bias (C)
Threshold Pulse
Subliminal+Threshold Pulse