netic link between these two conditions should be further investigated.

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Normal Intracortical Excitability in Developmental Stuttering

Martin Sommer, MD,* Stephan Wischer, MD, Frithjof Tergau, MD, and Walter Paulus, MD

Department of Clinical Neurophysiology, University of Göttingen, Göttingen, Germany

Abstract: Persistent developmental stuttering (PDS) shares clinical features with task-specific dystonias. In these dystonias, intracortical inhibition is abnormally weak. We therefore sought to determine intracortical inhibition and intracortical facilitation in PDS. In 18 subjects with PDS since childhood (mean age, 39.4 [SD 13.0] years) and 18 speech-fluent controls (43.6 [14.3] years), we investigated resting and active motor thresholds as well as intracortical inhibition and facilitation were normal. Normal intracortical excitability makes a pathophysiological analogy between focal dystonia and PDS less likely. The enhanced motor threshold suggests reduced motor cortical neuronal membrane excitability in PDS. © 2003 Movement Disorder Society

Key words: persistent developmental stuttering; transcranial magnetic stimulation; intracortical excitability

Persistent developmental stuttering (PDS) is characterized by intermittent dysfluencies of speech acquired in childhood that are persistent after puberty. The core symptoms are repetitions and prolongations of syllables or sounds, and transient cessation of speech due to a freezing of muscles of respiration, phonation, and articulation. PDS is one of the most frequent speech disorders, affecting approximately 1% of the population. PDS affects males more often than females, at a ratio of about 3 to 4:1.2 In contrast to neurogenic, late-onset stuttering, PDS is not linked to evident brain damage by trauma or stroke; morphological abnormalities are more subtle and comprise a disconnection of the left Rolandic operculum and slight gyral abnormalities of the adjacent left prefrontal operculum.

Clinically, PDS shares features of task-specific dystonias. Both disorders are task-specific disorders of fine
motor control that present with an excessive activation of task-related and task-unrelated muscles. Both PDS and focal dystonias are accentuated by emotional stress, are likely to have a genetic predisposition, and may occur during childhood or early adolescence. These clinical similarities incited speculations as to whether PDS may be a task-specific dystonia. PDS and dystonias differ in regard to the gender ratio, with males affected predominantly by PDS and females by focal dystonias, and the age of onset, which is usually earlier in PDS than in focal dystonias. 

A reduced intracortical inhibition in the focal dystonia of writer’s cramp has been demonstrated with a conditioning-test paired-pulse design of transcranial magnetic stimulation (TMS). We extended that finding to the cortical representation of a human muscle (abductor digiti minimi, ADM) of patients with the cranial dystonia of blepharospasm. This suggests that in cranial dystonias the disturbed tuning between motor cortical inhibition of facilitation spreads to the cortical representation of clinically uninvolved hand muscles.

Based on the clinical similarities of PDS and writer’s cramp, we hypothesized that intracortical inhibition may be reduced in PDS.

SUBJECTS AND METHODS

We investigated 18 subjects with PDS (mean age ± SD, 39.5 ± 13.0 years). They were recruited from the Göttingen stuttering self-help group and by advertisement at the University campus. At the beginning of the study, they were asked to give a report of their current activities and of their history of speech dysfluencies. All subjects showed core symptoms of stuttering (repetitions and prolongations of sounds, and speech blocks) in that interview. As healthy controls, we studied 18 subjects speech-fluent in a similar interview and with no personal history of stuttering (mean age, 43.6 ± 14.3 years). None of the subjects showed neurological or medical abnormality on routine examination; all had at least 8 of 10 points for right-handedness on the Oldfield handedness questionnaire. None of the subjects were taking CNS-active drugs at the time of the interviews. The protocol was approved by the ethics committee of the University of Göttingen, and written informed consent was obtained from all participants.

While the participants were sitting in a reclining chair, we delivered transcranial magnetic stimulation over the optimal representation of the ADM of the dominant hand. Stimuli were generated by two Magstim 200 stimulators connected via a bistimulation module to a figure-of-eight coil in which each wing had an outer diameter of 7 cm (Magstim Company, Whitland, Dyfed, UK). The coil was held in the optimal position, i.e., tangentially to the skull with the handle pointing backwards at about 45° laterally. We recorded motor evoked potentials (MEPs) from the ADM using silver–silver chloride electrodes in a belly–tendon montage and a digital device at a sampling rate of 5 kHz (Synamps; Neuroscan, Herndon, VA), recording 50 msec of prestimulus EMG to assess muscle relaxation. Data was filtered at 10 Hz and 2.5 kHz.

Reducing the stimulus intensity in steps of 1%, we defined the resting motor threshold (RMT) as the lowest intensity at which at least 5 of 10 consecutive MEPs were ≥50 μV in amplitude while the investigated muscle was at rest. Audio-visual EMG feedback was provided to control for muscle relaxation. The lowest intensity at which 5 of 10 consecutive MEPs were ≥200 to 300 μV in amplitude during voluntary abduction of the small finger was set as active motor threshold (AMT). 

For intracortical excitability, we delivered conditioning-test paired TMS pulses that consisted of a subthreshold conditioning stimulus (90% AMT) followed by a test pulse yielding MEPs of ~1 mV after an interval of 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20, or 30 msec, each interval being tested at least 10 times in random order. The MEPs elicited by the paired stimuli were expressed as a percentage of the MEP induced by the intermixed single test pulses. Trials with imperfect muscle relaxation in the prestimulus recording were rejected.

To test whether the higher conditioning pulse intensity in the stuttering group distorted the results, we also studied intracortical excitability in 3 stuttering subjects (2 men, 1 woman; mean age, 51.3 years) using conditioning stimulus intensities of 70, 80, and 90% AMT, test pulses yielding MEPs of ~1 mV, and conditioning-test intervals of 1, 2, 3, 4 and 10 msec, each interval being tested at least 10 times in random order. Data analysis was identical to the principal experiment.

For correlation analysis, we calculated Pearson’s correlation coefficient. All results are indicated as mean value ± SD, and the level of significance was set at P < 0.05.

RESULTS

In 2 subjects with PDS not included in the analysis, motor thresholds were too high to evoke reliable MEPs. In the remaining 16 subjects with PDS, mean motor thresholds were significantly higher than in controls (unpaired, two-tailed t test; RMT, P = 0.04; AMT, P = 0.02; Fig. 1). Consequently, the mean conditioning pulse of the paired-pulse paradigm was higher in subjects with PDS (38.6 ± 9.8% of stimulator output) than in controls (31.0 ± 4.5% unpaired, two-tailed t test, P = 0.02), as
was the test pulse (69.1 ± 16.1% vs. 62.9 ± 8.6% unpaired, two-tailed t test, P = 0.19).

The intracortical inhibition was similar in subjects with PDS and controls. There was no significant difference at any interstimulus interval (two-tailed, unpaired t tests, P = 0.1), or for the pool of inhibitory intervals (unpaired, two-tailed t test of intervals 1–5 msec, P = 0.28; Fig. 2).

The control experiment showed that reduced conditioning pulse intensities are less effective (Fig. 3). Hence, adjusting the conditioning pulse to the increased AMT in the stuttering group is necessary to detect the maximum intracortical excitability present in that group.

The resting and active motor thresholds were not correlated strongly with age either in subjects with PDS or in controls; correlation coefficients were between −0.25 and 0.25.

DISCUSSION

To our knowledge, this was the first assessment of motor thresholds and intracortical excitability in PDS. Our results for intracortical excitability were within normal ranges and did not match the reduced intracortical inhibition reported for writer’s cramp and for blepharospasm. Apparently, the pathophysiology of PDS is distinct from that of focal dystonias. This conclusion was supported further by the threshold elevation we found in PDS, because motor thresholds have been reported as unchanged in focal dystonias.

The intracortical inhibition is likely mediated by inhibitory motor cortical interneurons. Its reduction in focal dystonia suggests that these interneurons are under direct or indirect control of the basal ganglia output neurons. The reduced inhibition is rather unspecific, because it has been reported in a variety of neurological and psychiatric disorders. Intracortical inhibition is altered by drugs affecting dopaminergic, GABAergic, or glutamatergic transmission (see Ziemann et al. for overview). Our results suggested that synaptic transmission by these transmitters is unaffected in the motor cortex of subjects with PDS.

Motor thresholds show some interindividual variability, possibly related to the positioning of motor neurons and their afferent interneurons within the motor cortex, or to the density of corticospinal connections. Clinical studies demonstrated normal motor thresholds in focal dystonia. The motor threshold is decreased after transient or permanent deafferentation, but increased after lesions of the corticospinal tract, as in the course of amyotrophic lateral sclerosis or after stroke. We conclude that corticospinal motor tract excitability is abnormally high in PDS. The pattern of increased motor threshold and normal intracortical inhibition is reminiscent of the effect of the sodium channel blockers in controls.

An artifact of increased arousal in the PDS group is unlikely, because 1) prestimulus recordings of the recordings accepted for analysis did not show increased voluntary muscle activity; and 2) increased arousal would be expected to lower the motor thresholds rather than increase them.

One may object that the abductor digiti minimi is not a suitable muscle for studying PDS, and that a facial or
laryngeal muscle may have been more appropriate. The main argument for choosing the ADM was a technical one. In our experience, noninvasive surface EMG traces from facial muscles are contaminated usually by considerable background noise, making reliable assessment of intracortical excitability very difficult. Two other arguments supported the choice of a small hand muscle. First, speech muscle representations are linked closely to and reflect the excitability of hand muscle representations, as has been shown in a study of hand muscle MEP facilitation during speech. Second, reduced intracortical inhibition in dystonia is not limited to the representation of the body part affected clinically, but is much more widespread, involving hand muscle representations in cranial dystonia and even contralateral hand muscle representations in unilateral writer’s cramp. Hence, if there was a reduced intracortical inhibition in a face or speech muscle representation, there is good reason to expect that it would be present in hand muscle representations as well.

In summary, our results make a pathophysiological analogy between focal dystonias and PDS less likely.

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FIG. 3. Control experiment testing the intracortical excitability in 3 stuttering subjects at three different levels of conditioning pulse intensity. As in Figure 2, conditioned motor evoked potentials are expressed in percent of the unconditioned response (dashed line). The findings indicate that conditioning pulse intensities that are too low yield artificially low levels of intracortical inhibition. Hence, in the principal experiment it was necessary to adjust the conditioning pulse to the higher AMT of the stuttering subjects. All symbols represent the mean ± SD.