# Cortical and subcortical mechanisms in persistent stuttering

Dissertation

for the award of the degree
„Doctor rerum naturalium“
Division of Mathematics and Natural Sciences
of the Georg-August-Universität Göttingen

submitted by
Nicole Neef

from Karl-Marx-Stadt
Göttingen 2010

Doctoral Thesis Committee:

**PD Dr. med. Martin Sommer (Supervisor, Reviewer)**
Abteilung Klinische Neurophysiologie
Universitätsmedizin Göttingen
Robert-Koch-Straße 40
37075 Göttingen
**Prof. Dr. rer. nat. Julia Fischer (Reviewer)**
Deutsches Primatenzentrum
Abteilung Kognitive Ethologie
Kellnerweg 4
37077 Göttingen
**Prof. Dr. med.Walter Paulus**
Abteilung Klinische Neurophysiologie
Universitätsmedizin Göttingen
Robert-Koch-Straße 40
37075 Göttingen
**Prof. Dr. phil. Marcus Hasselhorn**
Georg-August-Universität Göttingen
Abt. 4: Pädagogische Psychologie und Entwicklungspsychologie
37075 Göttingen

Date of thesis submission: 30th November 2010
Date of the oral examination: 10th January 2011

## Statement of Originality

I hereby declare that this thesis is my own work and has been written independently, with no other sources and aids than quoted in the text, references and acknowledgements.

Göttingen, 30th November 2010

Nicole Neef

## Content

## Abbreviations

| | |
|---|---|
| AADC | Aromatic L-amino acid decarboxylase |
| AI | ambivalence interval |
| AMT | active motor threshold |
| ANOVA | analysis of variance |
| AWNS | adults who do not stutter |
| AWS | adults who stutter |
| CS | conditioning stimulus |
| CV | consonant-vowel |
| CVS | consonant-vowel-syllable-continua |
| DBS | deep brain stimulation |
| DIVA | directions into velocities of articulators model |
| DTI | diffusion tensor imaging |
| EEG | electroencephalography |
| EMG | electromyogram |
| FA | fractional anisotropy |
| FDI | first dorsal interosseous |
| fMRI | functional magnetic resonance imaging |
| FS | fluent speaker |
| GABA | γ-Aminobutyric acid |
| $ICC_{unjust}$ | unjust intra-class correlation coefficient |
| ICD | International Classification of Functioning, Disability and Health |
| ICF | intracortical facilitation |
| IFG | inferior frontal gyrus |
| ISI | inter-stimulus interval |
| ITI | inter-tap interval |
| M1 | primary motor cortex |
| MEG | magnetencephalography |
| MEP | motor evoked potential |
| MMN | mismatch negativity |
| MRI | magnetic resonance imaging |
| MT | motor threshold |
| NMDA | N-methyl-D-aspartate |
| PB | phoneme boundary |
| PET | positron emissions tomography |

| | |
|---|---|
| PM | premotor cortex |
| PMd | dorsolateral premotor cortex |
| PMv | ventral premotor cortex |
| rTMS | repetitive transcranial magnetic stimulation |
| SD | standard deviation |
| SEM | standard error of mean |
| SICI | short-term intracortical inhibition |
| SMA | supplementary motor area |
| SSI-3 | stuttering severity index 3th edition |
| STG | superior temporal gyrus |
| TMS | transcranial magnetic stimulation |
| TS | test stimulus |
| VOT | voice onset time |
| WHO | world health organization |

# 1 Introduction

Stuttering is a speech disorder that occurs without known origin between 3 and 8 years of age and often remits before puberty. When it persists after puberty it becomes a chronic adult speech disorder throughout the lifespan (Andrews et al., 1983). The advances in neuroimaging promoted insights into the highly distributed system of speech production and its alterations in adulthood stuttering. One important motivation in stuttering research is to separate neurobiological correlates of the core symptoms of stuttering from neurobiological correlates associated with compensation, attempts to avoid stuttering. Results so far indicate a variety of complex dysfunctional systems and it appeared problematic to distinguish between mechanisms responsible for speech dysfluencies and those connected to compensation in the adult system (Ludlow, 2000). The first study of this dissertation will tie in with this problem.

Another important aspect is again motivated by neuroimaging studies that stress irregularities in the activation of the primary motor cortex during different functional states associated with speech production. The regulation of blood supply which is the basis of functional magnetic resonance imaging (fMRI) is correlated with summed neuronal activity but conclusions about states of cortical excitability and thus neurophysiological mechanisms are indirect. The modulation of cortical excitability is an inherent principle in the encoding of output signal by the primary motor cortex and the method of choice to non-invasively study this in humans is transcranial magnetic stimulation (TMS). This method is well established in Professor Paulus' Department of Clinical Neurophysiology, for instance to investigate neuromodulation in the primary motor cortex representation of small hand muscles. One aim of the dissertation was to establish recordings of TMS induced motor evoked potentials (MEPs) from facial muscles. This enabled me to conduct the first study of the intracortical excitability of the primary tongue motor representation in adults who stutter.

A seminal work motivated the third study included in this dissertation: diffusion tensor imaging (DTI) identified reduced white matter integrity in fibres connecting frontal, temporal and parietal speech related areas (Sommer et al., 2002a). Affected are possibly fibres mediating the mapping of speech sounds to articulation. The interaction of speech production and speech perception and the interference of stuttering with this interaction is the topic of the third study reported in this dissertation.

During the course of my doctoral studies I furthermore contributed to a longitudinal DTI study aiming at identifying a biological marker of stuttering persistency at stuttering onset. In

addition I conducted an fMRI study of the neuroanatomical correlates of continuous performance in stuttering in cooperation with the Biomedical NMR Research GmbH at the Max Planck Institute for Biophysical Chemistry. An internship at the speech Laboratory of Purdue University allowed me to study the consolidation of speech motor learning in children who stutter by using the Optotrak, a system that delivers a 3D tracking and measuring of speech kinematics. These ongoing studies are not included here.
As the drafts of the studies themselves give only limited space to introduction of the topic, a more detailed introduction is given in sections 1.1 to 1.5.

## 1.1 Components of the process of fluent articulation

Stuttering is a disorder with intermittent interruptions of fluent articulation. Fluent articulation is one of human‘s most complex motor skills. It comprises the coordinated use of approximately 100 muscles (Ackermann, 2008) and it is fascinating how effortless this skill is managed by almost every human being. Rapid, complex movements are essential to articulate the sounds of speech. Here I briefly summarize the structures involved in articulation, which is the ultimate readout of language planning and speech motor control processes. Subsequently, I refer to influential theories on language planning and speech motor control because all these aspects are implied in different approaches to explain stuttering.

Articulation involves three anatomically distinct subsystems: the respiratory, laryngeal and supralaryngeal system. The respiratory system regulates the outflow of air during speech and thus provides the energy for the acoustic targets of speech. The core structures of the laryngeal system are the vocal folds, controlling voicing and loudness of speech. During voicing the oscillation of the vowel folds generates the fundamental frequency on which resonation builds. The larynx provides the quasiperiodic and tone-like sound fundamental for vowels and voiced consonants (e.g. [b], [z] and [m]). The supralaryngeal system contains the pharyngeal, oral and nasal cavities whose architecture and configuration shape the timbre and the sound of the generated acoustic signal. The supralaryngeal system also called the vocal tract can be constricted at different places for example via lip closure, lip protrusion, tongue tip or body elevation or retraction, and velum elevation. Characteristic sound features of speech vowels are generated by overlapping vocal tract actions such as jaw lowering, tongue body elevation, and lip protrusion. In contrast, the striking acoustic features of consonants are generated by the magnitude of obstruction, resulting in bursts due to closure and friction-like noise due to fine-tuned constriction.

The respiratory, laryngeal and supralaryngeal systems recruit distributed neural networks to channel the muscle activation into organized spatio-temporal speech movement patterns. The following neural structures are central for this function:

(1) Orofacial and laryngeal sensorimotor cortex and the corticobulbar and the corticospinal tracts
(2) Premotor cortex, insula, supplementary motor area, and cingulate motor area
(3) Motoneurons in the brainstem (nucleus trigeminus, nucleus facialis, nucleus glossopharyngeus, nucleus vagus, nucleus accessories, nucleus hypoglossus)
(4) Motoneurons and associated spinal interneurons which control the respiratory musculature are found distributed across cervical segments (C1-C8) and thoracic segments (T1-T12) of the spinal cord
(5) Peripheral nerve fibers of the mentioned motoneurons and their neuromuscular junctions
(6) Extrapyramidal tracts, basal ganglia-thalamocortical pathway
(7) Cerebellum with its efferent and afferent fibers, cerebello-thalamocortical pathway

Anatomy and physiology of speech production is comprehensively described by Steven M. Barlow or Kenneth N. Stevens (Barlow et al., 1999; Stevens, 2000).
In normal conversation, a speaker produces 3 to 5 intelligible syllables per second (Smith, 1992); thus, the nervous system manages to simultaneously control and coordinate the overlapping articulatory gestures to produce rapidly altering configurations of the multilevel executing speech organs.

Preceding and simultaneously, a message that is intended to be transferred to a communication partner has to be created and transformed into the verbal code. This cognitive process is detailed by Levelt in his influential model of speech production (Levelt, 1989c). A brief summary of this psycholinguistic model which shaped several theories on stuttering is given in Appendix A.

Speech motor control is a further aspect that needs to be considered for the complex process of speech production. A current model of speech motor control is the Directions into Velocities of Articulators model (DIVA; Golfinopoulos et al., 2010; Guenther, 1994, 1995). In this model speech motor control is based on a feed forward and a feedback control subsystem. The feedforward process is supposed to control the execution of speech movements. Additionally, the feedforward subsystem activates predictive internal models (efference copies) in the feedback subsystem. These internal models represent the expectation of the incoming somatosensory and auditory feedback resulting from current speech

movements which enable a fast detection and correction of articulation. Psycholinguistic aspects of language generation are not considered in the model. Rather it details the production process and the link of production perception interaction. By providing a neuroanatomical framework to understand fluent as well as stuttered (Civier et al., 2010; Max et al., 2004) speech production it is helpful to consider this model for studies on stuttering. More details on the DIVA model are given in Appendix A.

## 1.2 What is stuttering?

Stuttering is an impairment of "Speech that is characterized by frequent repetition or prolongation of sounds or syllables or words, or by frequent hesitations or pauses that disrupt the rhythmic flow of speech. It should be classified as a disorder only if its severity is such as to markedly disturb the fluency", ("International Classification of Functioning, Disability and Health" ICD-10 F98.5 A; WHO, 2007a). As a consequence of stuttering, the affected individual is disabled in performing daily tasks that rely on spoken communication. This handicaps the individual to maintain a desired occupation or to fulfill economic needs (Yaruss, 2010).

The core symptoms of stuttering are dysfluencies. These are features in speech production that can be observed to a different extent in everybody's speech. The discrimination between typical dysfluencies and stuttering-like dysfluencies requires their qualitative description. Typical or so called *other dysfluencies* include interjections ("mhm", "yes"), phrase repetitions ("this is a this is a phrase repetition"), multisyllabic repetitions ("multi multisyllabic"), revisions ("revi repetition") that are not perceived as stuttering. As to stuttering-like dysfluencies consensus exists regarding part word repetition (p-p-p-partword) and dysrythmic phonation such as unintended audible prolongations of sounds and unintended momentary cessation of phonation/articulation (block) (Yairi and Ambrose, 1992; Yairi and Ambrose, 2005). There is, however, an ongoing debate on whether undue tension or struggle is a criterion to rate a single syllable word repetition ("I-I-I see") as a stuttering-like dysfluency or not (Bloodstein and Ratner, 2008; Ward, 2006; Yairi and Ambrose, 2005) and whether a cut-off value (e.g. 3 % of stuttered syllables) is necessary to label stuttering (Sandrieser and Schneider, 2008; Ward, 2006). This debate reflects the two opposing views of stuttering as either a quantitative variation along the continuum of normal speech dysfluency (continuity hypothesis; Bloodstein, 1970; van Lieshout et al., 2007) or a qualitatively separate disorder with a distinction between stuttering and normal dysfluency (Johnson, 1959; Yairi and Ambrose, 2005). In the current studies I determined stuttering presence and severity

according to the German version of the stuttering severity index (Sandrieser and Schneider, 2008) as described in the methods sections of the included studies.

## 1.3 Subtypes of stuttering

Scientific approaches to explain stuttering are diverse and consequently many different attempts to classify the disorder exist. These attempts are clearly influenced by the Zeitgeist in which they emerged. Ehud Yairi wrote an excellent review on these attempts of subtyping stuttering (Yairi, 2007). A reliable and standardized categorization would obviously be of great advantage for scientific studies. A current PubMed search clearly indicates that a separation between acquired [neurogenic] stuttering, psychogenic stuttering, and persistent [developmental, idiopathic] stuttering is commonly used these days (Lundgren et al., 2010). Therefore this etiology-based classification is briefly introduced here.

### 1.3.1 Acquired stuttering

Acquired stuttering occurs in adulthood and is related to aberrant neurogenic conditions including for example cerebrovascular lesions, traumatic brain injuries, seizure disorders and Parkinson's disease (Lundgren et al., 2010). Various cortical and subcortical lesion sites are related to acquired stuttering (see Appendix B, Table B-1). There is a lot to gain from studies of acquired stuttering, where the causal disruption is more easily identified and the short period between onset and examination helps to assure that observed abnormalities are not secondary but indeed causal. Therefore, a detailed overview on locations of brain injuries that induce speech dysfluencies, criteria for the differential diagnosis, cases of chased stuttering due to brain lesions and current knowledge from deep brain simulation and stuttering is given in Appendix B.

### 1.3.2 Psychogenic stuttering

Psychogenic stuttering occurs in adulthood as a result of psychological trauma (Baumgartner and Duffy, 1997). A reliable differential diagnosis of acquired from psychogenic stuttering, based on perceptual features of speech characteristics, is problematic. It appears that the rapid, favorable response to the treatment serves best to differentiate the psychogenic cases from the neurologic cases (Lundgren et al., 2010).

### 1.3.3 Persistent stuttering

All studies introduced in this dissertation aim at elucidating pathomechanisms in persistent stuttering because it is a frequent disorder with unclear etiology. For that reason I give more details on this disorder. Persistent stuttering occurs in childhood without obvious reason. The

aforementioned description of the symptoms of stuttering including sound and part word repetitions, sound prolongations and blocks, are accompanied by further characteristics in persistent stuttering. There are physical concomitants as for example facial grimacing, fist clenching, and eye blinking. Additionally many persons with persistent stuttering develop negative emotions like fear and embarrassment and avoidance behavior including for example the avoidance of certain words or speech sounds that are expected to provoke stuttering, or do avoid situations such as telephoning or ordering food in a restaurant (Büchel and Sommer, 2004; Wingate, 1964).

### *Age of onset*

Persistent stuttering most often occurs in childhood between age 2 and 5 (Andrews and Harris, 1964; Dworzynski et al., 2007; Mansson, 2000; Yairi and Ambrose, 2005) without obvious reason. An extensive study on childhood stuttering yielded an onset of stuttering prior to the age of 3 in 85% of 103 examined children who stutter (Yairi and Ambrose, 2005). The sole epidemiological study that continued until the children were aged 15 reported 25 % of stuttering onset after the age of 8 (Andrews and Harris, 1964).

### *Incidence*

The risk of developing stuttering ranged between 5% and 7% depending on the age range and study duration (Andrews and Harris, 1964; Dworzynski et al., 2007; Mansson, 2000). A recent community-ascertained cohort study of 1619 Australian children recruited at 8 months of age reported a cumulative incidence of stuttering onset of 8.5% at age 3 (Reilly et al., 2009).

### *Recovery rate and prevalence*

2 to 6 years after stuttering onset recovery rates range between 65% and 85% (Mansson, 2000; Yairi and Ambrose, 2005). For a considerable number of affected individuals, however, stuttering continues unmitigated, resulting in a prevalence of about 1% among adults (Andrews and Harris, 1964; Yairi and Ambrose, 1999).

### *The sex ratio*

For stuttering the sex ratio appears to be roughly equal at the onset of the disorder (3 girls : 4 boys), and studies indicate that among those children who continue to stutter in adulthood, 75% to 80% are males (Bloodstein, 1970; Howell, 2007).

### *Genetic susceptibility*

Stuttering has been long recognized to have a genetic component (Suresh et al., 2006). Family clustering is frequently reported, several twin studies document a high degree of heritability and male relatives of female stutterers are at greater risk to develop stuttering; an excellent overview is given by Yairi and Ambrose (2005). The role of genetic contributions in the aetiology of stuttering is complex, multifactorial, and heterogeneous (Fisher, 2010). Genetic-linkage studies yielded suggestive evidence of linkage at multiple chromosomal sites with little overlap among independent data sets (Kang et al., 2010). One example of suggestive linkage has its locus on chromosome 12q and was found in a study which included consanguineous families in Pakistan (Riaz et al., 2005). A continuative analysis of chromosome 12q23.3 genomic region in consanguineous Pakistani families revealed genetic abnormalities in the lysosomal enzyme–targeting pathway (Kang et al., 2010).

## 1.4 Approaches to explain stuttering

The phenomenon of stuttering gave rise to manifold theories, each shaped by the perspective of a certain field such as for example analytic psychology (Damste et al., 1968), speech and language pathology e.g. (Bloodstein and Ratner, 2008; Van Riper, 1971; Yairi and Ambrose, 2005), psychology e.g. (Smith and Kelly, 1997; Starkweather and Gottwald, 1990), linguistics e.g. (Coulter et al., 2009; Howell, 2004; Postma and Kolk, 1993), biomechanics e.g. (Civier et al., 2010; Namasivayam et al., 2009; Van Lieshout, 2004) and neuroscience e.g. (Alm, 2004; Brown et al., 2005; Büchel and Sommer, 2004; Kell et al., 2009; Ludlow, 2000). This multiplicity of approaches is plausible due to the fact that a broad assortment of linguistic, cognitive, and sensorimotor processes is involved in speech production.

We focus on stuttering as a motor disorder. Before I detail this speech motor control perspective I briefly mention the psycholinguistic perspective, not only because it has strongly influenced stuttering research but also because this perspective was considered in the third study (phoneme identification) included in this dissertation. An awareness of the diverse approaches to problems in stuttering is important, because a certain experimental result may be given disparate interpretations by different investigators.

### 1.4.1 Psycholinguistic approach

It is still a matter of debate, whether stuttering is a language disorder or a motor control disorder (Kent, 2000). The challenge in understanding stuttering is the distinction between impairments of the language system and impairments of motor control per se (Kent, 2000). Several attempts to explain stuttering favor the fluency failure resulting from weakness in

encoding lexical, grammatical, phonological or suprasegmental (e.g. word stress) targets in speech production (Bloodstein and Ratner, 2008). Phonological encoding is the linguistic process that is most often considered to be disturbed in stuttering (Smith et al., 2010). Prominent theories are the neuropsycholinguistic theory (Perkins et al., 1991), the Covert Repair Hypothesis (Postma and Kolk, 1993) and the EXPLAN theory (Howell, 2004). These theoretical accounts posit that motor breakdowns result from slowed or faulty phonological encoding, a linguistic processing stage that precedes motor planning and execution as detailed in Appendix A. These accounts suggest primary a deficit in language competence and language performance. An elaborated review on psycholinguistic accounts is given in (Bloodstein and Ratner, 2008) and a brief summary, focusing on accounts of a phonological encoding deficit in stuttering, is given in Appendix C.

### 1.4.2 Motor deficit perspective

Persons who stutter exhibit difficulties in initiating and controlling speech movements (Peters et al., 2000). Mechanisms governing a precise adjustment of the respiratory, laryngeal and articulatory system are operating less efficiently or are disrupted in timing or coordination and thus interfere with the smooth course of articulatory movements (Adams, 1974; Kent, 1984; Van Riper, 1971; Zimmermann, 1980b).

Difficulties in *initiating* speech movements have been extensively examined by means of acoustic reaction time studies. Compared to control subjects, persons who stutter were slower in initiating speech movements unequivocally for the initiation of complex utterances (Peters et al., 1989). Because reaction time is a cumulative measure of linguistic and motor processes a general conclusion regarding the initiation of speech movements in stuttering is pending (Smits-Bandstra, 2010).

The control of *timing* is one important aspect of speech motor control and in several attempts it has been hypothesized that stuttering is a disorder of timing (Kent, 1984; Ludlow and Loucks, 2003; Olander et al., 2010). Several studies of perceptually fluent speech of persons who stutter reveal deviations in variability, speed and relative timing of speech movements (Kleinow and Smith, 2000; Max et al., 2003; Zimmermann, 1980a).

Comparisons of *non-speech* oral movements and finger movements between persons who stutter and control subjects suggest a general neuromotor deficit in stuttering (Cooper and Allen, 1977; Max et al., 2003; Zelaznik et al., 1997). Examinations of unimanual and bimanual rhythmic finger tapping or finger sequencing studies reveal unequivocal results and differences between persons who stutter and control subjects manifest mainly in complex conditions (Olander et al., 2010). To conclude, the complex spatial-temporal coordination

independent of the executing organs (orofacial /limb) is constrained in the system of persons who stutter.

### *Aberrant production-perception-interaction*

Current theories of speech production integrate perceptive processes and production-perception-interactions. Several researchers consider an aberrant sensory feedback system as potential cause of stuttering. Civier and Guenther (2010) distinguish three views:

(1) persons who stutter differ from control subjects by relying too heavily on sensory feedback (Tourville et al., 2008; van Lieshout et al., 1993);

(2) persons who stutter benefit from reliance on sensory feedback (Max et al., 2004; Namasivayam et al., 2008; van Lieshout et al., 1996);

(3) due to an impaired feedforward control system, persons who stutter rely more heavily on a feedback-based motor control strategy (Civier et al., 2010; De Nil et al., 2001; Kalveram and Jancke, 1989; Zimmermann, 1980b). This suggests that an over-reliance towards an auditory feedback control strategy increases the systems' vulnerability to produce errors. Those errors might cause the motor system to "reset" and repeat the current syllable (Civier et al., 2010). Repetitions would then result from the attempts to repair large sensorimotor errors as simulated in the computer model and proven in one person who stutters.

## 1.5 Neurophysiological approaches to explain stuttering

Since the formulation of the cerebral dominance theory (Orton, 1928) researchers have speculated about potential involvement of aberrant neural processes in the onset and development of stuttering (De Nil, 2004). Early research into the nature of these deviations was mainly based on behavioural observations and electromyographic measurements. With advances in neuroimaging techniques such as positron emissions tomography (PET) and magnetic resonance imaging (MRI) manifold findings about the neural differences between persons who stutter and control subjects has been aggregated, motivating the emergence of different hypothesis of brain function in stuttering. The following section targets to introduce three of these hypotheses leading to the motivation of the studies presented in this dissertation.

### 1.5.1 The cerebral dominance hypothesis

Already in 1931, Travis introduced the idea of the cerebral dominance theory of stuttering:

*"Stuttering is caused by aberrant interhemispheric relationships. These aberrancies could include the creation of a mistiming of nerve impulses to the bilateral speech musculatures."* (Travis, 1978)

The author took note of the fact that the midline speech structures such as jaw, lips, tongue, velum and glottis were innervated by separate sources of the two hemispheres of the brain. High spatio-temporal coordination of these structures during speaking depends on the precisely timed, synchronized streams of nerve impulses. To avoid competing timing signals, Travis hypothesized, one cerebral hemisphere dominates the other. Speech "breakdowns" were proposed to arise from insufficient dominance.

With the progress in neuroimaging techniques, it became possible to scrutinize the cerebral dominance hypothesis, and indeed several fMRI and PET studies revealed that the lateralized activation pattern during speech tasks differs between persons who stutter and control subjects. They found increased right-hemispheric activations and decreased left-hemispheric activations in stuttering. Specifically, hyperactivations were localized in right motor and premotor cerebral and left cerebellar areas, while absent or decreased activations were described in left auditory and sensory cortical areas (Brown et al., 2005). As interesting as these findings are, the interpretation with respect to functional alterations is unclear. PET and fMRI detect changes in the cerebral blood flow, the haemodynamic response, upon a particular behavior (e.g. speaking). While the haemodynamic response is thought to report quantitative changes in the average local neuronal activity, it reveals neither the quality, the *functional consequence* of these changes nor the *neurophysiological mechanisms* that underlie the aberrant activity patterns in persons who stutter. Using transcranial magnetic stimulation (TMS, see Appendix D), a neurostimulation technique that allows direct interference with local brain activity, I addressed those points in two studies.

Asking for the *functional consequence* of this right hemispheric hyperactivity in stuttering, neuroscientists suggest a compensatory role, because the level of activation for example in the right frontal operculum correlated negatively with stuttering severity (Preibisch et al., 2003). Fluency-inducing maneuvers, like choral reading or metronome speaking, which relieve the need for compensation, also reduce the right-hemispheric motor-system overactivations and left temporal auditory-system deactivations, this is, they approximate the activation pattern of persons who stutter to that of control subjects (Fox et al., 1996; Fox et al., 2000; Ingham et

al., 2004). A direct test of the role of right-hemispheric motor areas to proposed specific behaviors is so far missing in stuttering research.

In the first study of the current dissertation TMS was used to induce a virtual lesion in the dorsolateral premotor cortex (PMd) to test its role in movement timing in persons who stutter. In healthy subjects it has been reported that the left PMd is crucially involved in the control of paced finger movements (Pollok et al., 2008). It is unclear whether this cortical lateralization of timing control holds true in persons who stutter. Supporting evidence for an imbalanced functional lateralization of the control of finger tapping in stuttering is given by a recent fMRI study (Morgan et al., 2008). While in healthy subjects finger tapping with the right hand activated the contralateral motor and premotor cortex, in persons who stutter the precentral gyrus of either hemisphere was activated. In the study presented here we tested whether the right premotor cortex is indeed *functionally* involved in a paced finger tapping task in persons who stutter.

The second study included in this dissertation took aim at the *neurophysiological mechanisms* in the primary motor tongue representation. From a neurophysiological point of view, the right hemispheric hyperactivity of the primary motor cortex during symptom production (Braun et al., 1997; Fox et al., 1996; Fox et al., 2000) has been interpreted as increased cortical excitability (Ludlow and Loucks, 2003). By applying TMS it is possible to determine cortical excitability (see Appendix D). Although TMS is well established and a widely used technique there are only two reports on cortical excitability in stuttering research preceding this dissertation (Sommer et al., 2009a; Sommer et al., 2003). The objective of the most recent study (Sommer et al., 2009a) is to elucidate transcallosal interactions between the motor cortices in adults who stutter. The interplay between hemispheres which is operationalized with measures of transcallosal inhibition and ipsilateral silent period was normal in the cortical hand representation in stuttering, not indicating that this interplay between motor cortices is likely to play a decisive role in stuttering. The earlier study (Sommer et al., 2003) ascertains the intracortical excitability of the cortical representation of a right hand. The critical parameters are *intracortical inhibition* which is likely mediated by inhibitory motor cortical interneurons (Hallett, 2000), and *intracortical facilitation* which is hypothesized to be a net facilitation consisting of prevailing facilitation and weaker inhibition mediated, among other mechanisms, by glutamatergic N-methyl-D-aspartate (NMDA) receptors and γ-Aminobutyric acid (GABA)ergic receptors (Hanajima and Ugawa, 2008; Paulus et al., 2008). Again, intracortical inhibition and intracortical facilitation were found to be normal in the

motor hand area in adults who stutter. Thus, so far there is no evidence for an abnormal excitability of the primary motor representation in persons who stutter.

It is plausible to examine neurophysiological mechanisms in the primary motor hand representation in persons who stutter because various studies on finger movements indicate a compromised function on a subclinical level in stuttering (see section 1.4.2 and study 1) and a fMRI study indicates an altered activation pattern (Morgan et al., 2008). Nonetheless, two aspects should be considered: the *physiological state* and the *executing system* (limb system versus orofacial system).

On the one hand previous TMS measurements in stuttering reflect the *neurophysiological state* during rest and not during a mode in which the neural populations contribute to a certain function such as finger tapping or speaking. The context-dependent influence of remote brain areas interconnected with the primary motor cortex changes with the current functional state. Thus, the primary motor cortex provides not a fixed, context-invariant neurophysiological picture. The context dependence is clearly illustrated by neuroimaging studies on stuttering, reporting a right hemispheric overactivity of the primary motor cortex during symptom production (Braun et al., 1997; Fox et al., 1996; Fox et al., 2000), a bilateral overactivity during perceptively fluent speech production and a bilateral decreased activity during speech perception and speech planning (Chang et al., 2009). As a consequence, state-dependent measures are necessary to exclude an altered motor cortical excitability in stuttering.

On the other hand, one should be careful when generalizing mechanisms in the motor hand representation to that of *speech relevant structures*, as the underlying network architecture differs, providing bilateral innervation of midline speech structures. However, the recording of TMS induced motor evoked potentials (MEPs) in orofacial structures is challenging. The reasons for that are (1) the direct peripheral stimulation of the innervating nerve, (2) the short latency of the MEP which might be masked by the TMS artefact, (3) the persistent tonic activity of orofacial muscles, and (4) the relevant cortical representation lies beneath thicker skull or deeper inside (Devlin and Watkins, 2008). Although methodologically challenging, we were able to establish a set up to measure TMS induced potentials from the primary motor tongue representation. Thus the second study included in this dissertation is the first report of the neurophysiological properties of oral muscles in persons who stutter, measured by means of TMS at rest and under voluntary contraction. These properties were obtained from the primary motor cortices of both hemispheres to consider potential imbalances of cortical excitability measures between hemispheres as it is suggested by the cerebral dominance hypothesis.

The cerebral dominance hypothesis is not the only concept explaining stuttering as a motor-deficit. The *basal ganglia hypothesis* extends the view to subcortical structures and their involvement in motor control while the *disconnection hypothesis* broadens the picture to include the left-perisylvian deficit of white matter integrity (Sommer et al., 2002a). Both hypotheses and their relation to the studies in this dissertation are introduced in the next sections.

### 1.5.2 The basal ganglia hypothesis

The second hypothesis postulates an altered basal ganglia function in stuttering. Although the basal ganglia lie beyond the range of direct interference by TMS, the cortico-striato-thalamo-cortical loop is an important connection shaping the output of the primary motor cortex as well as the PMd, i.e. the stimulation sites targeted in the TMS studies included here. The basal ganglia comprise subcortical gray matter in the forebrain, diencephalon and midbrain. Macroscopically one can separate two primary input structures (striatum and subthalamic nucleus), two intrinsic nuclei (globus pallidus external segment, substantia nigra pars compacta), and two primary output structures (substantia nigra pars reticularis, globus pallidus internal segment, see Figure 1-1). Multiple loops between the cerebral cortex, the basal ganglia, thalamus and cerebellum contribute to the motor function such as planning, selecting, initiating and regulating voluntary movements. Excellent insights into the functional organization of the basal ganglia are given by Roberta M. Kelly and Peter L. Strick as well as by Jonathan W. Mink (Kelly and Strick, 2004; Mink, 1996).

Early findings supporting a basal ganglia involvement in stuttering came from pharmacological studies. Clinical trials with dopamine antagonists such as haloperidol, risperidone and olanzapine resulted in a fluency enhancement while dopamine agonists, including L-dopa, aggravate stuttering (Brady, 1991; Maguire et al., 2004). Moreover, long time medication with levodopa in Parkinson's disease is reported to be accompanied with acquired stuttering (Louis et al., 2001). That stuttering is likely to be related to abnormal elevations of cerebral dopamine activity was reinforced by an early study with PET. Wu and colleagues examined three persons who stutter and six control subjects. They labeled presynaptic dopamine production and reported an increased uptake of the administered ligand [6FDOPA, ligand for Aromatic L-amino acid decarboxylase (AADC) enzyme which generates dopamine] in medial prefrontal cortex, deep orbital cortex, insular cortex, extended amygdala, auditory cortex and caudate tails (Wu et al., 1997).

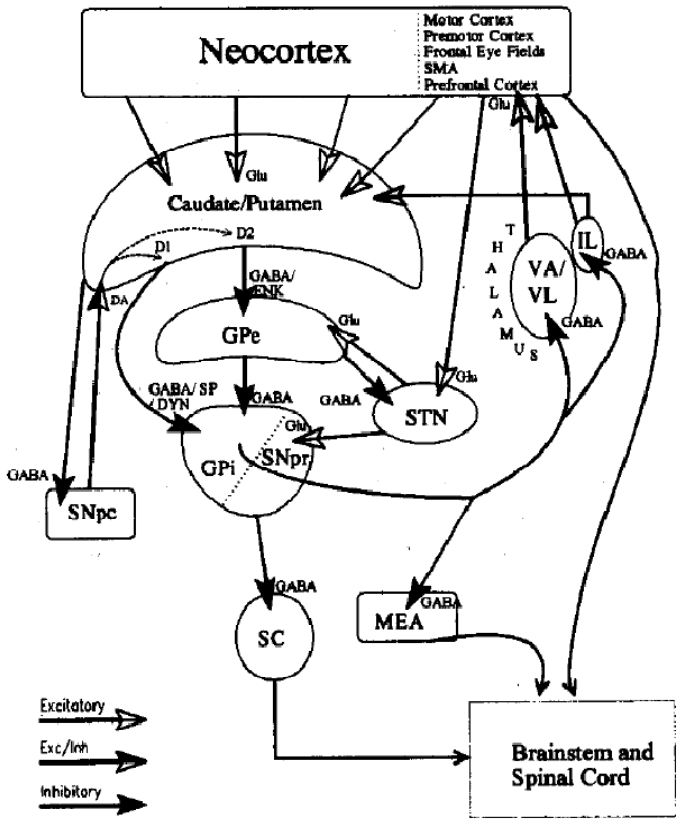


**Figure 1-1 from Mink, 1996: Schematic representation of the basal ganglia.** The striatum (consisting of the caudate and putamen) and the subthalamic nucleus (STN) are the input nuclei receiving *excitatory* input from various cortical regions such as the motor cortex, premotor cortex, supplementary motor area (SMA), prefrontal cortex and frontal eye field. The intrinsic nuclei are the globus pallidus external segment (GPe) and the substantia nigra pars compacta (SNpc). GPe receives *inhibitory* input by the striatum and excitatory input by the STN; and inhibits the STN, GP internal segment (GPi), and the SN pars reticulata (SNpr). SNpc contains mainly dopaminergic neurons and is extensively connected with the striatum. The output structures are the GPi and the SNpr, receiving both, fast excitatory and slow inhibitory input from the striatum. GPi and SNpr inhibit motor areas in the thalamus (ventral anterior thalamic nucleus VA; ventral lateral thalamic nucleus VL, intralaminar thalamic nuclei IL) and the brainstem. Further abbreviations: superior colliculus SC; midbrain extrapyramidal area MEA.

Recent neuroimaging studies consistently report aberrant basal ganglia activations in persons who stutter (Chang et al., 2009; Giraud et al., 2007; Lu et al., 2010; Lu et al., 2009a; Lu et al., 2009b; Watkins et al., 2008). Reported basal ganglia dysfunctions are listed in Table 1-1. All of these studies point towards aberrant basal ganglia circuits affecting planning, initiating, sequencing and executing speech in stuttering.

**Table 1-1 Recent neuroimaging studies revealing aberrant basal ganglia activity in stuttering**

| Reference | deviations | task |
|---|---|---|
| (Chang et al., 2009) | less activation in the left putamen | repeating syllables or non-speech sounds (cough) |
| (Giraud et al., 2007) | positive correlation between severity of stuttering and activity in the bilateral caudate nuclei | overt sentences reading |
| (Watkins et al., 2008) | overactivation in the substantia nigra, extending to the pedunculopontine nucleus, red nucleus and subthalamic nucleus | overt sentences reading sentences combined with altered auditory feedback |
| (Lu et al., 2009b) | weaker negative connectivity from the left posterior middle temporal gyrus to the putamen, but stronger positive connectivity from the putamen to the thalamus, from the thalamus to the posterior middle temporal gyrus and anterior supplementary motor area, and from the anterior superior temporal gyrus to the preSMA | covert picture naming |
| (Lu et al., 2009a) | altered connectivity in the basal ganglia-thalamic-cortical circuit | covert picture naming |
| (Lu et al., 2010) | aberrant basal ganglia-inferior frontal gyrus/premotor area circuit | covert picture naming |

Per Alm provides a detailed theoretical framework on deficient basal ganglia circuits in persistent stuttering (Alm, 2004). He hypothesized stuttering to arise from an impairment of the basal ganglia and cortico-striato-thalamo-cortical connections to produce timing cues for the initiation of the next motor segment in speech. A recent theoretical work incorporates the aspect of sequence skill learning and automatization of speech (Smits-Bandstra and De Nil, 2007): Dysfunctional cortico-striato-thalamo-cortical connections might hinder the timed stimulus response association learning. Smits-Bandstra and De Nil suggest that the motor memories, namely the neurochemical traces that developed due to continuous exposure to specific stimulus response associations, normally become increasingly resistant to interference as they become increasingly automatized. Proposing a deficit in automatization in persons who stutter, the authors suggest a need for additional attentional resources to speech. Being less automated, the speech skills would be relatively weak, unstable, and more susceptible to interference from ongoing activity.

A direct test of the basal ganglia hypothesis would require functional interference with the activity of this subcortical structure. As the basal ganglia lie beyond the range of TMS, this method can only probe potential consequences of chronically altered basal ganglia activity with respect to cortical properties. Paired-pulse TMS as described in Appendix D, has provided valuable insights in the modulation of cortical excitability in a number of basal ganglia disorders, including Parkinson's disease, Chorea and Gilles de la Tourette and

dystonia (Berardelli et al., 2008). In dystonia for example, reduced short-term intracortical inhibition (SICI) was reported during rest and certain active states (Beck and Hallett, 2010; Sommer et al., 2002b; Stinear and Byblow, 2004).

In the light of these findings, altered SICI and intracortical facilitation (ICF) in persons who stutter can not only be related to the cerebral dominance hypothesis, as detailed above, but can also be seen as a neurophysiological indication of an altered basal ganglia activity. This would be a valuable contribution to the research field which is dominated by evidence from neuro-imaging studies and theoretical works.

### 1.5.3 The disconnection hypothesis

In the third study included in this dissertation a psychophysical test was employed to determine the sensitivity of persons who stutter to identify phonemes. The third neurobiological hypothesis on stuttering, the disconnection hypothesis, is related to this experiment. Although there are only psychophysical data so far, the outcome of the psychophysical experiment and the disconnection hypothesis did motivate a forthcoming electrophysiological study already planned and approved from the ethics committee of the Göttingen University. Furthermore, because central for this dissertation are cortical and subcortical mechanisms in stuttering, this influencing hypothesis is introduced here.

The disconnection hypothesis originates from an advanced magnetic resonance imaging technique – diffusion tensor imaging. DTI enables us to measure the diffusion of water molecules in biological tissue in vivo. Diffusion describes how particles move about, driven by the thermal energy of the particles themselves. Due to random collisions the velocity and direction of motion perpetually change - the particles perform Brownian motion (Dhont, 2004). In the cerebro-spinal fluid water molecules diffuse equally in all directions - isotropic. In contrast, nerve fibers restrict the diffusion of water molecules due to the isolating myelin sheath. Water molecules diffuse mainly directed along a fiber – anisotropic. DTI detects water diffusion to characterize brain's white matter which mainly consists of nerve fibers connecting associated brain regions or projecting from or to peripheral organs. One DTI parameter is the fractional anisotropy (FA). This parameter indicates the similarity of directions of fiber tracts within each voxel, the smallest resolved box-shaped part of a three-dimensional space (Basser et al., 1994). A high density or number of white fibers or more extensive myelination result in an increased directionality of diffusion and thus in a high FA value. Consequently, gray matter has low FA values around 0.1, while white matter exhibits higher values for example 0.5 in the superior longitudinal fasciculus and 0.75 in the body of the corpus callosum (Yuan et al., 2007).

The first assessment of FA in brains of adults who stutter yielded one main result: The FA in the white matter underlying the left rolandic operculum was decreased compared to control subjects (Sommer et al., 2002a). Subsequent studies examining adults and adolescents who stutter, independently confirmed the finding of compromised white matter integrity in left frontal regions (Chang et al., 2008; Cykowski et al., 2010; Watkins et al., 2008).

These described brain alterations are evident in adults who stutter and adolescents. It is not clear yet, whether lifelong stuttering caused these deviations similar to reported training effects on white matter (Scholz et al., 2009; Takeuchi et al., 2010). Nonetheless, it is tempting to speculate that inborn, genetic aberrations are the cause of the observed white matter abnormalities (Büchel and Watkins, 2010). The latest indication in that direction came with the aforementioned discovery of stuttering related mutations of proteins controlling the lysosomal enzyme–targeting pathway (Kang et al., 2010). Other, apparently more severe, mutations in the same pathway lead to mucolipidosis type II and III, and affected subjects show severe white-matter abnormality (Folkerth, 1999).

The consequence of decreased fiber integrity in the frontal motor and premotor regions might be a vulnerability of speech relevant cortico-cortical (Salmelin et al., 2000) or cortical-subcortical connections in stuttering (Lu et al., 2009a). One important link for speech production is the neural link between the motor production of speech sounds and the representation of speech sounds in cortex (Hickok and Poeppel, 2007; Scott and Johnsrude, 2003), because the production of speech sounds is substantially modified by real-time auditory feedback. Altered auditory feedback of speech produces automatic adjustment by the speaker to compensate for the alteration such that feedback remains predictable (Houde and Jordan, 1998; Tourville et al., 2008). Moreover, experience with speech sounds shapes their perception (Nasir and Ostry, 2009; Shiller et al., 2009) suggesting that laryngeal disorders that affect speaking, such as spasmodic dysphonia, alaryngeal speech or stuttering, may have consequences on the perception of speech sounds in humans (Heiser and Cheung, 2008). These considerations motivated the experiment conducted in the third study presented in this dissertation.

**Table 1-2 Results from diffusion tensor imaging** yielded aberrant fractional anisotropy (FA) in persons who stutter. Most consistent is the observation of a reduced FA in the white matter of the left premotor region (italic font).

| Reference | lower FA | higher FA |
|---|---|---|
| (Sommer et al., 2002a) | *left rolandic operculum* | |
| (Watkins et al., 2008) | ▫pars orbitalis in the right inferior frontal gyrus<br>▫*left* and right *posterior inferior frontal gyrus*<br>▫*left* and right *precentral gyrus* (middle)<br>▫*left* and right *ventral premotor cortex*<br>▫right posterior supramarginal gyrus<br>▫left dorsal supramarginal gyrus<br>▫in the right and left cerebellar white matter<br>▫in white matter tracts such as the right corticospinal tract (at the level of the midbrain)<br>▫the medial lemniscus<br>▫right middle cerebellar peduncle | ▫left posterior inferior frontal gyrus (ventral to the area of decrease described above)<br>▫right postcentral gyrus<br>▫right supramarginal gyrus |
| (Chang et al., 2008) | ▫the corticospinal/corticobulbar tract bilaterally<br>▫*the left arcuate fasciculus in the left rolandic operculum region*<br>▫a posterior-lateral region underlying the supramarginal gyrus | |
| (Kell et al., 2009) | ▫*more anterior than rolandic operculum*<br>▫*left arcuate fasciculus* | ▫left anterior insula/inferior frontal region<br>▫the left orbitofrontal cortex<br>▫underneath the left intraparietal sulcus |
| (Cykowski et al., 2010) | ▫*a continuous region from the left forceps minor near its junction with the left anterior corona radiata, extending dorsally and caudally through the third division of the left superior longitudinal fasciculus (including and WM deep to Brodmann area BA 44)*<br>▫within the body of the corpus callosum | |
| (Chang et al., 2010) | | right rolandic operculum |

## 1.6 Scope of the dissertation

The objective of this dissertation is to explore cortical and subcortical mechanisms in stuttering.

In the first study, repetitive transcranial magnetic stimulation (rTMS) helped discovering a dysfunction of the *left dorsolateral premotor cortex* in control of paced finger movements and a compensatory role of its *right* hemispheric homologue in stuttering. While previous neuroimaging studies elucidated altered activation patterns, we were able to directly show for the first time that the right hemisphere might indeed play a compensatory rather than maladaptive role for non-speech functions in persistent developmental stuttering.

In the second study, we aimed at detecting neurophysiological changes in the primary motor tongue representation of the left and right hemisphere in adults with persistent stuttering. Overcoming methodological challenges of transcranial magnetic stimulation at orofacial structures, this is the first study demonstrating an abnormality in intracortical excitability in persistent stuttering.

The third study operationalized a behavioral approach to elucidate a possible disconnection between *parieto-temporal* regions involved in the phonological bottom up processing of speech stimuli and *frontal* regions mainly involved in the planning, programming and execution of speech movements. Behavioral deviations on a subclinical level might indicate a disturbed functional connectivity of these main networks of speech processing.

The following studies aim particularly:

(1) to test the lateralization of cortical control of paced finger movement timing in stuttering

(2) to detect neurophysiological changes in the intracortical excitability in the primary motor tongue representation of the left and right hemisphere by employing single-pulse and paired-pulse TMS in adults who stutter and matched control subjects

(3) to test the stability of phoneme percepts in stuttering by analyzing participants' sensitivity to identify voiced and voiceless stop-consonants near the phoneme boundary.

# 2 Original Articles

The following published and submitted articles are presented in this chapter:

I. Neef N .E., Jung, K., Rothkegel H., Pollok B., Wolff von Gudenberg A., Paulus W., Sommer M. **"Right-shift for non-speech motor processing in adults who stutter"** (2010 Jun 30. [Epub ahead of print]). The study was designed by Martin Sommer, Holger Rothkegel, Bettina Pollok and Nicole Neef. The program to present the stimuli was provided by Bettina Pollok. Nicole Neef wrote the ethic proposal, recruited the subjects, examined the subjects and analyzed the data. Reanalysis of the speech sample to test inter-rater reliability was performed by Kristina Jung. Statistics were performed by Martin Sommer and Nicole Neef. The manuscript was written by Martin Sommer and Nicole Neef with contributions of all authors.

II. Neef N. E., Paulus W., Neef A., Wolff von Gudenberg A., Sommer M. **"Reduced intracortical inhibition and facilitation in the primary motor tongue representation of adults who stutter"** (resubmitted after revision to *Clinical Neurophysiology;* version of November 26$^{th}$ 2010). The study was designed by Martin Sommer and Nicole Neef. Nicole Neef wrote the ethic proposal, recruited the subjects, examined the subjects and analyzed the data. A data browser was programmed by Andreas Neef. The quantification of the Electromyography (EMG) activity at baseline and area under the MEP amplitude were performed by Andreas Neef. Statistics were performed by Martin Sommer and Nicole Neef. The manuscript was written by Nicole Neef with contributions of all authors.

III. Neef N. E., Sommer M., Paulus W., Wolff von Gudenberg A., Wüstenberg T. **"Instable phoneme categorization in adults who stutter"** (under revision to resubmit to *Journal of Speech, Language, and Hearing Research;* version of November 30$^{th}$ 2010). This study was designed by Torsten Wüstenberg, Martin Sommer, Veronika Gutmann and Nicole Neef. Torsten Wüstenberg prepared the auditory stimuli and programmed the psychophysical test. Nicole Neef wrote the ethic proposal, recruited the subjects, examined the subjects and analyzed the data. Veronika Gutmann collected some of the pilot data. Statistics were performed by Torsten Wüstenberg, Martin Sommer and Nicole Neef. Graph 1 and 2 was prepared by Torsten Wüstenberg all other graphs were designed by Torsten Wüstenberg and Nicole Neef. The manuscript was written by Torsten Wüstenberg (methods sections: stimuli, data analysis, Appendix A and B) and Nicole Neef (introduction; methods sections: participants, fluency assessment, experimental procedure, statistics; results; discussion) with contributions of all authors.

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

Nicole E. Neef[1,2], Kristina Jung[3], Holger Rothkegel[1,2], Bettina Pollok[4],
Alexander Wolff von Gudenberg[3], Walter Paulus[1,2], and Martin Sommer[1,2]

[1]Department of Clinical Neurophysiology, Georg-August-University of Goettingen, Germany,
[2]Center for Systems Neuroscience, Goettingen, Germany
[3]Institut der Kasseler Stottertherapie, Bad Emstal, Germany
[4]Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University Duesseldorf, Germany

Running title: non-speech motor processing in stuttering

Address for correspondence:
Martin Sommer, M.D.
Department of Clinical Neurophysiology, University of Goettingen,
Robert-Koch-Str. 40, D-37075 Goettingen, Germany
Tel. +49-551-39 66 50, Fax. +49-551-39 81 26; Email: msommer@gwdg.de

## 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.

## Keywords

persistent developmental stuttering, repetitive transcranial magnetic stimulation, dorsolateral premotor cortex, compensatory mechanism

## 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 segments ((WHO), 2007a), 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, 1989c). In adults who stutter (AWS), acoustic-temporal and spatio-temporal characteristics are affected in stuttered and fluent speech on all these time scales (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 (Ivry and Spencer, 2004; Rao et al., 1997), 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; Zelaznik et al., 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 (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 et al., 2009; Siebner and Rothwell, 2003), 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; Pollok et al., 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 PMs 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 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).

# Methods

## 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., 2009b). 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 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), 2007b) 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.

please insert Tab. 1 about here

## 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; Riley, 1994), 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 (Riley, 1994). Software for offline analysis was 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.

### 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 hours 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.

### 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 degrees. 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 minutes 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).

### 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.

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).

## 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).

Please insert Fig. 1 about here

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

## 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.

### 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; Pollok et al., 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. (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. (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.

### 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., 2010) 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.

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

### 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., 2002a; 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., 2010) 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., 2009b; 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.

### 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; Howell et al., 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).

## 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.

## Funding

This work was supported by the Deutsche Forschungsgemeinschaft [SO 429/2-2 to M.S.]; Scholarship of the Stifterverband für die Deutsche Wissenschaft, Walter und Ilse Rose Stiftung [to W.P.]; the Bernstein Center for Computational Neuroscience (BCCN) [01GQ0432 to W.P.] and the Forschungskommission of the Medical Faculty of the Heinrich-Heine University. Duesseldorf [9772328 to B.P.]. Nicole Neef, Kristina Jung, Holger Rothkegel, Dr. Bettina Pollok, Dr. Alexander Wolff von Gudenberg, Prof. Dr. Walter Paulus and Dr. Martin Sommer reported no biomedical financial interests or potential conflicts of interest.

## Acknowledgements

We are thankful to Manuel Hewitt for the technical assistance, to Michael Nitsche for the support in statistical questions, to Per Alm, Veronika Gutmann, Anne Smith, Vincent Walsh and Christine Weber-Fox for fruitful discussions of the results, to Hayley Arnold for thoughtful comments and confirming correct English usage and syntax, and to the reviewers for their helpful feedback.

## References


(WHO) WHO. ICD-10 F98.5 Stuttering [Stammering]. Retrieved from http://apps.who.int/classifications/apps/icd/icd10online/, 2007a.

(WHO) WHO. ICD-10 F98.6 Cluttering Retrieved from www.who.int/classifications/apps/icd/icd10online, 2007b.

Abe M and Hanakawa T. Functional coupling underlying motor and cognitive functions of the dorsal premotor cortex. *Behavioural Brain Research,* 198 (1): 13-23, 2009.

Adams MR and Ramig P. Vocal characteristics of normal speakers and stutterers during choral reading. *Journal of Speech and Hearing Research,* 23 (2): 457-69, 1980.

Alm PA. Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of Communication Disorders,* 37 (4): 325-69, 2004.

Andrews G and Harris M. *The Syndrome of Stuttering*. London: Heinemann, 1964.

Antipova EA, Purdy SC, Blakeley M, and Williams S. Effects of altered auditory feedback (AAF) on stuttering frequency during monologue speech production. *Journal of Fluency Disorders,* 33 (4): 274-290, 2008.

Bengtsson SL, Ullen F, Ehrsson HH, Hashimoto T, Kito T, Naito E, Forssberg H, and Sadato N. Listening to rhythms activates motor and premotor cortices. *Cortex,* 45 (1): 62-71, 2009.

Biermann-Ruben K, Salmelin R, and Schnitzler A. Right rolandic activation during speech perception in stutterers: a MEG study. *Neuroimage,* 25 (3): 793-801, 2005.

Bishop JH, Williams HG, and Cooper WA. Age and task complexity variables in motor-performance of stuttering and nonstuttering children. *Journal of Fluency Disorders,* 16 (4): 207-217, 1991.

Bloodstein O and Ratner BN. *A Handbook on Stuttering*. Canada: Delmar Thomson Learning, 2008.

Boroojerdi B, Diefenbach K, and Ferbert A. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *Journal of the Neurological Sciences,* 144 (1-2): 160-70, 1996.

Braun AR, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, Carson RE, and Ludlow CL. Altered patterns of cerebral activity during speech and language production in developmental stuttering. An H2(15)O positron emission tomography study. *Brain,* 120 ( Pt 5): 761-84, 1997.

Brown S, Ingham RJ, Ingham JC, Laird AR, and Fox PT. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. *Human Brain Mapping,* 25 (1): 105-17, 2005.

Buchel C, Raedler T, Sommer M, Sach M, Weiller C, and Koch MA. White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cerebral Cortex,* 14 (9): 945-51, 2004.

Chang SE, Erickson KI, Ambrose NG, Hasegawa-Johnson MA, and Ludlow CL. Brain anatomy differences in childhood stuttering. *Neuroimage,* 39 (3): 1333-44, 2008.

Chang SE, Kenney MK, Loucks TMJ, and Ludlow CL. Brain activation abnormalities during speech and non-speech in stuttering speakers. *Neuroimage,* 46 (1): 201-212, 2009.

Chouinard PA, Van Der Werf YD, Leonard G, and Paus T. Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *Journal of Neurophysiology,* 90 (2): 1071-83, 2003.

Craig A, Hancock K, Tran Y, Craig M, and Peters K. Epidemiology of stuttering in the community across the entire life span. *Journal of Speech, Language, and Hearing Research,* 45 (6): 1097-105, 2002.

Curry FK and Gregory HH. The performance of stutterers on dichotic listening tasks thought to reflect cerebral dominance. *Journal of Speech and Hearing Research,* 12 (1): 73-82, 1969.

De Nil LF and Brutten GJ. Speech-associated attitudes of stuttering and nonstuttering children. *Journal of Speech and Hearing Research,* 34 (1): 60-6, 1991.

Del Olmo MF, Cheeran B, Koch G, and Rothwell JC. Role of the cerebellum in externally paced rhythmic finger movements. *Journal of Neurophysiology,* 98 (1): 145-52, 2007.

Doumas M, Praamstra P, and Wing AM. Low frequency rTMS effects on sensorimotor synchronization. *Experimental Brain Research,* 167 (2): 238-45, 2005.

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, and Marsden CD. Interhemispheric inhibition of the human motor cortex. *Journal of Physiology,* 453: 525-46, 1992.

Fink GR, Frackowiak RS, Pietrzyk U, and Passingham RE. Multiple nonprimary motor areas in the human cortex. *Journal of Neurophysiology,* 77 (4): 2164-74, 1997.

Fox PT, Ingham RJ, Ingham JC, Hirsch TB, Downs JH, Martin C, Jerabek P, Glass T, and Lancaster JL. A PET study of the neural systems of stuttering. *Nature,* 382 (6587): 158-61, 1996.

Fox PT, Ingham RJ, Ingham JC, Zamarripa F, Xiong JH, and Lancaster JL. Brain correlates of stuttering and syllable production. A PET performance-correlation analysis. *Brain,* 123 ( Pt 10): 1985-2004, 2000.

Gerschlager W, Christensen LO, Bestmann S, and Rothwell JC. rTMS over the cerebellum can increase corticospinal excitability through a spinal mechanism involving activation of peripheral nerve fibres. *Clinical Neurophysiology,* 113 (9): 1435-40, 2002.

Gerschlager W, Siebner HR, and Rothwell JC. Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology,* 57 (3): 449-55, 2001.

Gibbon J, Malapani C, Dale CL, and Gallistel C. Toward a neurobiology of temporal cognition: advances and challenges. *Current Opinion in Neurobiology,* 7 (2): 170-84, 1997.

Hallett M. Transcranial magnetic stimulation and the human brain. *Nature,* 406 (6792): 147-50, 2000.

Horne MK and Butler EG. The role of the cerebello-thalamo-cortical pathway in skilled movement. *Progress in Neurobiology,* 46 (2-3): 199-213, 1995.

Howell P. Assessment of Some Contemporary Theories of Stuttering That Apply to Spontaneous Speech. *Contemp Issues Commun Sci Disord,* 31: 122-139, 2004.

Howell P, Au-Yeung J, and Rustin L. Clock and motor variance in lip tracking: A comparison between children who stutter and those who do not. In W. Hulstijn, H. F. M. Peters, and Lieshout PHHMv (Eds.), *In Speech Production: Motor Control, Brain Research and Fluency Disorders*. Amsterdam: Elsevier, 1997, pp. 573-578.

Howell P, Davis S, and Williams R. Late childhood stuttering. *Journal of Speech, Language, and Hearing Research,* 51 (3): 669-87, 2008.

Howell P and Sackin S. Timing interference to speech in altered listening conditions. *Journal of the Acoustical Society of America,* 111 (6): 2842-2852, 2002.

Hulstijn W, Summers JJ, van Lieshout PH, and Peters HF. Timing in finger tapping and speech: A comparison between stutters and fluent speakers *Human Movement Science,* 11: 113-124, 1992.

Hunsley YL. Dysintegration in the speech musculature of stutterers during the production of a non-vocal temporal pattern. *Psychological Monographs,* 49 (1): 32-49, 1937.

Ingham RJ. Brain imaging studies of developmental stuttering. *Journal of Communication Disorders,* 34 (6): 493-516, 2001.

Ingham RJ and Carroll PJ. Listener judgement of differences in stutterers' nonstuttered speech during chorus- and nonchorus-reading conditions. *Journal of Speech and Hearing Research,* 20 (2): 293-302, 1977.

Ingham RJ, Fox PT, Costello Ingham J, and Zamarripa F. Is overt stuttered speech a prerequisite for the neural activations associated with chronic developmental stuttering? *Brain and Language,* 75 (2): 163-94, 2000.

Ingham RJ, Fox PT, Ingham JC, Xiong J, Zamarripa F, Hardies LJ, and Lancaster JL. Brain correlates of stuttering and syllable production: gender comparison and replication. *Journal of Speech, Language, and Hearing Research,* 47 (2): 321-41, 2004.

Ivry RB and Spencer RM. The neural representation of time. *Current Opinion in Neurobiology,* 14 (2): 225-32, 2004.

Ivry RB, Spencer RM, Zelaznik HN, and Diedrichsen J. The cerebellum and event timing. *Annals of the New York Academy of Sciences,* 978: 302-17, 2002.

Jancke L. Variability and duration of voice onset time and phonation in stuttering and nonstuttering adults. *Journal of Fluency Disorders,* 19 (1): 21-37, 1994.

Johansen-Berg H, Behrens TE, Robson MD, Drobnjak I, Rushworth MF, Brady JM, Smith SM, Higham DJ, and Matthews PM. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America,* 101 (36): 13335-40, 2004.

Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, and Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proceedings of the National Academy of Sciences of the United States of America,* 99 (22): 14518-23, 2002.

Kim JH, Lee JM, Jo HJ, Kim SH, Lee JH, Kim ST, Seo SW, Cox RW, Na DL, Kim SI, and Saad ZS. Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: functional connectivity-based parcellation method. *Neuroimage,* 49 (3): 2375-86, 2010.

Kleinow J and Smith A. Influences of length and syntactic complexity on the speech motor stability of the fluent speech of adults who stutter. *Journal of Speech Language and Hearing Research,* 43 (2): 548-559, 2000.

Kobayashi M, Hutchinson S, Theoret H, Schlaug G, and Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology,* 62 (1): 91-8, 2004.

Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez Sauco M, and Rothwell JC. Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. *Journal of Neuroscience,* 26 (28): 7452-9, 2006.

Kurata K, Tsuji T, Naraki S, Seino M, and Abe Y. Activation of the dorsal premotor cortex and pre-supplementary motor area of humans during an auditory conditional motor task. *Journal of Neurophysiology,* 84 (3): 1667-72, 2000.

Lehericy S, Ducros M, Krainik A, Francois C, Van de Moortele PF, Ugurbil K, and Kim DS. 3-D diffusion tensor axonal tracking shows distinct SMA and pre-SMA projections to the human striatum. *Cerebral Cortex,* 14 (12): 1302-9, 2004.

Levelt WJM. *Speaking: from intention to articulation*. Cambridge, MA: MIT Press, 1989.

Levit-Binnun N, Handzy NZ, Peled A, Modai I, and Moses E. Transcranial magnetic stimulation in a finger-tapping task separates motor from timing mechanisms and induces frequency doubling. *Journal of Cognitive Neuroscience,* 19 (5): 721-33, 2007.

Lewis PA and Miall RC. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. *Current Opinion in Neurobiology,* 13 (2): 250-255, 2003.

Lu C, Chen C, Ning N, Ding G, Guo T, Peng D, Yang Y, Li K, and Lin C. The neural substrates for atypical planning and execution of word production in stuttering. *Experimental Neurology,* 221 (1): 146-56, 2010.

Lu C, Peng D, Chen C, Ning N, Ding G, Li K, Yang Y, and Lin C. Altered effective connectivity and anomalous anatomy in the basal ganglia-thalamocortical circuit of stuttering speakers. *Cortex*, 2009.

Ludlow CL. Stuttering: dysfunction in a complex and dynamic system. *Brain,* 123 ( Pt 10): 1983-4, 2000.

Ludlow CL and Loucks T. Stuttering: a dynamic motor control disorder. *Journal of Fluency Disorders,* 28 (4): 273-95, 2003.

Malcolm MP, Lavine A, Kenyon G, Massie C, and Thaut M. Repetitive transcranial magnetic stimulation interrupts phase synchronization during rhythmic motor entrainment. *Neuroscience Letters,* 435 (3): 240-5, 2008.

Mansson H. Childhood stuttering: Incidence and development,. *Journal of Fluency Disorders,* 25: 47-57, 2000.

Mauk MD and Buonomano DV. The neural basis of temporal processing. *Annual Review of Neuroscience,* 27: 307-40, 2004.

Max L and Gracco VL. Coordination of oral and laryngeal movements in the perceptually fluent speech of adults who stutter. *Journal of Speech, Language, and Hearing Research,* 48 (3): 524-42, 2005.

Max L, Guenther FH, Gracco VL, Ghosh SS, and Wallace ME. Unstable or insufficiently activated internal models and feedback-biased motor control as sources of dysfluency: A theoretical model of stuttering. *Contemporary Issues in Communication Science and Disorders: CICSD,* 31: 105-122, 2004.

Max L and Yudman EA. Accuracy and variability of isochronous rhythmic timing across motor systems in stuttering versus nonstuttering individuals. *Journal of Speech, Language, and Hearing Research,* 46 (1): 146-63, 2003.

Melvine C, Williams H, Bishop J, McClenaghan B, Cooper W, and McDade H. Vocal and manual timing control of adult stutterers and nonstutterers. In Starkweather CW and Peters UFM (Eds.), *Stuttering: Proceedings of the first World Congress on Fluency Disorders.* Nijmegen, The Netherlands: University of Nijmegen, 1995, pp. 35-38.

Meyer-Lindenberg A, Ziemann U, Hajak G, Cohen L, and Berman KF. Transitions between dynamical states of differing stability in the human brain. *Proceedings of the National Academy of Sciences of the United States of America,* 99 (17): 10948-53, 2002.

Miniussi C, Cappa SF, Cohen LG, Floel A, Fregni F, Nitsche MA, Oliveri M, Pascual-Leone A, Paulus W, Priori A, and Walsh V. Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimulation,* 1 (4): 326-336, 2008.

Mochizuki H, Huang YZ, and Rothwell JC. Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. *Journal of Physiology,* 561 (Pt 1): 331-8, 2004.

Moore WH, Jr. and Lang MK. Alpha asymmetry over the right and left hemispheres of stutterers and control subjects preceding massed oral readings: a preliminary investigation. *Perceptual and Motor Skills,* 44 (1): 223-30, 1977.

Morgan A, Reilly S, Anderson A, Reutens D, and Wood A. *Functional brain activation differences for motor versus language regions in adults with and without stuttering: An fMRI study. Secondary Titl*. Oxford, 2008.

Netz J, Ziemann U, and Homberg V. Hemispheric asymmetry of transcallosal inhibition in man. *Experimental Brain Research,* 104 (3): 527-33, 1995.

O'Shea J, Sebastian C, Boorman ED, Johansen-Berg H, and Rushworth MF. Functional specificity of human premotor-motor cortical interactions during action selection. *European Journal of Neuroscience,* 26 (7): 2085-95, 2007.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia,* 9 (1): 97-113, 1971.

Perneger TV. What's wrong with Bonferroni adjustments. *BMJ,* 316 (7139): 1236-8, 1998.

Picard N and Strick PL. Imaging the premotor areas. *Current Opinion in Neurobiology,* 11 (6): 663-72, 2001.

Pollok B, Gross J, Muller K, Aschersleben G, and Schnitzler A. The cerebral oscillatory network associated with auditorily paced finger movements. *Neuroimage,* 24 (3): 646-55, 2005.

Pollok B, Krause V, Butz M, and Schnitzler A. Modality specific functional interaction in sensorimotor synchronization. *Human Brain Mapping,* 30 (6): 1783-90, 2009.

Pollok B, Rothkegel H, Schnitzler A, Paulus W, and Lang N. The effect of rTMS over left and right dorsolateral premotor cortex on movement timing of either hand. *European Journal of Neuroscience,* 27 (3): 757-64, 2008.

Preibisch C, Neumann K, Raab P, Euler HA, von Gudenberg AW, Lanfermann H, and Giraud AL. Evidence for compensation for stuttering by the right frontal operculum. *Neuroimage,* 20 (2): 1356-64, 2003.

Prins D and Hubbard CP. Constancy of interstress intervalls in the fluent speech of people who stutter during adaptation trials. *Journal of Speech and Hearing Research,* 35 (4): 799-804, 1992.

Ramnani N and Passingham RE. Changes in the human brain during rhythm learning. *Journal of Cognitive Neuroscience,* 13 (7): 952-66, 2001.

Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, and Binder JR. Distributed neural systems underlying the timing of movements. *Journal of Neuroscience,* 17 (14): 5528-35, 1997.

Riecker A, Groschel K, Ackermann H, Schnaudigel S, Kassubek JR, and Kastrup A. The role of the unaffected hemisphere in motor recovery after stroke. *Human Brain Mapping*, 2010.

Riecker A, Kassubek J, Groschel K, Grodd W, and Ackermann H. The cerebral control of speech tempo: opposite relationship between speaking rate and BOLD signal changes at striatal and cerebellar structures. *Neuroimage,* 29 (1): 46-53, 2006.

Riley GD. *The Stuttering Severity Instrument for Children and Adults- Third Edition (SSI-3)*. Austin, TX: Pro-Ed., 1994.

Rossi S, Hallett M, Rossini PM, and Leone AP. *Safety, Ethical Considerations, and Application Guidelines for the Use of Transcranial Magnetic Stimulation in Clinical Practice and Research. Secondary Titl*. Siena, 2009.

Salmelin R, Schnitzler A, Schmitz F, and Freund HJ. Single word reading in developmental stutterers and fluent speakers. *Brain,* 123 ( Pt 6): 1184-202, 2000.

Saltuklaroglu T, Teulings HL, and Robbins M. Differential levels of speech and manual dysfluency in adults who stutter during simultaneous drawing and speaking tasks. *Human Movement Science,* 28 (5): 643-54, 2009.

Samii A, Canos M, Ikoma K, Wassermann EM, and Hallett M. Absence of facilitation or depression of motor evoked potentials after contralateral homologous muscle activation. *Electroencephalography and Clinical Neurophysiology,* 105 (3): 241-5, 1997.

Sandrieser P and Schneider P. *Stottern im Kindesalter*. Stuttgart: Thieme, 2008.

Schluter ND, Rushworth MF, Passingham RE, and Mills KR. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain,* 121 ( Pt 5): 785-99, 1998.

Schubotz RI, von Cramon DY, and Lohmann G. Auditory what, where, and when: a sensory somatotopy in lateral premotor cortex. *Neuroimage,* 20 (1): 173-85, 2003.

Siebner HR, Hartwigsen G, Kassuba T, and Rothwell JC. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex,* 45 (9): 1035-42, 2009.

Siebner HR and Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Experimental Brain Research,* 148 (1): 1-16, 2003.

Smits-Bandstra S, De Nil LF, and Saint-Cyr JA. Speech and nonspeech sequence skill learning in adults who stutter. *Journal of Fluency Disorders,* 31 (2): 116-36, 2006.

Sommer M, Knappmeyer K, Hunter EJ, von Gudenberg AW, Neef N, and Paulus W. Normal interhemispheric inhibition in persistent developmental stuttering. *Movement Disorders*, 2009.

Sommer M, Koch MA, Paulus W, Weiller C, and Büchel C. Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet,* 360 (9330): 380-3, 2002.

Sommers RK, Brady WA, and Moore WH, Jr. Dichotic ear preferences of stuttering children and adults. *Perceptual and Motor Skills,* 41 (3): 931-8, 1975.

Spencer RM, Ivry RB, and Zelaznik HN. Role of the cerebellum in movements: control of timing or movement transitions? *Experimental Brain Research,* 161 (3): 383-96, 2005.

Spencer RM, Zelaznik HN, Diedrichsen J, and Ivry RB. Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. *Science,* 300 (5624): 1437-9, 2003.

Tourville JA, Reilly KJ, and Guenther FH. Neural mechanisms underlying auditory feedback control of speech. *Neuroimage,* 39 (3): 1429-43, 2008.

Van Riper C. The use of DAF in stuttering therapy. *British Journal of Disorders of Communication,* 5 (1): 40-5, 1970.

Wagner T, Rushmore J, Eden U, and Valero-Cabre A. Biophysical foundations underlying TMS: setting the stage for an effective use of neurostimulation in the cognitive neurosciences. *Cortex,* 45 (9): 1025-34, 2009.

Walsh V and Rushworth M. A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia,* 37 (2): 125-35, 1999.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology,* 108 (1): 1-16, 1998.

Watkins KE, Smith SM, Davis S, and Howell P. Structural and functional abnormalities of the motor system in developmental stuttering. *Brain,* 131 (Pt 1): 50-9, 2008.

Webster WG. Response sequence organization and reproduction by stutterers. *Neuropsychologia,* 24 (6): 813-821, 1986.

Webster WG. Principles of human brain organization related to lateralization of language and speech motor functions in normal speakers and stutterers. In Hulstijn W, Peters HFM, and Lieshout PHHMv (Eds.), *Speech Production: Motor Control, Brain Research and Fluency Disorders: Proceedings of the Third International Conference on Speech Motor Production and Fluency Disorders*. Amsterdam: Elsevier, 1997, pp. 119-139.

Webster WG and Ryan CR. Task complexity and manual reaction times in people who stutter. *Journal of Speech and Hearing Research,* 34 (4): 708-14, 1991.

Weiler F, Brandao P, Barros-Filho J, Uribe CE, Pessoa VF, and Brasil-Neto JP. Low frequency (0.5Hz) rTMS over the right (non-dominant) motor cortex does not affect ipsilateral hand performance in healthy humans. *Arquivos de Neuro-Psiquiatria,* 66 (3B): 636-40, 2008.

Wiener M, Turkeltaub P, and Coslett HB. The image of time: A voxel-wise meta-analysis. *Neuroimage,* 49 (2): 1728-1740, 2010.

Wing AM and Kristofferson AB. Response delays and the timing of discrete motor responses. *Perception and Psychophysics* (14): 5-12, 1973.

Wingate ME. *Foundations of stuttering*. San Diego: Academic Press, 2002.

Wise SP. The primate premotor cortex: past, present, and preparatory. *Annual Review of Neuroscience,* 8: 1-19, 1985.

Wohl MT. The electric metronome--an evaluative study. *British Journal of Disorders of Communication,* 3 (1): 89-98, 1968.

Zelaznik HN, Smith A, and Franz EA. Motor Performance of Stutterers and Nonstutterers on Timing and Force Control Tasks. *Journal of Motor Behavior,* 26 (4): 340-347, 1994.

Zelaznik HN, Smith A, Franz EA, and Ho M. Differences in bimanual coordination associated with stuttering. *Acta Psychologica,* 96 (3): 229-43, 1997.

Zelaznik HN, Spencer RM, Ivry RB, Baria A, Bloom M, Dolansky L, Justice S, Patterson K, and Whetter E. Timing variability in circle drawing and tapping: probing the relationship between event and emergent timing. *Journal of Motor Behavior,* 37 (5): 395-403, 2005.

Zelaznik HN, Spencer RMC, and Ivry RB. Dissociation of explicit and implicit timing in repetitive tapping and drawing movements. *Journal of Experimental Psychology-Human Perception and Performance,* 28 (3): 575-588, 2002.

**Tab. 1 Characteristics of participants** 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; * = median; 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[23]; stuttered syllables were mean percentage out of not less than 340 read and 500 spoken syllables.

## Tab. 1 Characteristics of participants

| | | age | gender | education | instrument | handedness | mother tongue | AMT right FDI | AMT left FDI | suttered syllables | SSI-3 score | age of 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** | | **3** | | **77.5** | | **50** | **52** | **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** | | **5** | | **70** | | **48** | **47** | **.5** | | |
| | **mean** | **28.1** | | | | **76.0** | | **46.6** | **46.8** | **.6** | | |
| | **sd** | **5.0** | | | | **18.1** | | **7.8** | **8.15** | **.4** | | |
| **test** | | **T = .65** | | **Z = -1.28** | | **Z = -.73** | | **F = 1.87** | | **Z = -4.6** | | |
| **(p)** | | **(.5)** | | **(.2)** | | **(.46)** | | **(.18)** | | **(< .001)** | | |

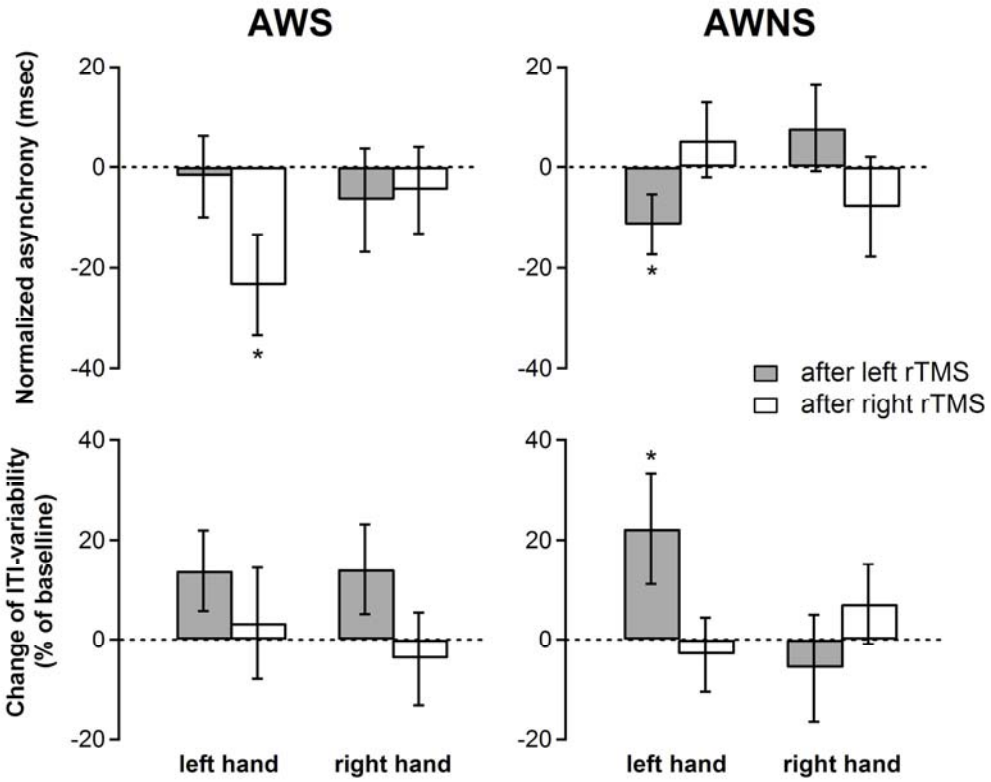


**Fig. 1:** Mean values (± standard error) of normalized asynchrony (upper graphs) and change of normalized inter-tap interval (ITI)-variability in percent with respect to baseline (lower graphs) after repetitive transcranial magnetic stimulation (rTMS) over the left and right dorsolateral premotor cortex (PMd) in adults who stutter (AWS) and adults who do not stutter (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*). rTMS 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 $p < .05$).

## 2.2 Reduced intracortical inhibition and facilitation in the primary motor tongue representation of adults who stutter

**Authors:** N. E. Neef, W. Paulus, A. Neef, A. Wolff von Gudenberg, M. Sommer

**The work was done at:** Department of Clinical Neurophysiology, Georg-August-University, Göttingen

**Corresponding author:** Martin Sommer, Georg-August-University, Department of Clinical Neurophysiology, Robert-Koch-Str. 40, 37075 Göttingen, Germany**; phone:** +49 551 39 8463; **fax:** +49 551 39 8126, **email:** msommer@gwdg.de

**Keywords** stuttering, primary motor tongue representation, trancranial magnetic stimulation, intrahemispheric inhibition, intrahemispheric facilitation, MEP input-output curve

**Acknowledgements:** We thank Dr. M. Röbel from the University Medicine Göttingen, Department of Otorhinolaryngology and Prof. W. Engelke from the University Medicine Göttingen, Department of Maxillofacial Surgery for technical assistance. This work was supported by the Stifterverband für die Deutsche Wissenschaft, Walter und Ilse Rose Stiftung [NN], the Deutsche Forschungsgemeinschaft [SO 429/2-2] and by the German Ministry of Health [BMBF 01GQ0811 (AN); 01GQ0810 (WP)].

**Abstract**

**Objective:** This study aimed at detecting neurophysiological changes, in the primary motor tongue representation of the left and right hemisphere in adults with persistent stuttering.

**Methods:** Excitability was examined in 12 patients and in 14 control subjects. Using transcranial magnetic stimulation (TMS) we examined motor threshold, motor-evoked potential (MEP) input-output curves, short-term intracortical inhibition (SICI) and intracortical facilitation (ICF).

**Results:** In control subjects a significant inhibition of the MEP-amplitude at short inter-stimulus interval (ISI) as well as a significant facilitation of the MEP-amplitude at long ISIs was evident. Patients with persistent stuttering showed an inhibition at ISI 3ms and lower inhibition at 2 ms interval, not reaching statistical significance; this delay of inhibitory activity was especially prominent in the right hemisphere. Facilitation was reduced at ISI 10 and 15 ms in patients. Furthermore, MEP input-output curve was steeper in patients with persistent stuttering. Motor thresholds did not differ between groups.

**Conclusions:** In persistent stuttering intracortical excitability of the primary motor tongue representation is altered with a deviant time course for inhibitory activity in the right hemisphere and reduced paired-pulse facilitation.

**Significance:** These results specify changes in intracortical networks possibly mediated by altered GABAergic regulations in persistent stuttering. Thus, a better understanding of disease mechanisms and a potential role in understanding pharmacological treatment response emerges by using TMS in persistent stuttering.

## 1. Introduction

Speech-relevant cortical and subcortical neural systems appear to be malfunctioning in persistent stuttering (Brown et al., 2005; Fox et al., 1996; Ludlow and Loucks, 2003). This speech disorder affects approximately 1% of the adult population, severely compromising their quality of life (Bloodstein and Ratner, 2008; Craig et al., 2002). Stuttering is characterized by involuntary, intermittent interruptions of fluent speech. Speech sound and syllable repetitions, sound prolongations and speech blocks are prominent signs. It is still unclear which changes in motor cortical function contribute to these disruptions to a smooth execution of complex spatiotemporal commands of articulatory gestures.

Current knowledge about cortical mechanisms in stuttering relies mainly on imaging studies reporting for instance a right-hemispheric hyperactivity in the primary motor cortex during dysfluent speech (Braun et al., 1997; Fox et al., 1996; Fox et al., 2000). This hyperactivity has been speculated to be related to an increased cortical excitability (Ludlow and Loucks, 2003). In physiological terms motor cortical excitability can be explored using transcranial magnetic stimulation (TMS). TMS-studies in stuttering are scarce, although this technique is an established tool to assess noninvasively the functional integrity of descending corticospinal and corticonuclear pathways of the human motor cortex. Activating descending pathways originating from layer 5 pyramidal cells in the primary motor cortex requires suprathreshold TMS stimuli and results in brief muscle response, the motor-evoked potential (MEP). Subthreshold TMS stimuli can activate intracortical circuits in the motor cortex (Paulus et al., 2008). Paired-pulse stimulation with a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS) induces either a reduced motor cortex excitability, short-term intracortical inhibition (SICI); or an increased motor cortex excitability, the intracortical facilitation (ICF). SICI and ICF depend on the length of the inter-stimulus interval (ISI) between CS and TS (Kujirai et al., 1993; Ziemann et al., 1998). Figure 1 depicts modulated intracortical excitability in a typical healthy subject. Hence, TMS is a tool for transynaptically activating cortical neurons, providing a method to assess the strength of intracortical synaptic connections.

Neurons of the primary motor cortex (M1) rececive influential input from frontal cortex regions and from the basal ganglia; their descending output innervates coordinated, voluntary movements. Intracortical inhibitory and facilitatory networks within M1 may promote the selection and initiation of target movements and suppress synergisms. Speech requires a highly coordinated interplay between different subsystems innervated bilaterally by six different cranial nerves (V, VII, IX, X, XI, XII). Respiratory activity has to be synchronized

as well, again involving paired spinal nerves. The excitability of the cortical neurons that project through corticobulbar pathways to the target cranial nerves and further to the target muscles is shaped by subcortical and intercortical as well as intracortical circuity. Intracortical excitability modulations are induced by interactions of inhibitory and excitatory circuits.

A disturbed intracortical excitability of neurons in the primary motor cortex (M1) that project to speech relevant muscles is a potential reason for the dysfluent speech (Ludlow and Loucks, 2003), but the intracortical excitability of speech relevant motor cortex regions had not been investigated in adults who stutter (AWS). An adjacent region in M1, the hand representation, was studied in our group (Sommer et al., 2003) with the finding of an unaltered intracortical excitability in AWS.

Altered intracortical inhibition in stuttering might be a reasonable expectation because imbalanced cortical excitability in motor regions has been implicated by functional neuroimaging during symptom production (Brown et al., 2005). Besides; stuttering shares clinical features of other movement disorders: tic-like involuntary movements (Mulligan et al., 2003), focal dystonia -like excessive activation of task-related and task-unrelated muscles (Sommer et al., 2003), and Parkinsonism-like freezing of articulatory gestures (Alm, 2008). All these movement disorders are characterize by a reduced SICI (Berardelli et al., 2008).

In the present study, we used TMS elicited motor evoked potentials (MEPs) to test the hypothesis that intracortical excitability in the M1 tongue representation is altered in adults who stutter (AWS). Specifically, we hypothesized that the excitability of inhibitory circuits within M1tongue representation is reduced in AWS. A decreased intracortical inhibition may lead to a reduced inhibition for the prevention of movements (Stinear et al., 2009) thereby contributing to the intermittent dysfluencies in stuttering.

## 2. Methods

### *2.1 Subjects*

Twelve AWS (three female; mean 29.9 years, *SD* 8.2) and fourteen fluent speakers (FS, 3 females, mean 29.5 years, *SD* 7.6) participated in this study. Adults who stutter were recruited from the local stuttering support group and the Institute for the Kassel Stuttering Therapy (Euler et al., 2009). Fluent speakers were recruited by advertisement. The groups were matched for age, handedness (Oldfield, 1971) and education. Seven AWS reported a family history of stuttering. None of the FS reported having a family history of speech or language disorders. Expect from stuttering in the AWS group, participants reported no medical history, neurological impairment or drug use that would potentially affect their neurological function.

Before experimental measures were obtained with TMS, all subjects were screened for exclusion criteria using a standard TMS safety screen (Keel et al., 2001). All subjects provided written informed consent prior to inclusion into the study. This study received ethical approval from the Goettingen Ethics Committee.

### *2.2 Fluency assessment*

To judge stuttering severity, fluency assessments were performed regarding 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 and analyzed by a qualified speech-language pathologist. SSI-3 norms were adapted from Riley (Riley, 1994) . 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) as well as sound and syllable repetitions were counted as stuttered syllables. Monosyllabic words that were repeated with apparent undue stress or tension were counted. 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 Experimental procedures*

Subjects were seated in a comfortable chair. Bilateral simultaneous surface recordings of the lingual muscle were taken with two pairs of disposable pre-gelled silver/silver chloride ring electrodes (5 mm x 100 mm, Viasys Neurocare, Hoechberg, Germany). Electrodes were mounted at a customized spoon-shaped silicon mouthpiece. Contact area at the tongue was 5 mm x 10 mm at longitudinal and lateral inter-electrode distances of 25 and 20 mm, respectively. The mouthpiece was placed on the upper surface of the tongue, and the subjects were asked to close their lips and teeth leisurely without additional pressure and to hold the end of the mouthpiece with the hand ipsilateral to TMS stimulation site, with the elbow comfortably supported. While recording participants were asked to push the tongue tightly against the electrodes and their lower teeth. This procedure was adapted from (Rödel et al., 2003).

Surface EMG signals were recorded using a CED power 1401 interface with a sampling frequency of 5 KHz, amplified × 1000 and Butterworth bandpass filtered between 20 Hz and 2000 Hz. Recordings were controlled by Signal Software (Cambridge Electronic Design, version 2.13).

### *2.4 Transcranial Magnetic Stimulation*

*Experiment 1*

TMS was applied while participants sat comfortably in a reclining chair. Subjects were instructed to stay relaxed throughout the assessment. The voluntary background contraction of the tongue was maintained at approximately 10% of maximum activity (Muellbacher et al., 2001). Muscle activation was controlled through visual feedback of EMG activity. TMS was achieved using a monophasic stimulus applied through a figure-of-eight coil with an outer wing diameter of 70 mm. The coil was positioned tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane. In this position, the induced current flow in the brain was in the posterior–anterior direction. The scalp surface was explored systematically and the position for consistently inducing maximal MEPs in the contralateral tongue site at the lowest stimulus strength was identified as the "hot spot" and marked with a pen to ensure accurate coil placement throughout the experiment (Muellbacher et al., 2001). We found the motor tongue representation to be slightly more anterior and more lateral than what we usually observe for the hand representation which is consistent with the literature (Svensson et al., 2003). Motor threshold for SICI and ICF was assessed with the coil connected to a Bistim module (Magstim Company Ltd., Whitland, Wales), which connected two identical Magstim200 stimulators. Single TMS pulses were applied to determine the minimal stimulus intensity to the nearest 1% of the maximum stimulator output required to produce MEPs of greater than 100 μV in at least 3 of 6 consecutive stimuli. This intensity defines the motor threshold (MT). Intracortical excitability was assessed according to a paired conditioning test stimulus paradigm (Kujirai et al., 1993; Muellbacher et al., 2001), with a subthreshold conditioning stimulus followed by a suprathreshold test stimulus at different inter-stimulus intervals (ISIs). Four ISIs, 2, 3, 10, and 15 ms were tested and randomly intermixed with the test stimulus given alone. Each of the four ISIs was applied 8 times while the test stimulus alone was applied 18 times. The conditioning stimulus was applied at 90% MT and the test stimulus was set at 130% MT. These ISIs and stimulation intensities were chosen based on findings of a previous study to obtain sizeable SICI and ICF in lingual muscles (Muellbacher et al., 2001).

This protocol was conducted in 14 FS and in 12 AWS in both hemispheres in a pseudo-randomized order in two separate sessions.

*Experiment 2*

Motor threshold was reassessed and MEP input-output curves was determined with the same coil, positioned as described before, but this time connected to a single pulse Magstim200 stimulator (Magstim Company Ltd., Whitland, Wales). The MEP input–output curve was recorded using six intensity levels between 90% and 140% of MT (10% increments). Five stimuli were applied at each intensity level in a consecutive order every 4 s. Afterwards the MEP input-output curve was recorded while participants were asked to contract their tongue with about 60 % maximum activity with a short (one minute) break between intensity levels.

This protocol was conducted in both hemispheres in a pseudo-randomized order in two separate sessions, in 12 FS and 8 AWS who also participated in experiment 1.

### *2.6 Data analysis*

Altogether participant recruitment comprised 17 AWS and 17 FS. We did not conduct the whole procedure in 4 AWS and in 3 FS because M1 tongue representation could not be determined properly in one or both hemispheres of these subjects. One other AWS was excluded because fluency assessment yielded an additional cluttering component in this patient. According to the definition ((WHO), 2007b) cluttering was recognized by rapid, erratic, and dysrhythmic speech dysfluency with distinct speech timing abnormalities.

To determine pre-TMS tongue activity we analyzed the EMG signal of all valid recordings of every single subject. Recordings with TMS artifacts outlasting the motor evoked response were excluded. For the paired-pulse protocol 60 ms of the EMG signal immediately before the TMS artifact and for the input-output curve data 79 ms of the EMG signal were considered. These signals were corrected for offset, rectified and averaged using Matlab.

Motor evoked potential peak-to-peak amplitudes were analyzed with Signal 4.04 (Cambridge Electronic Design). Mean peak-to-peak amplitudes were calculated for each condition, including unconditioned MEP amplitudes of the MEP input-output curve procedure and of the paired-pulse procedure, and conditioned MEP amplitudes of the paired-pulse procedure for ISI 2, 3, 10 and 15 ms for either projection and either hemisphere. The conditioned MEP amplitudes were normalized and are given as ratios of the unconditioned MEP amplitude recorded in the paired-pulse protocol.

In addition to the peak-to-peak amplitude, MEP magnitude was also estimated by the area under the baseline corrected and rectified EMG signal, where baseline was defined as average pre-TMS amplitude of the EMG. The time interval of significant MEP response was defined manually for each trial and each recording site. The interval selection was guided by the

overall shape of the MEP amplitude envelope and by the rate of change of MEP amplitude. Selection of intervals and computation of the area under the curve was performed in a custom written EMG-Browser in Igor Pro (Wavemetrics).

### *2.7 Statistical analysis*

To test for group differences for the variables age and percentage of stuttered syllables we used two-tailed *t*-tests for independent samples; for the *t* of percentage of stuttered syllables heterogeneity of variance was stated; education and handedness were analyzed with Mann-Whitney *U*-tests. Nonparametric testing was chosen since education is an ordinally scaled variable (1 = school, 2 = high school, 3 = less than 2 years college, 4 = 2 years college, 5 = 4 years college, 6 = postgraduate) and handedness did not show normal distribution in either group.

*Experiment 1*

*Motor threshold* comparison was calculated with repeated-measures ANOVA with hemisphere (left, right) as a within-subjects factor and group (AWS, FS) as a between-subjects factor.

*Unconditioned MEP amplitudes* were tested by 2x2x2 repeated measures ANOVA with the between-subjects factor group (AWS, FS) and the within-subjects factors hemisphere (left, right) and projection (contralateral, ipsilateral).

For *SICI* and *ICF* analyses, conditioned MEP amplitudes were expressed as a percentage of unconditioned MEP amplitudes (test stimulus only condition), employing a 2x2x2x2x4 omnibus ANOVA with the between-subjects factor group (AWS, FS) and the within-subjects factors hemisphere (left, right), projection (contralateral, ipsilateral) and ISI (2 ms, 3ms, 10 ms, 15 ms).

Separate 2 x 2 x 2 x 2 repeated-measures ANOVAs were performed on SICI and ICF data with the within-subjects factors hemisphere (left, right), projection (contralateral, ipsilateral) and ISI (ICI: 2 ms, 3ms; ICF: 10 ms, 15 ms) and the between-subjects factor group (AWS, FS). Post-hoc unpaired, two-tailed *t*-tests were conducted to determine group differences considering single conditions.

*Pre-TMS tongue activity* and *unconditioned MEP amplitude* were assessed separately using 2 x 2 x 2 repeated measures ANOVAs with within-subjects factor hemisphere (left, right) and tongue site (left, right) and between-subjects factor group (AWS, FS).

*Experiment 2*

*Motor threshold* comparison was calculated with repeated-measures ANOVA with hemisphere (left, right) as a within-subjects factor and group (AWS, FS) as a between-subjects factor.

*MEP input-output curves* were explored by analyzing MEP amplitudes and MEP areas separately. A 2 x 2 x 2 x 6 x 2 repeated measures ANOVA with modus (10%contraction, 60%contraction), hemisphere (left, right), projection (contralateral, ipsilateral) and intensity (90, 100, 110, 120, 130, 140% MT) as within-subjects factors and group (AWS, FS) as a between-subjects factor served for these analyses.

*Pre-TMS tongue activity* of the input-output curve data were analyzed with a 2 x 2 x 2 x 6 x 2 repeated measures ANOVA with modus (10%contraction, 60%contraction), hemisphere (left, right), tongue site (left, right) and intensity (90, 100, 110, 120, 130, 140% MT) as within-subjects factors and group (AWS, FS) as a between-subjects factor.

Values were considered statistically significant if $p < .05$. Statistics were performed by SPSS Statistics 17.0 (http://www.spss.com/de/software).

## 3. Results

### *3.1 Experiment 1*

*Participants*

The groups matched for age, $t(24) = -0.13$, $p = .9$ (unpaired two tailed *t*-test), handedness, $p = .980$; *U*-test) and education, $p = .206$ (*U*-test). Adults who stutter produced more stuttered syllables than fluent speakers, $t(11.054) = -4.96$; $p < .001$ (unpaired two tailed *t*-test, heterogeneity of variance). Stuttering severity was very mild in five, mild in two, moderate in two, severe in two and very severe in one AWS. Averaged stuttering onset was at age 4.5±2.8 (see Table 1 for demographics and fluency scores).

*Motor threshold*

The values of MT are given in Table 1. Analysis of variance considering the factors group and hemisphere yielded no effects or interaction. Previous TMS studies of the primary motor hand area in AWS resulted in contradictory observations reporting increased motor thresholds in AWS relative to FS (Sommer et al., 2003), as well as no differences (Neef et al., 2010; Sommer et al., 2009a).

*Pre-TMS tongue activity*

Pre-TMS tongue activity in the paired-pulse protocol was similar in both groups (Figure 2A). ANOVA yielded no effect for hemisphere, projection and group as well as no interactions.

Please insert Figure 1 around here

*Unconditioned MEP amplitude*

A single unconditioned TMS pulse with 130% MT results in similar MEP amplitudes for FS and AWS, ANOVA detected no effect of group. MEP amplitudes at contralateral projections were significantly larger than at ipsilateral projections (effect of projection $F(1,24) = 15.44$, $p = .001$). Post-hoc group-wise comparisons of contralateral and ipsilateral MEP amplitudes via two-tailed, paired *t*-tests yielded significant differences for all conditions, expect the right hemisphere projections in FS (see Table 2). This finding is in accordance with previous studies and likely reflects a predominance of the contralateral projections present even in the tongue (Meyer et al., 1997; Rödel et al., 2003). Analysis of variance yielded no other effects.

Please insert Table 2 around here

*Intracortical Excitability*

In FS ISIs of 2 and 3ms lead to inhibition of the MEP amplitude, whereas ISIs of 10 and 15 ms lead to facilitated the MEP amplitude (Figure 2B). Post hoc paired *t*-tests revealed significant changes in intracortical exitability for all ISIs in FS with a significance level consistently smaller than .0001. These results agree in time course and magnitude with a previous report (Muellbacher et al., 2001). In AWS excitability was significantly changed for ISI 3ms, $t(11) = -4.9$, $p < .0001$; 10 ms $t(11) = 3.75$, $p = .003$; and 15 ms $t(11) = 2.4$, $p = .035$); but inhibition at ISI 2 ms did not reach significance, $t(11) = -1.5$, $p = .15$. Figure 2B depicts the main effect of ISI with $F(1,24) = 87.72$, $p < .0001$ Thus, short ISIs at 2 and 3 ms significantly inhibited the MEP amplitude in both groups expect for ISI 2 ms in AWS, while longer ISIs at 10 and 15 ms significantly augmented motor evoked responses. The interaction between ISI and group with $F(3,22) = 7.69$, $p < .0001$ indicates that the magnitude of the effect differs between the two groups.

*SICI*

Short-term intracortical inhibition was reduced for the right hemispheric projections at an ISI 2 ms in AWS compared to FS (Figure 2D and F). ANOVA yielded an effect of projection $F(1,24) = 4.36$, $p = .048$; an effect of ISI $F(1,24) = 9.34$, $p = .005$; an interaction of ISI and

group $F(1,24) = 4.59$, $p = .043$; and an interaction of hemisphere, ISI and group $F(1,24) = 5.41$, $p = .027$.

Post-hoc *t*-tests revealed a significantly reduced SICI of the ipsilateral projections of the right hemisphere at an ISI of 2 ms in AWS $t(24) = -2.1$; $p = .046$; for the same hemisphere and ISI, SICI trends to decreased inhibition for the contralateral projection $t(24) = -2.0$; $p = .056$).

Analysis of variance yielded no other effects. Additionally we calculated separate 2x2 ANOVAs for each hemisphere and its contralateral projection and show the results in Table 4.

Please insert Table 3 around here

Please insert Table 4 around here

*ICF*

Intracortical facilitation was consistently reduced in AWS (Figure 2C-F). ANOVA yielded an effect of group $F(1,24) = 10.34$, $p = .004$; and an interaction of hemisphere and projection $F(1,24) = 6.06$, $p = .021$.

Post-hoc unpaired, two-tailed *t*-tests revealed significantly reduced ICFs for right hemispheric contralateral projection at either ISI (10 ms, $p = .005$; 15 ms, $p = .011$) and for the ipsilateral projection at ISI 15 ms ($p = .024$). Left hemispheric contralateral projections exhibited a significantly reduced ICF at ISI 10 ms ($p = .034$). Table 3 contains *p* values for all conditions documenting a reduced ICF for all conditions at a level of marginally significance ($p < .1$) in AWS related to FS. Analysis of variance yielded no other effects. Additionally we calculated separate 2x2 ANOVAs for each hemisphere and its contralateral projection and show the results in Table 4.

Please insert Figure 2 around here

### 3.3 Experiment 2

*Participants*

The groups matched for age, $t(20) = -0.24$, $p = .811$ ( unpaired two tailed *t*-test), handedness, $p = .680$ (*U*-test) and education, $p = .205$(*U*-test). Adults who stutter produced more stuttered syllables than fluent speakers, $t(7.02) = -3.91$; $p = .006$ (unpaired two tailed *t*-test, heterogeneity of variance). Stuttering severity was very mild in three, mild in two, moderate

in one, severe in one and very severe in one AWS. Averaged stuttering onset was at age 5.1±3.3 (see Table 1 for demographics and fluency scores).

*Motor threshold*

In FS MT was for the left and right hemisphere 42.6±6.7% and 44.3±8.8% maximum stimulator output, respectively. AWS had a MT for the left and right hemisphere of 42.8±8.4 and 40.8±5.9% maximum stimulator output. ANOVA yielded no significant effects or interaction (see Table 1 and Figure 3B).

*Pre-TMS tongue activity*

Pre-TMS tongue activity in the MEP input-output curve data did not differ between groups (Figure 3A). ANOVA yielded a significant effect of mode $F(1,18) = 9.33$; $p = .007$, with an increased tongue activation at a contraction of approximately 60 % of maximum contraction 0.048±0.05 mV versus tongue activation at a contraction of approximately 10 % of maximum contraction 0.014±0.01mV (see Figure 3A).

*MEP input-output curve*

The ANOVA considering MEP peak-to-peak amplitude revealed an effect of mode, $F(1,18) = 11.45$, $p = .003$ which reflects that MEP amplitudes are larger while the tongue is more strongly contracted (mean MEP 1.01± 0.67 mV) compared to less contraction (mean MEP 0.55± 0.28 mV). Furthermore, analysis yielded an effect of projection, $F(1,18) = 31.29$, $p < .001$ with larger MEP amplitudes in the contralateral projection (0.91±0.48 mV) than in the ipsilateral projection (0.65±0.38 mV). This again reflects slightly stronger contralateral projections and is in accordance with previous reports from other labs (Muellbacher et al., 2001).The effect of stimulus intensity, $F(5,14) = 16.49$, $p < 0.0001$, is reflected in the steady increase of MEP amplitudes with increasing stimulus intensity (90% 0.31±0.19 mV, 100% 0.44±0.27, 110% 0.65±0.35, 120% 0.91±0.55, 130% 1.1±0.68, 140% 1.28±0.62; see Figure 3C). Analysis yielded an interaction between stimulus intensity and group, $F(5,14) = 2.74$, $p = .023$, because MEP recruitment was steeper in AWS related to FS (Figure 3B). Post-hoc unpaired *t*-tests of MEP amplitudes yielded no significant differences between groups for separate conditions. Additionally, we found an interaction between mode and stimulus intensity, $F(1,18) = 3.86$, $p = .003$, because the slope of the recruitment curve under 10% contraction was steeper at lower intensities and flatter at higher intensities compared to the recruitment curve under 60% contraction which showed the reversed pattern (Figure 3E). Finally, there was an effect of mode, hemisphere and projection, $F(5,14) = 6.23$ $p = .02$, because under 60% contraction motor responses were enlarged in the contralateral projection

of the left hemisphere (1.29± 1.06 mV) compared to the contralateral projection of the right hemisphere (1.05±0.66mV).

The ANOVA considering MEP area yielded one additional interaction between projection and stimulus intensity with $F(5,15) = 20.76$; $p < .0001$. Areas of the MEP of the contralateral projection had a steeper slope compared to the MEP areas of the ipsilateral projection (Figure 3F).

Furthermore, the ANOVA with MEP areas yielded almost the same effects compared to the ANOVA with MEP peak-to-peak amplitudes: effect of mode $F(1,18) = 10.95$; $p = .004$; effect of projection $F(1,18) = 34.12$, $p < .0001$, effect of stimulus intensity $F(5,14) = 30.9$; $p < .0001$; an interaction of mode, hemisphere and projection $F(5,14) = 4.92$, $p = .04$; and an interaction between mode, stimulus intensity and group $F(5,14) = 2.38$; $p = .045$. Post hoc repeated measures ANOVAS separated for mode yielded in an significant interaction between group and intensity at 60% of maximum contraction, $F(5,14) = 2.55$; $p = .033$. This interaction was missing in the 10% of maximum contraction mode. Post hoc unpaired *t*-tests yielded no differences between groups concerning the MEP area at 60% maximum contraction at 140% MT or at 130% MT although the slope is steeper in AWS in this condition (Figure 3D).

Please insert Figure 3 around here

## 4. Discussion

Here we present the first assessment of intracortical excitability in the M1 representations of the lingual muscle in stuttering. The reduction of short-term intracortical inhibition at ISI 2ms in our sample of stuttering subjects partly confirms our hypothesis of a reduced ICI. Unexpected were the observations of a generally reduced intracortical facilitation, and of a steeper MEP recruitment in adults who stutter related to fluent speakers.

### *4.1 Reduction of short-term intracortical inhibition in stuttering*

The reduction of SICI indicates an altered excitability modulation of intracortical neural networks in stuttering. Due to the local action of TMS and the limited conduction velocities and synaptic delays it is assumed that SICI is mediated by the local neuronal circuits in the motor cortex (Di Lazzaro et al., 1998; Ziemann and Rothwell, 2000). At intervals larger than 1 ms SICI is caused by the activation of GABAergic interneurons and the subsequent inhibition of excitatory neurons (Fisher et al., 2002; Hanajima et al., 2003). We speculate that

in AWS's M1 tongue representation the interneuronal inhibitory network is less active at early times. In the next paragraph we shortly introduce the cellular physiology framework to discuss the effect.

A TMS pulse stimulates nerve fibers most likely at their terminations (Maccabee et al., 1993; Rotem and Moses, 2008) thereby activating synaptic terminals in all cortical layers. A suprathreshold TMS pulse activates enough excitatory synapses to elicit action potentials in layer 5 excitatory cells, the cortical output responsible for muscle activation. The layer 2/3 excitatory cells are activated as well, and in turn stimulate layer 5 cells, thereby prolonging and increasing the motor output. If the TMS pulse is weaker, excitatory cells are not sufficiently activated to fire action potentials, no motor response is elicited; the TMS stimulus is called subthreshold. Even in this case, however, the inhibitory interneurons are depolarized enough to fire action potentials. Those action potentials reach inhibitory (GABAergic) synapses onto the layer 2/3 and layer 5 excitatory neurons after a distance dependent conduction delay of 0-1 ms (Esser et al., 2005). Over the next 2 ms the inhibitory postsynaptic currents in the excitatory neurons increase. If a second, stronger TMS pulse is applied during this period, it might still suffice to activate the excitatory layer 5 neurons, that cause the motor response but due to the built up inhibition, the excitation of layer 5 and especially layer 2/3 neurons is weaker, leading to a reduction of action potential number, when compared to a single, unconditioned TMS stimulus. This view is supported by large scale modeling (Esser et al., 2005).

Our findings indicate that at an ISI of 2ms for FS there is significant inhibition but not in AWS. In the right hemisphere in AWS the inhibition takes longer to develop. This delay of the peak inhibitory activity implies that inhibitory inputs on the excitatory cells develop with a slower time course in AWS. The reasons can be diverse, including altered kinetics of synaptic signaling (altered subunit composition of GABA receptor complexes), longer conduction delays (a larger fraction of long range, i.e. 1 mm, inhibitory connections; (Kang et al., 1994) or short term synaptic plasticity e.g synaptic depression due to depletion of release-competent synaptic vesicles at the excitatory synapses innervating the layer 5 excitatory neurons.

GABAeric interneurons seem to play a key role in mediating the effect of intracortical inhibition. Therefore it is interesting to note that stuttering can be induced by theophylline (Movsessian, 2005) an adenosin receptor antagonist which has been previously described to reduce the binding of GABA to $GABA_A$ receptors via a decoupling of the benzodiazepine binding site that is present on the receptor (Roca et al., 1990). Additionally, theophylline

plasma concentration correlates positively with a reduction of SICI in healthy subjects (Nardone et al., 2004). SICI is mediated by either the α2- or α3-subunit of the $GABA_A$ receptor (Di Lazzaro et al., 2006). Thus, the susceptibility of the speech motor system in stuttering might be mediated by $GABA_A$ neurons.

### *4.2 Reduced intracortical facilitation in stuttering*

One possible explanation for a generally reduced ICF in stuttering might be a different level of pre TMS tongue activation. It is known that orofacial muscles are rarely at rest (Devlin and Watkins, 2008) and that muscle activation reduces ICF suggesting that voluntary drive reduces the excitability of intracortical circuits (Ridding et al., 1995). Therefore one might conclude that the pre TMS tongue activity was higher in AWS and hence ICF was reduced. However, the comparison of pre TMS tongue activity revealed no group differences. Consistent with this, previous EMG studies in stuttering do not provide evidence for elevated tonic activity or a co-activation in the laryngeal or orofacial muscles, neither during fluent speech nor during dysfluent speech (Smith et al., 1996; Smith et al., 1993). Even at rest lower lip activity did not differ between AWS and FS, while upper lip activity has been reported to be lower in AWS (de Felicio et al., 2007).

Another possible explanation for a reduced ICF might be that the MEP amplitude was already saturated in AWS at a test pulse intensity of 130% MT. This point also does not hold true because the MEP recruitment until 140% MT resulted in a steeper slope in AWS and the comparison of MEP areas between groups yielded no differences. Thus, our findings implicate a diminished excitability of excitatory neuronal circuits in motor cortex in the sample of AWS examined in the current study.

While ICF is normal in the M1 hand representation in AWS (Sommer et al., 2003) the current data imply a reduced intracortical facilitation for the M1 tongue representation. In contrast to ICI which is reduced in several movement disorders, reduced ICF has been described only in few movement disorders; unequivocally in cerebellar ataxia and equivocally in Huntington's disease (Berardelli et al., 2008). The fact, that these movement disorders as well as movement disorders that are characterized by reduced ICI are related to a dysfunction of the basal ganglia or the cerebellum, suggests that the dysfunction in these structures might influence intracortical circuits that modulate motor cortex excitability. In stuttering the contribution of altered cerebello-cortical loops (Lu et al., 2010) as well as deviant basal ganglia function are proposed (Alm, 2004). Clinical trials with dopamine antagonists resulted in a positive effect on speech fluency (Burns et al., 1978; Maguire et al., 2010) while dopamine agonists

enhanced dysfluency. An early study with Positron Emission Tomography reports an increased uptake of presynaptic dopamine in stuttering which indicates that stuttering is related to a hyper-dopaminergic status (Wu et al., 1997). Although, physiological mechanisms of ICF are not well understood we here speculate that the reduced ICF might be mediated by disturbed interaction between cortical and subcortical networks modulating inhibitory and facilitatory intracortical circuits.

Although, TMS paired-pulse techniques employed to study SICI and ICF in different movement disorders provide important information about the pathophysiologies in the primary motor cortex (Hanajima and Ugawa, 2008), the exact mechanisms of these modulations of cortical excitability are still a matter of debate (Reis et al., 2008). Furthermore, literature on intracortical excitability in speech relevant muscles is scarce. Because the tongue muscles are rarely at rest and the innervations occurs bilaterally a direct comparison with previous literature on SICI and ICF is limited and restricts general conclusions.

### *4.3 MEP recruitment*

The recording of the MEP input-output curve was necessary to address the question, whether MEP amplitude was already statured in AWS in the facilitatory paired-pulse condition. To take care for a potential ceiling effect we obtained MEP input-output curves under different conditions of tongue activity. While recruitment under 10% of maximum tongue contraction was characterized by a steep slope at high intensities, MEP recruitment seems to reach staturation at high intensities under 60% contraction (Figure 3E). Figure 3C and 3D detail that this saturation is more clearly displayed in FS compared to AWS were recruitment between 130 and 140% of maximum stimulator output shows a further trend towards a larger MEP amplitude and MEP area. It was not possible to win all AWS that participated in the ICI/ICF session to participate in the MEP input-output curve session. Thus, the data result from a subsample of AWS of the first experiment which limits their interpretation.

### *4.5 Implications*

We specified a reduced and possibly delayed SICI in the right hemisphere and a reduced ICF in either hemisphere which implies altered intracortical modulation of inhibitory as well as facilitatory circuits in stuttering. As the final cortical processing stage for voluntary movement, the primary motor cortex is a critical site for the integration of movement selection, initiation and prevention processes. Upcoming studies might further elucidate state-

dependent modulation of intracortical inhibition to conceive pathomechanisms of dysfluent speech production in stuttering. Furthermore, single-pulse and paired-pulse TMS can be employed to study underlying physiological mechanisms of a pharmacologically induced enhancement of speech fluency and to compliment current pharmacological approaches.

## Disclosure

The authors report no conflicts of interest.

## References

WHO. ICD-10 F98.6 Cluttering 2007:Retrieved from www.who.int/classifications/apps/icd/icd10online.

Alm PA. Stuttering and the basal ganglia circuits: a critical review of possible relations. J Commun Disord. 2004 Jul-Aug;37(4):325-69.

Alm PA. Fluency disorders: a discussion of possible causes and mechanisms, from a neuroscience perspective. 8th Oxford Dysfluency Conference; 2008; Oxford, UK. 2008.

Berardelli A, Abbruzzese G, Chen R, Orth M, Ridding MC, Stinear C, et al. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul. 2008 Jul;1(3):183-91.

Bloodstein O, Ratner BN. A Handbook on Stuttering. 6 ed. Canada: Delmar Thomson Learning; 2008.

Braun AR, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, et al. Altered patterns of cerebral activity during speech and language production in developmental stuttering. An H2(15)O positron emission tomography study. Brain. 1997 May;120 ( Pt 5):761-84.

Brown S, Ingham RJ, Ingham JC, Laird AR, Fox PT. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. Hum Brain Mapp. 2005 May;25(1):105-17.

Burns D, Brady JP, Kuruvilla K. The acute effect of haloperidol and apomorphine on the severity of stuttering. Biol Psychiatry. 1978 Apr;13(2):255-64.

Craig A, Hancock K, Tran Y, Craig M, Peters K. Epidemiology of stuttering in the community across the entire life span. J Speech Lang Hear Res. 2002 Dec;45(6):1097-105.

de Felicio CM, Freitas RL, Vitti M, Regalo SC. Comparison of upper and lower lip muscle activity between stutterers and fluent speakers. Int J Pediatr Otorhinolaryngol. 2007 Aug;71(8):1187-92.

Devlin JT, Watkins KE. Investigating language organization with TMS. In: Wassermann EM, Epstein CM, Ziemann U, Walsh V, Paus T, Lisanby SH, editors. The Oxford Handbokk of Transcranial Magnetic Stimulation. New York: Oxford University Press; 2008. p. 479-99.

Di Lazzaro V, Pilato F, Dileone M, Ranieri F, Ricci V, Profice P, et al. GABAA receptor subtype specific enhancement of inhibition in human motor cortex. J Physiol. 2006 Sep 15;575(Pt 3):721-6.

Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res. 1998 Mar;119(2):265-8.

Esser SK, Hill SL, Tononi G. Modeling the effects of transcranial magnetic stimulation on cortical circuits. J Neurophysiol. 2005 Jul;94(1):622-39.

Euler HA, Gudenberg AWv, Jung K, Neumann K. Computergestützte Therapie bei Redeflussstörungen: Die langfristige Wirksamkeit der Kasseler Stottertherapie. Sprache, Stimme, Gehör. 2009;33(4):193-97.

Fisher RJ, Nakamura Y, Bestmann S, Rothwell JC, Bostock H. Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. Exp Brain Res. 2002 Mar;143(2):240-8.

Fox PT, Ingham RJ, Ingham JC, Hirsch TB, Downs JH, Martin C, et al. A PET study of the neural systems of stuttering. Nature. 1996 Jul 11;382(6587):158-61.

Fox PT, Ingham RJ, Ingham JC, Zamarripa F, Xiong JH, Lancaster JL. Brain correlates of stuttering and syllable production. A PET performance-correlation analysis. Brain. 2000 Oct;123 ( Pt 10):1985-2004.

Hanajima R, Furubayashi T, Iwata NK, Shiio Y, Okabe S, Kanazawa I, et al. Further evidence to support different mechanisms underlying intracortical inhibition of the motor cortex. Exp Brain Res. 2003 Aug;151(4):427-34.

Hanajima R, Ugawa Y. Paired-pulse measures. In: Wassermann EM, Epstein CM, Ziemann U, Paus T, Lisanby SH, editors. The Oxford handbook of transcranial magnetic stimulation. New York: Oxford Univerity Press; 2008.

Kang Y, Kaneko T, Ohishi H, Endo K, Araki T. Spatiotemporally differential inhibition of pyramidal cells in the cat motor cortex. J Neurophysiol. 1994 Jan;71(1):280-93.

Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol. 2001;112(4):720.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993 Nov;471:501-19.

Lu C, Chen C, Ning N, Ding G, Guo T, Peng D, et al. The neural substrates for atypical planning and execution of word production in stuttering. Exp Neurol. [; Research Support, Non-U.S. Gov't]. 2010 2010 Jan (Epub;221(1):146-56.

Ludlow CL, Loucks T. Stuttering: a dynamic motor control disorder. J Fluency Disord. 2003 Winter;28(4):273-95.

Maccabee PJ, Amassian VE, Eberle LP, Cracco RQ. Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. J Physiol. 1993 Jan;460:201-19.

Maguire G, Franklin D, Vatakis NG, Morgenshtern E, Denko T, Yaruss JS, et al. Exploratory randomized clinical study of pagoclone in persistent developmental stuttering: the Examining Pagoclone for peRsistent dEvelopmental Stuttering Study. J Clin Psychopharmacol. 2010 Feb;30(1):48-56.

Meyer BU, Liebsch R, Roricht S. Tongue motor responses following transcranial magnetic stimulation of the motor cortex and proximal hypoglossal nerve in man. Electroencephalogr Clin Neurophysiol. 1997 Feb;105(1):15-23.

Movsessian P. Neuropharmacology of theophylline induced stuttering: the role of dopamine, adenosine and GABA. Med Hypotheses. 2005;64(2):290-7.

Muellbacher W, Boroojerdi B, Ziemann U, Hallett M. Analogous corticocortical inhibition and facilitation in ipsilateral and contralateral human motor cortex representations of the tongue. J Clin Neurophysiol. 2001 Nov;18(6):550-8.

Mulligan HF, Anderson TJ, Jones RD, Williams MJ, Donaldson IM. Tics and developmental stuttering. Parkinsonism Relat Disord. 2003 Jun;9(5):281-9.

Nardone R, Buffone E, Covi M, Lochner PG, Tezzon F. Changes in motor cortical excitability in humans following orally administered theophylline. Neurosci Lett. 2004 Jan 23;355(1-2):65-8.

Neef N, Jung K, Rothkegel H, Pollok B, Wolff von Gudenberg A, Paulus W, et al. Right-shift for non-speech motor processing in adults who stutter. Cortex. 2010.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971 Mar;9(1):97-113.

Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, et al. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul. 2008 Jul;1(3):151-63.

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol. 2008 Jan 15;586(2):325-51.

Ridding MC, Taylor JL, Rothwell JC. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J Physiol. 1995 Sep 1;487 ( Pt 2):541-8.

Riley GD. The Stuttering Severity Instrument for Children and Adults- Third Edition (SSI-3). Austin, TX: Pro-Ed.; 1994.

Roca DJ, Schiller GD, Friedman L, Rozenberg I, Gibbs TT, Farb DH. gamma-Aminobutyric acidA receptor regulation in culture: altered allosteric interactions following prolonged exposure to benzodiazepines, barbiturates, and methylxanthines. Mol Pharmacol. 1990 May;37(5):710-9.

Rödel RM, Laskawi R, Markus H. Tongue representation in the lateral cortical motor region of the human brain as assessed by transcranial magnetic stimulation. Ann Otol Rhinol Laryngol. 2003 Jan;112(1):71-6.

Rotem A, Moses E. Magnetic stimulation of one-dimensional neuronal cultures. Biophys J. 2008 Jun;94(12):5065-78.

Sandrieser P, Schneider P. Stottern im Kindesalter. 3 ed. Stuttgart: Thieme; 2008.

Smith A, Denny M, Shaffer LA, Kelly EM, Hirano M. Activity of intrinsic laryngeal muscles in fluent and disfluent speech. J Speech Hear Res. 1996 Apr;39(2):329-48.

Smith A, Luschei E, Denny M, Wood J, Hirano M, Badylak S. Spectral analyses of activity of laryngeal and orofacial muscles in stutterers. J Neurol Neurosurg Psychiatry. 1993 Dec;56(12):1303-11.

Sommer M, Knappmeyer K, Hunter EJ, Gudenberg AW, Neef N, Paulus W. Normal interhemispheric inhibition in persistent developmental stuttering. Mov Disord. 2009 Apr 15;24(5):769-73.

Sommer M, Wischer S, Tergau F, Paulus W. Normal intracortical excitability in developmental stuttering. Mov Disord. 2003 Jul;18(7):826-30.

Stinear CM, Coxon JP, Byblow WD. Primary motor cortex and movement prevention: where Stop meets Go. Neurosci Biobehav Rev. 2009 May;33(5):662-73.

Svensson P, Romaniello A, Arendt-Nielsen L, Sessle BJ. Plasticity in corticomotor control of the human tongue musculature induced by tongue-task training. Exp Brain Res. 2003 Sep;152(1):42-51.

Wu JC, Maguire G, Riley G, Lee A, Keator D, Tang C, et al. Increased dopamine activity associated with stuttering. Neuroreport. 1997 Feb 10;8(3):767-70.

Ziemann U, Rothwell JC. I-waves in motor cortex. J Clin Neurophysiol. 2000 Jul;17(4):397-405.

Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol. 1998 Aug 15;511 ( Pt 1):181-90.

**Figure 1 Intracortical inhibition and facilitation in a fluent speaking control.** Depicted are motor evoked potentials (MEP) elicited in the contralateral (left) and ipsilateral (right) tongue muscle by transcranial magnetic stimulation (TMS) of the left primary motor cortex. Upper traces depict MEPs (gray) of single pulse TMS with an unconditioned test pulse at 130% motor threshold (MT). The black trace constitutes the averaged MEP. The contralateral response is larger than the ipsilateral response. Lower traces depict responses after paired-pule TMS. Test pulse intensity was set at 130% MT and conditioned stimulus intensity was set at 90% MT. ISIs were set at 2, 3, 10 and 15 ms. The dotted line shows the averaged unconditioned MEP. While short ISIs at 2 and 3 ms inhibit the MEP, longer ISIs at 10 and 15 ms facilitate the MEP.

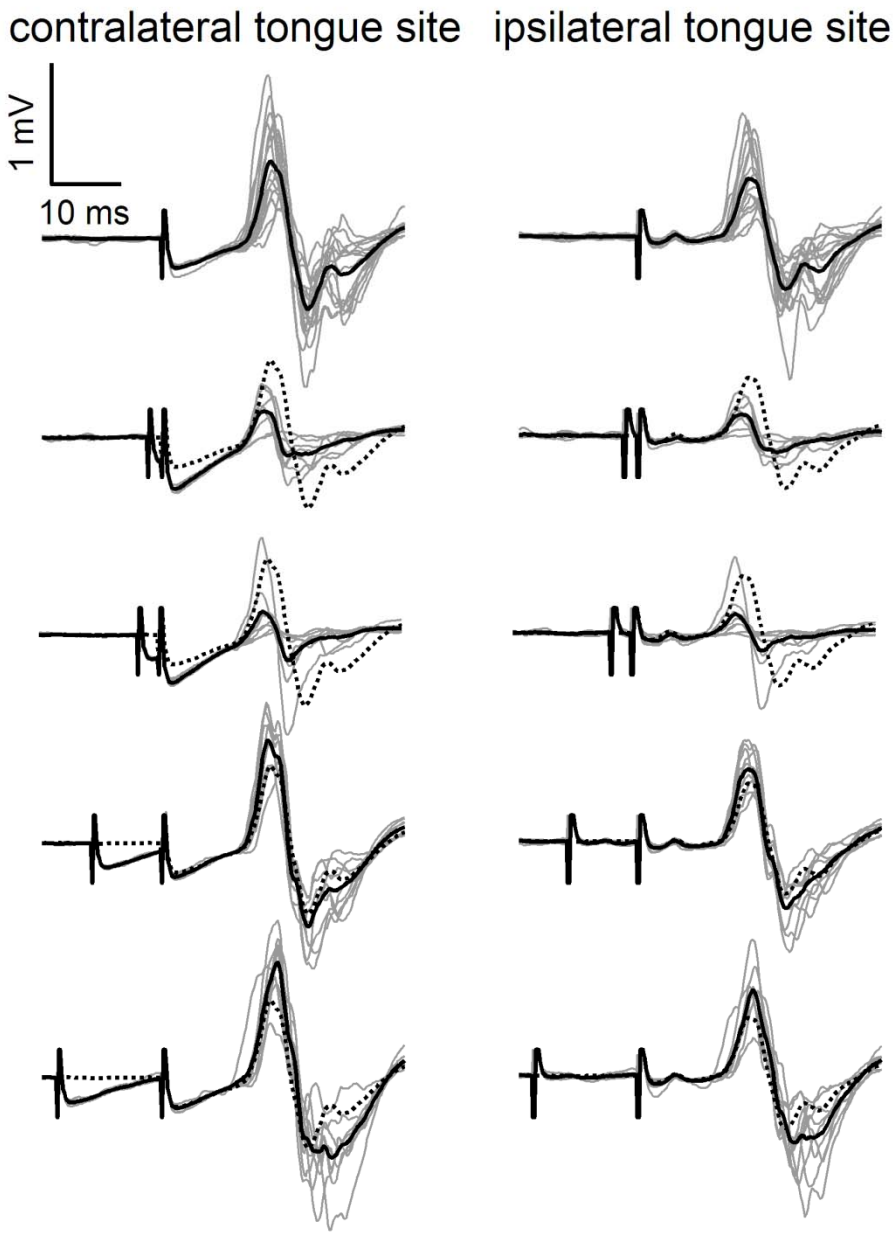
contralateral tongue site
ipsilateral tongue site
1 mV
10 ms

**Figure 1**

**Figure 2 Reduction of intracortical excitability in AWS**. (A) Pre-TMS tongue activity averaged over 60 ms of the offset corrected rectified EMG-signal immediately before the TMS pulse was applied. Participants were asked to press the tongue tightly, with about 60% of maximum contraction against the mouth piece. There were no significant differences, neither between tongue sites nor between groups. (B-F) Depicted are the MEP amplitudes, normalized to unconditioned MEP amplitudes for the paired-pulse TMS with inter-stimulus intervals (ISI) at 2, 3, 10 and 15 ms. All values are given ± SEM. Significant difference from unconditioned MEP amplitude is labeled by filled markers, significant differences between AWS and FS is labeled by * for $p < .05$ and ** for $p < .01$. (B) Shown are the averages of fluent speakers (FS, squares) and adults who stutter (AWS, triangles) over all conditions which are separately depicted in (C) contralateral projection for left, (D) and right hemispheric stimulation, (E) ipsilateral projection for left and (F) right hemispheric stimulation. AWS exhibited no intracortical inhibition at ISI 2 ms. Intracortical facilitation at ISIs 10 and 15 ms are generally reduced in AWS compared to FS.

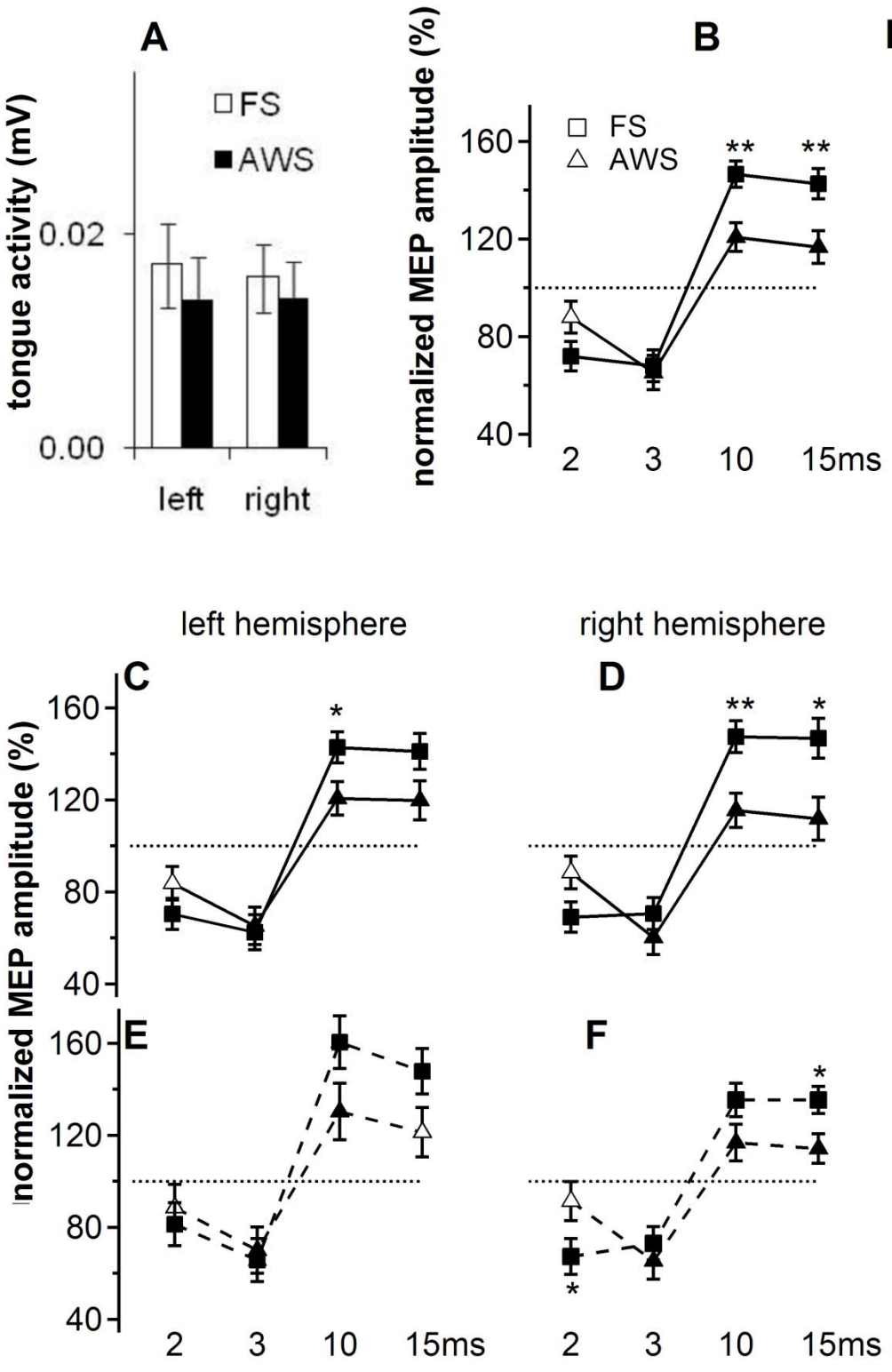
A
FS
AWS
tongue activity (mV)
0.02
0.00
left
right
B
normalized MEP amplitude (%)
FS
AWS
160
120
80
40
**
**
2
3
10
15ms
left hemisphere
right hemisphere
C
D
E
F
normalized MEP amplitude (%)
160
120
80
40
*
**
*
*
2
3
10
15ms

**Figure 2**

**Figure 3 Steeper MEP recruitment in stuttering.** (A) Pre transcranial magnetic stimulation (TMS) tongue activity averaged over 79 ms of the offset corrected rectified EMG-signal immediately before the TMS pulse was applied. Values are given for fluent speakers (FS, white bars) and adults who stutter (AWS, black bars). The contraction of the tongue with approximately 60% maximum contraction resulted in a significant increase in the EMG response compared to 10% of maximum contraction. Further differences appeared neither between tongue sites nor between groups. (B) Motor threshold (MT) shown for FS (white bars) and AWS (black bars) given in percent of maximum stimulator output do not differ between groups or hemispheres. (C) Mean amplitude of motor evoked potential (MEP) (D) and mean MEP area in FS (white squares) and AWS (black triangles) under 10% of maximum contraction (dashed line) and 60% of maximum contraction (solid line) at different stimulus intensities. Both parameters illustrate a steeper recruitment in AWS related to FS especially under 60% of maximum contraction. (E) Interaction between mode and intensity for MEP amplitude: MEP recruitment was flatter at lower intensities and steeper at higher intensities at 10% of maximum tongue contraction, but steeper at lower intensities and flatter at higher intensities at 60% of maximum tongue contraction. (F) Interaction between intensity and projection for MEP area: MEP recruitment was steeper in the contralateral projection related to the ipsilateral projection independent of stimulated hemisphere and group. All values are given ± SEM.

**Figure 3**

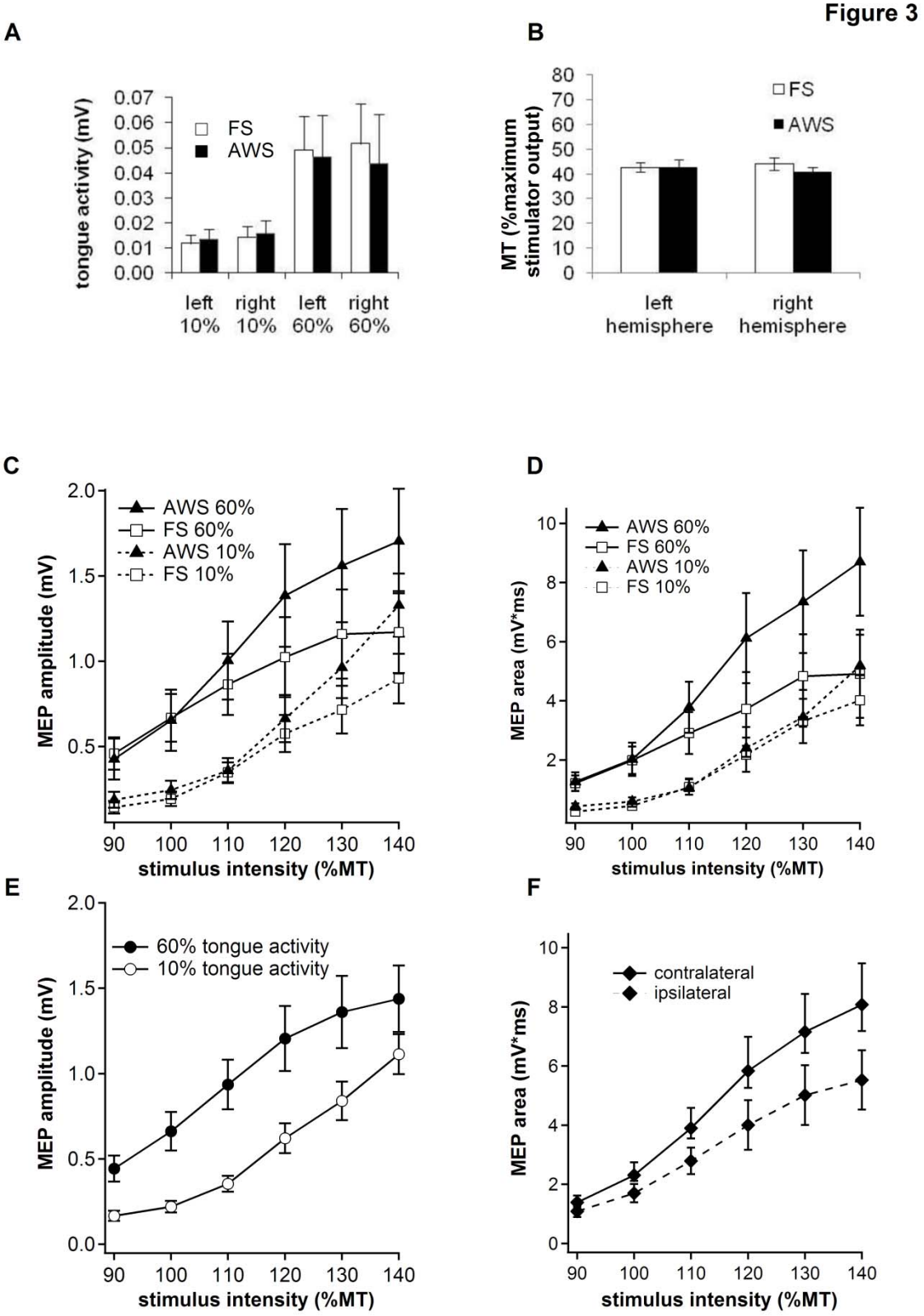
A
tongue activity (mV)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
FS
AWS
left 10%
right 10%
left 60%
right 60%
B
MT (%maximum stimulator output)
80
70
60
50
40
30
20
10
0
FS
AWS
left hemisphere
right hemisphere
C
MEP amplitude (mV)
2.0
1.5
1.0
0.5
AWS 60%
FS 60%
AWS 10%
FS 10%
90 100 110 120 130 140
stimulus intensity (%MT)
D
MEP area (mV*ms)
10
8
6
4
2
AWS 60%
FS 60%
AWS 10%
FS 10%
90 100 110 120 130 140
stimulus intensity (%MT)
E
MEP amplitude (mV)
2.0
1.5
1.0
0.5
0.0
60% tongue activity
10% tongue activity
90 100 110 120 130 140
stimulus intensity (%MT)
F
MEP area (mV*ms)
10
8
6
4
2
0
contralateral
ipsilateral
90 100 110 120 130 140
stimulus intensity (%MT)

**Table 1 Description of the samples.** Given are the means ± standard deviations; minimum – maximum. Stuttering onset and age were documented in years; stuttering severity was estimated with the Stuttering Severity Index (Sandrieser and Schneider, 2008); stuttered syllables were mean percentage out of not less than 340 read and 500 spoken syllables; handedness index was calculated Oldfield (1971); education was classified as follows: 1 = school, 2 = high school, 3 = less than 2 years college, 4 = 2 years college, 5 = 4 years college, 6 = postgraduate; motor threshold (MT) was quantified in percent of maximum stimulator output in the left and right hemisphere, MT_2 threshold determinate with the Bistim module, and MT_1 threshold determined with a single Magstim200 stimulator. Note that MT_2 yields higher values than MT_1 because of the power loss due to the bistimulation module.

| | **adults who stutter** | | **fluent speakers** |
|---|---|---|---|
| | **experiment 1** | **experiment 2** | |
| | (N = 12) | (N = 8) | (N = 14) |
| stuttering onset | 4.5±2.8; 2.0-10.0 | 5.1±3.3; 2-10 | NA |
| stuttering severity | 23.3±9.3; 10-39 | 22.8±10.2; 10-39 | 0±0 |
| stuttered syllables | 6.7±3.8; 1.9-13.3 | 5.9±4.1, 1.9-13.3 | 0.3±0.2; 0.0-0.8 |
| age | 29.9±8.2; 21.3-47.1 | 30.4±8.8; 21.4-47.1 | 29.5±7.6; 22.0-45.1 |
| handedness index | 93.9±10.2; 71.4-100 | 95.8±8.6; 76.5-100 | 94.1±9.4; 74.5-100 |
| education | 3.3±1.8; 1-6 | 3.1±2.0; 1-6 | 4.2±1.2; 2-6 |
| MT left_2 | 48.5±9.8; 38-64 | | 46.5±7.3; 38-62 |
| MT right_2 | 44.7±8.7; 36-67 | | 49.0±8.2; 38-61 |
| MT left_1 | | 42.8±8.4; 30-54 | 42.6±6.7; 35-57 |
| MT right_1 | | 40.8±5.9; 33-49 | 44.3±8.8; 33-59 |

**Table 2 Unconditioned MEP amplitudes** separated for adults who stutter (AWS) and fluent speakers (FS) and for hemisphere and projection. Given are the mean (*M*) of absolute values; standard deviation (*SD*); and *p*-values of paired, two-tailed t-tests.

| | | **left hemisphere** | | | **right hemisphere** | | |
|---|---|---|---|---|---|---|---|
| | **projection** | ***M* (mV)** | ***SD* (mV)** | ***p*** | ***M* (mV)** | ***SD* (mV)** | ***p*** |
| **AWS** | **contralateral** | 0.95 | .690 | **.027** | 1.13 | 0.772 | **.021** |
| | **ipsilateral** | 0.65 | .609 | | 0.71 | .616 | |
| **FS** | **contralateral** | 0.80 | .422 | **.018** | 0.74 | .676 | .310 |
| | **ipsilateral** | 0.63 | .312 | | 0.64 | .493 | |

**Table 3 Group differences for intracortical excitability** determined with unpaired two-tailed t-tests. Each *p*-values represents a group comparison of normalized conditioned MEP amplitudes for left and right hemispheric contralateral and ipsilateral projections for inhibitory inter-stimulus intervals (ISI, 2 ms and 3 ms) and facilatory ISIs (10 ms and 15 ms). Significant differences are indicated with values printed in bold.

| **projection** | **contralateral** | | | | **ipsilateral** | | | |
|---|---|---|---|---|---|---|---|---|
| **ISI** | **2 ms** | **3 ms** | **10 ms** | **15 ms** | **2 ms** | **3 ms** | **10 ms** | **15 ms** |
| **left hemisphere** | .189 | .812 | **.034** | .079 | .606 | .758 | .087 | .082 |
| **right hemisphere** | .056 | .320 | **.005** | **.011** | **.046** | .482 | .099 | **.024** |

**Table 4 Effects yielded by separate two-way ANOVAS** with group as between subject factor and inter-stimulus interval (ISI) as with-in subject factor. ANOVAS were separated for hemispheres, inhibitory and facilitatory ISIs and considered only the contralateral projection.

| | **left hemisphere** | **right hemisphere** |
|---|---|---|
| **SICI** | ISI $F(1,24) = 7.62$, p = .011 | ISI $F(1,24) = 7.0$, $p = .014$<br>ISI x Group $F(1,24) = 8.8$, $p = .007$ |
| **ICF** | Group $F(1,24) = 4.9$, p = .037 | Group $F(1,24) = 9.9$, $p = .004$ |

## 2.3 Instable phoneme categorization in adults who stutter

Authors:
Nicole E. Neef
Martin Sommer
Walter Paulus
Department of Clinical Neurophysiology, Georg-August-University of Goettingen
Alexander Wolff von Gudenberg
Institut der Kasseler Stottertherapie, Bad Emstal, Germany
Torsten Wüstenberg
Department of Psychiatry and Psychotherapy, Charité Universitaetsmedizin Berlin

Running Head: Phoneme Categorization in Stuttering

Corresponding Author:
Martin Sommer, M.D
Department of Clinical Neurophysiology
Robert-Koch-Str. 40
D-37075 Goettingen, Germany
Phone: +49-551-39 66 50
Email: msommer@gwdg.de

## Abstract

*Purpose:* It is currently unknown if persistent stuttering is accompanied by an irregular sublexical speech perception. We tested the stability of phoneme percepts by analyzing participants' ability to discriminate between voiced and voiceless stop-consonants.

*Method:* In two synthetically generated syllable continua (/bə/-/pə/, /də/-/tə/), voice onset time was systematically modified. We determined the phoneme discrimination ability of twenty patients and twenty matched control subjects by computing the phoneme boundaries, and by quantifying the ambivalence interval - the interval of voice onset times where phonemes were perceived ambiguously.

*Results:* Patients showed larger and less stable ambivalence intervals compared to healthy subjects, while no difference between patients and controls was revealed concerning phoneme boundaries.

*Conclusion:* Persistent developmental stuttering is associated with unreliable phonological percepts, supporting current theories regarding the sensory-motor interaction in human speech. Particularly, our findings might implicate an affected auditory feedback control subsystem in AWS.

## Introduction

Stuttering is characterized by sudden interruptions of fluent speech due to an intermittent loss of motor control (Ludlow and Loucks, 2003). The dynamic, multifactorial view of stuttering postulates nonlinear interaction between a vulnerable speech motor system and factors like genetic predisposition, emotional and autonomic arousal, linguistic and other cognitive processing demands (Smith and Kelly, 1997; Smith et al., 2010). Although stuttering manifests in the articulatory domain, speech perception is the focus of several studies designed to elucidate its role in stuttering. Because proper articulation results in distinguishable auditory targets, audition is a modality that serves mainly to control success of articulation. Speech acquisition comprises subtle refinement of articulatory configurations resulting in fine-tuned phonematic features relevant to distinguish meanings. Fine-tuning requires the representation of a produced sound in the processing system and a mapping between auditory target and produced item. This process is still active in adulthood, demonstrated by the relation between a speaker's production of a phoneme contrast and his or her perception of this contrast (Newman, 2003; Perkell et al., 2004) and the influence of speech motor learning on adult speaker's auditory maps (Nasir & Ostry, 2009). Because of the tight link between production and perception it has been suggested that pathological speech patterns are connected to altered speech perception (Heiser and Cheung, 2008).

The temporal processing demands of auditory and proprioceptive information during speaking are presumed to challenge the speech motor system of adults who stutter (AWS) (Kent, 2000). The auditory and proprioceptive information that is to be expected during speech production are proposed to be held in internal models of speech sounds. The speech motor control deficit is possibly linked to instability of these internal sensory models or to insufficient access on them, restricting the feed forward control mechanisms in speech production (Max et al., 2004).

The concept of instable speech sound maps in stuttering together with the demonstrated link between speech production and perception lead us to probe a speech perception ability of AWS – the phoneme categorization. Only few behavioral studies investigated speech sound perception on the sublexical level in stuttering (Blood, 1996; Kramer et al., 1987). Sublexical speech stimuli are eligible to test phoneme perception without contextually driven top down information which facilitates recognition. We are not aware of a behavioral study investigating phoneme categorization in AWS.

In contrast, sublexical speech perception abilities have been studied in a few Electroencephalography (EEG) and Magnetencephalography (MEG) studies in AWS. Corbera

and colleagues (2005) recorded the mismatch negativity (MMN) event-related brain potential elicited to simple tone contrasts and to vowel contrasts. The MMN results from the detection of a deviant stimulus. For example, in Corbera's vowel contrast condition participants listened to the repeated presentation of /o/. The unexpected presentation of /e/ resulted in an enlarged electrophysiological response which indicated a detected mismatch between the previous presented /o/ and the now presented /e/. This increase of the MMNs was significantly larger in the left supratemporal region in AWS compared to control subjects. A larger MMN indicates a higher sensitivity of the neural population to a certain deviation. Thus, the authors suggest an abnormal speech sound representation within the auditory region of the left hemisphere in AWS.

The MEG study demonstrates altered cortical activation patterns upon perception of an unexpected phoneme. It remained unclear whether the performance in the underlying categorization is also different in AWS on a subclinical level. This information is provided by the psychophysical phoneme identification study presented here. One phonetically relevant property of speech is the voice onset time (VOT). Differences in VOT are perceptually essential to discriminate voiced from voiceless stop consonants. In word-initial position, German voiced stops like /b/ and /d/ are typically produced with short VOTs or, in some cases, with prevoicing; and German voiceless stops like /p/ and /t/ are produced with longer VOTs (Keating, 1984). The stimuli of the present study were created by systematic variation of the VOT, creating a /b/-/p/ and a /d/-/t/ continuum. Each VOT continuum can be separated in three different sections according to the listener's performance in the psychophysical test. Two sections contain those stimuli that are reliably identified as the voiced respectively voiceless phoneme. Between those sections lies a range of VOT in which no reliable identification is possible and the listener reports different percepts upon repeated presentation. The *width* of this section is termed here ambivalence interval (AI). It is directly related to the slope of the psychometric function describing the discriminatory performance (see Appendix B). The position of AI is conveniently defined by the VOT where discrimination is at chance level. This VOT is here termed phoneme boundary PB. These two parameters were extracted for each listener by fitting the results of the identification task with a logistic curve (Fig 2 and Appendix B). The AI is a possible quantifier of ambiguity. A narrow AI, corresponding to a steep slope, indicates a small range where stimuli are perceived as ambiguous. Accordingly a wide AI (i.e. shallow slope) indicates that the range where stimuli are not reliably identified is large (Fig 2). This concept has been employed in a recent

publication by Möttönen and Watkins (2009), who studied the influence of lip primary motor cortex inhibition on phoneme categorization and discrimination. A logistic psychometric function was used to fit the listener's performance in a phoneme identification task (e.g. in the acoustic /ba/-/da/ continuum). The slope of the function served as quantification of the listener's discrimination ability. It was reduced following inhibition of the primary motor lip area.

Our study is designed to determine the ambivalence intervals and the phoneme boundaries of two consonant-vowel (CV) continua (/bə/-/pə/ and /də/-/tə/). We choose two different CV continua to determine a general effect. We test the following specific hypotheses: First, compared to fluently speaking participants, AWS will show broader ambivalence intervals, indicating less stable phoneme representations on a subclinical level. Second, AWS and fluently speaking participants will not differ in phoneme boundaries, a feature that depends mainly on the native language and the idiom of the subjects (Braun, 1996; Lisker and Abramson, 1964).

## Methods

*Participants*

Twenty AWS (aged 32.2±12.6 years, five women) and twenty control subjects (aged 31.9±11.0, four women) participated in the study. AWS were recruited from the local stuttering support group and the Institute for the Kassel Stuttering Therapy. Control subjects were recruited by advertisement. The groups were matched for age ($t(39) = -0.09$, $p = .16$; unpaired two tailed $t$ Test), level of education ($p = .64$; $U$ test) and handedness ($p = .43$; $U$ test). Three AWS and one control subject were left handed according to the Edinburgh inventory (Oldfield, 1971). AWS produced more stuttered syllables than control subjects (German version of the SSI-3, mean±$SD$ 11.83±9.45, vs. 0.27±0.23; $p < .001$; $U$ test). Stuttering severity was very mild in six, mild in two, moderate in three, severe in four and very severe in five AWS (Sandrieser and Schneider, 2008). Averaged stuttering onset was at age 5.0±2.6. Detailed description of participants is reported in Table 1.

All participants were native speakers of German, none of them was bilingual. Fifteen AWS reported a family history of stuttering. None of the control subjects reported having a family history of speech or language disorders. None of the participants reported a speech, language or hearing deficit, except of stuttering in the stuttering group; or showed neurological abnormalities on routine examination. No participant was taking drugs affecting the central

nervous system at the time of the study. The Göttingen Ethics Committee approved the study, and all participants gave written informed consent. All participants were paid for their participation.

*Fluency Assessment*

To judge stuttering severity, fluency assessments were performed regarding 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 and analyzed by a qualified speech-language pathologist. SSI-3 norms were adapted from Riley (Riley, 1994). 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) as well as sound and syllable repetitions were counted as stuttered syllables. Monosyllabic words that were repeated with apparent undue stress or tension were counted. Furthermore, the estimated duration of the three longest blocks and observation of physical concomitants were included for the estimate of stuttering severity in AWS.

*Stimuli*

Synthetically generated sets of /bə/-/pə/ and /də/-/tə/consonant-vowel CV continua with a varying VOT from 7 to 61 ms served as stimuli. These sets were created within a five step process: (i) Voiceless syllables were generated using the AT&T Bell-Research Lab speech synthesizer (http://www2.research.att.com/~ttsweb/tts/; sample rate = 16 kHz, number of bits per sample = 16). (ii) Spectrograms of these syllables were computed with the software package Praat (http://www.fon.hum.uva.nl/praat/). (iii) The first three formats of the vowel were extracted from these spectrograms. (iv) Stimuli were segmented into consonant and vowel regarding the formant with the earliest onset. (v) To form the CV continua, the resulting segments were superimposed with a step width of 1 millisecond using an in house made algorithm written in the MatLab programming language (MatLab 7.4, Release 2007a, Mathworks, Inc., Natick, MA).

*Experimental Procedure*

Participants sat in front of a computer in a quiet room. Stimuli were presented binaurally via dynamic, closed-ear headphones (Sennheiser HD 280; up to 32dB attenuation of outside noise) at a comfortable hearing level they regulated by themselves. The two sets of CV

continua were presented in separate blocks in a balanced order. Each block comprised five trial series. Each series started off with a staircase search for the approximate position of the phoneme boundary. This was followed by a random sequence of stimuli with VOTs covering 20 ms around the tentative phoneme boundary. Participants were asked to listen to the stimuli and to press the left mouse button when they perceive a /be/ and the right mouse button when they perceive a /pe/. As a reminder this information was depicted on the screen during the entire trial series. By pressing the space bar participants were able to repeat the last stimulus until indicating their final decision by mouse button press in a two alternative forced choice. The two blocks were separated by a 15-minute break. Speech samples for the SSI-3 fluency assessment were recorded during this break.

The adaptive computation of stimulus VOTs was based on an accelerated stochastic approximation (see Appendix – A) as described by Kesten (1958; Treutwein, 1995). The staircase procedure started by a randomly chosen VOT and was aborted after ten reversals. For the /bə/-/pə/continuum control subjects required a mean of 35.95 (±2.87) and AWS a mean of 36.77 (±5.24) trials. For the /də/-/tə/continuum the average amount of trials for one repetition was 36.93 (±4.5) for control subjects and 38.06 (±5.96) for AWS. The adaptive estimation of the phoneme boundary took about three minutes each.

It is an intrinsic property of the applied adaptive algorithm that in the last third of each repetition, consecutive stimuli near the phoneme boundary, and thus within the ambivalence interval, are presented. For control subjects 28.4% of /bə/-/pə/ and 29.1% of /də/-/tə/ stimuli were presented in ambivalence interval. For AWS this ratio was slightly higher: 30.6% for the /bə/-/pə/ and 35.2% for the /də/-/tə/continuum (see Figure 1). This supports an optimal fit of the later described psychometric model to the data.

The experiment was run on presentation software version 0.71 (Neurobehavioral Systems, http://www.neurobs.com/).

---

Please insert Figure 1 about here.

---

*Data Analysis*

To estimate the phoneme boundary and the ambivalence interval, we fitted a logistic psychometric function $\Psi(\mathrm{VOT})$ for the voiceless percept to the data, including the trials of the staircase search and the following catch trials, (see Appendix – B) using a maximum likelihood algorithm (psygnifit, http://www.bootstrap-software.org/psignifit/; Wichmann and

Hill, 2001b, a). After modeling the data, phoneme boundary was estimated by the null of the second derivative $\frac{d^2\Psi}{dVOT^2}$ of the psychometric function. The ambivalence interval was estimated by computing the absolute difference between the two nulls of the third derivative $\frac{d^3\Psi}{dVOT^3}$ of the psychometric function (see Figure 2).

---

Please insert Figure 2 about here.

---

*Statistics*

To test the differences between groups, we entered the values of the ambivalence interval in a three-factorial mixed design omnibus ANOVA for repeated measures with the between-subjects factor Group (AWS; control subjects) and the within-subjects factors CV-continuum (/bə/-/pə/, /də/-/tə/) and Repetition (1 to 5). A similar analysis was computed for the estimates of the phoneme boundary. Main effects and interactions were tested via post hoc *t* tests.

To test potential correlations between stuttering severity and ambivalence interval as well as phoneme boundary, we calculated Spearman's correlation coefficient between the stutterer's SSI-3 overall-scores and the ambivalence interval or phoneme boundary values respectively.

Statistics were performed with the Software Package for the Social Sciences (SPSS 17.0, http://www.spss.com/de/software).

## Results

*ANOVA regarding the ambivalence interval* affirmed the following significant main effects and interactions: (i) a main effect for the Group, $F(1,38) = 4.46$, $p = .041$, with a significant greater ambivalence interval for AWS, $t(39) = -2.12$, $p = .026$; (ii) a main effect for CVS-continuum, $F(1,38) = 7.45$, $p = .01$, with a greater ambivalence interval for the /də/-/tə/ continuum, $t(39) = -2.91$, $p = .006$; (iii) a main effect of Repetition, $F(4,35) = 5.43$, $p = .002$, with a greater ambivalence interval for the first repetition (r1) compared with the second, third and fourth repetition, $t(39)$ (r1>r2) = 2.99, $p = .048$; $t(39)$ (r1>r3) = 3.41, $p = .015$ and $t(39)$ (r1>r4) = 3.48, $p = .013$ (all *p*-values were Bonferroni corrected for multiple comparisons); (iv) an interaction between repetition and group, $F(4,35) = 3.59$, $p = .015$. Looking for the effect of repetition for either group as indicated by a main interaction of these two factors, in control subjects a significant decrease of the ambivalence interval already was found for

repetition 2, $t(19) = 3.713$, $p = .001$ (Bonferroni corrected for multiple comparisons) while in AWS this decrease is only significant for repetition 3, $t(19) = 2.84$, $p = .01$ (uncorrected). Moreover, a significant increase of the ambivalence interval which is evident between the third and fifth repetition, $t(19) = -2.57$, $p = .019$ (uncorrected), occurred in AWS (Figure 3 C, D).

*The ANOVA regarding the phoneme boundary* revealed no significant main effect for Group, $F(1,38) = 2.4$, $p = .127$. As well known from the literature (e.g. (Phillips et al., 2000) phoneme boundary of the /bə/-/pə/continuum differed significantly from that of /də/-/tə/continuum, $F(1,38) = 274.95$, $p < .001$.

*Correlation analyses* yielded no correlation between stuttering severity and ambivalence interval, $-.36 < r_s < .25$; $p > .12$ or phoneme boundary, $-.24 < r_s < .22$; $p > .30$, respectively.

---

Please insert Figure 3 about here.

---

## Discussion

The aim of the present study was to substantiate a putative dysfunction of phoneme categorization in stuttering. While previous studies indicated neuroanatomical and neurofunctional alterations in brain regions relevant for speech perception, behavioural evidence for associated speech perception impairment is so far missing. Our results indicate a diminished phoneme discriminatory power in AWS. We conclude that an instable speech perception adds to the prominent motor disturbances in AWS. The broader ambivalence intervals and less reliable phoneme categorization suggest less stable phoneme percepts in AWS.

*The repetition effect*

Noteworthy is the delayed repetition effect in AWS relative to fluent speakers. This observation is in line with previous reports from speech production experiments where a delayed improvement of performance occurs in AWS (Smits-Bandstra and De Nil, 2009). That an improvement is not maintained in AWS has also been described (Smits-Bandstra et al., 2006). We assume that this variability in performance reflects the speech system's instability in AWS which is also prone to other than speech related disturbances like fluctuations in attention or vigilance (Bosshardt, 2006), and therefore unable to maintain the

acquired improvement of performance. On a broader level, this is reminiscent of a tendency of relapse in AWS after successful fluency-shaping therapy (Euler, von Gudenberg, Jung & Neumann, 2009).

*Processes involved in phoneme categorization*

State-of-the-art accounts of sublexical speech perception refer to four different processes: acoustic processing, phonetic processing, phonological processing and categorical phoneme perception (Turkeltaub and Coslett, 2010). (i) Acoustic processing concerns the spectrotemporal analysis of speech and non-speech auditory signals independent of language experience; (ii) phonetic processing is shaped by language experience and is speech-specific; (iii) phonological processing selects from discrete abstract symbolic mental representations of speech sounds of the language-specific phonemic system; and (iv) categorical phoneme perception concerns assigning phoneme labels to speech sounds.

While each of these processes could contribute to our findings, literature on the initial three in AWS is remarkably scarce. The current study therefore aimed at the fourth process: discrimination of speech sounds within phoneme boundaries; a meta-linguistic process which does not lead to lexical access or further semantic processing. Rather it includes acoustic and phonetic processing which operate on continuous, analog auditory signals, possibly mediated through a comparison between phonological features and an articulatory plan (Rauschecker and Scott, 2009; Turkeltaub and Coslett, 2010).

(i) Acoustic processing

Spectrotemporal analysis of non-speech or speech auditory signals is assumed to be computed in bilateral dorsal superior temporal lobe areas including Herschel's gyrus and planum temporale (e.g. (Overath et al., 2008), and speech auditory signals additionally in the bilateral dorsal superior temporal gyrus (e.g. (Hickok and Poeppel, 2007). In AWS, EEG and MEG studies indicated differences in the timing and amplitude of neurophysiologic responses of the auditory cortex to auditory presented speech stimuli (Beal et al., 2010; Hampton and Weber-Fox, 2008) and may be based on structural alterations in Herschel's gyrus and the planum temporale (Beal et al., 2007; Foundas et al., 2001; Foundas et al., 2004).

(ii) Phonetic processing

Phoneme perception involves the superior temporal gyrus, specifically the planum temporale (Jäncke et al., 2002; Zatorre et al., 1996). Confirming our hypothesis, our sample of AWS

exhibited broader ambivalence intervals. This finding indicates an overlapping of the acceptable ranges of the encoded acoustic reference frame of a certain phonemic feature such as VOT in AWS relative to control subjects. Maybe this blurring is related to a different and asynchronous neural timing in auditory cortices in AWS. A recent magnetencephalography study documented the M 100 latencies (a response to the onset properties of an auditory stimulus) to the auditory presented vowel /i/ to be delayed in AWS's right hemisphere. This delay was related to the M 100 in AWS's left hemisphere as well as to the bilateral M 100 in fluent speakers (Beal et al., 2010). It is therefore conceivable that deviant phonetic processing contributed to the behavioral findings in the current study.

A broadened ambivalence interval is a behavioral deviant on a subclinical level in AWS. As expected, all AWS were able to solve the task properly by identifying phonemes at VOTs, which were distant from phoneme boundaries. We did not expect any group difference concerning the phoneme boundaries itself, because this feature depends primarily on idiom and mother tongue (Braun, 1996; Lisker and Abramson, 1964), and we did not control for idiom in the present study. Unexpectedly, our data show a trend towards increased phoneme boundaries in AWS, indicating that AWS demand longer VOT to perceive a stop consonant as voiceless. This observation supports previous reports: EEG-mismatch negativities to auditory presented phonetic contrasts embedded in meaningless syllables was significantly enhanced in left supratemporal regions in AWS indicating a deviant phoneme perception (Corbera et al., 2005). Thus, AWS exhibit abnormal behavioral and cortical processing in phoneme perception tasks.

(iii) Phonological processing

The current study asked participants to decide whether a presented stop consonant embedded in a consonant-vowel syllable was voiced or voiceless. This decision required access to the discrete phonological feature: voicing.

Several theories on stuttering postulate an imprecise phonological encoding in speech *production* (Sasisekaran et al., 2006). These theories comprise the Covert Repair Hypothesis (Postma and Kolk, 1993), the EXPLAN theory (Howell, 2007), the neurolinguistic model (Perkins et al., 1991) and the Fault line Hypothesis (Wingate, 1988). However, little is known regarding phonological processing during sublexical speech *perception* in AWS. Evidence for deviant phonological processing has been suggested by a recent functional magnetic resonance imaging (fMRI) study; auditory presented meaningless speech syllables resulted in a decreased activity in the left superior temporal gyrus in AWS (Chang et al., 2009).

With regard to our results, we cannot exclude alterations of sublexical speech perception abilities in AWS. It might be possible that these alterations are caused by an instable speech production, or vice versa. Thus, studying the interaction of speech perception and speech production is likely to expand our understanding about stuttering. The interface for the mapping between perceived and produced speech is probably located in the left supramarginal and angular gyrus (Rauschecker and Scott, 2009; Turkeltaub and Coslett, 2010). It is assumed, that categorical perception involves these areas.

(iv) Phoneme categorization

Deciding whether the presented phoneme is either voiced or voiceless most likely requires the activation of the articulatory model of the specific phoneme (Meister et al., 2007; Turkeltaub and Coslett, 2010), the so called speech sound map in the ventral premotor cortex and posterior inferior frontal gyrus (Golfinopoulos et al., 2010). In our experiment, due to the presentation of a third of the stimuli within the ambivalence interval, the task demand was quite high. With increasing ambiguity of the presented syllables, task demand increases as indicated in a previous study by the significant increase of response times around the phoneme boundary (Wüstenberg and Mattler, 2008). Repetitive matching requires a high level of functional connectivity within the described network. An intense neural communication requires an intact anatomical architecture and an undisturbed neural synchronization. If connections were malfunctioning, discriminatory power is likely to be impaired and ambivalence interval is broadened.

Supporting a disturbance of this internal matching process, left perisylvian fibers exhibit reduced integrity in AWS (Cykowski et al., in press; Sommer et al., 2002; Watkins et al., 2008). The dual-stream model of functional anatomy of language postulates the dorsal stream to be mainly involved in this mapping (Hickok and Poeppel, 2007). Fibers linking the superior temporal lobe and the premotor cortices via the dorsal stream are the arcuate and superior longitudinal fascicle (Saur et al., 2008). A recent analysis of resting-state-functional-connectivity confirms this cortico-cortical connectivity between Brodmann area (BA) 6 and rostral supramarginal gyrus, and between BAs 44 and 45 and caudal supramarginal gyrus and angular gyrus (Kelly et al.). Thus, less coherent connections in AWS might slow down the transfer of information or diminish the quality of the transported signals, which challenges discriminatory power under difficult conditions such as near the phoneme boundary.

*Direction into Velocities of Articulators model as a possible explanatory framework*

Expanding a possible sensory-motor inter-areal disconnection contributing to our finding, the effect of perceptual instability could be related to difficulties matching an encoded phoneme with an internal model representing the relationship between articulation and its sensory consequence.

The Directions into Velocities of Articulators (DIVA) model (Golfinopoulos et al., 2010; Guenther, 1995) of speech production and its neural implementation proposes a motor feedforward and a sensory feedback control system. So far, only the feedforward control system was proposed to be disturbed in AWS (Max et al., 2004). Our findings suggest a more extended dysfunction within the proposed model, including parts of the feedback control system.

---

Please insert Figure 4 about here.

---

Conceptually, the feedback control subsystem (Figure 4) enables the detection and correction of current speech motor programs, especially for novel or difficult speech tasks. Proposed feedforward projections from the 'Speech Sound Map' activate expected auditory targets in the 'Auditory Target Map'. Encoded are acceptable ranges in acoustic reference frames (Guenther 1995). The auditory response to self-generated speech is represented in the 'Auditory State Map'. If the incoming auditory response falls outside the acceptable range of the expected auditory target, the 'Auditory Error Map' will generate an error signal. Ultimately, the 'Feedback Control Map' generates corrective motor commands in the 'Articulator Velocity and Position Maps'.

The current finding of broadened ambivalence intervals within phoneme boundaries might indicate a dysfunctional auditory feedback subsystem in AWS. Overlapping acceptable ranges in acoustic reference frames for representations in the 'Auditory State Map' as well as in the 'Auditory Target Map' might prevent the creation of an error signal in the 'Auditory Error Map' if the produced speech sound falls in this overlapping area. As a consequence no corrective motor commands would be activated in the 'Feedback Control Map' which results in the production of speech sounds that fall into larger acceptable ranges. Indeed, an increased within-subject variability of produced phonemic features has already been described in AWS (e.g.(Jancke, 1994; Max and Gracco, 2005; Smith et al., 2010).A dysfunctional connection between 'Speech Sound Map' and trans-cerebellar pathway, which is assumed to provide

precise temporal information in the processing of time intervals during speech perceptual tasks (Ackermann, 2008), might also contribute to the broadened ambivalence intervals. In AWS a dysfunctional right cerebellar/ left frontal loop was recently described (Lu et al., 2010).

## Conclusion

In conclusion, our results demonstrate behavioral evidence for an altered speech perception in AWS, underpinning neuroimaging studies that demonstrate irregularities in neuroanatomic correlates of speech perception. In addition, our data help expand a theoretical framework on stuttering assuming less stable speech sound representations or an insufficient access to them, thereby highlighting the role of auditory perception in persistent developmental stuttering. Future studies should evaluate the link between sublexical speech perception and production to further elucidate the nature of stuttering. Such studies would provide data to complete theoretical models of stuttering as well as of speech processing and its neural implementation in general.

ACKNOWLEDGEMENT

This work was supported by the Stifterverband für die Deutsche Wissenschaft, Walter und Ilse Rose Stiftung and the Deutsche Forschungsgemeinschaft [SO 429/2-2]. We thank Veronika Gutman for her help in subject recruitment and testing.

## References

Ackermann H. Cerebellar contributions to speech production and speech perception: psycholinguistic and neurobiological perspectives. *Trends in Neurosciences,* 31 (6): 265-72, 2008.

Anderson JD, Wagovich SA, and Hall NE. Nonword repetition skills in young children who do and do not stutter. *J Fluency Disord,* 31 (3): 177-99, 2006.

Beal DS, Cheyne DO, Gracco VL, Quraan MA, Taylor MJ, and De Nil L. Auditory evoked fields to vocalization during passive listening and active generation in adults who stutter. *Neuroimage,* 52 (4): 1645-53, 2010.

Beal DS, Gracco VL, Lafaille SJ, and De Nil LF. Voxel-based morphometry of auditory and speech-related cortex in stutterers. *Neuroreport,* 18 (12): 1257-60, 2007.

Blood IM. Disruptions in auditory and temporal processing in adults who stutter. *Perceptual and Motor Skills,* 82 (1): 272-4, 1996.

Bosshardt HG. Cognitive processing load as a determinant of stuttering: summary of a research programme. *Clin Linguist Phon,* 20 (5): 371-85, 2006.

Braun A. Zur regionalen Distribution von VOT im Deutschen. In Braun A (Ed.) *Untersuchungen zu Stimme und Sprache. Papers on Speech and Voice*. Stuttgart: Franz Steiner, 1996, pp. 19-32.

Chang SE, Kenney MK, Loucks TMJ, and Ludlow CL. Brain activation abnormalities during speech and non-speech in stuttering speakers. *Neuroimage,* 46 (1): 201-212, 2009.

Corbera S, Corral MJ, Escera C, and Idiazabal MA. Abnormal speech sound representation in persistent developmental stuttering. *Neurology,* 65 (8): 1246-52, 2005.

Cykowski MD, Fox P, Ingham RJ, Ingham JC, and A. RD. A study of the reproducibility and etiology of diffusion anisotropy differences in developmental stuttering: A potential role for impaired myelination. *Neuroimage*, in press.

Foundas AL, Bollich AM, Corey DM, Hurley M, and Heilman KM. Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. *Neurology,* 57 (2): 207-15, 2001.

Foundas AL, Bollich AM, Feldman J, Corey DM, Hurley M, Lemen LC, and Heilman KM. Aberrant auditory processing and atypical planum temporale in developmental stuttering. *Neurology,* 63 (9): 1640-6, 2004.

Golfinopoulos E, Tourville JA, and Guenther F. The integration of large-scale neural network modeling and functional brain imaging in

speech motor contro. *Neuroimage*: doi:10.1016/j.neuroimage.2009.10.023, 2010.

Guenther FH. Speech sound acquisition, coarticulation, and rate effects in a neural network model of speech production. *Psychological Review,* 102 (3): 594-621, 1995.

Hampton A and Weber-Fox C. Non-linguistic auditory processing in stuttering: evidence from behavior and event-related brain potentials. *J Fluency Disord,* 33 (4): 253-73, 2008.

Heiser MA and Cheung SW. Cortical representations of communication sounds. *Curr Opin Otolaryngol Head Neck Surg,* 16 (5): 478-84, 2008.

Hickok G and Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci,* 8 (5): 393-402, 2007.

Howell P. The effects of gated speech on the fluency of speakers who stutter. *Folia Phoniatrica et Logopedica,* 59 (5): 250-5, 2007.

Jancke L. Variability and duration of voice onset time and phonation in stuttering and nonstuttering adults. *Journal of Fluency Disorders,* 19 (1): 21-37, 1994.

Jäncke L, Wüstenberg T, Scheich H, and Heinze H. Phonetic perception and the temporal cortex. *Neuroimage,* 15 (4): 733-46, 2002.

Keating PA. Phonetic and phonological representation of stop consonant voicing. *Language,* 60, (2): 286-319, 1984.

Kelly C, Uddin LQ, Shehzad Z, Margulies DS, Castellanos FX, Milham MP, and Petrides M. Broca's region: linking human brain functional connectivity data and non-human primate tracing anatomy studies. *European Journal of Neuroscience*.

Kent RD. Research on speech motor control and its disorders: a review and prospective. *Journal of Communication Disorders,* 33 (5): 391-427; quiz 428, 2000.

Kesten H. Accelerated stochastic approximation. *Annals of Mathematical Statistics,* 29: 41-59, 1958.

Kramer MB, Green D, and Guitar B. A comparison of stutterers and nonstutterers on masking level differences and synthetic sentence identification tasks. *Journal of Communication Disorders,* 20 (5): 379-90, 1987.

Lisker L and Abramson AS. A cross-language study of voicing in initial stops: acoustical measurements. *Word,* 20: 384-422, 1964.

Lu C, Chen C, Ning N, Ding G, Guo T, Peng D, Yang Y, Li K, and Lin C. The neural substrates for atypical planning and execution of word production in stuttering. *Experimental Neurology,* 221 (1): 146-56, 2010.

Ludlow CL and Loucks T. Stuttering: a dynamic motor control disorder. *Journal of Fluency Disorders,* 28 (4): 273-95, 2003.

Max L and Gracco VL. Coordination of oral and laryngeal movements in the perceptually fluent speech of adults who stutter. *Journal of Speech, Language, and Hearing Research,* 48 (3): 524-42, 2005.

Max L, Guenther FH, Gracco VL, Ghosh SS, and Wallace ME. Unstable or insufficiently activated internal models and feedback-biased motor control as sources of dysfluency: A theoretical model of stuttering. *Contemporary Issues in Communication Science and Disorders: CICSD,* 31: 105-122, 2004.

Meister IG, Wilson SM, Deblieck C, Wu AD, and Iacoboni M. The essential role of premotor cortex in speech perception. *Current Biology,* 17 (19): 1692-6, 2007.

Möttönen R and Watkins KE. Motor representations of articulators contribute to categorical perception of speech sounds. *Journal of Neuroscience,* 29 (31): 9819-25, 2009.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia,* 9 (1): 97-113, 1971.

Overath T, Kumar S, von Kriegstein K, and Griffiths TD. Encoding of spectral correlation over time in auditory cortex. *Journal of Neuroscience,* 28 (49): 13268-73, 2008.

Perkins WH, Kent RD, and Curlee RF. A theory of neuropsycholinguistic function in stuttering. *Journal of Speech and Hearing Research,* 34 (4): 734-52, 1991.

Phillips C, Pellathy T, Marantz A, Yellin E, Wexler K, Poeppel D, McGinnis M, and Roberts T. Auditory cortex accesses phonological categories: an MEG mismatch study. *Journal of Cognitive Neuroscience,* 12 (6): 1038-55, 2000.

Postma A and Kolk H. The covert repair hypothesis: prearticulatory repair processes in normal and stuttered disfluencies. *Journal of Speech and Hearing Research,* 36 (3): 472-87, 1993.

Rauschecker JP and Scott SK. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. *Nature Neuroscience,* 12 (6): 718-24, 2009.

Riley GD. *The Stuttering Severity Instrument for Children and Adults- Third Edition (SSI-3)*. Austin, TX: Pro-Ed., 1994.

Sandrieser P and Schneider P. *Stottern im Kindesalter*. Stuttgart: Thieme, 2008.

Sasisekaran J, De Nil LF, Smyth R, and Johnson C. Phonological encoding in the silent speech of persons who stutter. *J Fluency Disord,* 31 (1): 1-21; quiz 19, 2006.

Saur D, Kreher BW, Schnell S, Kummerer D, Kellmeyer P, Vry MS, Umarova R, Musso M, Glauche V, Abel S, Huber W, Rijntjes M, Hennig J, and Weiller C. Ventral and dorsal

pathways for language. *Proceedings of the National Academy of Sciences of the United States of America,* 105 (46): 18035-40, 2008.

Smith A and Kelly E. Stuttering: A dynamic multifactorial model. In Curlee RF and Seigel GM (Eds.), *Nature and treatment of stuttering: New directions*. New York: Allyn & Bacon, 1997, pp. 204-217.

Smith A, Sadagopan N, Walsh B, and Weber-Fox C. Increasing phonological complexity reveals heightened instability in inter-articulatory coordination in adults who stutter. *J Fluency Disord,* 35 (1): 1-18, 2010.

Smits-Bandstra S and De Nil L. Speech skill learning of persons who stutter and fluent speakers under single and dual task conditions. *Clinical Linguistics & Phonetics,* 23 (1): 38-57, 2009.

Smits-Bandstra S, De Nil LF, and Saint-Cyr JA. Speech and nonspeech sequence skill learning in adults who stutter. *Journal of Fluency Disorders,* 31 (2): 116-36, 2006.

Sommer M, Koch MA, Paulus W, Weiller C, and Büchel C. Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet,* 360 (9330): 380-3, 2002.

Treutwein B. Adaptive Psychophysical Procedures. *Vision Research,* 35 (17): 2503-2522, 1995.

Turkeltaub PE and Coslett HB. *Localization of sublexical speech perception components*. *Secondary Titl*. 114: 1-15, 2010.

Watkins KE, Smith SM, Davis S, and Howell P. Structural and functional abnormalities of the motor system in developmental stuttering. *Brain,* 131 (Pt 1): 50-9, 2008.

Wichmann FA and Hill NJ. The psychometric function: I. Fitting, sampling, and goodness of fit. *Perception and Psychophysics,* 63 (8): 1293-313, 2001a.

Wichmann FA and Hill NJ. The psychometric function: II. Bootstrap-based confidence intervals and sampling. *Perception and Psychophysics,* 63 (8): 1314-29, 2001b.

Wingate ME. *The structure of stuttering*. New York: Springer, 1988.

Wüstenberg T and Mattler U. Functional lateralization of feature specific processing in a phonetic classification task. *International Journal of Psychophysiology,* 69 (3): 215, 2008.

Zatorre RJ, Meyer E, Gjedde A, and Evans AC. PET studies of phonetic processing of speech: review, replication, and reanalysis. *Cerebral Cortex,* 6 (1): 21-30, 1996.

# Appendix

A

*Adaptive Procedure*: The adaptive computation of stimulus voice onset times (VOT) is based on an accelerated stochastic approximation as described by Kesten (Kesten, 1958; Treutwein, 1995).

$$\mathrm{VOT}_{n+1} = \mathrm{VOT}_n - \frac{\Delta\mathrm{VOT}_0}{2 + m_{shift}}(C_n - \phi)$$

Whereas

$\Delta\mathrm{VOT}_n$ and $\Delta\mathrm{VOT}_{n+1}$ are the voice onset times of the $n^{th}$ or $n+1^{st}$ trial respectively,

$\Delta\mathrm{VOT}_0$ is the initial step width of 40 ms;

$\phi$ is the phoneme boundary probability of 0.5;

$m_{shift}$ is the number of shifts in response category (reversals) and

$C_n$ is the response category of the $n^{th}$ trial, $C_n = \begin{vmatrix} 0, \text{voiced} \\ 1, \text{voicless} \end{vmatrix}$.

B

*Psychophysical Model:* To estimate phoneme boundary and ambivalence interval, we fitted a logistic psychometric function $\Psi(\mathrm{VOT})$ for the voiceless percept to the data using a maximum likelihood algorithm [psygnifit, http://www.bootstrap-software.org/psignifit/, (Wichmann and Hill, 2001b, a)]:

$$\Psi(\mathrm{VOT}, \alpha, \beta, \gamma, \lambda) = \frac{\gamma + (1 - \gamma - \lambda)}{1 + e^{-\left(\frac{\mathrm{VOT} - \alpha}{\beta}\right)}},$$

where

$\alpha$ denotes the inflection point of the function,

$\beta$ defines the steepness of $\Psi(\mathrm{VOT})$,

$\gamma$ the guessing rate and

$\lambda$ the lapsing rate, which describes the amount of responses caused by lapses.

The guessing rate is fixed by the experimental design and can be computed to 1/number of choices. All other parameters are estimated while the model is fitted into the data using a maximum likelihood algorithm. The phoneme boundary was estimated by the null of the second derivative $\frac{d^2\Psi}{d\mathrm{VOT}^2}$ of the psychometric function. The ambivalence interval was

estimated by computing the absolute difference between the two nulls of the third derivative $\frac{d^3\Psi}{dVOT^3}$ of the psychometric function (see Figure 2).

*Table 2 Description of participants*

| Subject | Age | Sex | Edu-cation | Handedness | Family History | Suttered Sylla-bles | SSI-3 score | Age of Onset |
|---|---|---|---|---|---|---|---|---|
| AWS 1 | 24 | m | 1 | -57.9 | no | 18.6 | 36 | 8.0 |
| AWS 2 | 24 | f | 2 | 100.0 | yes | 27.9 | 48 | 4.0 |
| AWS 3 | 25 | m | 5 | 100.0 | yes | 1.5 | 7 | 12.0 |
| AWS 4 | 33 | m | 5 | 88.9 | yes | 20.8 | 42 | 4.0 |
| AWS 5 | 28 | f | 6 | 100.0 | yes | 18.3 | 47 | 3.0 |
| AWS 6 | 14 | m | 1 | 90.0 | no | 6.5 | 32 | 6.0 |
| AWS 7 | 43 | m | 5 | 87.5 | no | 25.2 | 33 | 5.0 |
| AWS 8 | 24 | m | 2 | -40.0 | yes | 1.8 | 12 | 2.5 |
| AWS 9 | 18 | m | 1 | 100.0 | yes | 29.0 | 41 | 7.5 |
| AWS 10 | 33 | m | 1 | - 90.0 | no | 15.1 | 31 | 10.0 |
| AWS 11 | 26 | m | 4 | 100.0 | yes | 3.0 | 17 | 2.5 |
| AWS 12 | 47 | m | 6 | 79.0 | yes | 10.7 | 26 | 3.0 |
| AWS 13 | 40 | m | 6 | 100.0 | yes | 3.1 | 17 | 3.0 |
| AWS 14 | 49 | m | 5 | 100.0 | yes | 1.8 | 14 | 3.5 |
| AWS 15 | 36 | f | 6 | 100.0 | yes | 5.6 | 25 | 3.5 |
| AWS 16 | 54 | m | 1 | 100.0 | no | 2.8 | 17 | 5.0 |
| AWS 17 | 57 | f | 5 | 100.0 | yes | 2.5 | 18 | 2.0 |
| AWS 18 | 32 | f | 1 | 100.0 | yes | 22.4 | 36 | 5.0 |
| AWS 19 | 22 | m | 1 | 80.0 | yes | 11.0 | 37 | 5.0 |
| AWS 20 | 15 | m | 1 | 11.1 | yes | 9.1 | 22 | 4.5 |
| median | 30 | | 3 | 77.5 | | 9.9 | 28.5 | 4.25 |
| mean | 32.2 | | 3.25 | 79.0 | | 11.8 | 27.9 | 4.95 |
| sd | 12.62 | | 2.17 | 19.8 | | 9.5 | 12.1 | 2.62 |
| C 1 | 33 | f | 5 | 100.0 | no | 0.1 | | |
| C 2 | 33 | f | 6 | 100.0 | no | 0.2 | | |
| C 3 | 35 | m | 6 | 100.0 | no | 0.4 | | |
| C 4 | 21 | m | 3 | 100.0 | no | 0.3 | | |
| C 5 | 36 | m | 4 | 100.0 | no | 0.9 | | |
| C 6 | 28 | m | 4 | 79.0 | no | 0.3 | | |
| C 7 | 22 | m | 3 | 100.0 | no | 0.5 | | |
| C 8 | 23 | m | 4 | 100.0 | no | 0.3 | | |
| C 9 | 26 | m | 3 | 80.0 | no | 0.6 | | |
| C 10 | 27 | m | 3 | 100.0 | no | 0.1 | | |
| C 11 | 28 | m | 4 | 100.0 | no | 0.6 | | |
| C 12 | 28 | m | 4 | 100.0 | no | 0.1 | | |
| C 13 | 25 | f | 4 | 88.9 | no | 0.1 | | |
| C 14 | 26 | m | 4 | 87.5 | no | 0.0 | | |
| C 15 | 40 | m | 3 | 87.5 | no | 0.3 | | |
| C 16 | 15 | m | 1 | 100.0 | no | 0.15 | | |
| C 17 | 32 | m | 5 | 62.5 | no | 0.2 | | |
| C 18 | 45 | m | 2 | -17.65 | no | 0.0 | | |
| C 19 | 54 | m | 1 | 100.0 | no | 0.1 | | |
| C 20 | 60 | f | 5 | 100.0 | no | 0.0 | | |
| median | 28 | | 4 | 70 | | 0.2 | | |
| mean | 31.9 | | 3.7 | 76.0 | | 0.26 | | |
| sd | 11.0 | | 1.4 | 18.1 | | 0.24 | | |
| *p* value | $p = .16$ | | $p = .64$ | $p = .43$ | | $p < .001$ | | |

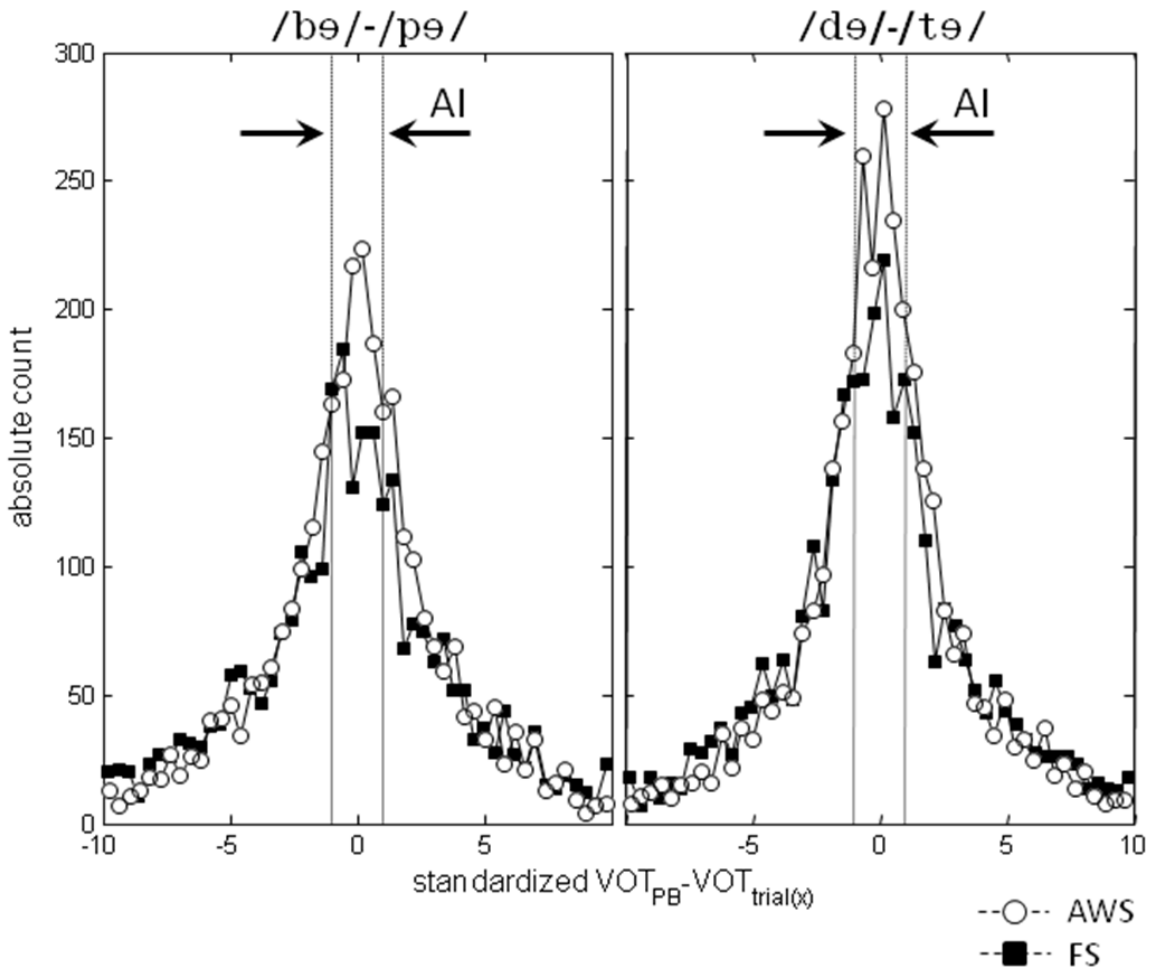


Figure 1. Standardized Distribution of Stimuli for /bə/-/pə/ and /də/-/tə/continuum**.** Standardization was computed as follows: $\Delta VOT_{standardized} = \frac{2(PB - VOT_{trial(x)})}{AI}$. After standardization lower and upper borders of ambivalence interval are equal 1 or -1 respectively. *Abbreviations:* VOT – voice onset time; AI – ambivalence interval; PB – phoneme boundary; SE – standard error; AWS – adults who stutter; C – fluent speakers. (courtesy of Torsten Wüstenberg)

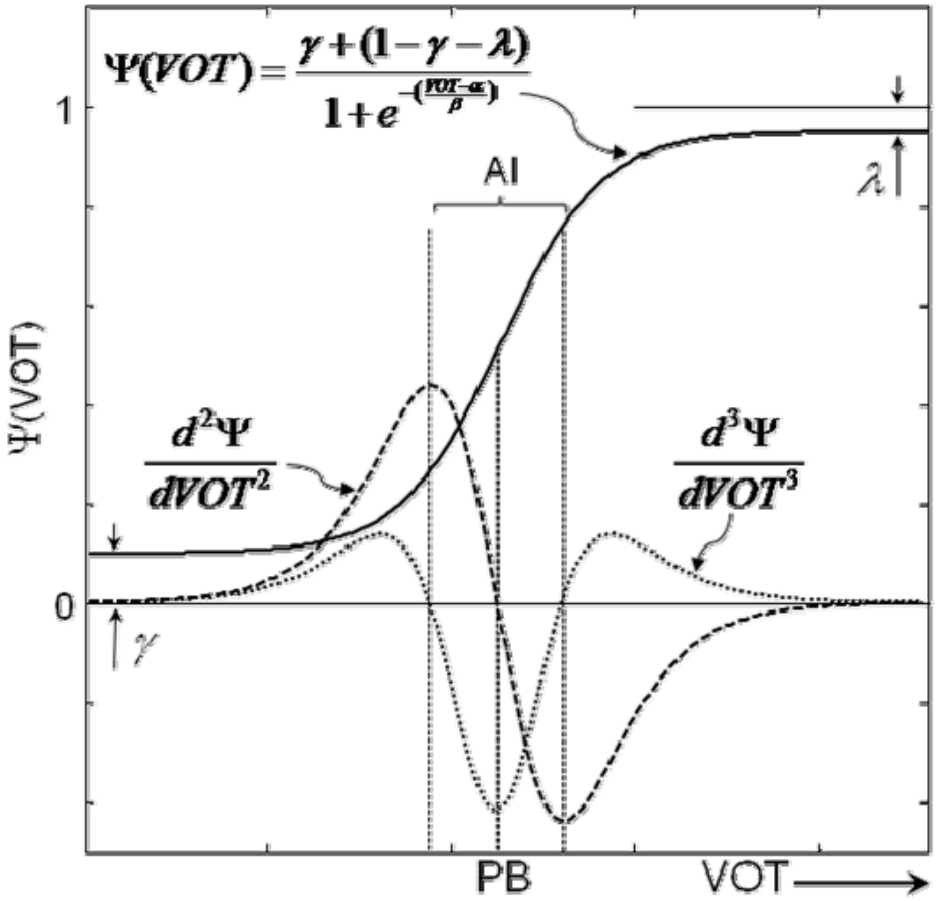


Figure 2. Psychometric model and schematic depiction of the mathematical basics for the estimation of phoneme boundary and ambivalence interval. *Abbreviations:* VOT – voice onset time; AI – ambivalence interval; PB – phoneme boundary. (courtesy of Torsten Wüstenberg)

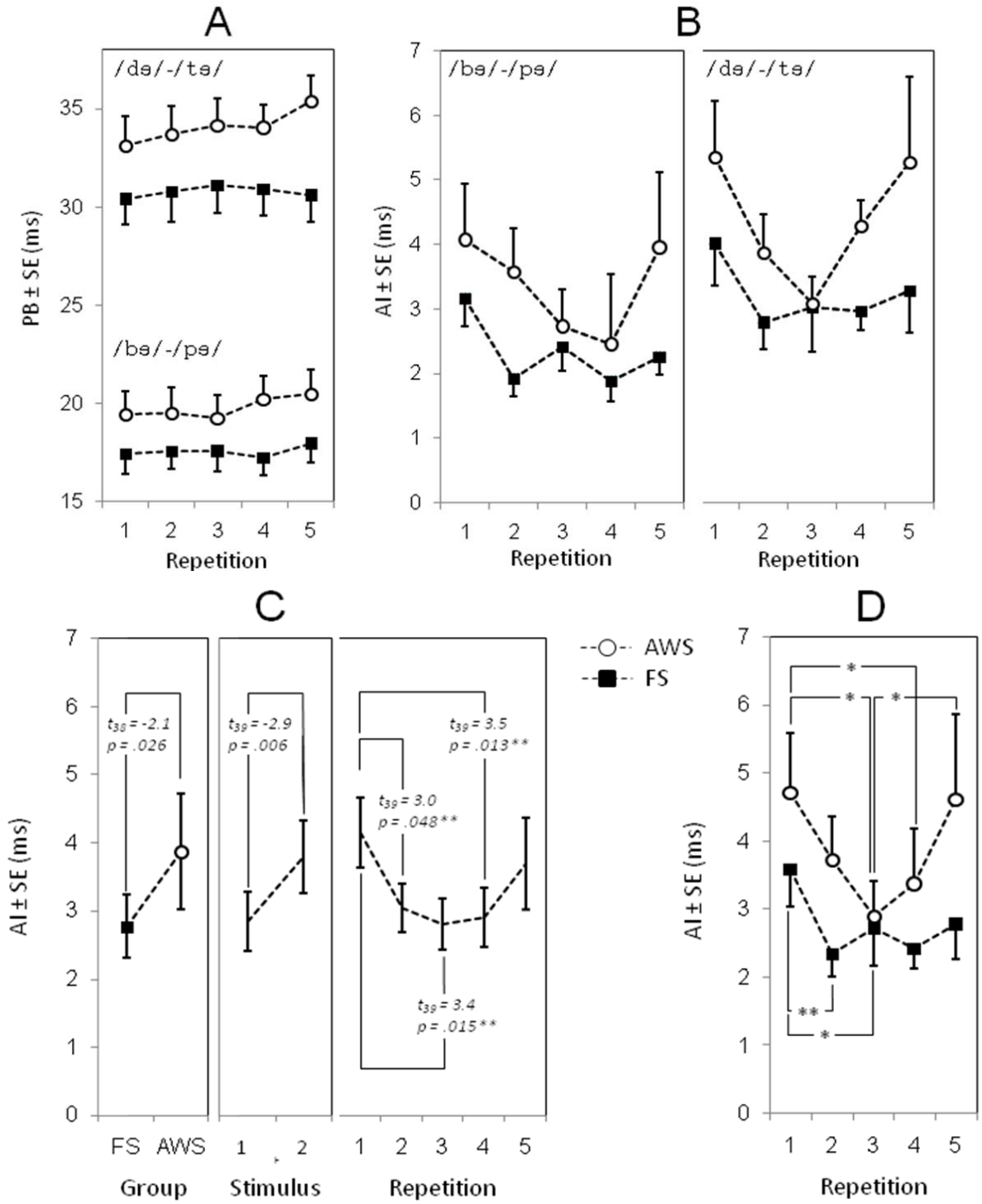


Figure 3. Descriptive Statistics. (A) ambivalence intervals and (B) phoneme boundaries for the /bə/-/pə/ and /də/-/tə/continuum. *Inference statistics - results of ANOVA for ambivalence interval.* (C) Main effects for Group, CV continuum (1 /bə/-/pə/, 2 /də/-/tə/) and Repetition as well as (D) the interaction Group*Repetition (* uncorr, ** Bonferroni corr). Results of post-hoc t-tests are marked within the corresponding graphs. *Abbreviations:* AI – ambivalence interval; PB – phoneme boundary; CV – consonant-vowel-continuum; SE – standard error; AWS – adults who stutter; C – fluent speakers.

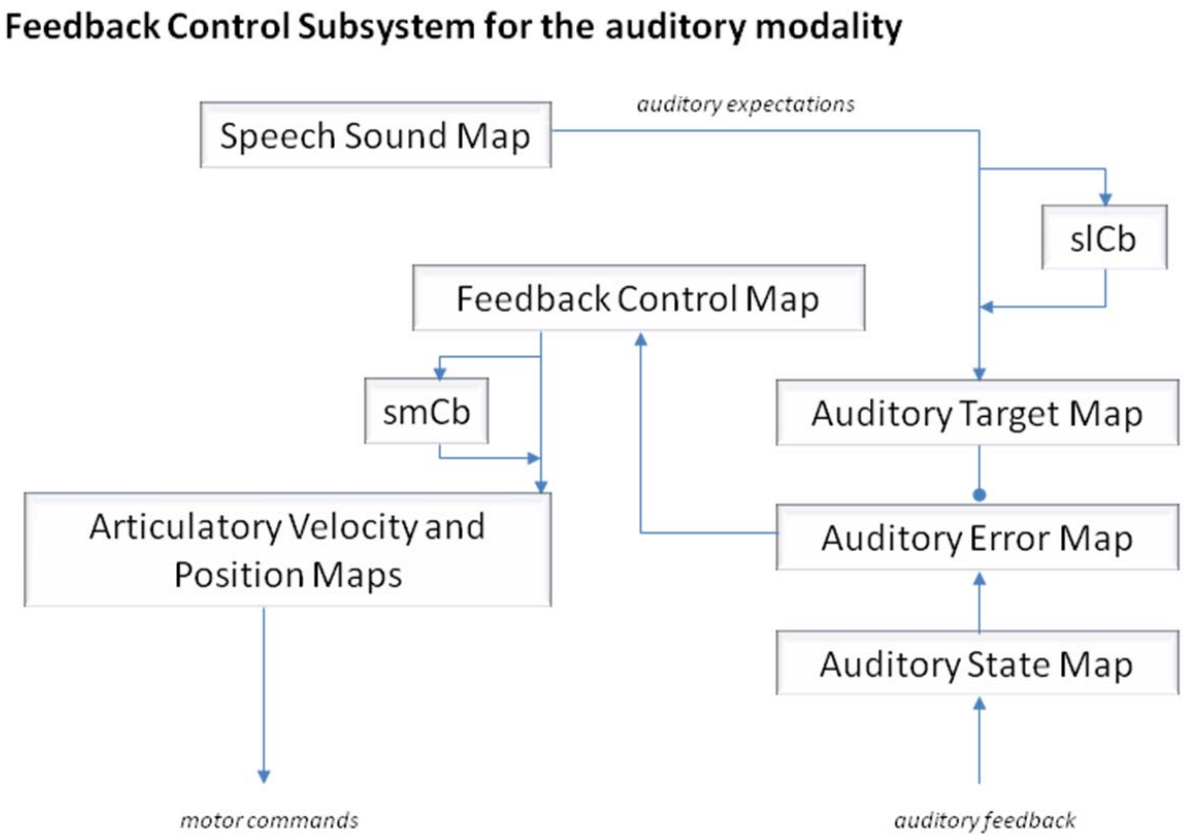


Figure 4. Subcomponents of the auditory feedback control subsystem of the DIVA model. Proposed neuroanatomical locations are: the left posterior inferior frontal gyrus und ventral premotor cortex for the 'Speech Sound Map'; the Heschl's gyrus and the planum temporale for the 'Auditory State Map'; the planum temporal and the superior temporal gyrus for the 'Auditory Error Map' as well as the 'Auditory Target Map'; the right ventral premotor cortex for the 'Feedback Control Map'; and the ventral motor cortex for the motor cortex. Additional loops integrate the superior lateral cerebellum and the ventral anterior nucleus of the cerebellum (slCB), and the superior medial cerebellum and the ventral lateral nucleus of the thalamus (smCb) (Golfinopoulos et al. 2010).

# 3 Summary

The three presented studies yielded the following results:

(1) *Non-speech motor processing in stuttering:* In control subjects rTMS to the left PMd did interfere with paced finger movements while rTMS to the right PMd yielded no altered tapping performance. This pattern was reversed in persons with persistent stuttering who showed an altered performance after right hemispheric rTMS and no effect of the left-hemispheric rTMS. Stutterers thus appeared to recruit the right-hemispheric PMd even for non-speech motor performance, possibly compensating for a left-hemispheric deficit.

(2) *Excitability of the primary motor tongue representation in stuttering:* Patients with persistent stuttering exhibited a normal short intracortical inhibition in the primary motor tongue representation of the left hemisphere. In contrast, right-hemispheric short intracortical inhibition was delayed. Additionally, intracortical facilitation was reduced but MEP input-output curve showed a steeper slope in patients with persistent stuttering compared to control subjects.

(3) *Instable phoneme categorization in stuttering:* The discriminatory power to the voiced/voiceless contrast of stop-consonants is weaker in persons who stutter. The range of voice onset times, in which phonemes are perceived ambiguous was larger in stuttering. In addition the discriminatory performance was less stable over consecutive runs.

The relation of the individual results to the stuttering literature has been discussed in the drafts. The following section focuses on a synopsis and the implications for future research.

# 4 Conclusions and Future Prospects

## 4.1 The TMS approach

The causes and underlying pathomechanisms of persistent stuttering have been obscure for a long time. Neuroimaging studies, EEG and MEG studies and behavioral studies suggest a maladaptive cortical and subcortical morphology and compromised related neural computations of sensory-motor information including speech as well as non-speech domains. Additional TMS studies are desirable because this method allows a direct interference with brain functions enabling us to test hypothesis derived from neuroimaging studies. Although there is a need to elucidate functional relations and cortical neuropathology with TMS this kind of research is still in its infancy.

*Both stu*dies with TMS included in this dissertation were designed to elucidate potential differences between the cerebral hemispheres in persistent stuttering and the findings of both studies direct attention to the right hemisphere: The rTMS study suggests that the right PMd plays a functional role in the control of non-speech movement timing in persons with persistent stuttering, whereas the paired-pulse study indicates altered intracortical inhibitory neuronal circuits in the right primary motor tongue representation in persons with persistent stuttering. Thus, the TMS studies substantiate cortical deviations prominent in the right frontal motor and premotor regions in stuttering.

The laterality-shift for the control of movement timing towards the right hemisphere suggests a compensatory role of the right PMd in stuttering. A very recent study reports that in a subgroup of young children who stutter a task as simple as hand clapping is demanding and characterized by remarkably higher variability levels of inter-clap interval compared to age-matched controls (Olander et al., 2010). The poor performance indicates a neuromotor deficit exceeding the speech domain. In adulthood this neuromotor deficit is evident only in complex tasks including finger tap sequencing and speaking (Smits-Bandstra and De Nil, 2007). It is tempting to speculate that a functional organization in the presence of an underlying neuromotor deficit is achieved by recruiting right hemispheric regions.

The delay in intracortical inhibition in the right primary motor presentation of the tongue is a different aspect, possibly reflecting causal *neurophysiological aberrations*, without an indication for a compensatory role.

Additionally aberrant was the modulation of intracortical facilitation which affected the primary motor cortices of both hemispheres. This diminished modulation might directly

contribute to the intermittent involuntary loss of speech-control, interrupting fluent speech in stuttering. Interneuronal modulation of primary motor cortex' excitability is an important neurobiological principle enabling this neural structure to encode signals contributing to the selection, initiation and inhibition of complex spatial-temporal speech movements (Stinear et al., 2009). The study included here, is the first step towards a systematic neurophysiological evaluation of the primary motor tongue representation in stuttering. As it receives input from frontal cortical regions and the basal ganglia and drives the corticobulbar projection, changes in its excitability are likely to reflect an altered modulation of corticobulbar neurons by basal and frontal regions. Neuroimaging studies suggest that this modulation is state dependent (Chang et al. 2009). So far, we examined the intracortical excitability and its modulation at rest and under voluntary contraction. Having established MEP recordings from the tongue, we can now advance towards function-related questions.

### *Current studies*

In direct extension of the tongue-MEP-project a current study of our laboratory integrates speech production. Here we study the modulation of the excitability of the primary motor tongue representation during the preparation of a subsequent articulatory gesture (Hoang et al., in preparation). Preliminary results show that excitability is indeed state dependent, increasing before initiation of the new gesture. While at *rest* the left *and* right primary motor representation show a reduced intracortical facilitation, during a speech related mode only the left primary motor cortex exhibits a reduced facilitation in persons who stutter; the right primary motor cortex shows the tendency to more facilitation. This state-dependent dissociation between the two hemispheres evokes the question for underlying mechanisms. Is the interplay between the speech motor cortices via the corpus callosum impaired? Or are those intercortical connections altered, which are involved in the regulation of excitation to initiate efferent volleys of motor commands and to prevent unwanted movements? It seems that the cerebral dominance hypothesis, although well advanced in years, comes to the fore again.

## 4.2 The speech perception approach

### *Mapping of sounds to articulation*

In adults who stutter the phoneme categorization study suggested a diminished sensitivity to identify voiced and voiceless plosives near the phoneme boundary. One possible interpretation attributes this vulnerability to the decreased integrity of fiber tracts of the

fasciculus longitudionalis superior which has been consistently reported by four independent research groups (Chang et al., 2008; Cykowski et al., 2010; Sommer et al., 2002a; Watkins et al., 2008). It is not exactly clear yet, which fiber tracts are affected: fiber tracts connecting Broca's area (inferior frontal gurus) with the ventral premotor and primary motor cortex, related to the encoding of the phonetic plan (Lu et al., 2009a; Salmelin et al., 2000), or connections of the dorsal route between premotor areas and superior temporal lobe related to the sensory-motor mapping of sound to articulation (Chang et al., 2008; Cykowski et al., 2010; Neef et al., 2009). Therefore we already planned the following future studies:

(1) A study with transcranial magnetic stimulation to elucidate whether the lesioning of critical cortical sites influences the identification of the contrast of voicing. Planned stimulation sites are the left superior temporal gyrus, the left ventral premotor cortex and the left primary motor cortex. An effect of stimulation will be operationalized by quantifying and comparing ambivalence intervals before and after stimulation. (i) We expect a broadening of the ambivalence intervals due to a lesioning of the STG because this cortical region is mainly involved in speech perception. (ii) A broadening of the ambivalence interval due to an inhibition of the ventral premotor cortex might indicate an increased vulnerability of the dorsal route (connection between PMv and STG). (iii) An effect of lesioning the primary motor cortex might indicate that the motor programs themselves may constitute phonological primitives, which as a consequence would demand a rethinking of the targeted reference frame in speech production.

(2) A study with electroencephalography (EEG) will elucidate the temporal coordination of neural activity and thus will answer the question whether the neural populations in frontal and temporal regions are simultaneously engaged in the mentioned phoneme identification task as it is proposed for a sensory-motor mapping of sound to articulation. By using distributed source models we will estimate the functional connectivity of the dorsal route for the processing of perceptually ambiguous and unambiguous stimuli, respectively. In control subjects the phoneme identification task is expected to be mirrored in a quantifiable functional connectivity during the perception of unambiguous stimuli. This functional connectivity is expected to be diminished during the perception of ambiguous stimuli. In persons who stutter a deficient dorsal route caused by diminished fiber integrity is expected to be mirrored in an altered time pattern.

### *Continuous performance*

Besides the diminished sensitivity to perceive phonetic feature near the phoneme boundary stuttering subjects were characterized by a delayed familiarity effect and a significant fatigue. As mentioned in the discussion of the perception study, a pattern of inconsistent performance ties in with observations of other studies on continuous performance in stuttering (Howell et al., 2009, Smith et al., 2010, Smits-Bandstra et al., 2006) and might be related to fluctuations in attention or vigilance (Bosshardt, 2006). On a broader level, this is reminiscent of a tendency of relapse in AWS after successful fluency-shaping therapy (Euler et al., 2009).

Inconsistent performance as well as stuttering relapse after fluency-shaping therapy has been connected to basal ganglia activation. We explored this hypothesis further, conducting a continuous performance task in a functional magnetic imaging experiment (Neef et al., in preperation) we determined functional irregularities in the activation pattern in adults who stutter (n = 10) compared to control subjects (n = 10). Preliminary results show less activation of the left insula, the left putamen, and the left frontal orbital cortex extending to the inferior frontal cortex in adults who stutter compared to control subjects (Figure 4-1). Affected intermediate and subcortical regions are proposed to selectively gate the influence of attention on working memory, specifically the basal ganglia contributing to the disinhibition of thalamocortical loops, thereby biasing the encoding towards the most relevant information (McNab and Klingberg, 2008).

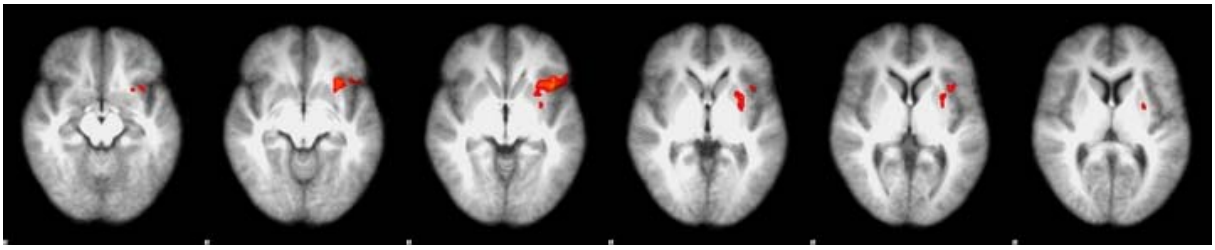

**Figure 4-1 Progress: analysis of MRI-data courtesy by Tibor Auer (post-doctoral fellow at the Biomedical NMR Research GmbH, Max-Planck-Institute for Biophysical Chemistry)**

It was already mentioned in the introduction that the literature on stuttering contains a multitude of supportive findings for different hypotheses, e.g. the cerebral dominance, disconnection or the basal ganglia hypothesis. The studies presented in this dissertation were likewise motivated and found supportive evidence for different hypothesis. What is missing, not only from this work, but also from the literature is a framework that allows to tie in the different aspects, incorporating the different neurophysiological explanatory approaches *and* the theories on motor as well as cognitive functions like attention, speech and language.

## 4.3 Future directions

Future efforts to unravel the causes of stuttering might profit from a change in perspective. New inputs could come from the research on the cortical and subcortical reorganizations underlying skill acquisition and automation. It might account for the connection between aberration in basal ganglia function and a pathological interplay between hemispheres in the emergence of dysfluent speech movements. Interestingly, the extent of the basal ganglia involvement in a skill is related to the skill's degree of automaticity. During maturation speaking becomes an automatized skill. The automation of a skill involves a restructuring of implementation and a reorganization of functional anatomy including a decreased activation of cortical areas and an increased activation of the intermediate cortical structures and the basal ganglia (Saling and Phillips, 2007).

Fluency-enhancing techniques such as speaking with a gentle voice onset and no voice offset or speaking under altered auditory feedback invokes additional monitoring to control for the target speech pattern. This shifts the speaking away from automatized toward a monitored, controlled process involving additional cortical resources. Both referred methods are very efficient at the beginning of an intervention but prone to become less beneficial with time exercised (Euler et al., 2009). This suggests that an increasing automaticity which is related to an increasing involvement of the basal ganglia leads to reoccurrence of the dysfluent symptoms.

The modulation of cortical excitability also plays a role in skill acquisition: when new motor patterns are acquired, initially some degrees of freedom which are redundant, not crucial for the task, are "frozen". This reduces the capacity needed for monitoring and thus speeds up motor learning. When automation sets in, however, the degrees of freedom are freed again. Freezing and freeing involves the modulation of cortical inhibition (Salling and Phillips, 2007), which brings in other aspect of this dissertation, the excitability of primary motor cortex and the contribution of other cortical areas like premotor cortex.

Whether the field of automaticity-related restructuring of cortical and subcortical processing can help to create an integrative framework in which different aspects and hypothesis on the cause of stuttering can be tied in, is not clear. Thus, a promising direction in stuttering research might lie in studies that correlate shifts in activation from cortical towards subcortical structures with the behavioural changes associated with automation. For me, this option is an attractive perspective in future works on stuttering.

# Appendix A – Levelt's psycholinguistic model and the DIVA model

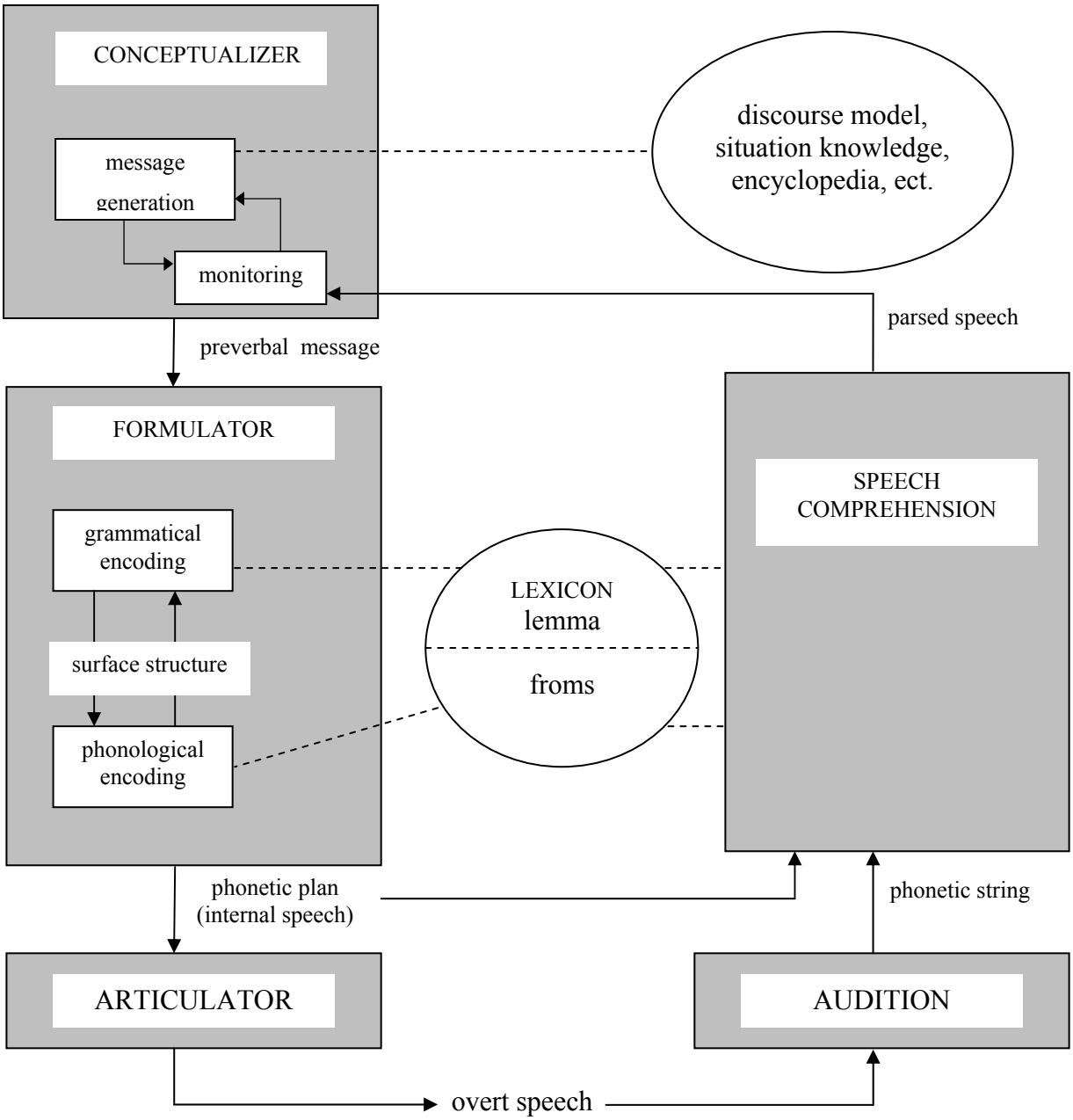


**Figure A-1 "A blueprint for the speaker"** (Levelt 1989, see (Payne and Whitney, 2002). The generation of fluent speech involves various processes that are portioned in processing components (boxes) and knowledge stores (circle and ellipse).

The most influential model of speech production is Levelt's "blueprint for the speaker" (Figure A-1; Levelt, 1989b). Levelt segregates knowledge stores and particular processing components. According to the model, one of the stores represents the speaker's obtained knowledge about discourse regulation such as a discourse record mutually maintained by a speaker and listener. Another store provides lexical knowledge. Processing components

include the conceptualizer, the formulator, the articulator, audition and speech comprehension. Each of the processing components receives input and generates output. The output of an upstream component serves as input of a downstream component. The initial point is the conceptualizer, which generates the preverbal message, consisting of prelinguistic conceptual information which the speaker intends to express. The formulator generates the phonetic plan which requires lexical selection, grammatical and phonological/prosidic encoding. Subsequently the articulator generates the acoustic pattern of overt speech by enfolding and executing the phonetic plan as a series of neuromuscular orders. The speech comprehension system provides a feedback of the produced speech, which enables the speaker to monitor his own production.

A part of the model has been realized in the elaborated computational model of word production (WEAVER++) that retains the discrete ordered stages of linguistic operations (Levelt et al., 1999). Its detailed and explicit formulation is mainly based on behavioral studies in which the reaction time (e.g. picture naming latency) is the crucial indicator for the establishment of separate processing stages (Levelt, 2001). Recent intracranial electrophysiological data do indeed provide evidence for a spatio-temporal distinct neural activity consecutively processing lexical, grammatical and phonological information (Hagoort and Levelt, 2009; Sahin et al., 2009).

Phonological encoding or form encoding is one of the psycholinguistically proposed processes that is mostly suggested to be disturbed in stuttering (Howell, 2004; Perkins et al., 1991; Postma and Kolk, 1993; Wingate, 1988). Therefore, I'm going to explain this process in more detail for the example word "stuttering": Lexical selection ends with the activation of the *lemma*, an abstract representation of meaning.

After the lemma is selected, the first step in form encoding is the retrieval of morphemic phonological codes: the code for the head morpheme <stutter> and the code for the grammatical morpheme <ing>. The output of this stage is the representation of the phonological code (Figure A-2).

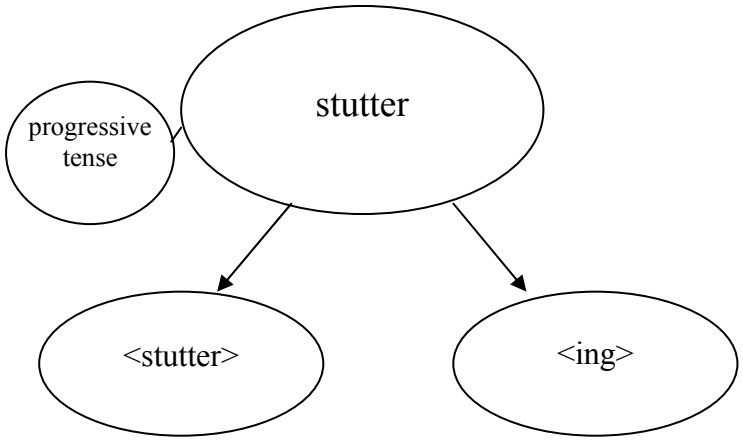


**Figure A-2 Accessing the morpho-phonological code**

The second stage processes the phonological spell-out: each segment of the morphological code is selected /stʌtə/ and /ɪŋ/; separately the metrical code of <stutter> is spelled-out. It specifies that word stress must go to the first syllable. The affix does not have a metrical code (Figure A-3).

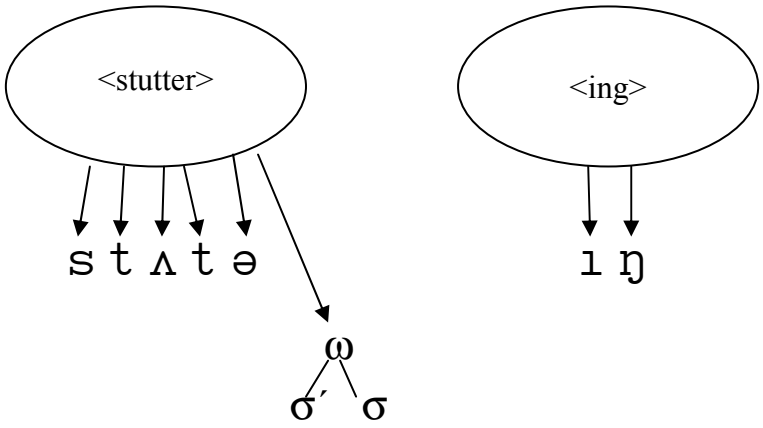


**Figure A-3 Spelling out the phonological and metrical code** The symbol ω represents the phonological word, σ is the unstressed syllable and σ´ the stressed syllable.

In the third step the spelled out segments are mapped to the metrical frame following the phonotactic rules (Levelt, 1999). The output of this stage constitutes the phonetic plan (Figure A-4).

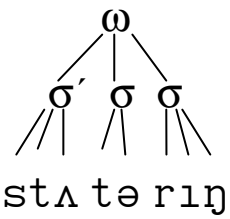


Figure A-4 Prosodification

Levelt's model has been influential, that it also formed the basis for a large number of theories on the underlying causes of stuttering (Bloodstein and Ratner, 2008). They are detailed in Appendix C.

Being a linguistic theory, based on psychophysical evidence from speech production experiments, the neural basis of the proposed modules (components and stores) the implementation in the human brain had not been accounted for. Only later a meta analysis attempted to relate the functional components of the model to regions in a cerebral network (Indefrey and Levelt, 2004). Neural implementation and articulation, which is also addressed in Levelt's model, are the central aspects in the second model introduced here.

### *DIVA model of speech motor control*

In order to take care of executive aspects Levelt refers to Perkell's model of speech production (Levelt, 1989a; Perkell, 1980). The advanced and current version of Perkell's model of speech production is represented by the Directions Into Velocities of Articulators (DIVA model; Golfinopoulos et al., 2010; Guenther, 1994).

This neurocomputational model provides a mechanistic account of acoustic, kinematic, and functional magnetic resonance imaging (fMRI) data on speech acquisition and production. It is composed of interconnected components whose cell activities and synaptic weights are governed by differential equations. The model and its neural implementation propose a motor feedforward and a sensory feedback control system regarding cortical as well as subcortical neural networks.

A good starting point to explore the DIVA model is he module 'Articulator Velocity and Position Maps' (Figure A-5). Here, the integrated signals of the feedforward and the feedback control subsystem generate the speech motor command. These maps are the core elements of the integrated Maeda speech synthesizer (Maeda, 1990). Each map consists of eight

antagonistic pairs of cells, corresponding to eight degrees of freedom of the vocal tract: jaw height, tongue shape, tongue body position, tongue tip position, lip protrusion, larynx height, upper lip height, and lower lip height. The 'Articulator Velocity and Position Maps' are thought to correspond to neuron pools in the caudoventral portion of the precenetral gyrus, also called primary motor cortex.

The activation of the 'Articulator Velocity and Position Maps' by the feedforward control subsystem is mediated through projections from the 'Speech Sound Maps' which are hypothesized to lie in the left posterior inferior frontal gyrus and adjacent ventral premotor cortex. The 'Speech Sound Maps' are postulated to correspond to Levelt's "mental syllabary" (Levelt et al., 1999). But initiation of the 'Speech Sound Maps' results rather in an activation of cells, which represent phonemes or multi-phonemic speech sounds than in the generation of a phonetic plan. Thus, the activation of one of these cells will initiate for example a time series of articulatory gestures in order to produce the corresponding speech sound. This precisely timing is proposed to be mediated by a trans-cerebellar pathway. Only the corresponding driver-like input from the 'Initiation Map' leads to a release of the commands from the 'Articulator Velocity and Position Maps' to the articulators. This map is supposed to lie bilaterally in the supplementary motor area and its activation depends on basal ganglia activity.

Conceptually, the feedback control subsystem enables the detection and correction of current speech motor programs, especially for novel or difficult speech tasks. Proposed feedforward projections from the 'Speech Sound Map' activate expected auditory targets in the 'Auditory Target Map'. Encoded are acceptable ranges in acoustic reference frames (Guenther 1995). The auditory response to self-generated speech is represented in the 'Auditory State Map'. If the incoming auditory response falls outside the acceptable range of the expected auditory target, the 'Auditory Error Map' will generate an error signal. Ultimately, the 'Feedback Control Map' generates corrective motor commands in the 'Articulator Velocity and Position Maps'.

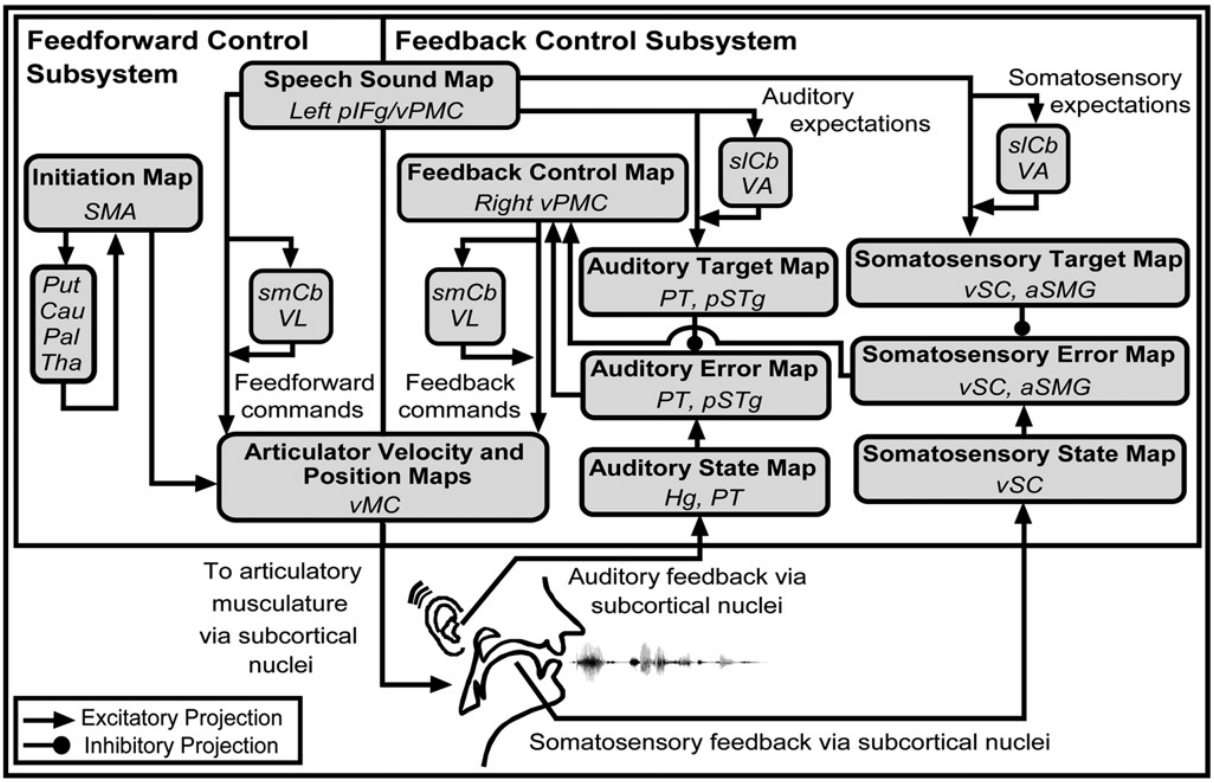


**Figure A-5 Directions into velocities of articulators model DIVA** (Figure by Golfinopoulos et al., 2010) – a neural network model of speech acquisition and production which characterizes proposed processing stages of speech motor control. Abbreviations: aSMg=anterior supramarginal gyrus; Cau=caudate; Pal=pallidum; Hg=Heschl's gyrus; pIFg=posterior inferior frontal gyrus; pSTg=posterior superior temporal gyrus; PT=planum temporale; Put=Putamen; slCB=superior lateral cerebellum; smCB=superior medial cerebellum; SMA=supplementary motor area; Tha=thalamus; VA=ventral anterior nucleus of the cerebellum; VL=ventral lateral nucleus of the thalamus; vMC=ventral motor cortex; vPMC=ventral premotor cortex; vSC=ventral somatosensory cortex.

DIVA can generate time varying sequences of articulatory positions and formant frequencies and it is possible to simulate and test the model against recorded acoustic, kinematic and neuroimaging data of speech production. This has been considered to study fluent (Guenther et al., 2006) as well as dysfluent (Civier et al., 2010; Max et al., 2004) speech production.

# Appendix B - Stuttering and acquired brain lesions

This dissertation focuses on cortical and subcortical mechanisms in persistent developmental stuttering. Due to the long course and the often very long delay between onset and examination in a study, the causal origins of developmental stuttering are notoriously hard to address and consequently they are still largely unclear. There is, however, a lot to gain from studies of the related acquired and induced stuttering, where the causal disruption is more easily identified and the short period between onset and examination helps to assure that observed abnormalities are not secondary but indeed causal. Similarly to aphasiology where lesion studies elucidated and facilitated the understanding of language processing in the brain I am going to give a short review on locations of brain injuries that induces speech dysfluencies to further understand the emergence of stuttering and general processes of speech production.

## *Acquired stuttering*

In 1835, Franz Joseph Gall and Johann Gaspar Spurzheim might have delivered the first report on acquired [neurogenic] stuttering (Andy and Bhatnagar, 1992). They mentioned a patient with a sword wound across the left nasal fossa and a penetrated internal posterior part of the anterior left lobe of the brain which was followed by speech and voice problems, hemiplegia and loss of vision. Later on only a slight stuttering remained. 150 years later, Nancy Helm and colleagues provided the first comprehensive description of the syndrome (Helm et al., 1978) but guidelines in its assessment were critically reviewed e.g. (Lundgren et al., 2010; Ringo and Dietrich, 1995) because the perceptual distinction between developmental and acquired stuttering remains indefinite (Van Borsel and Taillieu, 2001). A diagnosic certainty is possible if a documented neurologic condition and the following behaviors are associated: (1) dysfluencies occurre at a similar rate on open class words (e.g. nouns, verbs, adjectives) as well as on closed class words (pronouns, determiners, conjunctions, prepositions, particles); (2) repetitions, prolongations, and blocks occur in all positions in words; (3) dysfluencies occur consistently across speech tasks (e.g. free speech production, reading); (4) patients appear not overtly anxious about the stuttering behavior; (5) accompanying physical concomitants (facial grimacing, fist clenching, and eye blinking) occur rarely and; (6) no adaptation effect is evident (repeated reading of a passage enhances fluency) (Jokel et al., 2007; Lundgren et al., 2010). Challenging aspects among the differential diagnosis of acquired stuttering are the distinction of dysfluency from those

associated with dysarthria, aphasia and apraxia of speech, and the exclusion of a possible psychological or neuropsychiatric genesis (Lundgren et al., 2010).

Acquired stuttering results from various neurologic conditions involving focal and multi-site cerebrovascular lesion (e.g. Ardila and Lopez, 1986; Fawcett, 2005), traumatic brain injury (e.g. Ludlow et al., 1987), seizure disorder (e.g. Chung et al., 2004; Lebrun, 1991; Michel et al., 2004), dialysis dementia (e.g. Madison et al., 1977) Parkinsons's syndrome (e.g. Koller, 1983; Sakai et al., 1992) and Parkinons's disease (e.g. Benke et al., 2000). Examples for neuropathological correlates of acquired stuttering following a cerebrovasculare lesion due to stroke or traumatic brain injury are given in Table B-1. Lesion-based studies implicate the perisylvian language cortex, homologue regions of the right hemisphere, the right parietal cortex as well as subcortical regions, namely the basal ganglia, thalamus, pons and the cerebellum with dysfluencies. At the first glance, this seems puzzling and gives no insight into a plausible mechanism (Bhatnagar and Buckingham, 2010)

**Table B-1 Lesion sites of acquired stutteirng**

| pathology | lesion site | sex | age | history | reference |
|---|---|---|---|---|---|
| vascular lesion | left frontotemporoparietal | male | 68 | | (Grant et al., 1999) |
| | the left posterior temporal lobe and bilateral cerebellum | male | 59 | + | |
| | right parietal cortex | male | 59 | + | |
| | medial left occipital lobe | male | 55 | | |
| | pontine, cerebellar | male | 53 | | (Ciabarra et al., 2000) |
| | left basal gangla (putamen, caudate, corona radiate) | female | 54 | | |
| | left corona radiata, putamen,subinsula | female | 63 | | |
| | left basal ganglia | female | 84 | | (Fawcett, 2005) |
| | orbital surface of the right frontal lobe and the pons | male | 57 | | (Balasubramanian et al., 2003) |
| | midbrain upper pons | male | 60 | | (Doi et al., 2003) |
| | left ventrolateral thalamus | male | 38 | | (Van Borsel et al., 2003) |
| | left parietal | male | 61 | | (Turgut et al., 2002) |
| | left precentral circunvolution | male | 53 | | (Franco et al., 2000) |
| traumatic brain injury | right parietal lobe and mesial aspects of the left parietal lobe | male | 23 | | (Lebrun et al., 1990) |
| | diffuse axsonal inyury, additionally right frontal/parietal lesion | female | 30 | | (Helm-Estabrooks and Hotz, 1998) |

### *Disappearance with acquired brain lesion*

Neurologic conditions can also have the opposite effect, changing lifelong stuttering to fluent speech. In 1986 Helm-Estabrooks and colleagues reported the disappearance of stuttering in a patient after head injury. In another case the occlusion of the mesencephalic artery, generated the infarction in the bilateral medial thalamus and rostral mesencephalic tegmentum and

ceased stuttering (Muroi et al., 1999). In two cases the progress of multiple sclerosis ceased stuttering (Miller, 1985). An elaborated study of four cases documents the disappearance of stuttering after neurosurgery (Jones, 1966). In all four cases neurosurgery was required on one cerebral hemisphere because of a neurologic disease (aneurysm clipping following a haemorrhage, tumour resection). Whereas pre-operative intracarotid amytal tests yielded a bilateral cerebral representation of language, post-operatively language function was shifted to the non-operated hemisphere in all patients. This co-occurrence of emerging language dominance with cessation of stuttering fits nicely with the *cerebral dominance theory*, a hypothesis that postulated that stuttering might be caused by an aberrant cerebral language lateralization (Travis, 1978).

### *Brain stimulation*

Further cues towards a neurobiological understanding of the phenomenon stuttering has been delivered by a contemporary surgical treatment: deep brain stimulation (DBS). An implanted multicontact electrode stimulates the brain tissue with high-frequency electric current pulses. First implantations provided efficient relief from symptoms of advanced Parkinson's disease: for example an improvement from rigidity when delivered to the *subthalamic nucleus* (Lanotte et al., 2002), a decrease of tremor when delivered to the *thalamic nucleus ventralis intermedius* (Benabid et al., 1991; Benabid et al., 1987); or relieve from dyskinesia when delivered to the *internal pallidum* (Limousin-Dowsey et al., 1999). DBS is now employed to treat a broad range of chronic brain disorders in patients resistant to pharmacological therapies, including dystonia, epilepsy, pain, obsessive compulsive disorders, Gilles de la Tourette syndrome, depression and to improve the condition of brain-injured patients in a vegetative or minimally conscious state (Deniau et al., 2010; Schiff et al., 2007). Although DBS can be an effective symptomatic therapy, it is accompanied by adverse effects e.g. (Seijo et al., 2007; Voges and Krauss, 2010).

In October 2010, a PubMed recherché with the keywords "deep brain stimulation" and "stuttering" yielded five articles, included in Table B-2. Most frequent are case reports on cessation of acquired stuttering due to DBS on the *left thalamus centromedian nucleus* (Bhatnagar and Buckingham, 2010; Bhatnagar and Andy, 1989). In three cases, DBS in patients with dystonia induced stuttering as an adverse effect. While stuttering ceased under

**Table B-2 Tuning of fluency by Deep Brain Stimulation**

| fluency | pathology | stimulation site | sex | implantation at age | last follow up | Reference |
|---|---|---|---|---|---|---|
| acquired stuttering, ceased | trigeminal neuralgia | left thalamus centromedian nucleu | male | 60 | 2.5 years later | (Bhatnagar and Andy, 1989) |
| acquired stuttering, ceased | trigeminal neuralgia and subcortical discharges, pain, dyskinesia of tremor type, sensory loss, | left thalamus centromedian nucleus | male | 58 | 7 years later | (Andy and Bhatnagar, 1992; Bhatnagar and Buckingham, 2010) |
| acquired stuttering, ceased | childhood hydrocephalus, subcortical discharges, pain, anger, amnesia | left thalamus centromedian nucleus | male | 17 | 7 years later | |
| acquired stuttering, ceased | seizures-bitemporal, pain, torticollis | left thalamus centromedian nucleus | female | 38 | 8 years later | |
| DBS induced stuttering , ceased | dystonic tremor of the trunk | bilateral thalamus ventral intermediate nucleus | female | 30 after 3 years and 8 months replacement of impulse generators | 2 years later | (Allert et al., 2010) |
| acquired stuttering, ceased | Parkinson's disease | left subthalamic nucleus | male | n.n. | n.n. | (Walker et al., 2009)abstract |
| adverse effect, induced stuttering by DBS | generalized Dystonia (DYST-1 mutation) | bilateral internal globus pallidus | male | 28 | 3 years later | (Nebel et al., 2009) |
| adverse effect, induced stuttering and dysarthria by DBS | segmental dystonia, DYT1-negative, involving neck, trunk, upper limbs | bilateral internal globus pallidus | male | 43 | 14 month later | |
| developmental stuttering ceased at age 9, re-emerged with PD, not ceased with DBS | Parkinson's disease | bilateral subthalamic nucleus | male | 58 | 4 month later | (Burghaus et al., 2006) |

adjusted stimulation of bilateral *thalamic nucleus ventralis intermedius* (Allert et al., 2010), it persisted under bilateral simulation of the *internal globus pallidus* (Nebel et al., 2009).

# Appendix C - Psycholinguistic approaches to explain stuttering

The neuropsycholinguistic theory suggests that fluency breakdowns result from a desynchronized arrival of segmental (phonological) and suprasegemental (stress pattern) information which are processed by different neural systems that converge on a common output system. Time pressure forces the speaker to begin, continue, or accelerate an utterance which results in a loss of motor control – stuttered dysfluencies (Perkins et al., 1991).

The Covert Repair Hypothesis is extensively pursued in recent years. The hypothesis targets the pre-articulatory internal monitor established in Levelts psycholinguistic model. The authors propose internal error sources such as phonemic encoding error detected *before* word execution has started (resulting in a block), phonemic encoding error detected *after* word execution has been produced (resulting in a prolongation or a repetition), phonemic encoding error detected *after* the first sound has been produced (resulting in a prolongation of the initial sound(s) or in a mid-syllable block) (Postma and Kolk, 1993).

The Execution and Planning model (EXPLAN) distinguishes between linguistic planning and motor execution of utterance components. The theory proposes an incremental processing in spontaneous speech production, which means, the planning of an upcoming utterance component is simultaneously processed to the execution of the current utterance component. In stuttering the motor execution plan is not available due to planning difficulties caused by potential phonetic or lexical complexity, resulting in speech dysfluencies (Howell, 2004).

# Appendix D - Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive technique used to stimulate a subset of the neurons in a small part, approximately 1 $cm^3$, of the cerebral cortex. The technique uses the principle of electromagnetic induction; a very brief magnetic pulse induces an electrical field and thereby an electrical current in conductive brain tissue.

The mechanisms by which the brief electrical current stimulates neurons are not entirely clear. Strong stimuli (suprathreshold) applied over the motor cortex directly elicit motor evoked potentials (MEP) in the target muscles of the stimulated area. It is thought that the electric stimulus suffices to depolarize the axons of the layer 5 pyramidal cells above action potential threshold. Weaker stimuli alter the excitatory state even when no muscle evoked potentials are detectable (see below: paired-pulse TMS). It is thought that these subthreshold stimuli only depolarize presynaptic terminals of interneurons increasing inhibitory input to the primary neurons (Esser et al., 2005).

Different TMS protocols specifically manipulate stimulated neural populations. For example, the repetitive stimulation (rTMS) of the primary motor cortex with subthreshold stimulation intensity and a low frequent pulse rate of 1 Hz over 10 minutes results in a temporary reduction of the excitability of the stimulated neuron pool (Romero et al., 2002). This reduced excitability is for example reflected in diminished amplitudes of the motor potentials evoked by single suprathreshold TMS pulses applied over the same stimulation site. The same stimulation protocol applied over Wernicke's area resulted in slowed picture word verification (Drager et al., 2004). The temporary reduction in excitability that is introduced by this TMS protocol is termed "virtual lesion".

Intracortical excitability can be obtained by positioning one TMS coile at a target site of the primary motor cortex. A subthreshold conditioning stimulus precedes a suprathreshold test stimulus which elicites a motor evoked potential (MEP) with an amplitude that depends on the time interval between the pulses. In healthy subjects, short inter-stimulus intervals (1 - 6 ms) inhibit the motor responses and long inter-stimulus intervals (10-15 ms) facilitate them (Kujirai et al., 1993). The intracortical inhibition is likely mediated by inhibitory motor cortical interneurons (Hallett, 2000) whereas intracortical facilitation is hypothesized to be a net facilitation consisting of prevailing facilitation and weaker inhibition mediated by glutamatergic N-methyl-D-aspartate receptors (NMDA receptors; Hanajima and Ugawa, 2008). Paired-pulse paradigms, where conditioning and test pulse are applied to separate sites,

are useful tools to investigate intracortical and intercortical connectivity (e.g.Mochizuki et al., 2004).

## Literatur

Ackermann H. Cerebellar contributions to speech production and speech perception: psycholinguistic and neurobiological perspectives. Trends in Neurosciences, 31 (6): 265-72, 2008.

Adams MR. A physiologic and aerodynamic interpretation of fluent and stuttered speech. Journal of Fluency Disorders, 1 (1): 35-47, 1974.

Allert N, Kelm D, Blahak C, Capelle HH, and Krauss JK. Stuttering induced by thalamic deep brain stimulation for dystonia. Journal of Neural Transmission, 117 (5): 617-20, 2010.

Alm PA. Stuttering and the basal ganglia circuits: a critical review of possible relations. Journal of Communication Disorders, 37 (4): 325-69, 2004.

Andrews G, Craig A, Feyer AM, Hoddinott S, Howie P, and Neilson M. Stuttering: a review of research findings and theories circa 1982. Journal of Speech and Hearing Disorders, 48 (3): 226-46, 1983.

Andrews G and Harris M. The Syndrome of Stuttering. London: Heinemann, 1964.

Andy OJ and Bhatnagar SC. Stuttering acquired from subcortical pathologies and its alleviation from thalamic perturbation. Brain and Language, 42 (4): 385-401, 1992.

Ardila A and Lopez MV. Severe stuttering associated with right hemisphere lesion. Brain and Language, 27 (2): 239-46, 1986.

Balasubramanian V, Max L, Van Borsel J, Rayca KO, and Richardson D. Acquired stuttering following right frontal and bilateral pontine lesion: a case study. Brain and Cognition, 53 (2): 185-9, 2003.

Barlow SM, Andreatta RD, and Kahane J. Chapter 1. Muscle systems of the vocal tract. In Barlow SM (Ed.) Handbook of clinical speech physiology. San Diego: Singular Publishing Group, Inc., 1999, pp. 1-99.

Basser PJ, Mattiello J, and LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. Journal of Magnetic Resonance. Series B, 103 (3): 247-54, 1994.

Baumgartner J and Duffy JR. Psychogenic stuttering in adults with and without neurologic disease. Journal of Medical Speech-Language Pathology, 5 (2): 75–95, 1997.

Beck S and Hallett M. Surround inhibition is modulated by task difficulty. Clinical Neurophysiology, 121 (1): 98-103, 2010.

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, and de Rougemont J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet, 337 (8738): 403-6, 1991.

Benabid AL, Pollak P, Louveau A, Henry S, and de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Applied Neurophysiology, 50 (1-6): 344-6, 1987.

Benke T, Hohenstein C, Poewe W, and Butterworth B. Repetitive speech phenomena in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry, 69 (3): 319-24, 2000.

Berardelli A, Abbruzzese G, Chen R, Orth M, Ridding MC, Stinear C, Suppa A, Trompetto C, and Thompson PD. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul, 1 (3): 183-91, 2008.

Bhatnagar S and Buckingham H. Neurogenic stuttering: its reticular modulation. Curr Neurol Neurosci Rep, 10 (6): 491-8, 2010.

Bhatnagar SC and Andy OJ. Alleviation of acquired stuttering with human centremedian thalamic stimulation. Journal of Neurology, Neurosurgery and Psychiatry, 52 (10): 1182-4, 1989.

Bloodstein O. Stuttering and normal nonfluency a continuity hypothesis. British Journal of Disorders of Communication, 5 (1): 30-9, 1970.

Bloodstein O and Ratner BN. A Handbook on Stuttering. Canada: Delmar Thomson Learning, 2008.

Bosshardt HG. Cognitive processing load as a determinant of stuttering: summary of a research programme. Clin Linguist Phon, 20 (5): 371-85, 2006.

Brady JP. The pharmacology of stuttering: a critical review. American Journal of Psychiatry, 148 (10): 1309-16, 1991.

Braun AR, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, Carson RE, and Ludlow CL. Altered patterns of cerebral activity during speech and language production in developmental stuttering. An H2(15)O positron emission tomography study. Brain, 120 ( Pt 5): 761-84, 1997.

Brown S, Ingham RJ, Ingham JC, Laird AR, and Fox PT. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. Human Brain Mapping, 25 (1): 105-17, 2005.

Büchel C and Sommer M. What causes stuttering? PLoS Biol, 2 (2): E46, 2004.

Büchel C and Watkins KE. Genetic susceptibility to persistent stuttering. New England Journal of Medicine, 362 (23): 2226; author reply 2227, 2010.

Burghaus L, Hilker R, Thiel A, Galldiks N, Lehnhardt FG, Zaro-Weber O, Sturm V, and Heiss WD. Deep brain stimulation of the subthalamic nucleus reversibly deteriorates stuttering in advanced Parkinson's disease. Journal of Neural Transmission, 113 (5): 625-31, 2006.

Chang SE, Erickson KI, Ambrose NG, Hasegawa-Johnson MA, and Ludlow CL. Brain anatomy differences in childhood stuttering. Neuroimage, 39 (3): 1333-44, 2008.

Chang SE, Kenney MK, Loucks TMJ, and Ludlow CL. Brain activation abnormalities during speech and non-speech in stuttering speakers. Neuroimage, 46 (1): 201-212, 2009.

Chang SE, Synnestvedt A, Ostuni J, and Ludlow CL. Similarities in speech and white matter characteristics in idiopathic developmental stuttering and adult-onset stuttering. J Neurolinguistics, 23 (5): 455-469, 2010.

Chung SJ, Im JH, Lee JH, and Lee MC. Stuttering and gait disturbance after supplementary motor area seizure. Movement Disorders, 19 (9): 1106-9, 2004.

Ciabarra AM, Elkind MS, Roberts JK, and Marshall RS. Subcortical infarction resulting in acquired stuttering. Journal of Neurology, Neurosurgery and Psychiatry, 69 (4): 546-9, 2000.

Civier O, Tasko SM, and Guenther FH. Overreliance on auditory feedback may lead to sound/syllable repetitions: simulations of stuttering and fluency-inducing conditions with a neural model of speech production. J Fluency Disord, 35 (3): 246-79, 2010.

Cooper MH and Allen GD. Timing control accuracy in normal speakers and stutterers. Journal of Speech and Hearing Research, 20 (1): 55-71, 1977.

Coulter CE, Anderson JD, and Conture EG. Childhood stuttering and dissociations across linguistic domains: a replication and extension. J Fluency Disord, 34 (4): 257-78, 2009.

Cykowski MD, Fox PT, Ingham RJ, Ingham JC, and Robin DA. A study of the reproducibility and etiology of diffusion anisotropy differences in developmental stuttering: a potential role for impaired myelination. Neuroimage, 52 (4): 1495-504, 2010.

Damste PH, Zwaan EJ, and Schoenaker TJ. Learning principles applied to the stuttering problem. Folia Phoniatrica, 20 (5): 327-41, 1968.

De Nil L. Recent developments in brain imaging research in stuttering. In Maasan B, Kent RD, Peters HFM, Van Lieshout PHMM, and Hulstijn W (Eds.), Speech motor control in normal and disorderd speech. New York: Oxford University Press, 2004, pp. 113-137.

De Nil LF, Kroll RM, and Houle S. Functional neuroimaging of cerebellar activation during single word reading and verb generation in stuttering and nonstuttering adults. Neuroscience Letters, 302 (2-3): 77-80, 2001.

Deniau J-M, Degos B, Bosch C, and Maurice N. Deep brain stimulation mechanisms: beyond the concept of local functional inhibition. European Journal of Neuroscience, 32 (7): 1080-1091, 2010.

Devlin JT and Watkins KE. Investigating language organization with TMS. In Wassermann EM, Epstein CM, Ziemann Uet al (Eds.), The Oxford Handbokk of Transcranial Magnetic Stimulation. New York: Oxford University Press, 2008, pp. 479-499.

Dhont JKG. Translational Brownian motion. In Gerhard Gompper UBK, Jan K.G. Dhont, Dieter Richter, Roland G. Winkler (Ed.) Physics Meets biology: From Soft

Matter to Cell Biology, 35th Spring School of the Institut of Solid State Research. Jülich: Forschungszentrum Jülich, 2004.

Doi M, Nakayasu H, Soda T, Shimoda K, Ito A, and Nakashima K. Brainstem infarction presenting with neurogenic stuttering. Internal Medicine, 42 (9): 884-7, 2003.

Drager B, Breitenstein C, Helmke U, Kamping S, and Knecht S. Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. European Journal of Neuroscience, 20 (6): 1681-7, 2004.

Dworzynski K, Remington A, Rijsdijk F, Howell P, and Plomin R. Genetic etiology in cases of recovered and persistent stuttering in an unselected, longitudinal sample of young twins. Am J Speech Lang Pathol, 16 (2): 169-78, 2007.

Esser SK, Hill SL, and Tononi G. Modeling the effects of transcranial magnetic stimulation on cortical circuits. Journal of Neurophysiology, 94 (1): 622-39, 2005.

Euler HA, Gudenberg AWv, Jung K, and Neumann K. Computergestützte Therapie bei Redeflussstörungen: Die langfristige Wirksamkeit der Kasseler Stottertherapie. Sprache, Stimme, Gehör, 33 (4): 193-97, 2009.

Fawcett RG. Stroke-associated acquired stuttering. CNS Spectr, 10 (2): 94-5, 2005.

Fisher SE. Genetic susceptibility to stuttering. New England Journal of Medicine, 362 (8): 750-2, 2010.

Folkerth RD. Abnormalities of developing white matter in lysosomal storage diseases. Journal of Neuropathology and Experimental Neurology, 58 (9): 887-902, 1999.

Fox PT, Ingham RJ, Ingham JC, Hirsch TB, Downs JH, Martin C, Jerabek P, Glass T, and Lancaster JL. A PET study of the neural systems of stuttering. Nature, 382 (6587): 158-61, 1996.

Fox PT, Ingham RJ, Ingham JC, Zamarripa F, Xiong JH, and Lancaster JL. Brain correlates of stuttering and syllable production. A PET performance-correlation analysis. Brain, 123 ( Pt 10): 1985-2004, 2000.

Franco E, Casado JL, Lopez Dominguez JM, Diaz Espejo C, Blanco A, and Robledo A. [Stuttering as the only manifestation of a cerebral infarct]. Neurologia, 15 (9): 414-6, 2000.

Giraud AL, Neumann K, Bachoud-Levi AC, von Gudenberg AW, Euler HA, Lanfermann H, and Preibisch C. Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. Brain and Language, 2007.

Golfinopoulos E, Tourville JA, and Guenther F. The integration of large-scale neural network modeling and functional brain imaging in speech motor contro. Neuroimage: doi:10.1016/j.neuroimage.2009.10.023, 2010.

Grant AC, Biousse V, Cook AA, and Newman NJ. Stroke-associated stuttering. Archives of Neurology, 56 (5): 624-7, 1999.

Guenther FH. A neural network model of speech acquisition and motor equivalent speech production. Biological Cybernetics, 72 (1): 43-53, 1994.

Guenther FH. Speech sound acquisition, coarticulation, and rate effects in a neural network model of speech production. Psychological Review, 102 (3): 594-621, 1995.

Guenther FH, Ghosh SS, and Tourville JA. Neural modeling and imaging of the cortical interactions underlying syllable production. Brain and Language, 96 (3): 280-301, 2006.

Hagoort P and Levelt WJ. Neuroscience. The speaking brain. Science, 326 (5951): 372-3, 2009.

Hallett M. Transcranial magnetic stimulation and the human brain. Nature, 406 (6792): 147-50, 2000.

Hanajima R and Ugawa Y. Paired-pulse measures. In Wassermann EM, Epstein CM, Ziemann U, Paus T, and Lisanby SH (Eds.), The Oxford handbook of transcranial magnetic stimulation. New York: Oxford Univerity Press, 2008.

Heiser MA and Cheung SW. Cortical representations of communication sounds. Curr Opin Otolaryngol Head Neck Surg, 16 (5): 478-84, 2008.

Helm-Estabrooks N and Hotz G. Sudden onset of "stuttering" in an adult: neurogenic or psychogenic? Seminars in Speech and Language, 19 (1): 23-9, 1998.

Helm NA, Butler RB, and Benson DF. Acquired stuttering. Neurology, 28 (11): 1159-65, 1978.

Hickok G and Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci, 8 (5): 393-402, 2007.

Hoang LN, Neef NE, Neef A, Ambrus G, Paulus W, Wolff von Gudenberg A, and Sommer M. Inter-gestural motor cortex excitability of the tongue representation in adults who stutter. in preparation.

Houde JF and Jordan MI. Sensorimotor adaptation in speech production. Science, 279 (5354): 1213-6, 1998.

Howell P. Assessment of Some Contemporary Theories of Stuttering That Apply to Spontaneous Speech. Contemp Issues Commun Sci Disord, 31: 122-139, 2004.

Howell P, Anderson AJ, Bartrip J, and Bailey E. Comparison of acoustic and kinematic approaches to measuring utterance-level speech variability. Journal of Speech, Language, and Hearing Research, 52 (4): 1088-96, 2009.

Howell P. Signs of developmental stuttering up to age eight and at 12 plus. Clinical Psychology Review, 27 (3): 287-306, 2007.

Indefrey P and Levelt WJ. The spatial and temporal signatures of word production components. Cognition, 92 (1-2): 101-44, 2004.

Ingham RJ, Fox PT, Ingham JC, Xiong J, Zamarripa F, Hardies LJ, and Lancaster JL. Brain correlates of stuttering and syllable production: gender comparison and replication. Journal of Speech, Language, and Hearing Research, 47 (2): 321-41, 2004.

Johnson W. The onset of stuttering: Research findings and implications. Minneapolis: University of Minnesota, 1959.

Jokel R, De Nil LF, and Sharpe AK. Speech disfluencies in adults with neurogenic stuttering associated with stroke and traumatic brain injury. Journal of Medical Speech-Language Pathology, 14: 243-261, Retrieved at http://goliath.ecnext.com/coms2/gi_0199-7265968/Speech-disfluencies-in-adults-with.html, 2007.

Jones RK. Observations on stammering after localized cerebral injury. Journal of Neurology, Neurosurgery and Psychiatry, 29 (3): 192-5, 1966.

Kalveram KT and Jancke L. Vowel duration and voice onset time for stressed and nonstressed syllables in stutterers under delayed auditory feedback condition. Folia Phoniatrica, 41 (1): 30-42, 1989.

Kang C, Riazuddin S, Mundorff J, Krasnewich D, Friedman P, Mullikin JC, and Drayna D. Mutations in the lysosomal enzyme-targeting pathway and persistent stuttering. New England Journal of Medicine, 362 (8): 677-85, 2010.

Kell CA, Neumann K, von Kriegstein K, Posenenske C, von Gudenberg AW, Euler H, and Giraud AL. How the brain repairs stuttering. Brain, 132 (Pt 10): 2747-60, 2009.

Kelly RM and Strick PL. Macro-architecture of basal ganglia loops with the cerebral cortex: use of rabies virus to reveal multisynaptic circuits. Progress in Brain Research, 143: 449-59, 2004.

Kent RD. Stuttering as a temporal programming disorder. In Curlee RF and Perkins WH (Eds.), Nature and treatment of stuttering: new directions. San Diego: College-Hill Press, 1984.

Kent RD. Research on speech motor control and its disorders: a review and prospective. Journal of Communication Disorders, 33 (5): 391-427; quiz 428, 2000.

Kleinow J and Smith A. Influences of length and syntactic complexity on the speech motor stability of the fluent speech of adults who stutter. Journal of Speech Language and Hearing Research, 43 (2): 548-559, 2000.

Koller WC. Dysfluency (stuttering) in extrapyramidal disease. Archives of Neurology, 40 (3): 175-7, 1983.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, and Marsden CD. Corticocortical inhibition in human motor cortex. Journal of Physiology, 471: 501-19, 1993.

Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, and Lopiano L. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. Journal of Neurology, Neurosurgery and Psychiatry, 72 (1): 53-8, 2002.

Lebrun Y. Stuttering and epilepsy. Journal of Neurolinguistics, 6 (4): 433–444, 1991.

Lebrun Y, Bijleveld H, and Rousseau JJ. A case of persistent neurogenic stuttering following a missile wound. Journal of Fluency Disorders, 15 (5-6): 251-258, 1990.

Levelt WJ. Chapter 11. Articulating. In Joshi A (Ed.) Speaking. From intention to articulation. Cambridge, MA: MIT Press, 1989a, pp. 413-457.

Levelt WJ. Models of word production. Trends in Cognitive Sciences, 3 (6): 223-232, 1999.

Levelt WJ. Spoken word production: a theory of lexical access. Proceedings of the National Academy of Sciences of the United States of America, 98 (23): 13464-71, 2001.

Levelt WJ, Roelofs A, and Meyer AS. A theory of lexical access in speech production. Behavioral and Brain Sciences, 22 (1): 1-38; discussion 38-75, 1999.

Levelt WJM. Chapter 1. The speaker as information processor. In Joshi A (Ed.) Speaking. From Intention to articulation. Cambridge, Ma: MIT Press, 1989b.

Levelt WJM. Speaking: from intention to articulation. Cambridge, MA: MIT Press, 1989c.

Limousin-Dowsey P, Pollak P, Van Blercom N, Krack P, Benazzouz A, and Benabid A. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. Journal of Neurology, 246 Suppl 2: II42-5, 1999.

Louis ED, Winfield L, Fahn S, and Ford B. Speech dysfluency exacerbated by levodopa in Parkinson's disease. Movement Disorders, 16 (3): 562-5, 2001.

Lu C, Chen C, Ning N, Ding G, Guo T, Peng D, Yang Y, Li K, and Lin C. The neural substrates for atypical planning and execution of word production in stuttering. Experimental Neurology, 221 (1): 146-56, 2010.

Lu C, Ning N, Peng D, Ding G, Li K, Yang Y, and Lin C. The role of large-scale interactions for developmental stuttering. Neuroscience, 161 (4): 1008-1026, 2009a.

Lu C, Peng D, Chen C, Ning N, Ding G, Li K, Yang Y, and Lin C. Altered effective connectivity and anomalous anatomy in the basal ganglia-thalamocortical circuit of stuttering speakers. Cortex, 2009b.

Ludlow CL. Stuttering: dysfunction in a complex and dynamic system. Brain, 123 ( Pt 10): 1983-4, 2000.

Ludlow CL and Loucks T. Stuttering: a dynamic motor control disorder. Journal of Fluency Disorders, 28 (4): 273-95, 2003.

Ludlow CL, Rosenberg J, Salazar A, Grafman J, and Smutok M. Site of penetrating brain lesions causing chronic acquired stuttering. Annals of Neurology, 22 (1): 60-6, 1987.

Lundgren K, Helm-Estabrooks N, and Klein R. Stuttering Following Acquired Brain Damage: A Review of the Literature. J Neurolinguistics, 23 (5): 447-454, 2010.

Madison DP, Baehr ET, Bazell M, Hartman RW, Mahurkar SD, and Dunea G. Communicative and cognitive deterioration in dialysis dementia: two case studies. Journal of Speech and Hearing Disorders, 42 (2): 238-46, 1977.

Maeda S. Compensatory articulation during speech: evidence from the analysis and synthesis of vocal tract shapes using an articulatory model. In Hardcastle WJ and Marchal A (Eds.), Speech Production and Speech Modeling. Boston: Kluwer Academic Publishers, 1990, pp. 131–149.

Maguire GA, Yu BP, Franklin DL, and Riley GD. Alleviating stuttering with pharmacological interventions. Expert Opin Pharmacother, 5 (7): 1565-71, 2004.

Mansson H. Childhood stuttering: Incidence and development,. Journal of Fluency Disorders, 25: 47-57, 2000.

Max L, Caruso AJ, and Gracco VL. Kinematic analyses of speech, orofacial nonspeech, and finger movements in stuttering and nonstuttering adults. Journal of Speech, Language, and Hearing Research, 46 (1): 215-32, 2003.

Max L, Guenther FH, Gracco VL, Ghosh SS, and Wallace ME. Unstable or insufficiently activated internal models and feedback-biased motor control as sources of dysfluency: A theoretical model of stuttering. Contemporary Issues in Communication Science and Disorders: CICSD, 31: 105-122, 2004.

Michel V, Burbaud P, Taillard J, Gaida T, Joseph PA, Duche B, and Bioulac B. Stuttering or reflex seizure? A case report. Epileptic Disord, 6 (3): 181-5, 2004.

Miller AE. Cessation of stuttering with progressive multiple sclerosis. Neurology, 35 (9): 1341-3, 1985.

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Progress in Neurobiology, 50 (4): 381-425, 1996.

Mochizuki H, Huang YZ, and Rothwell JC. Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. Journal of Physiology, 561 (Pt 1): 331-8, 2004.

Morgan A, Reilly S, Anderson A, Reutens D, and Wood A. Functional brain activation differences for motor versus language regions in adults with and without stuttering: An fMRI study. Secondary Titl. Oxford, 2008.

Muroi A, Hirayama K, Tanno Y, Shimizu S, Watanabe T, and Yamamoto T. Cessation of stuttering after bilateral thalamic infarction. Neurology, 53 (4): 890-1, 1999.

Namasivayam AK, van Lieshout P, and De Nil L. Bite-block perturbation in people who stutter: immediate compensatory and delayed adaptive processes. Journal of Communication Disorders, 41 (4): 372-94, 2008.

Namasivayam AK, van Lieshout P, McIlroy WE, and De Nil L. Sensory feedback dependence hypothesis in persons who stutter. Human Movement Science, 28 (6): 688-707, 2009.

Nasir SM and Ostry DJ. Auditory plasticity and speech motor learning. Proceedings of the National Academy of Sciences of the United States of America, 106 (48): 20470-5, 2009.

Nebel A, Reese R, Deuschl G, Mehdorn HM, and Volkmann J. Acquired stuttering after pallidal deep brain stimulation for dystonia. Journal of Neural Transmission, 116 (2): 167-9, 2009.

Neef N, Auer T, Frahm J, Paulus W, and Sommer M. Continuous performance test discovered less activation of the verbal working memory network in stuttering. in preperation.

Neef N, Paulus W, and Sommer M. Dem Stottern auf der Spur. L.O.G.O.S. Interdiziplinär, 17 (2): 129-135, 2009.

Olander L, Smith A, and Zelaznik H. Evidence That a Motor Timing Deficit Is a Factor in the Development of Stuttering. Journal of Speech, Language, and Hearing Research, 2010.

Orton ST. A physiological theory of reading disability and stuttering in children. New England Journal of Medicine, 199 (21): 1045-1052, 1928.

Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, Pascual-Leone A, Rosenow F, Rothwell JC, and Ziemann U. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul, 1 (3): 151-63, 2008.

Payne JS and Whitney PJ. Developing L2 Oral Proficiency through Synchronous CMC: Output, Working Memory, and Interlanguage Development. CALICO, 20: 7-32, 2002.

Perkell JS. Phonetic features and the physiology of speech production. In Butterworth B (Ed.) Language Production: Vol. 1. Speech and talk. London: Academic Press, 1980, pp. 337-372.

Perkins WH, Kent RD, and Curlee RF. A theory of neuropsycholinguistic function in stuttering. Journal of Speech and Hearing Research, 34 (4): 734-52, 1991.

Peters HF, Hulstijn W, and Starkweather CW. Acoustic and physiological reaction times of stutterers and nonstutterers. Journal of Speech and Hearing Research, 32 (3): 668-80, 1989.

Peters HF, Hulstijn W, and Van Lieshout PH. Recent developments in speech motor research into stuttering. Folia Phoniatrica et Logopedica, 52 (1-3): 103-19, 2000.

Pollok B, Rothkegel H, Schnitzler A, Paulus W, and Lang N. The effect of rTMS over left and right dorsolateral premotor cortex on movement timing of either hand. European Journal of Neuroscience, 27 (3): 757-64, 2008.

Postma A and Kolk H. The covert repair hypothesis: prearticulatory repair processes in normal and stuttered disfluencies. Journal of Speech and Hearing Research, 36 (3): 472-87, 1993.

Preibisch C, Neumann K, Raab P, Euler HA, von Gudenberg AW, Lanfermann H, and Giraud AL. Evidence for compensation for stuttering by the right frontal operculum. Neuroimage, 20 (2): 1356-64, 2003.

Reilly S, Onslow M, Packman A, Wake M, Bavin EL, Prior M, Eadie P, Cini E, Bolzonello C, and Ukoumunne OC. Predicting stuttering onset by the age of 3 years: a prospective, community cohort study. Pediatrics, 123 (1): 270-7, 2009.

Riaz N, Steinberg S, Ahmad J, Pluzhnikov A, Riazuddin S, Cox NJ, and Drayna D. Genomewide significant linkage to stuttering on chromosome 12. American Journal of Human Genetics, 76 (4): 647-51, 2005.

Ringo CC and Dietrich S. Neurogenic stuttering: An analysis and critique. Journal of Medical Speech-Language Pathology, 3 (2): 111-122, 1995.

Romero JR, Anschel D, Sparing R, Gangitano M, and Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clinical Neurophysiology, 113 (1): 101-7, 2002.

Sahin NT, Pinker S, Cash SS, Schomer D, and Halgren E. Sequential processing of lexical, grammatical, and phonological information within Broca's area. Science, 326 (5951): 445-9, 2009.

Sakai T, Miyamura M, and Kuzuhara S. [Palilalia and acquired stuttering in a case of Parkinson's disease]. Rinsho Shinkeigaku. Clinical Neurology, 32 (8): 859-63, 1992.

Saling LL and Phillips JG. Automatic behaviour: efficient not mindless. Brain Research Bulletin, 73 (1-3): 1-20, 2007.

Salmelin R, Schnitzler A, Schmitz F, and Freund HJ. Single word reading in developmental stutterers and fluent speakers. Brain, 123 ( Pt 6): 1184-202, 2000.

Sandrieser P and Schneider P. Stottern im Kindesalter. Stuttgart: Thieme, 2008.

Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, and Rezai AR. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature, 448 (7153): 600-3, 2007.

Scholz J, Klein MC, Behrens TE, and Johansen-Berg H. Training induces changes in white-matter architecture. Nature Neuroscience, 12 (11): 1370-1, 2009.

Scott SK and Johnsrude IS. The neuroanatomical and functional organization of speech perception. Trends in Neurosciences, 26 (2): 100-7, 2003.

Seijo FJ, Alvarez-Vega MA, Gutierrez JC, Fdez-Glez F, and Lozano B. Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. Acta Neurochirurgica, 149 (9): 867-75; discussion 876, 2007.

Shiller DM, Sato M, Gracco VL, and Baum SR. Perceptual recalibration of speech sounds following speech motor learning. Journal of the Acoustical Society of America, 125 (2): 1103-13, 2009.

Smith A. The control of orofacial movements in speech. Critical Reviews in Oral Biology and Medicine, 3 (3): 233-67, 1992.

Smith A and Kelly E. Stuttering: A dynamic multifactorial model. In Curlee RF and Seigel GM (Eds.), Nature and treatment of stuttering: New directions. New York: Allyn & Bacon, 1997, pp. 204-217.

Smith A, Sadagopan N, Walsh B, and Weber-Fox C. Increasing phonological complexity reveals heightened instability in inter-articulatory coordination in adults who stutter. J Fluency Disord, 35 (1): 1-18, 2010.

Smits-Bandstra S. Methodological considerations in the measurement of reaction time in persons who stutter. J Fluency Disord, 35 (1): 19-32, 2010.

Smits-Bandstra S and De Nil LF. Sequence skill learning in persons who stutter: implications for cortico-striato-thalamo-cortical dysfunction. J Fluency Disord, 32 (4): 251-78, 2007.

Smits-Bandstra S, De Nil L, and Rochon E. The transition to increased automaticity during finger sequence learning in adult males who stutter. Journal of Fluency Disorders, 31 (1): 22-42; quiz 39-40, 2006.

Sommer M, Knappmeyer K, Hunter EJ, Gudenberg AW, Neef N, and Paulus W. Normal interhemispheric inhibition in persistent developmental stuttering. Movement Disorders, 24 (5): 769-73, 2009.

Sommer M, Koch MA, Paulus W, Weiller C, and Büchel C. Disconnection of speech-relevant brain areas in persistent developmental stuttering. Lancet, 360 (9330): 380-3, 2002a.

Sommer M, Ruge D, Tergau F, Beuche W, Altenmuller E, and Paulus W. Intracortical excitability in the hand motor representation in hand dystonia and blepharospasm. Movement Disorders, 17 (5): 1017-25, 2002b.

Sommer M, Wischer S, Tergau F, and Paulus W. Normal intracortical excitability in developmental stuttering. Movement Disorders, 18 (7): 826-30, 2003.

Starkweather CW and Gottwald S. The demands and capacities model. II: Clinical applications. Journal of Fluency Disorders, 15: 143-157, 1990.

Stevens KN. Chapter 1. Anatomy and physiology of speech production In Stevens KN (Ed.) Acoustic phonetics. Cambridge, MA: MIT Press, 2000, pp. 1-54.

Stinear CM and Byblow WD. Elevated threshold for intracortical inhibition in focal hand dystonia. Movement Disorders, 19 (11): 1312-7, 2004.

Stinear CM, Coxon JP, and Byblow WD. Primary motor cortex and movement prevention: where Stop meets Go. Neuroscience and Biobehavioral Reviews, 33 (5): 662-73, 2009.

Suresh R, Ambrose N, Roe C, Pluzhnikov A, Wittke-Thompson JK, Ng MC, Wu X, Cook EH, Lundstrom C, Garsten M, Ezrati R, Yairi E, and Cox NJ. New complexities in the

genetics of stuttering: significant sex-specific linkage signals. American Journal of Human Genetics, 78 (4): 554-63, 2006.

Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, Yamanouchi T, Suzuki S, and Kawashima R. Training of working memory impacts structural connectivity. Journal of Neuroscience, 30 (9): 3297-303, 2010.

Tourville JA, Reilly KJ, and Guenther FH. Neural mechanisms underlying auditory feedback control of speech. Neuroimage, 39 (3): 1429-43, 2008.

Travis LE. The cerebral dominance theory of stuttering: 1931--1978. Journal of Speech and Hearing Disorders, 43 (3): 278-81, 1978.

Turgut N, Utku U, and Balci K. A case of acquired stuttering resulting from left parietal infarction. Acta Neurologica Scandinavica, 105 (5): 408-10, 2002.

Van Borsel J and Taillieu C. Neurogenic stuttering versus developmental stuttering: an observer judgement study. Journal of Communication Disorders, 34 (5): 385-95, 2001.

Van Borsel J, van der Made S, and Santens P. Thalamic stuttering: a distinct clinical entity? Brain and Language, 85 (2): 185-9, 2003.

Van Lieshout P. Dynamical Systems Theory and its application in speech. In Maasan B, Kent R, Peters H, Van Lieshout P, and Hulstijn W (Eds.), Speech motor control in normal and disordered speech. New York: Oxford University Press, 2004, pp. 51-81.

Van Lieshout P, Hulstijn W, and Peters H. Searching for the weak link in the speech production chain of people who stutter: a motor skill approach. In Maassen B, Kent R, Peters H, Lieshout Pv, and Hulstijn W (Eds.), Speech Motor Control in Normal and Disordered Speech. New York: Oxford University Press, 2007, pp. 313-356.

Van Lieshout PH, Hulstijn W, and Peters HF. From planning to articulation in speech production: what differentiates a person who stutters from a person who does not stutter? Journal of Speech and Hearing Research, 39 (3): 546-64, 1996.

Van Lieshout PH, Peters HF, Starkweather CW, and Hulstijn W. Physiological differences between stutterers and nonstutterers in perceptually fluent speech: EMG amplitude and duration. Journal of Speech and Hearing Research, 36 (1): 55-63, 1993.

Van Riper C. The nature of stuttering. Prentice-Hall: Englewood Cliffs, NJ, 1971.

Voges J and Krauss JK. [Neurological and technical aspects of deep brain stimulation]. Nervenarzt, 81 (6): 702-10, 2010.

Walker HC, Phillips DE, Boswell DB, Guthrie BL, Guthrie SL, Nicholas AP, Montgomery EB, and Watts RL. Relief of acquired stuttering associated with Parkinson's disease by

unilateral left subthalamic brain stimulation. Journal of Speech, Language, and Hearing Research, 52 (6): 1652-7, 2009.

Ward D. Stuttering & Cluttering: Frameworks for Understanding and Treatment. Hove, East Sussex: Psychology Press, 2006.

Watkins KE, Smith SM, Davis S, and Howell P. Structural and functional abnormalities of the motor system in developmental stuttering. Brain, 131 (Pt 1): 50-9, 2008.

WHO. ICD-10 F98.6 Cluttering Retrieved from www.who.int/classifications/apps/icd/icd10online, 2007.

Wingate ME. A Standard Definition of Stuttering. Journal of Speech and Hearing Disorders, 29: 484-9, 1964.

Wingate ME. The structure of stuttering. New York: Springer, 1988.

Wu JC, Maguire G, Riley G, Lee A, Keator D, Tang C, Fallon J, and Najafi A. Increased dopamine activity associated with stuttering. Neuroreport, 8 (3): 767-70, 1997.

Yairi E. Subtyping stuttering I: a review. J Fluency Disord, 32 (3): 165-96, 2007.

Yairi E and Ambrose N. A longitudinal study of stuttering in children: a preliminary report. Journal of Speech and Hearing Research, 35 (4): 755-60, 1992.

Yairi E and Ambrose NG. Early childhood stuttering I: persistency and recovery rates. Journal of Speech, Language, and Hearing Research, 42 (5): 1097-112, 1999.

Yairi E and Ambrose NG. Early childhood stuttering. Austin, TX: Pro-Ed, 2005.

Yaruss JS. Assessing quality of life in stuttering treatment outcomes research. J Fluency Disord, 35 (3): 190-202, 2010.

Yuan W, Holland SK, Schmithorst VJ, Walz NC, Cecil KM, Jones BV, Karunanayaka P, Michaud L, and Wade SL. Diffusion tensor MR imaging reveals persistent white matter alteration after traumatic brain injury experienced during early childhood. AJNR. American Journal of Neuroradiology, 28 (10): 1919-25, 2007.

Zelaznik HN, Smith A, Franz EA, and Ho M. Differences in bimanual coordination associated with stuttering. Acta Psychologica, 96 (3): 229-43, 1997.

Zimmermann G. Articulatory dynamics of fluent utterances of stutterers and nonstutterers. Journal of Speech and Hearing Research, 23 (1): 95-107, 1980a.

Zimmermann G. Stuttering: a disorder of movement. Journal of Speech and Hearing Research, 23 (1): 122-36, 1980b.

## Acknowledgements

The work included in this thesis would never have been possible without abundant expert support. First and foremost, I would like to express my deepest gratitude to Dr. Martin Sommer for his constant and terrific support, academic supervision, innovative ideas and patience provided the basis for the work included in my thesis. I am very grateful for his guidance, the numerous opportunities he offered me during the course of the years and for the independence with which I could conduct this research.

I like to express my sincere gratitude to Professor Walter Paulus. Without him, giving me the chance to work in his department and constantly supporting the ambitioned DTI study with children who stutter the progress during the course would never have been possible. Furthermore, he introduced me the fascinating field of brain stimulation.

I am very grateful to the members of my thesis committee Professor Julia Fischer and Professor Marcus Hasselhorn for their important advices and constructive criticism, advancing my progress over the years.

I wish to thank all members of the Institute of the Kasseler stuttering therapy. My special thanks goes to Dr. Alexander Wolff von Gudenberg for giving us the opportunity to recruit persons who stutter at his Institute and to Kristina Jung, without her help the measurement of the inter-rater reliability of the stuttering severity of the subjects in the fingertapping study would not have been possible.

I am very grateful to Torsten Wüstenberg for his tremendous support in the study on phoneme categorization in stuttering.

I would also like to thank Dr. Bettina Pollok for introducing me to the exciting topic of movement timing.

In addition I would like to thank all members of the Department of Clinical Neurophysiology who have supported me. I especially would like to acknowledge Dr. Andrea Antal for the inspiring journal clubs and Holger Rothkegel, Manuel Hewitt, Nivethida Tirugnanasambandam, Géza Ambrus, Klara Boros and Linh Hoang supporting me in various technical and practical TMS issues. A very special note of gratitude also goes to Marion Kurze helping me in a variety of organizational situations.

Furthermore, I deeply acknowledge the help of the members of the Göttingen stuttering support group and all the persons participating in the current studies promoting the research in stuttering.

I thank Tibor Auer for his constant and patient help in questions concerned with magnetic resonance imaging and I thank Professor Jens Frahm for giving me the opportunity to visit a methods course at the Biomedical NMR Research GmbH and to conduct an fMRI study with adults who stutter there.
I thank Dr. M. Röbel from the Department of Otorhinolaryngology and Prof. W. Engelke from the Department of Maxillofacial Surgery for their technical assistance concerning the tongue MEP recordings.
I acknowledge the supported by the „Stifterverband für die Deutsche Wissenschaft“, „Walter und Ilse Rose Stiftung“.
I would also like to acknowledge the valuable help of Prof. J. Gärtner, director of the Department of Pediatrics and Pediatric Neurology; Dr. Ch. Eich, consultant at the Department of Anaesthesiology, Emergency and Intensive Care Medicine; Dr. M. Röbl, consultant at the Pädiatrie 2 of the University Medicin Göttingen; Dr. Helms, physicist at the MR-Research in Neurology and Psychiatry; and D. Wettschereck, referee at the ethics committee of the University Medicin Göttingen for supporting the important DTI project to investigate a potential biomarker in stuttering at its onset.
Finally, I would like to express my deepest gratitude to my husband Andreas Neef, who has been a source of inspiration and analytical solutions, and to the members of my family who have always supported me, gave me the time to visit conferences and a speech science laboratory abroad.