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Research report

Right-shift for non-speech motor processing in adults who stutter

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ABSTRACT

Introduction: In adults who do not stutter (AWNS), the control of hand movement timing is assumed to be lateralized to the left dorsolateral premotor cortex (PMd). In adults who stutter (AWS), the network of speech motor control is abnormally shifted to the right hemisphere. Motor impairments in AWS are not restricted to speech, but extend to non-speech orofacial and finger movements. We here investigated the lateralization of finger movement timing control in AWS.
Methods: We explored PMd function in 14 right-handed AWS and 15 age matched AWNS. In separate sessions, they received subthreshold repetitive transcranial magnetic stimulation (rTMS) for 20 min at 1 Hz over the left or right PMd, respectively. Pre- and post-stimulation participants were instructed to synchronize their index finger taps of either hand with an isochronous sequence of clicks presented binaurally via earphones. Synchronization accuracy was measured to quantify the effect of the PMd stimulation.
Results: In AWNS inhibition of left PMd affected synchronization accuracy of the left hand. Conversely, in AWS TMS over the right PMd increased the asynchrony of the left hand.
Conclusions: The present data indicate an altered functional connectivity in AWS in which the right PMd seems to be important for the control of timed non-speech movements. Moreover, the laterality-shift suggests a compensatory role of the right PMd to successfully perform paced finger tapping.

1. Introduction

Fluent speech requires the well timed selection, initiation, execution and monitoring of motor sequences. The relevant cortical and subcortical neural systems appear to be malfunctioning in developmental stuttering (Brown et al., 2005; Fox et al., 1996; Ludlow and Loucks, 2003). Stuttering is characterized by an impairment of speech rhythm or fluency (Bloodstein and Ratner, 2008). Speech disruptions typically include blocks, repetitions, or prolongations of speech

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segments (WHO, 2007b), and may be accompanied by movements of face and limb muscles and by negative emotions such as fear or embarrassment. About 5% of the population stutters at some point during childhood (Mansson, 2000). Although spontaneous recovery rate is high, stuttering without obvious neurological origin persists after puberty in about 1% of adults (Andrews and Harris, 1964; Bloodstein and Ratner, 2008; Craig et al., 2002). Exploring the underlying neural mechanisms of this disorder provides insights into mechanisms of dysfluent speech production and into models of speech planning and production in general. These insights into the physiology of stuttering may ultimately serve to improve treatments enhancing speech fluency.

Temporal patterns in speech occur on multiple timescales (i.e., subsegmental, segmental and suprasegmental, Levelt, 1989). In adults who stutter (AWS), acoustic-temporal and spatio-temporal characteristics are affected in stuttered and fluent speech on all these timescales (Jancke, 1994; Kleinow and Smith, 2000; Max and Gracco, 2005; Prins and Hubbard, 1992). Most consistent are the observations of increased variability of duration and relative timing of acoustic and kinematic features. Additionally, stuttering has been associated with altered auditory feedback control mechanisms (Max et al., 2004; Tourville et al., 2008). Altogether, these facts underline a deficit of speech motor timing and the impact of the timing of auditory information during speaking in AWS.

Alterations of timing abilities in AWS exceed the domain of speech and affect the motor control of non-speech movements as well. For example, AWS performed poorly in reproducing varying rhythmic patterns (Hunsley, 1937) or unpredictable digit sequences (Webster, 1986). Additionally, AWS exhibit prolonged initiation and execution times in finger movement sequencing tasks (Smits-Bandstra et al., 2006; Webster, 1997) and increased manual reaction times (Bishop et al., 1991; Webster and Ryan, 1991). Phase variability is greater during bimanual coordination of auditory paced movements (Zelaznik et al., 1997) and movement variability is increased during simultaneous synchronization of speech and hand movements (Hulstijn et al., 1992). However, studies on auditory paced isochronous finger movements did not find differences of timing accuracy and timing variability between AWS and controls (Hulstijn et al., 1992; Max and Yudman, 2003; Melvine et al., 1995; Zelaznik et al., 1994).

Two separate processes have been related to timing accuracy: a neural clock mechanism (Rao et al., 1997; Ivry and Spencer, 2004), and an emergent property of the kinematics of movements itself (Ivry and Spencer, 2004; Mauk and Buonomano, 2004). This dissociation between event timing and emergent timing has been corroborated by previous findings (Spencer et al., 2003; Zelaznik et al., 2005, 2002). Timing in the sub- and supra-second range involves dissociable neural networks (Gibbon et al., 1997; Lewis and Miall, 2003; Wiener et al., 2010). Sub-second timing engages cerebello-thalamo-cortical network (Pollok et al., 2005), whereas supra-second timing tasks were more prone to activate cortical structures such as supplementary motor area (SMA) and prefrontal cortex (Wiener et al., 2010). For an event timing task like self-paced finger tapping, Wing and Kristofferson (1973) indicate a dichotomy between central clock and motor execution by suggesting that a central timekeeper supplies intervals of the adequate length and drives motor commands at the end of each interval. The original Wing–Kristofferson model was concerned with the special case of self-paced finger tapping and therefore neglected the process of integrating external cues. This contrasts with finger tapping in synchrony with an acoustically presented pacer, a timed motion task that additionally involves the integration of the external event and the monitoring of the synchrony of the pacer and the tapping.

Finger tapping accuracy can be disturbed by transcranial magnetic stimulation (TMS) (Doumas et al., 2005; Levit-Binnun et al., 2007; Malcolm et al., 2008; Pollok et al., 2008), a neurophysiological technique inducing a brief electric current in the brain using a magnetic field to pass the scalp and the skull safely and painlessly. Repetitive TMS (rTMS) is capable of inducing excitability changes of neural networks outlasting the stimulation period (Hallett, 2000; Miniussi et al., 2008; Siebner and Rothwell, 2003; Siebner et al., 2009), thereby temporarily disrupting activity in local or remote cortical areas (Wagner et al., 2009; Walsh and Rushworth, 1999). Thus, rTMS disrupts brain functions for a finite time with relatively high spatial resolution.

In the present study rTMS was employed to induce a transient virtual lesion of the dorsolateral premotor cortex (PMd). Traditionally the premotor cortices (PM) were assumed to be key structures in the motor domain and thereby associated with the preparation and the organization of movements and actions (Wise, 1985). Imaging studies suggest a specific significance of the PMd for cognitive functions (Abe and Hanakawa, 2009), sensorimotor integration (Pollok et al., 2009; Schubotz et al., 2003) and rhythm perception (Bengtsson et al., 2009), as well. Recent studies provide evidence for a specific role of the left PMd for movement timing of both hands (Pollok et al., 2009, 2008). Interestingly, externally paced finger movements as well as syllable repetition seem to recruit the same cerebral network involving the left PMd (Riecker et al., 2006). However, the PMd seems to play a role during fluency enhancing mechanisms in AWS. Fluency is reliably enhanced when speech is timed to a pacer: either an external pacer such as a rhythmic beat (Wingate, 2002; Wohl, 1968), the unison speaking with another person (Adams and Ramig, 1980; Ingham and Carroll, 1977; Saltuklaroglu et al., 2009), or an internal pacer such as rhythmic arm swinging or a finger tapping (Bloodstein and Ratner, 2008). Alternative fluency enhancing techniques are delayed or frequency shifted auditory feedback (Antipova et al., 2008; Van Riper, 1970). Such fluency enhancing mechanisms involve right premotor regions as well as the cerebellum (Braun et al., 1997; Fox et al., 1996; Tourville et al., 2008; Watkins et al., 2008). Hence, the PM seem to play an important role for motor timing control as well as the implementation of fluency enhancing techniques.

Theoretical frameworks on stuttering suggest an aberrant timing of neural activity in different brain regions that are relevant for speech processing (Alm, 2004; Howell, 2004; Ludlow and Loucks, 2003). Specifically, the basal ganglia-cortical route might be impaired in providing internal cues for the exact timing of movements, while the PMd in concert with the cerebellum successfully utilizes external time cues resulting in enhanced fluency for example during metronome speaking (Alm, 2004). Interestingly, in AWS even a non-speech motor task like externally paced finger tapping mirrored an

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irregular right-shifted activation (Morgan et al., 2008). This increased right pre-central activation suggests that the cortical contribution to the process of timed movements is less left lateralized. The present study aims at further investigating the assumption of a hemispheric shift of motor functions in AWS by means of an induced virtual lesion of the left and right PMd in AWS and adults who do not stutter (AWNS).

2. Methods

2.1. Participants

Fourteen right-handed AWS [mean age 30.3 ± 11.4 (SD); one female] and fifteen AWNS [mean age 28.1 ± 5.0 (SD); one female] participated in this study. Table 1 contains details of the participants. Stuttering participants were recruited from the Stuttering self-help group of Goettingen and the Institute for the Kassel Stuttering Therapy. Three AWS had already taken part in an earlier TMS study (Sommer et al., 2009). The groups were matched and statistics did not yield any group differences for age ($T = .65$, $p = .5$), handedness (Oldfield, 1971; $Z = -.73$, $p = .46$) and level of education ($Z = -1.28$, $p = .2$), amount of musical training and gender. AWS produced significantly more stuttered syllables than AWNS [mean_{AWS} 9.0 ± 8.0 (SD), mean_{AWNS} .6 ± .4 (SD); $Z = -4.6$; $p < .001$; for details on statistics see data analysis section]. Stuttering severity was very mild in five, mild in three, moderate in two, severe in two and very severe in two AWS according to the Stuttering Severity Index (SSI-3). Inter-rater reliability analysis

Table 1 – Characteristics of participants.

		Age	Gender	Education	Instrument	Handedness	Mother tongue	AMT right FDI	AMT left FDI	Suttered syllables	SSI-3 score	Age of stuttering onset
AWS		38	m	6	Yes	100	G	39	42	3.1	17	3.5
		27	m	6	Yes	100	G	43	36	6.9	21	6
		21	m	3	No	100	G	45	50	1.9	8	2.5
		44	m	2	Yes	60	G	57	54	2.9	14	2
		42	m	6	No	70	G	38	40	25.2	33	5
		18	m	3	No	90	G	49	44	23.8	43	4.5
		18	m	1	Yes	80	G	68	73	16.3	40	4
		28	m	6	Yes	90	K	54	57	9.8	28	4.5
		33	m	6	No	70	T	44	57	3.8	27	2.5
		19	f	2	Yes	70	G	63	46	4.5	23	2.5
		54	m	1	No	75	G	57	63	1.5	7	4
		28	m	6	Yes	30	G	38	36	16.5	32	4.5
		36	m	2	No	70	G	63	68	3.2	16	5
		18	m	1	Yes	100	G	51	59	5.9	18	6
	Median	28.0		3		77.5		50.0	52.0	5.2	22.0	4.3
	Mean	30.3				79.0		50.6	51.8	9.0	23.4	4.0
	SD	11.4				19.8		10.0	11.7	8.2	11.0	1.3
AWNS		29	m	5	No	60	G	40	43	.4		
		25	m	3	No	100	G	48	54	1.5		
		39	m	6	No	57	G	50	54	1.1		
		34	m	6	No	100	G	55	58	.9		
		23	m	4	Yes	100	G	41	40	.3		
		27	f	6	No	80	H	28	30	.5		
		31	m	6	Yes	70	I	48	41	.5		
		33	m	6	No	90	G	47	50	.4		
		30	m	6	No	63	G	46	42	.2		
		20	m	3	Yes	70	G	56	56	.3		
		25	m	3	Yes	60	G	38	50	.8		
		24	m	3	Yes	50	G	51	47	.3		
		24	m	4	Yes	60	G	57	57	.5		
		31	m	3	No	80	G	52	40	.3		
		27	m	5	No	100	G	42	40	.8		
	Median	27.0		5		70.0		48.0	47.0	.5		
	Mean	28.1				76.0		46.6	46.8	.6		
	SD	5.0				18.1		7.8	8.15	.4		
Test (p)		$T = .65$ (.5)		$Z = -1.28$ (.2)		$Z = -.73$ (.46)		$F = 1.87$ (.18)		$Z = -4.6$ (<.001)		

AWS = adults who stutter; m = male, f = female; SD = standard deviation; AMT = active motor threshold; FDI = first dorsal interosseous; G = German, K = Kannada, T = Turkish, H = Hungarian, I = Italian; level of education was estimated as follows: 1 = school, 2 = high school, 3 = less than 2 years college, 4 = 2 years college, 5 = 4 years college, 6 = postgraduate; handedness was quantified with the 10-item scale of the Edinburgh Handedness Inventory; stuttered syllables were mean percentage out of not less than 340 read and 500 spoken syllables.

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yielded an unjust intra-class correlation coefficient (ICC_{unjust}) of .94 (95% CI .82 -.98) and intra-rater reliability analysis yielded an ICC_{unjust} of .97 (95% CI .81 - .98).

None of the participants had a self-reported history of speech, language or hearing problems, with the exception of stuttering in AWS. According to the definition (WHO, 2007a) cluttering was recognized by rapid, erratic, and dysrhythmic speech dysfluency with distinct speech timing abnormalities. On this ground we excluded one fifteenth putative participant who exhibited both stuttering and cluttering. None of the participants showed neurological or medical abnormalities on routine examination. None of the participants were taking drugs affecting the central nervous system at the time of the study. The local Ethics Committee approved the study and all participants gave written informed consent according to the declaration of Helsinki.

2.2. *Fluency assessment*

The fluency assessments were performed and independently analyzed by a qualified speech-language pathologist (N.N.) and a qualified clinical linguist (K.J.). In compliance with the German version of the SSI-3 (Sandrieser and Schneider, 2008), speech samples of all participants containing a conversation about job or school and a reading task were videotaped (Sony Handycam DCR-TRV16E Mini DV digital Camcorder) and audio recorded (Edirol R-09; sample rate: 16 bit/44.1 kHz; format: WAV). SSI-3 norms were adapted from Riley (1994). Software for offline analysis were DivX player (DivX software, San Diego) and WavePad (NCH software, Canberra). The offline analysis of dysfluencies included 500 syllables for the conversation and not less than 340 syllables for the reading task. Sound prolongations, blocks (silent prolongation of an articulatory posture), sound and syllable repetitions were counted as stuttered syllables. Monosyllabic words that were repeated with apparent undue stress or tension were counted too (Sandrieser and Schneider, 2008). Furthermore, the estimated duration of the three longest blocks and observation of physical concomitants were included for the estimate of stuttering severity in AWS.

2.3. *Procedure*

The experiment consisted of two sessions, one for stimulating the left and the other for stimulating the right PMd. During each session participants performed one run of left index and one run of right index finger tapping before rTMS. Both runs were repeated immediately (about 30 sec) after rTMS. The order of stimulation site and hand was counterbalanced across participants. To avoid carry-over effects of the magnetic stimulation the second rTMS session was performed not less than 48 h after the first one.

Participants sat in a silent room in front of a computer keyboard connected to the computer via a PS/2 cable. The keyboard was shielded to the participant's visual field. Participants were requested to synchronize their unimanual index finger taps with a metronome. The acoustically presented metronome signals contained clicks of 10 msec duration with an inter click interval of 800 msec. Each experimental run comprised a continuous series of 56 clicks. The clicks were presented binaurally via dynamic, closed-ear headphones (Sennheiser HD 280; up to 32 dB attenuation of outside noise). Click intensity was individually adjusted to a level perceived as loud by the participants. The pacing signal was triggered and the onsets of space bar presses were recorded by using Eprime (http://www.pstnet.com). We quantified performance by calculating (1) the asynchrony, the averaged temporal distance between the onset of the pacing signal and finger taps, and (2) the inter-tap interval (ITI)-variability, the variation of the time between two consecutive taps.

2.4. *Stimulation technique*

TMS was applied while participants sat comfortably in a reclining chair. A figure-8-shaped stimulation coil connected to a Magstim rapid2 stimulator (Magstim Company, Dyfed, Wales, UK) was positioned tangentially to the scalp with the handle pointing backwards and rotated away from the midline by 45°. The junction of the two wings of the figure-8-coil was held flat on the skull. The pulse configuration was biphasic with an initial posterior–anterior current flow in the brain. The motor hot spot was localized at the optimal point for eliciting motor evoked potentials (MEPs) in the contralateral first dorsal interosseous (FDI) muscle over the primary motor cortex (M1). Active motor threshold (AMT) was determined as the minimum intensity needed to evoke MEPs in the tonically contracted contralateral FDI muscle of about 200 μV in five of ten consecutive trials. For the rTMS of the PMd the intersection of the coil was placed 2.5 cm anterior to the M1 representational hot spot of FDI. This procedure is in accordance with previous studies (Doumas et al., 2005; Mochizuki et al., 2004; Pollok et al., 2008; Schluter et al., 1998) and fits with functional imaging data displaying the PMd to be positioned about 1.8–2.5 cm (Picard and Strick, 2001) and 2.0 cm (Fink et al., 1997) anterior to the M1 hand area. The coil was held with the handle pointing backward and rotated away from the midline by 45° to induce a final anterior–posterior directed current in the stimulated cortex. Surface electromyogram (EMG) was recorded from the FDI through a pair of silver–silver chloride surface electrodes in a belly-tendon montage. Raw signals were amplified, band-pass filtered (2–2500 Hz), digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, United Kingdom) and controlled by Signal Software (Cambridge Electronic Design, version 2.13). Complete muscle relaxation was controlled through visual feedback of EMG activity. Subthreshold rTMS was applied at 90% of ipsilateral AMT intensity for 20 min at 1 Hz over the left PMd in one session and the right PMd in another. This rTMS protocol has been shown to decrease cortico-spinal excitability for several minutes (Gerschlager et al., 2001; Walsh and Rushworth, 1999) and complies with safety recommendations (Rossi et al., 2009; Wassermann, 1998).

2.5. *Data analysis*

The mean values of the two dependent variables, asynchrony and ITI-variability, were calculated separately for each group (AWNS/AWS), each hand (left hand/right hand) and each site of stimulation (left rTMS/right rTMS); thus, yielding 16 values of asynchrony and ITI-variability, respectively.

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To control for group differences in the finger tapping performance before rTMS we compared the individual mean baseline asynchrony values using a two-way mixed design analysis of variance (ANOVA) with the between-subjects factor group (AWS/AWNS) and the within-subjects factor hand (left/right). A similar ANOVA was calculated with the baseline ITI-variability.

At baseline finger taps preceded the acoustic signal in most participants resulting in negative asynchrony values. However, there were two AWS and seven AWNS that showed a positive asynchrony in most runs. To test the impact of rTMS we therefore normalized the asynchrony after stimulation for each participant and each session by subtracting the asynchrony before stimulation.

We entered the normalized values in a three-way mixed design ANOVA with the between-subjects factor group (AWS/AWNS) and the within-subjects factors stimulation site (rTMS over the left PMd/rTMS over the right PMd) and hand (left/right). In addition, the expected rTMS-induced increases of asynchrony values (Pollok et al., 2008) were tested with one-tailed *t*-tests. We tested the impact of rTMS on ITI-variability similarly by entering the normalized to baseline values.

To exclude differences of age between groups we used a two-tailed *t*-test for independent samples, for education, handedness and percentage of stuttered syllables, we used Mann–Whitney *U*-tests. Nonparametric testing was chosen since education is an ordinally scaled variable and handedness as well as percentage of stuttered syllables did not show normal distribution in AWNS. The AMT comparison was calculated with a repeated measures ANOVA with hand as a within-subjects factor and group as a between-subjects factor.

Statistics were performed by SPSS Statistics 17.0 (http://www.spss.com/de/software).

3. Results

At baseline the two-way mixed design ANOVA with asynchrony values before rTMS as dependent variable revealed no significant difference between AWS and AWNS (factor group $F_{1,27} = 1.4$; $p = .3$). However, the ANOVA revealed a more pronounced negative asynchrony in the right hand than in the left hand [factor hand $F_{1,27} = 7.73$, $p = .01$; left hand -28 ± 52 msec (mean ± SD) *vs* right hand -39 ± 60 msec]. Analysis yielded no further effect. ITI-variability before rTMS revealed no main effect or interaction for group and hand.

After rTMS, the analysis of normalized asynchrony values revealed no main effects of hand ($F_{1,27} = 1.5$, $p = .2$), stimulation site ($F_{1,27} = .4$, $p = .5$) and group ($F_{1,27} = .6$, $p = .4$) but a significant interaction between hand, stimulation site and group ($F_{1,27} = 5.82$, $p = .023$). Post-hoc one-tailed *t*-tests, not corrected for multiple comparisons (Perneger, 1998), revealed that rTMS over the left PMd significantly increased left hand asynchrony in AWNS ($T = 1.9$, $p = .036$) as previously shown (Pollok et al., 2008). By contrast, in AWS rTMS over the right PMd resulted in a significant increase of left hand asynchrony ($T = 2.34$, $p = .015$) (Fig. 1).

After rTMS the analysis of normalized ITI-variability revealed no main effects of group, stimulation site or hand

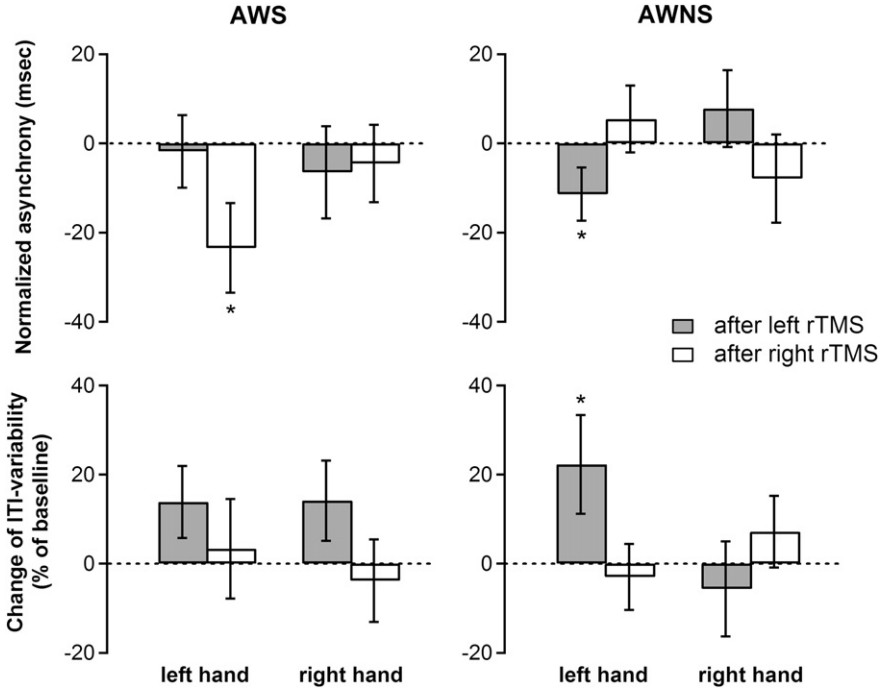

Fig. 1 – Mean values (±standard error) of normalized asynchrony (upper graphs) and change of normalized ITI-variability in percent with respect to baseline (lower graphs) after rTMS over the left and right PMd in AWS and AWNS. The analysis of asynchrony values yielded a three-way interaction between group (*AWS/AWNS*), hand (*left/right*) and localization of rTMS (*left PMd/right PMd*). Repetitive TMS over the left hemisphere prolonged left hand asynchrony in AWNS, but not in AWS. By contrast, right rTMS prolonged left hand asynchrony in AWS, but not in AWNS. ITI-variability increased after rTMS over the left PMd in AWNS. There was no significant rTMS effect on ITI variability in AWS. Asterisks indicate $p < .05$.

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and no interactions of any of these factors. Interaction between group, hand and stimulation site was marginally significant ($F_{1,27} = 5.82$, $p = .06$). Post-hoc one-tailed t-tests, not corrected for multiple comparisons, yielded in an increased normalized ITI-variability after rTMS over the left PMd in the left hand of AWNS ($T = -2.01$, $p = .032$). This is in concordance with previous findings (Pollok et al., 2008). All other statistics yielded no significant differences (Fig. 1).

4. Discussion

We studied the cortical control of auditory paced finger movements in AWS and AWNS. In AWNS, rTMS over the left PMd increased left hand asynchrony and increased ITI-variability, whereas rTMS over the right PMd was ineffective. By contrast, in AWS rTMS over the left PMd was ineffective, whereas rTMS over the right PMd prolonged left hand asynchrony.

4.1. *Left-hemispheric dominance on movement timing control in AWNS*

In AWNS rTMS over the left PMd increased asynchrony and ITI-variability of the left hand. This finding agrees well with previous studies confirming a particular role of the left PMd in auditory paced rhythmic finger tapping (Pollok et al., 2009, 2008). Although it is not entirely clear via which connections the left PMd exerts dominance over the right hemisphere, a specific significance of direct left PMd – right M1 connections (Pollok et al., 2008; Boroojerdi et al., 1996; Ferbert et al., 1992) as well as subcortical circuits (Chouinard et al., 2003) has been evidenced. It is well established that the cerebellum is closely connected to the cerebral cortex via a cerebello-thalamo-cortical loop (Horne and Butler, 1995) and that auditory paced isochronous tapping engages the cerebellum (Ivry et al., 2002; Spencer et al., 2005). Even perception of an isochronous rhythm involves the left PMd in concert with the right cerebellum in healthy subjects suggesting the engagement of prediction mechanisms that are used for motor preparation (Bengtsson et al., 2009). Therefore, the left PMd might serve as an interface between sensory prediction and temporally precise motor initiation (Kurata et al., 2000; Ramnani and Passingham, 2001). Consequently, an rTMS-induced dysfunction of the left PMd might alter the functional connectivity of the cerebello-thalamo-cortical loop which results in less precise timed motor behavior.

This finding is consistent with a hemispheric dominance of the left PMd in AWNS reported by Koch et al. (2006) during a response selection task and by Pollok et al. (2008) for movement timing during auditory paced finger tapping. Nevertheless, this hypotheses is not unchallenged since in a response selection experiment, O'Shea et al. (2007) did not find evidence for such a hemispheric dominance. Rather, they demonstrated that changes in functional connectivity occur in the pathway linking PMd and contralateral M1.

4.2. *Right-shifted control of movement timing in AWS*

In contrast to AWNS, right rTMS prolonged left hand asynchrony in AWS, whereas left rTMS was ineffective. Previous behavioral (Curry and Gregory, 1969; Sommers et al., 1975), physiological (Biermann-Ruben et al., 2005; Moore and Lang, 1977) and neuroimaging studies (Braun et al., 1997; De Nil and Brutten, 1991; Ingham et al., 2004; Preibisch et al., 2003) provide evidence for a cerebral imbalance in AWS with an increased involvement of the right hemisphere during speech production. Our results are in line with neural imaging studies suggesting an aberrant role of the left PMd (Lu et al., 2010a) and an additional involvement of the right PMd during speech (Braun et al., 1997; Fox et al., 1996; Ingham, 2001) and even non-speech tasks in AWS (Chang et al., 2009; Morgan et al., 2008). Accordingly, using functional magnetic resonance imaging right hand finger tapping has been shown to be associated with bilateral pre- and post-central activation with increased activation of the right hemisphere in AWS as compared to AWNS (Morgan et al., 2008). Thus, less activation of the left premotor area and stronger activation of the right premotor area are not specific for speech in AWS, an interpretation corroborated by the present findings.

4.3. *No effects on right hand performance in both groups*

Previous studies documented contradictory data resulting from rTMS over the left PMd on right hand movement timing in non-stuttering adults (Del Olmo et al., 2007; Doumas et al., 2005; Pollok et al., 2008). The present study showed an effect of left PMd rTMS on the subdominant left hand only. Within our sample of fluently speaking participants right handedness was less strongly developed (group average 76; median 70). Thus, one might speculate that the rTMS effect occurs in strongly developed right handedness only (i.e., Edinburgh Inventory score of 90–100). To insure that the degree of handedness did not interfere with our main result we recalculated our statistics with three-way mixed analyses of covariance (ANCOVAs) with handedness scores as additional covariate. The ANCOVAs confirmed the three-way interaction between hand, site and group for asynchrony ($F_{1,26} = 6.28$, $p = .019$) and the marginal interaction of the same factors for ITI-variability ($F_{1,26} = 3.58$, $p = .07$). ANCOVAs yielded no further effects.

Hence, the lack of modulation of right hand asynchrony cannot be explained by less pronounced right handedness within the present sample. Our data suggest that networks controlling the performance of the non-dominant hand may be more susceptible to rTMS effects than those controlling the dominant hand (Meyer-Lindenberg et al., 2002). This idea is also supported by a former diffusion tensor imaging study showing decreased fractional anisotropy underneath the precentral gyrus of the non-dominant hand related to the dominant hand (Buchel et al., 2004). Thus, morphologically the non-dominant hand relies on white matter with less integrity contrasted to the dominant hand. Furthermore, rTMS studies demonstrate an improvement of non-dominant left hand performance after inhibition of the ipsilateral left M1 (Kobayashi et al., 2004), but no improvement of dominant right hand performance after inhibition of the ipsilateral right M1 (Weiler et al., 2008). Additionally, in AWNS, interhemispheric inhibition from the dominant to the non-dominant M1 is stronger than vice versa (Netz et al., 1995; Samii et al., 1997). These results are compatible with our hypothesis that the

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network subserving motor control of the dominant hand might be more stable and thus, less prone to disturbance.

4.4. *Why did right PMd stimulation affect the contralateral hand in AWS, while left PMd stimulation did affect the ipsilateral hand in AWNS?*

In both groups rTMS affected the subdominant hand. but, in AWNS this effect occurred after left PMd stimulation, whereas in AWS right PMd stimulation yielded reduced timing accuracy. Although speculative, this result supports the hypothesis that in AWS motor functions are shifted to the right hemisphere. Thus, rTMS of the dominant hemisphere might affect temporal accuracy of the subdominant hand.

Interestingly, the present data did not indicate differences between AWS and AWNS prior to rTMS. Nevertheless, even a task which is not impaired in AWS, like unimanual auditory paced finger tapping (Hulstijn et al., 1992; Max and Yudman, 2003; Melvine et al., 1995; Zelaznik et al., 1994), is associated with altered brain functions. Since in our study, inhibition of the right PMd elicited an aggravation of asynchrony but inhibition of the left PMd did not elicit an effect, we assume that the right PMd involvement reflects a compensatory mechanism rather than malfunction (Braun et al., 1997; Fox et al., 2000; Ludlow, 2000; Preibisch et al., 2003).

This compensatory mechanism might be needed because in AWS a basal neural deficit has been described in a left frontal brain region near the stimulation site. White matter integrity is reduced in the left Rolandic Operculum in adults (Sommer et al., 2002; Watkins et al., 2008) and adolescents who stutter (Chang et al., 2008). This results in a disconnection within the cerebral network processing speech motor behavior. Evidence in favor of such a weakened connection has been given by an abnormal activating time course of left premotor and primary motor regions (Salmelin et al., 2000) and altered left frontal-right cerebellar interactions (Lu et al., 2010a) in AWS.

The integration of motor areas of an undamaged hemisphere to adaptively compensate for damaged or disconnected regions has been recently identified in recovered stroke patients (Johansen-Berg et al., 2002; Riecker et al., 2010). Interestingly, a functional connectivity analysis pinpointed the SMAs to provide a driver-like input to the contralesional premotor and sensorimotor cortices in stroke patients (Riecker et al., 2010).

Anterior parts of the SMA are mainly connected with M1, PM and the putamen, posterior parts are mainly connected with the inferior frontal gyrus, medial parietal, superior frontal cortex and the caudatum (Johansen-Berg et al., 2004; Kim et al., 2010; Lehericy et al., 2004). In AWS, SMA shows increased activation during speech production (Chang et al., 2009) and even a more pronounced activation during stuttered as compared to fluent speech production (Ingham et al., 2000), which is also mirrored in a correlation between stutter-rate and SMA activation (Fox et al., 2000). Additionally, the involvement of the putamen, which interacts with the SMA as well as with M1 and PM, is also altered in AWS (Braun et al., 1997; Lu et al., 2010b; Ludlow and Loucks, 2003; Watkins et al., 2008). This over-activation may be related to the fact that the SMA supports the involvement of different neural populations like the right PMd that are additionally recruited for functional reorganization.

4.5. *Limitations of the study*

Although we used a standard procedure for determining rTMS location, we did not verify the exact PMd localization by structural or functional imaging. We therefore cannot rule out an aberrant structural or functional organization of the left PMd in AWS. Cerebellar regions play an important role for event timing (Spencer et al., 2003) and altered auditory feedback (Howell and Sackin, 2002; Tourville et al., 2008), and behavioral evidence indicated cerebellar deficits in children who stutter (Howell et al., 1997, 2008). However, we did not stimulate the cerebellum, because this procedure is quite uncomfortable and may induce changes of the cortico-spinal excitability. This effect is related to the peripheral stimulation of the neck muscles rather than the stimulation of the cerebellum itself (Gerschlager et al., 2002).

5. Conclusion

The present findings indicate a right-shifted neuronal organization for movement timing in AWS supporting the hypothesis of a generally altered neurophysiological organization of the motor control system in AWS. Since synchronization accuracy prior to rTMS did not differ between AWS and AWNS we suggest that the increased involvement of the right PMd in non-speech and possibly also in speech tasks represents a compensatory rather than a maladaptive process.

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