Brain-activity-based vibrotactile stimulation for dystonia

Background and Aims

Dystonia is a disabling and highly heterogenous movement disorder, which can cause involuntary twisting of the neck, cramping of the hand, tremor, or tonic muscle contractions in multiple parts of the body. In the UK more than 100 000 people are affected by dystonia[1]. The causes of primary dystonia are still poorly understood, and the condition can be difficult to diagnose and manage. In many cases it takes years before receiving a correct diagnosis and suitable treatment.

Dystonia is not a neurodegenerative condition, but a network disorder, which can be triggered by injuries, infections, medication, toxins or even stressful life events combined with a genetic predisposition[2,3]. In idiopathic cases no clear cause is apparent. Speculations about the neural mechanisms causing dystonia have included reduced cortical inhibition, maladaptive plasticity and dysfunctional sensory integration, but so far have failed to create new treatment options[4]. Currently available treatments include medication, injections of botulinum toxin, physiotherapy and invasive deep brain stimulation surgery, however they carry risks and unwanted side effects and the level of symptom relief that can be achieved is highly variable[5,6]. Pain caused by dystonic muscle spasms and compensatory postural changes can be a major source of disability, forcing some patients to give up work.

One remarkable phenomenon is that so-called 'sensory tricks', for example touching the cheek lightly or wearing a scarf, can intermittently relieve excessive muscle contractions. Individual cases of effective sensory tricks have been observed for all forms of dystonia, although not all patients have an effective sensory trick and it is more common in primary dystonia[7–9]. Based on this observation, a study in the early 90s showed that somatosensory input in the form of vibrotactile stimulation (VTS) delivered to the head, neck or back, could alleviate muscle contractions in 5 of the 11 studied patients. One exciting aspect of this study is that VTS could relieve symptoms even in some cases that had no alternative effective sensory trick[10].

Surprisingly, even though similar studies have been published more recently[11,12], no study to date has tested the viability of vibrotactile stimulation for providing long-term, possibly daily relief. One concern that might have prevented such studies is the possibility that brain activity might simply adapt to persistent sensory stimulation, resulting in rebounding symptoms, and in the worst-case scenario perhaps even reduced efficacy of simple touch-based sensory tricks.

Based on latest neuroscientific findings on the pathophysiology of dystonia[13], we set out to develop and test a vibrotactile stimulation protocol that responds to ongoing brain activity in an adaptive manner, to "outsmart" internally generated neural activity and avoid habituation. Our project capitalized on a recently published computer algorithm that can manipulate brain activity with high temporal precision. In this study (funded by a Rosetrees Seedcorn award and MRC/EPSRC funding), we targeted neural low-frequency oscillations, which correlate positively with dystonia severity[14–17]. We recorded brain activity using electroencephalography (EEG) and applied brain-activity-based VTS in 7 participants affected by dystonia (6 focal neck dystonia, 1 axial torso dystonia). In line with our hypothesis, **we found that repeatedly targeting a specific phase of the pathological oscillation can be highly effective in relieving symptoms. This was effective in 4 of 7 patients, potentially mildly effective in 2 (but would require further tests and parameter optimization)** and ineffective in one participant.

The principle of phase-locked stimulation has been used successfully in proof-of-principle studies suppressing essential tremor and manipulating pathological oscillations in Parkinsonian brains[18–21], but ours is the first study that successfully applies the concept to develop a new treatment for dystonia.

Supporting data

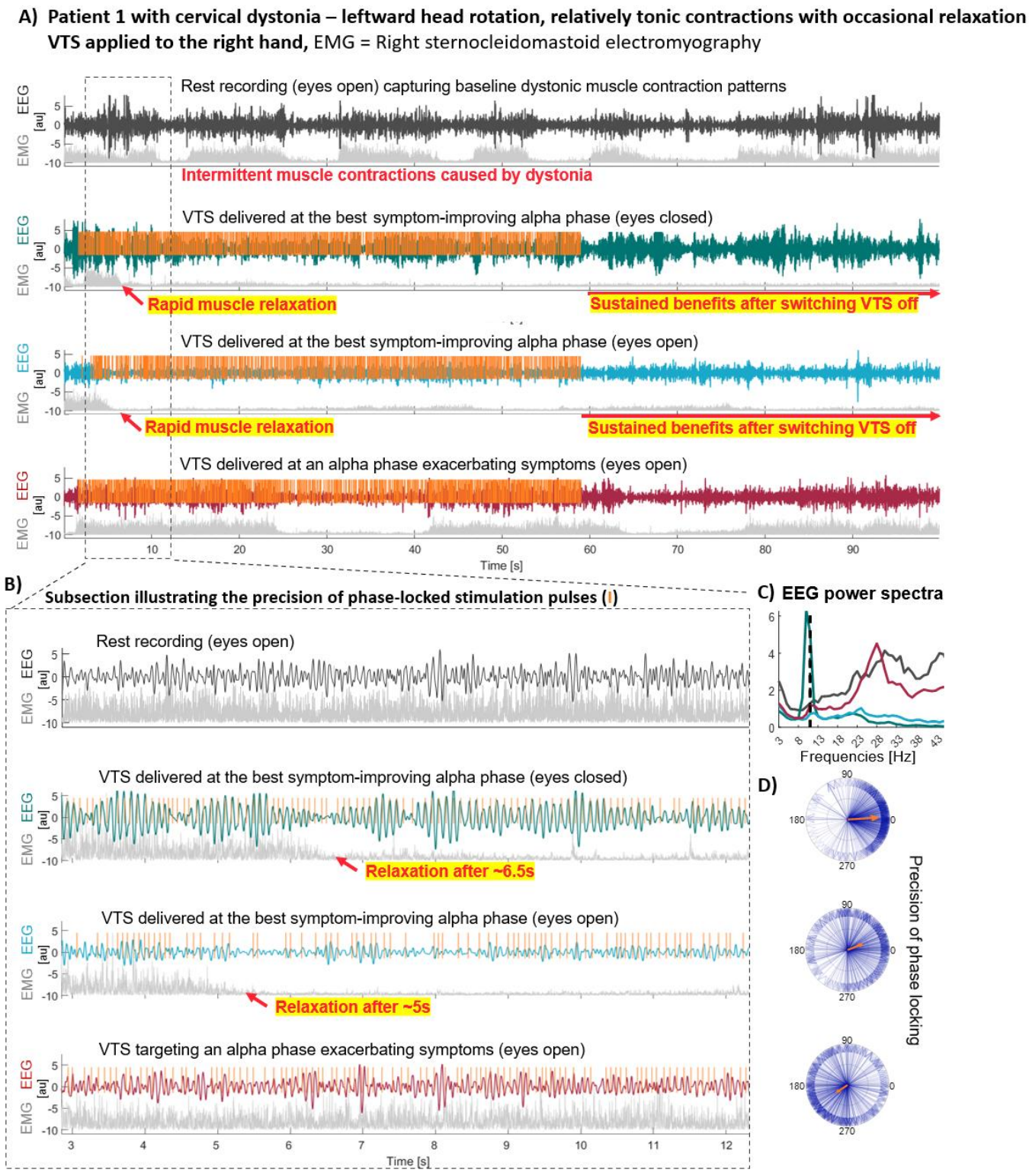

Figure 1 | *A) Example EEG and EMG data shown from one typical responder. Bursts of EMG activity (light grey) show dystonic muscle contractions, which are alleviated briefly after the effective stimulation setting (orange pulses, 2nd and 3rd row) is switched on. Stimulating at the opposite phase (4th row) prolonged the muscle contractions. B) Subsection of the start of the recording showing the precision of phase tracking. C) Power spectra showing strongest alpha synchronization when the patient's eyes were closed. The power difference in higher frequencies is due to the stronger muscle activation when VTS was off or was applied at a symptom-exacerbating phase. D) Blue arrows show the phase of the EEG tracking signal at the time of stimulation. The length of the orange arrow depicting the mean indicates the precision.*

The key findings of our pilot tests are:

1) **Stimulation timing (i.e. the target phase) matters more than the location of delivery.**
One key finding of our initial experiments was that the precise VTS location was less crucial for clinical efficacy than the timing of the vibration pulses (**Fig. 1+2**). Stimulation of the hand or wrist was most effective in alleviating dystonia symptoms despite the involuntary dystonic contractions occurred in neck or back muscles. "Clinical efficacy" here refers to a relaxation of the affected muscles, increased control over them, an increased range of movement and a return of the head orientation to a relatively central position. Moving the vibration device onto affected muscles was less effective, likely because the vibration was barely perceptible due to the lower density of neck/back mechanoreceptors compared to the hand[22]. It implies that wrist-worn vibrating devices might be well suited for providing daily relief.
Our four responders reported large subjective symptom improvements during their best stimulation settings (0-10 scale with 0=no dystonia, 10=worst dystonia; baseline severity/improved severity of 10/1, 7/1, 7/1.5, 8/2). Among them was a patient with axial torso dystonia, who has been suffering from disabling pain rendering them unable to work or do household chores. They had no effective sensory trick, but still benefitted from our intervention, allowing them to perform a much wider range of movements pain-free. Improvements in "mild responders" were 8/6.5 and 6/1, but were less consistently linked to a specific stimulation setting.

2) **Some variability in timing is acceptable.** Phase-specific stimulation requires tracking and processing of brain activity in real time, ideally as fast as possible with minimal delays. The oscillating signal in the brain is not perfectly regular – some cycles are shorter, some longer, hence if communication delays between devices are too long, the phase precision of the stimulation timing would deteriorate, and stimulation might be delivered randomly instead of targeting a specific point of the oscillatory cycle. Our EEG data transfer via USB and data processing in Python was fast enough to target sub-sections of 8-12 Hz alpha oscillations with sufficiently high precision (**Fig. 1B+D**). Alpha oscillations become stronger and more regular when participants close their eyes, which also increases the stimulation timing precision (**Fig. 1D**, compare stronger vs. reduced precision in the top vs. middle plot). But even when participants had their eyes open, resulting in reduced alpha synchronization, a much weaker peak in the power spectra (**Fig. 1C**, blue line) and decreased precision of phase-locking, we achieved substantial symptom reduction (**Fig. A+B,** blue line, 3rd row).

3) **Stimulation parameters within patients appear to be stable across multiple sessions.**
One patient participated in four repeated visits over the course of five months and their optimal stimulation parameters remained stable. Patients reported a strong relief of their dystonic muscle contractions and a much wider movement range, which exceeded what their sensory tricks could achieve.

4) **EEG tracking is necessary.**
Importantly, participants were blinded to the stimulation conditions. Nevertheless, we found that targeting a specific phase in one individual was consistently effective in alleviating dystonia symptoms. Stimulating at the phase opposite to the one that was most beneficial exacerbated symptoms. Furthermore, a "replay control condition", which simply replayed a pulse pattern, which was previously generated by phase-tracking, showed that the same vibration pattern is only effective for symptom relief when it is triggered based of brain activity, but not when it is simply replayed without tracking brain activity. As stimulation is active in all conditions and perceptually indistinguishable, our effects cannot be simply explained by psychological reactions to the intervention. Instead, our findings suggest that brain activity tracking is necessary to achieve maximum symptom relief. In two responders, continuous 80 Hz stimulation also provided some symptom relief, however the effects were less pronounced.

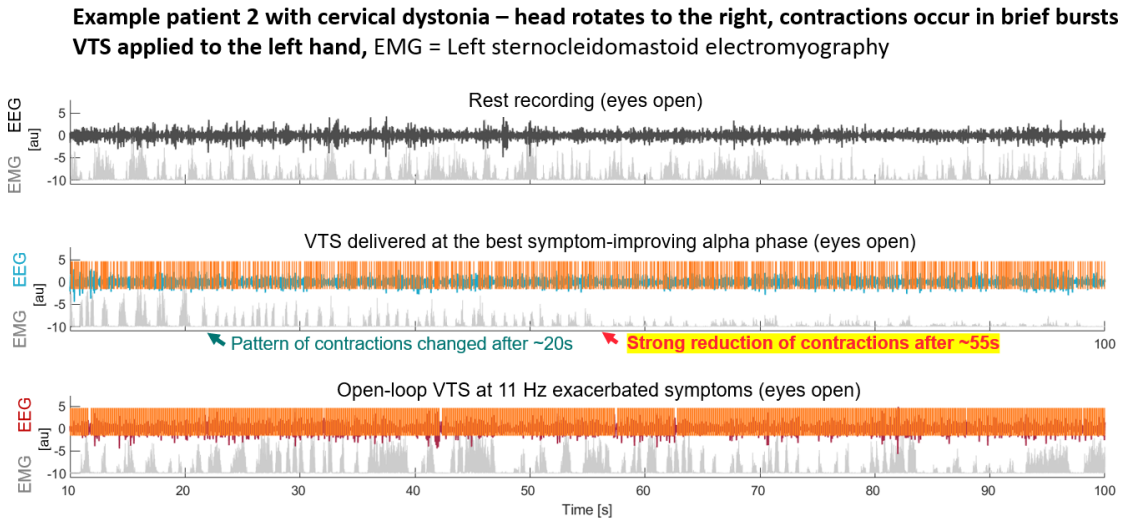

Figure 2 *| Example data of another typical responder experiencing dystonic contractions in brief bursts rather than sustained periods. It took longer for symptoms to subside in this case (~55 seconds), but once they improved, they remained strongly reduced for several minutes after stimulation was stopped (not shown in this figure).*

References

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