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Treatment of writer's cramp based on current pathophysiological concepts

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Task specific dystonia belongs to the group of focal dystonias. They are debilitating movement disorders that present with co-contraction of antagonist muscles during a specific task. The most common one is writer's cramp. Botulinum toxin is the symptomatic standard treatment. Its response rate is 50% after 1 year, and the overall efficacy limited due to unwanted weakness in not injected muscles. The pathophysiology of writer's cramp remains unclear, but genetic and additional environmental causes have been proposed. A possible underlying mechanism may be maladaptive reorganization in the sensorimotor cortex. Based on this background alternative treatment strategies were developed such as several different sensory and motor training programs that have been applied to reverse these brain abnormalities. In some studies, sensory and motor training were combined and adjunct with fitness exercises. They were conducted either as an outpatient setting or were established home based. Clinical outcome was measured with different clinical scales such as the writer's cramp rating scale, the arm dystonia rating scale or the Burke, Fahn Marsden Scale. For objective assessment, kinematic handwriting parameters were analyzed. Functional or structural changes of the sensorimotor cortex were estimated using functional magnetic tomography, magnetencephalography and voxel-based morphometry. The results of these training programs were promising; however, one drawback is that the number of patients studied were small and the programs were not controlled since it is difficult to establish a control training to conduct a randomized controlled study.

KEYWORDS

writer's cramp, treatment, pathophysiology, sensorimotor disorganization, structural and functional imaging

Introduction

Writer's cramp (WC) is the most common task specific form of dystonia. With a prevalence of 3.8–80/1,000,000 people it ranks among the orphan diseases (1). The mean age of onset is 38 years. Clinically, patients present with co-contraction of antagonist muscles during writing. In some cases, involuntary flexion of one or several fingers and/or the wrist are the main complaints. Others show extension of their fingers and/or the wrist

during writing or the abnormal posture may be accompanied by tremor (2) (see Figure 1). Mirror dystonia may occur in up to 44.6% of patients in the affected, resting hand, when they are asked to write with their contralateral, non - affected hand (3). In simple writer's cramp co-contraction presents mainly during writing, while in more complex forms other fine motor tasks are also affected (4). In the literature, the complex forms of writer's cramp have also been referred to as dystonic writer's cramp because of the occurrence of dystonia during other activities (5). Patients with writer's cramp often use a high pen pressure and increased axial pressure during writing (6–8). The writing speed and frequency are often reduced and the writing movement is irregular (9). Moreover, with high sensitivity and specificity abnormal word legibility and peak accelerations have been discovered when using a handwriting recognition software to record word legibility in an automated manner (10).

Task specific dystonia may also affect other professions such as musician's, golfer's, typists or hairdressers. In musician's dystonia the fingers are most commonly affected, rather than the hand. Task specific dystonia impacts patient's livelihood and has substantial socio-economic impact, causing many patients to give up their profession (11). The standard treatment includes botulinum toxin (BoNT) injections into affected muscles. However, BoNT injections are not always helpful and may cause a number of side effects (12). As alternative treatment approaches training programs have been developed (13). In this review we will focus on these treatment strategies that are based on the current neurophysiological findings and discuss their methodology and outcome. We will also discuss future perspectives.

Pathophysiology of writer's cramp

The pathophysiology is multifactorial and has been linked to environmental and genetic factors (14–17). It is considered a motor network disorder including the sensorimotor cortex, basal ganglia, thalamus and cerebellum and provides a model for other forms of task specific dystonia areas (18–21). Several studies demonstrated impaired sensory function (13, 22–27), abnormal reorganization of the somatosensory cortex (S1) (28, 29) and sensorimotor integration (30) as result of maladaptive neural plasticity (31), alterations in motor planning with a lack of neuronal inhibition (13, 17), and cerebellar dysfunction (19, 32, 33). These areas are also involved during writing (34–36). Probably, not only the planning of a writing movement is affected (37), but it seems like the parieto-premotor-M1 network, which codes well-trained and skillful tasks, is deficient (38, 39).

The sensory system is deficient in writer's cramp

Several structural and functional imaging as well as neurophysiological methodologies have been implemented to understand the deficient sensory system in writer's cramp. The general view is that maladaptive reorganization of the somatotopic finger representations within the primary somatosensory cortex is a pathogenic feature in task specific dystonia.

For example functional connectivity was strengthened between the somatosensory cortical-putamen loop during a visuo-motor control task (40). The putamen seems to play a major role as its grey matter volume is elevated (39, 41). The thalamus, another area that contributes to sensory processing, is considered as a central dysfunctional hub integrating basal ganglia and cerebellar output and gating sensory streams (26). Here, grey matter decreases were found bilaterally in affected patients (42).

Beside imaging studies there are a number of neurophysiological studies that demonstrated abnormalities of the sensory system in writer's cramp. First, proprioceptive processing was defective as shown in a tonic vibration task (43, 44). Second, contact heat-evoked potentials and pain rating were reduced using quantitative sensory testing (45). Third, tactile information processing was impaired (26). Specifically, temporal (26, 48) and spatial discrimination thresholds (SDT) (22, 48, 49) are increased. Fourth, fine force regulation was disturbed. Patients with writer's cramp had not only deficits in the coordination of grip and lift load (50), but also in scaling of the precision grip force in a drawer opening task (51). A grip force overshoot during the initial lifts of an

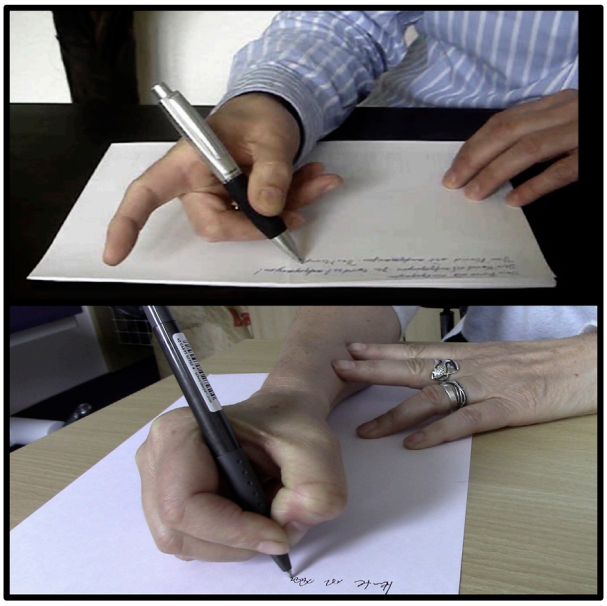

FIGURE 1
Figure shows two different types of writer's cramp. The upper patient presents with extension of the index finger during writing. In the bottom part of the figure the patient has flexion of the thumb with contraction of flexor pollicis longus muscle.

unfamiliar object has been described (52). Fifth, patients with writer's cramp showed increased error, greater variability, and longer release in a force tracking task indicating a generalized deficit in sensorimotor integration (53). Finally, they presented with an abnormal rate of force production and relaxation during wrist movements when measuring peak torque output at the elbow joint and in multiple flexor and extensor muscle groups (54). They had difficulties in adjusting the pressure of their index finger to rather low force plateaus given by visual cues (55). In a probabilistic cued fine motor task writer's cramp patients were capable of anticipatory adaptation of forces, but could not utilize the decision range in motor planning and adjust their force (23).

Writer's cramp is a sensorimotor network disorder

Functional and structural imaging studies have advanced our understanding of the pathophysiology in WC (21). Studies examining the morphometric changes in focal dystonia detected either increased or decreased grey matter volume, in some studies bilaterally, in the putamen or globus pallidus (41, 56–59). In patients with writer's cramp, voxel-based analysis showed larger grey matter volume bilateral in the posterior part of the putamen and globus pallidus (39). Conversely, decreased grey matter density was found in the hand area of the left primary sensorimotor cortex, bilaterally in the cerebellum, and subcortically in the thalamus in the same patient group (42). Diffusion tensor imaging (60) identified lower fractional anisotropy in the tracts between the middle frontal gyrus and putamen (61). In contrast, higher fractional anisotropy has been reported bilaterally between the posterior internal capsule and the ventroposteriolateral thalamic nucleus. Tractography demonstrated that changes involved fiber tracts connecting the primary sensorimotor or the brainstem (62). Finally, more recent work included diffusion-weighted imaging (DWI) and graph theoretical analysis to examine the structural connectome. The structural regional networks in dystonic patients showed a reduction in the number of nodes mainly in the bilateral putamen. In writer's cramp, the abnormalities occurred bilateral in the insula and the anterior and middle cingulate cortex. The cerebellar vermis, the left cerebellar lobule VIII and the inferior temporal gyrus were also affected. Thus, structural changes in areas that are involved in dystonia represented nodes of a large structural network disruption that were related to areas responsible for sensorimotor planning and processing during writing (18).

Using functional imaging, patients with WC exhibited abnormal blood oxygenation level dependent (BOLD) activity in the sensorimotor cortex, cerebellum and possibly thalamus during writing in an fMRI study (63). The BOLD response was decreased in cortical and subcortical areas during a finger tapping tasks in patients with in simple and/or complex WC compared to controls (39, 64), the hippocampus (65) and the hippocampal-striatal functional connectivity reduced, while the activity was increased in the putamen (65). After practice, premotor-striatal areas, which connectivity correlated with motor performance, were overactive (65). Dynamic causal modelling techniques revealed that patients with WC used the same neural network as healthy individuals during finger tapping, but the effective connectivity patterns differed between both groups. Specifically, the effective connectivity between the globus pallidus' inhibitory influence on the motor cortex (M1) was weakened while M1 inhibited the putamen stronger in WC. Furthermore, connectivity between M1 and the cerebellum and the cerebellum and the putamen was altered in WC (20). Functional network changes have further been explored using graph theoretical analysis approaches. Here, hub analysis revealed alterations in communication patterns of the primary motor cortex, the thalamus and the cerebellum. Especially the abnormal activity in the cerebellum had been attributed to compensatory rerouting at an early stage of the disease (33) (see Figure 2).

The influence of writing on the cortical and subcortical network

The premotor cortex is involved in planning and monitoring writing movements while the superior parietal cortex controls the somatosensory information and integration into a motor plan (34–36). In an executed writing compared to an imagined writing task the activated network was the same, although during writing the activation of the fronto–parieto-temporal network was clearly more pronounced during the execution of writing in a group of healthy individuals (Figure 3). In contrast, WC patients displayed reduced connectivity between the dorsal premotor and superior parietal cortex (66) that was positively correlated with the severity of dystonic symptoms. They demonstrated a more pronounced BOLD signal in the contralateral sensorimotor cortex, the supplementary- and dorsal premotor cortex as well as in the putamen and thalamus during motor imagery of writing (66). Motor imagery of grasping a pencil for writing lead to an elevated BOLD response in the supplementary-, dorsal pre- and motor cortex (BA 6) indicating alterations in planning a writing movement (37). In the task specific network of the dominant hand, WC patients showed a deficient parieto-premotor-M1 network, which codes well-trained and skillful tasks (38, 39). The cerebellum (vermis und lobulus VI) and the anterior, associative putamen showed decreased activation in writer's cramp patients that were unrelated to the specific task (38).

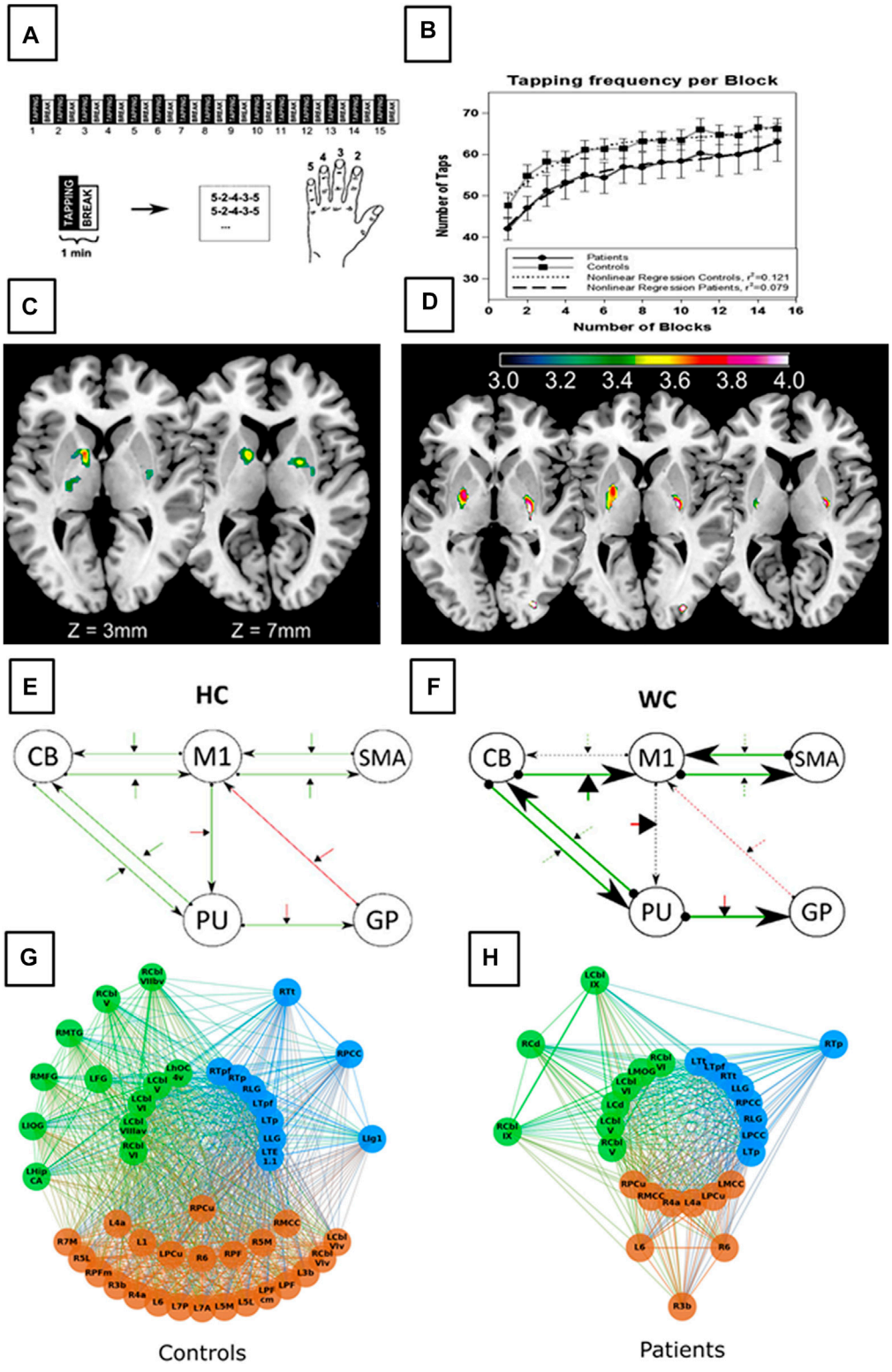

FIGURE 2
Figure displays morphometric alterations and functional disturbances in network communication in WC patients compared to healthy controls (HC). The task included a block-wise executed sequential finger-tapping task **(A)** of the non-dominate hand to avoid dystonic contraction during tapping. Behavioural results demonstrate comparable motor performance in HC and WC patients **(B)**. Voxel based morphometry demonstrate increase grey matter density within the basal ganglia in WC patients **(C)**. Functional magnetic resonance imaging revealed altered basal ganglia

(*Continued*)

FIGURE 2 (Continued)
activation **(D)** in WC patients (putamen and globus pallidus). In addition, altered network functions in WC patients can be demonstrated using dynamic causal modeling **(E,F)** with stronger task activated connectivity in both, the cortico-cerebellar and the cortico-basal ganglia loops. Graph theorem analysis revealed altered modular hub formation in WC patients. The order of the circles display different hierarchical hubs, starting with the connector hubs in the innermost circle, provincial hubs in the intermediate circle and high influence nodes on the outer circle. WC patients network architecture differs in terms of the number of hubs per network (blue the front-occipital module, green the parietal module and brown a subcortical module) and a reduction in high influence nodes, and provincial hubs. These results together identifie WC as a network disorder even detectable in the non-dystonic hand (Figures 1A–D adapted from Zeuner et al. (39); Figures 1E, F adapted from Rothkirch et al. (20); Figures 1 G, F adapted from Schill et al. (33).

Increased excitability and loss of inhibition in writer's cramp

Reduced inhibitory control over cortical motor areas might be responsible for sustained muscle contraction in patients with writer's cramp (31). For decades, not only loss of inhibition, but also increased excitability at multiple levels have been discussed as an underlying pathophysiological feature in patients with writer's cramp (67). This includes the motor cortex (M1), premotor cortex, somatosensory cortex (S1), and the cerebellum. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. GABAergic deficits have been described in the sensorimotor cortex and in the cerebellum and might be an explanation for the loss of inhibitory control resulting from maladaptive plasticity and abnormal surround inhibition (68).

Treatment of writer's cramp

Standard treatment of writer's cramp

The standardized therapy, botulinum neurotoxin (BoNT) injections into affected muscles, has been shown to be effective in a number of uncontrolled (69) and one randomized, placebo controlled study (12, 70). Kruisdjik et al. (2007) included 40 patients writer's cramp (12). Their patients received either BoNT or placebo EMG guided in a randomized manner twice with 1 month apart in case they were unsatisfied with the treatment effect. The primary outcome measure was the patients' decision to either continue or stop the injections after 3 months. They were followed for a year. Fourteen from 20 patients reported a positive effect from BoNT and chose to continue the treatment, while in the placebo group 13 of 19 patients wished to stop with the injections. The positive results were supported by improvements in the visual analogue scale (writing), the writer's cramp rating scale, the writing speed and the symptom severity scale. Ideally, the application of the toxin should be performed with ultrasound or with stimulation through the EMG needle in order to target the correct muscle for injection (69, 71, 72). However, most patients display several ways to compensate their dystonic posture, so frequently it is difficult to identify the dystonic muscles (70). Hence, just 50% of patients, who were treated for 1 year (12) decided to continue with BoNT treatment. In a retrospective 10 years follow-up, only 20/214 patients continued this treatment. The reasons for discontinuation included a lack of treatment efficacy or involuntary paresis in not injected muscles probably caused by spreading of the toxin into neighboring muscles. Affected patients might then show a paresis in both, the injected and non-injected muscles, which can result in restraints in their daily activities that are more severe than the disability in writing (73).

Sensorimotor training based on pathophysiological concepts

Alternative treatment approaches based on the pathophysiology of writer's cramp have been developed. This includes re-training programs with different concepts. The purpose of these training programs was to achieve a long-term effect.

One of the first training programs that had been developed aimed at re-organizing the disturbed somatosensory maladaptation and disorganization in the sensory cortex by implementing a sensory training with Braille reading (74). As an objective parameter the grating orientation task was used. Patients improved their writing and their performance in the grating orientation task, but a long-term effect remained only as long as they trained (75).

In subsequent motor training programs with (76) or without precedent immobilization (77, 78) patients learned individualized finger movements. Immobilization was carried out continuously with a splint for the wrist and the finger joints. Patients with writer's cramp have difficulties in activating fingers individually, because they often present with co-contraction. Therefore, therapeutic putty has been used to teach patients moving each finger separately. Pathophysiologically the intention was to reverse cortical disorganization, enhance the training efficacy and normalize sensorimotor integration. Their efficacy on writing was measured with kinematic analyses of writing movements (6, 9, 76–78). The purpose of those motor training programs was to decrease the abnormally increased writing pressure (6), disturbed regularity of movement kinematics (9, 78) and dystonic symptoms (6, 76, 78). Training without

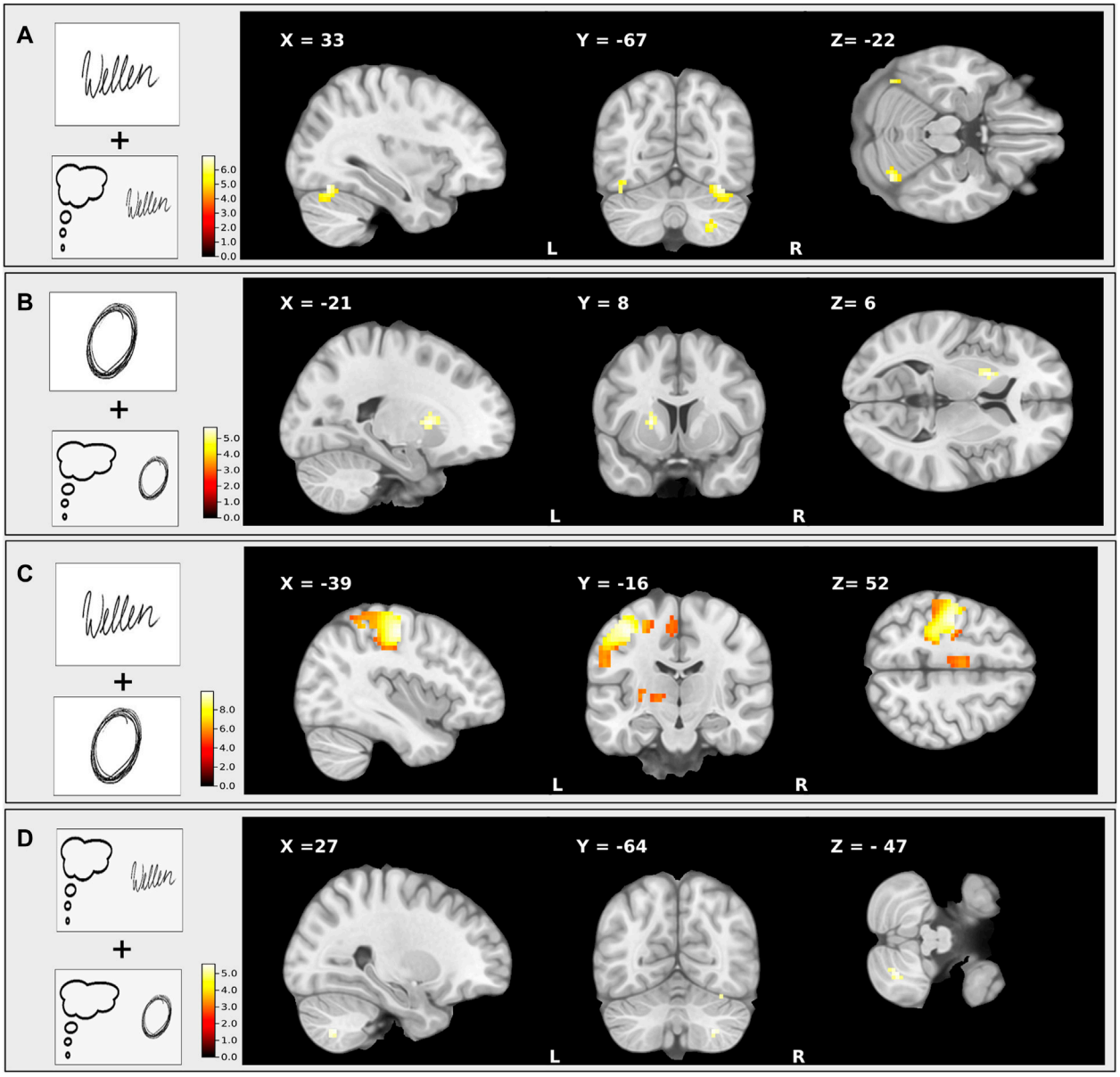

FIGURE 3
This figure shows the T-maps of four different conjunction contrasts: **(A)** executed writing and imagined writing were accompanied by an increased activity of the ipsilateral cerebellum and the contralateral sensorimotor cortex; **(B)** executed drawing and imagined drawing revealed elevated activity of a fronto–parieto-temporal network; **(C)** executed writing and executed drawing induced an enhanced activation of the left somatosensory and premotor area; **(D)** imagined writing and imagined drawing revealed a higher involvement of occipital activation during. The clusters were significant within the ROI analysis after FWE-correction on $p < 0.05$. This figure is adapted from Baumann et al. (36).

immobilization led to mild improvement in simple handwriting parameters (77), while the combination of a 4 weeks forearm immobilization with subsequent re-training over 8 weeks improved the writing fluency, and patients exerted less vertical force on the digitizing tablet (76). In addition, there was significantly clinical improvement as indexed by a decrease in the writer's cramp rating scale (79) and an increase in the arm dystonia rating scale (80). Transcranial magnetic stimulation (TMS) was implemented to test concurrent changes in regional excitability. Grey matter changes in the contralateral primary motor hand area (M1HAND) were evaluated utilizing voxel-based morphometry (VBM). Specifically, either suppression of regional excitability or grey matter decrease after immobilization or enhancement and grey matter increase after re-training of the right, dominant hand were analyzed in the contralateral left M1HAND area. While immobilization reduced corticomotor

excitability and caused relative grey matter decrease in the contralateral left M1HAND, subsequent training reversed the effects of immobilization, causing an increase in regional grey matter density and excitability (41).

Sensory discriminative and motor training has also been combined with fitness and resulted in clinical gains of motor control, motor accuracy, sensory discrimination and physical performance (81, 82). After 6 months, all 11 patients were contacted. Ten out of 11 patients returned to work, and the improvement was scored 84%–90% for the specific task that was impaired. Patients, whose training was supervised, showed a better outcome (81). Enlarged and disorganized hand representations were reversed after prolonged rehabilitation of 5.5 months investigated with magnetencephalography (MEG) and 3D-MRI 3D brain reconstructions that were paralleled with clinical recovery and improved writing performance (83). There was, however no long-term follow up, so it remains unclear, whether patients continued their training, and how long the positive training effect lasted. That program included several different training aspects including relaxation techniques, elementary movement and postures correction, pen control. Several studies started with simple movements and progressed to more complex movements during the course of the training (6, 76, 78, 83).

Biofeedback to reverse abnormally high muscle activity

Biofeedback is another technique that had been used to treat writer's cramp. This approach was based on faulty inhibition due to the abnormal reorganization in the sensorimotor cortex. Therefore, the training approach was to teach patients active inhibition of proximal muscles and thus reduce the overflow of motor areas pertaining to them. The authors implemented auditorial EMG feedback from affected muscles with abnormally high activity during writing. This feedback served as a control measure to teach patients writing in a relaxed manner (84). Patients received practice sessions once every 2 weeks and instructions for a home-based training program. On a visual analogue scale, nine of 10 patients reported an overall improvement ranging from 37.5% to 93.4% (84). To reverse decreased striatal D2 receptor-binding, as measured with single-photon emission computed tomography (SPECT) with [123I] iodobenzamide (IBZM), patients were instructed to visually maintain the EMG motor unit amplitude at the minimum possible level while writing exercises (85). The authors concluded from their data that with a biofeedback-based sensorimotor training it was possible to reorganize the activity in the nigrostriatal dopaminergic pathway (85).

A different biofeedback method that lead to a significant improvement in writing was auditory grip force feedback (86). In that study the authors used a pen wrapped with a force sensor matrix. Writer's cramp patients received 7 h training sessions that was distributed over several weeks. They performed the specialized training with a standard pen over 50 min, and for the last 10 minutes with the force sensor matrix wrapped writing stylus to measure grip force and to give auditory grip force feedback. Patients improved their handwriting performance, the writing pressure, and reported to have less pain (86).

Non-invasive brain stimulation techniques to reverse abnormal excitability

Furthermore, non-invasive stimulation techniques have been investigated using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (67, 87–92). The purpose was to reduce deficient inhibition. Low- (<1 Hz) frequency TMS decreases cortical excitability and had been applied in patients with writer's cramp to improve handwriting. The area that had been stimulated included the premotor cortex, the primary motor cortex and the supplementary motor area with the intention to improve handwriting and pen pressure (69, 87–91). In most studies showed short-term positive effects after 15–30 min and in some studies 10–15 days post stimulation (67). More recent studies imply that repetitive sessions over consecutive days are necessary to achieve therapeutic effects (67). In a tDCS study that applied anodal, cathodal, or sham tDCS to the cerebellum the authors reported improved writing kinematics with reduced cerebellar inhibition with anodal tDCS (92). However, there are a number of tDCS studies with negative results according to clinical parameters that were investigated (67).

Discussion and future directions

Writer's cramp is a rare task specific form of dystonia. In their medical history, many affected patients report long daily writing hours and often they have professions, in which writing is required. Therefore, the impact on patients' everyday life is tremendous, especially when they are working. BoNT offers one treatment possibility. However, over the years, a high percentage of patients refrain from BoNT injections. The main reasons are that this treatment form is not efficient for the patient's daily life or the side effects are not tolerable. For example, severe paresis may occur in the injected muscles. Sometimes the toxin spreads to neighboring muscles causing involuntary paresis and can cause constraints in daily life, even if writing has improved.

Therefore, based on the pathophysiology, several rehabilitative treatment approaches have been suggested (69). Studies with re-training programs for several weeks were designed to reverse abnormal sensorimotor reorganization and to achieve long-lasting therapeutic effects. In a subsequent study

biofeedback was combined with a re-training program to improve muscle co-contraction. Low-frequency rTMS studies have to be considered as short -term projects. Positive effects were measured during the first 30 min post-stimulation or a maximum of 15 days. There is ongoing discussion, whether the stimulation has to be repeated after a certain time to achieve long-term results in rTMS (67).

Currently, writer's cramp is considered as a network disorder affecting the sensory system, the motor system, the basal ganglia and the cerebellum. Especially, maladaptive reorganization in the sensory cortex (30), increased excitation or faulty inhibition have been reported in a number of studies (13, 17, 31). However, this view has been challenged due to the development of new technologies for examining brain region reorganization and it is expected that further advances will be made leading to additional changes in our understanding. For example, normal digit representation maps between fingers in patients with musician's dystonia have been reported very recently using an optimized spatial metric multivariate pattern analysis (93). So, perhaps, as we get a deeper understanding of the pathophysiology, it is necessary to reconsider current treatment approaches. This may also apply to the way, how writing has been evaluated. Mostly, a kinematic writing analysis has been used, and parameters such as increased axial pressure, decreased writing frequency, and irregular writing movements have been found to be characteristic features in writer's camp (9, 86). On the other hand, a handwriting recognition software has been recently applied for writer's cramp patients to evaluate word legibility in an automated manner. In that study, patients with writer's cramp showed abnormal word legibility and peak accelerations (10) with high sensitivity and specificity, but mean axial pen pressure, average velocity, stroke length, or CV of peak vertical velocity were normal. Therefore, it is conceivable that re-training should focus on alternative aspects of writing.

One major problem that applies to all treatment studies is the small number of patients. It is not possible to compare any occupational treatment to normal controls, therefore a randomized controlled study is not feasible. Another challenge is to establish a control training. It is impossible to introduce a control motor training, because any motor training will always have an influence on the sensorimotor network, independently of its specificity. A control training that includes no motor aspects might unblind writer's cramp patients, who expect some way of motor intervention to treat this motor disorder.

Therefore, future studies with new technologies have to be performed with larger sample sizes to either confirm or reject the current view of the pathophysiology. Depending on the results, the rehabilitative treatment approaches have to be reassessed and adapted. Ideally, future treatment studies should be performed in a multicentre setting with a higher number of patients and a control training needs to established.

Author contributions

KEZ developed the concept and wrote the first draft of the manuscript. AB and KW reviewed and revised the manuscript for content. In addition, they provided the figures.

Conflict of interest

KEZ has received research support from the Christa and Hans-Peter Thomsen Foundation, the German Research Foundation (DFG 5919/4-1) and from Strathmann GmbH & Co. KG. She reports speaker's honoraria from Bayer Vital GmbH, BIAL, Alexion, AbbVie Allergan and Merz outside the submitted work. She has served as a consultant and received fees from Merz, Ipsen, Alexion and the German Federal Institute for Drugs and Medical Devices (BfArM). KW receives research support for the German Research Foundation (DFG GK 2783) and form STADAPHARM. He serves as a consultant for BIAL and receives speaker's honoraria form BIAL, STADAPHARM and Boston Scientific.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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