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CNV amplitude as a neural correlate for stuttering frequency: A case report of acquired stuttering

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ABSTRACT

A neural hallmark of developmental stuttering is abnormal articulatory programming. One of the neurophysiological substrates of articulatory preparation is the contingent negative variation (CNV). Unfortunately, CNV tasks are rarely performed in persons who stutter and mainly focus on the effect of task variation rather than on interindividual variation in stutter related variables. However, variations in motor programming seem to be related to variation in stuttering frequency. The current study presents a case report of acquired stuttering following stroke and stroke related surgery in the left superior temporal gyrus. A speech related CNV task was administered at four points in time with differences in stuttering severity and frequency.

Unexpectedly, CNV amplitudes at electrode sites approximating bilateral motor and left inferior frontal gyrus appeared to be *inversely* proportional to stuttering frequency. The higher the stuttering frequency, the lower the activity for articulatory preparation. Thus, the amount of disturbance in motor programming seems to determine stuttering frequency. At right frontal electrodes, a relative increase in CNV amplitude was seen at the test session with most severe stuttering. Right frontal overactivation is cautiously suggested to be a compensation strategy. In conclusion, late CNV amplitude elicited by a relatively simple speech task seems to be able to provide an objective, neural correlate of stuttering frequency. The present case report supports the hypothesis that motor preparation has an important role in stuttering.

1. Introduction

Stuttering is a speech disorder primarily characterized by the occurrence of speech blocks, prolongations and/or repetitions of sound or syllables. When the disorder begins in early childhood, it is called developmental stuttering (Bloodstein and Ratner, 2008). However, an acquired form of stuttering following brain damage exists as well. This form is referred to as neurogenic stuttering and typically has its onset during adulthood (Van Borsel, 1997; Duffy, 2013). Neurogenic stuttering has been associated with a variety of lesions that can be located in all cortical lobes of both hemispheres as well as in the basal ganglia, thalamus, cerebellum, corpus callosum and brain stem (for a review, see Van Borsel, 1997; De Nil et al., 2009). Many of these areas are also assumed to be involved in developmental stuttering (e.g. Chang et al., 2009; Lu et al., 2010; Watkins and Klein 2011; Xuan et al., 2012). Although

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originally thought to be two different entities, it now seems that both types of stuttering may share common neural characteristics (Theys et al., 2012).

A neural hallmark of developmental stuttering is abnormal motor programming. Several studies found anatomical and functional disturbances in left inferior frontal gyrus (IFG), the core cortical region of motor preparation, and its connections. Besides structural anomalies in gray and white matter (Sommer et al., 2002; Chang et al., 2008, 2011; Watkins et al., 2008; Kell et al., 2009; Cykowski et al., 2010), uni- and bilateral hypo- and hyperactivations have been described in both silent reading and overt speech production (Fox et al., 1996; De Nil et al., 2000, 2003; Watkins et al., 2008). The most recurrent finding is an anomalous right laterality of the frontal operculum, the homolog of Broca's area (for a meta-analysis, see Brown et al., 2005). Increased activity in left IFG has also been observed during rest (Xuan et al., 2012). Magneto-encephalography revealed that adults who stutter (AWS) first activate left motor cortex and secondly left IFG during overt reading. Thus, AWS seem to initiate motor programs before preparing the articulatory code (Salmelin et al., 2000).

One of the electrophysiological substrates of motor preparation is the contingent negative variation (CNV). The CNV is an event-related, slow negative potential that occurs between two defined stimuli. The first stimulus is the warning stimulus (S1) which announces the imperative stimulus (S2) which on his turn requires a response (Walter et al., 1964; Rohrbaugh and Gaillard, 1983; McCallum, 1988; Regan, 1989; Golob et al., 2005). This response is typically a motor response though cognitive tasks have been reported as well (e.g. Cui et al., 2000; Bares et al., 2007). If the interval between the onset of S1 and S2 is ≥ 2 s, two CNVs can be distinguished within this interstimulus interval. The first one, the initial CNV, is related to orientation and is induced by the warning stimulus. It has its greatest amplitude at frontal sites within the first second following S1. The second one, the late CNV, occurs before S2 and has a wide cortical distribution with a maximum amplitude at central electrodes (Walter et al., 1964; Loveless and Sanford, 1974; Rohrbaugh and Gaillard, 1983; McCallum, 1988; Regan, 1989). The late CNV is reported to have multiple cortical and subcortical generators: prefrontal, premotor, primary motor, anterior cingulate, somatosensory and parietal regions as well as the basal ganglia and thalamus. Hence, the late CNV is generally accepted to measure the neuronal activity with in the cortico-basal ganglia-thalamic-cortical loop (Lamarche et al., 1995; Hamano et al., 1997; Gomez et al., 2003; Bares et al., 2007; Fan et al., 2007). This late CNV is suggested to represent primarily motor preparation, and, additionally, sensory anticipation for S2 (Bender et al., 2004; Bares et al., 2007).

CNV research mostly implies a motor response from the limbs. Only a few speech related CNV studies have been performed (e.g. Michalewski and Weinberg, 1977; Mock et al., 2011) and they rarely concerned stuttering. Pinsky and McAdam (1980) found no significant difference in speech CNV amplitude between 5 AWS and 5 control participants. Prescott and Andrews (1984), and Prescott (1988) evaluated the influence of the complexity of the speech response on the CNV amplitude in AWS. In their first study, no significant results were found (Prescott and Andrews, 1984). In the second study, AWS displayed larger CNV amplitudes than fluent speakers for familiar words, which are highly practiced speech responses and therefore very likely to be completely pre-programmed, suggesting that AWS have difficulties establishing efficient motor programs (Prescott, 1988). While these 2 studies mainly focused on the effect of task complexity on motor preparation, the effect of individual variation in stuttering severity has not been explored thus far. Nonetheless, Zimmerman and Knott (1974) observed large interindividual variations among stuttering participants in CNV amplitude and morphology. Several stuttering frequency and severity measures are repeatedly reported to correlate positively with cortical regions (Braun et al., 1997; Fox et al., 2000; Chang et al., 2009; Kell et al., 2009; Ingham et al., 2012) and subcortical brain structures like thalamus and basal ganglia (Braun et al., 1997; Giraud et al., 2008; Kell et al., 2009, Ingham et al., 2012) known to be involved in motor preparation. As on one hand, these regions are part of the cortico-basal ganglia-thalamic-cortical loop and on the other hand, the late CNV is known to measure the activity in this loop (Fan et al., 2007), a positive association between CNV amplitude and stuttering frequency/severity may be expected. More specifically, the amplitude of the late CNV during a speech production task is hypothesized to increase with increasing stuttering severity/frequency.

The current study presents a case of acquired stuttering following stroke in left superior temporal gyrus (STG) and stroke related surgery. A speech related CNV task was administered by use of electro-encephalography (EEG) at four points in time with differences in stuttering frequency. Due to its excellent temporal resolution, EEG allows one to look at a particular process with millisecond precision. Due to its limited spatial resolution however, EEG data can only provide activation information of broad neurological areas, not of specific brain regions.

2. Method

2.1. Participant

2.1.1. General information

MH is a 28-year-old right-handed, highly educated woman and native speaker of Dutch. At the time she suffered a stroke, she was working as a psychologist. There was no history of hearing complaints, psychiatric disorders, dyslexia or other speech-language problems prior to her neurological event. In addition, there was no family history of recovered or persistent developmental stuttering or cluttering. MH has a corrected-to-normal vision and took no medication apart from contraception. She gave her written informed consent to participate in this study, in accordance with the declaration of Helsinki. The study was approved by the local ethics committee.

2.1.2. Medical history

At birth, MH suffered from sepsis for which she spent several weeks in an incubator. Her psychomotor development, however, was normal. In 2010, after 7 years of complaints of fatigue and a regular occurrence of headache, a tentative diagnose of narcolepsy was made based on a polysomnography with a Multiple Sleep Latency Test. No cataplexy, sleep paralysis or hypnagogic hallucinations occurred. A brain MRI was normal. Methylphenidate, and subsequently modafenil were prescribed; however without any adequate effect. At the time of the stroke, fatigue had diminished and MH no longer took these medications.

2.1.3. Case report

Over a period of 2.5 months, MH sustained 5 hemorrhagic strokes from a cavernoma in the left temporal area. They were characterized by linguistic disturbances, especially auditory comprehension problems that took on average 60 min after which MH recovered completely. No other motor or cognitive disturbances were reported. Stuttering symptoms started to appear a few days after the third stroke. A detailed time line of the neurologic events, hospitalizations and neurophysiologic evaluations can be found in Fig. 1.

After this third stroke, MH was admitted to the hospital for the first time. On admission, clinical neurologic assessment was normal. An urgent brain MRI revealed a subacute intraparenchymatic hematoma in the left STG with moderate perilesional edema suggestive for a venous cavernoma (Fig. 2A). Conventional angiography showed no abnormalities. Because the linguistic symptoms appeared intermittently, a possible epileptic nature was suspected. Therefore, levetiracetam, 2×500 mg/day, was started. A few days after the third stroke, stuttering started to emerge. Since no increase in bleeding was seen on a brain Computerized Tomography (CT), an increase in edema was suggested to be the origin of stuttering onset. Behavioral assessment revealed no linguistic problems. MH obtained the maximum score on both the Token Test of the Aachen Aphasia Test (AAT – Dutch edition; Graetz et al., 1991) and the writing-on-dictate subtest (test 42) of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay et al., 1992) – Dutch edition (Bastiaanse et al., 1995).

After a fourth episode of aphasia, MH was re-admitted. The stuttering now seemed to be worse. Clinical neurological examination was normal. CT revealed a

slight increase of the intracerebral bleeding in the left temporal area. An additional Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan showed hypoperfusion near the left STG. About 10 days later, another episode of phatic problems occurred.

Due to the rapid recurrence of the events, a resection of the lesion was performed. Histopathology revealed an arteriovenous malformation (AVM). Initially after surgery, very discrete linguistic problems were noted which normalized rapidly without substantial logopaedic support. A few days after surgery the Token Test of the AAT was re-administered. Due to the localization of the lesion in the left STG, a more comprehensive evaluation of phonological processing skills was performed as well. These phonological processes include detection, identification and discrimination of spoken phonemes and the recognition of a spoken word as being part of the mental lexicon (McClelland and Elman, 1986; Poeppel et al., 2008). This can be evaluated by subtests 1, 2 and 5 of the PALPA (Kay et al., 1992; Bastiaanse et al., 1995). Phoneme discrimination was assessed by having MH judge whether aurally presented minimal pairs of pseudowords (subtest 1) and real words (subtest 2) were similar or not. Lexical decision was measured by subtest 5 in which 80 real and 80 pseudowords were presented aurally. On all these tests, MH obtained the maximum score. Nevertheless, mild stuttering persisted. Both selective angiography and MRI showed a favorable post-surgery image with no arguments for a residual AVM (Fig. 2B).

About 13 weeks after surgery, MH was re-admitted to the hospital due to a sudden increase in stuttering severity. Clinical neurological examination was normal. Both angiography and MRI were unchanged. No venous anomaly, arteriovenous fistula or AVM could be seen and MH was dismissed. Five months after surgery, MH resumed work on a part-time basis. No speech therapy was initiated for her stuttering. Anti-epileptic treatment was ultimately stopped.

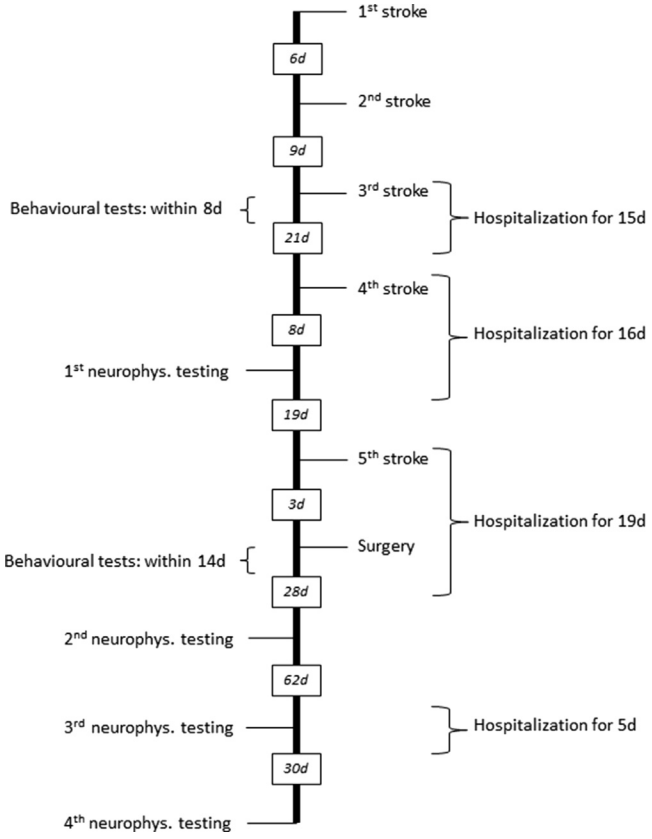

Fig. 1. A detailed time scale of all events. Durations are expressed in number of days (d).

2.2. Procedure

The neurophysiological testing was executed once pre-surgery and 3 times post-surgery: (1) after 1 month (2) after 3 months (3) after 4 months. Each evaluation followed the same procedure. First, speech and reading samples were collected. Secondly, the CNV paradigm was performed. Finally, three additional phonological tasks were administered that were presented in a randomized order over test session. The CNV task was always performed before the phonological tasks to limit the influence of fatigue. At the 4th testing, the phonological tasks were not administered. There were no differences between test sessions concerning medication status as at all test moments, only levetiracetam (2×500 mg/day) was taken.

2.2.1. Speech samples

On each test moment, a conversational and reading speech sample was collected. MH read the Dutch translation of the text 'The north wind and the sun' (International Phonetic Association, 1974). During the conversational speech sample MH engaged a conversation with the investigator about work/family/hobby. Due to a sudden increase in stuttering severity, a more extensive speech evaluation was done at the 3rd testing. Automatic speech (counting, reciting the days of the week and the months of the year) and repetition of words and sentences with increasing length was included as well. Speech samples were videotaped using a Canon ACV HD (1920×1080) camera and audiotaped in PRAAT, a free software program for acoustical analysis (Boersma & Weenink, Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands) using a Samsung CU01 microphone placed 50 cm in front of the participant.

Speech samples were judged for stuttering severity by means of the Stuttering Severity Instrument, fourth edition (SSI-4; Riley, 2008) and percent stuttered syllables (%SS) was calculated following the principles of the Stuttering Measurement System (Ingham and Ingham, 2011). Part-word (sound/syllable) repetitions, prolongations, blocks, broken words and tense pauses (American Speech-Language-Hearing Association, 1999; Yaruss, 1997) were counted as stuttered syllables. It is an ongoing debate whether or not to count monosyllabic word repetitions as stutters (Einarsdottir and Ingham, 2005). In this study, repetitions of monosyllabic words were considered as stuttered dysfluencies when they were repeated at a high rate (Bezemer et al., 2010; Guitar, 2006), with apparent undue stress, tension or struggle (American Speech-Language-Hearing Association, 1999; Van Zaalen and Winkelman, 2009) or when the number of repetition units was 3 or more (Boey et al., 2009; Gregory, 1993). Because stuttering severity can vary

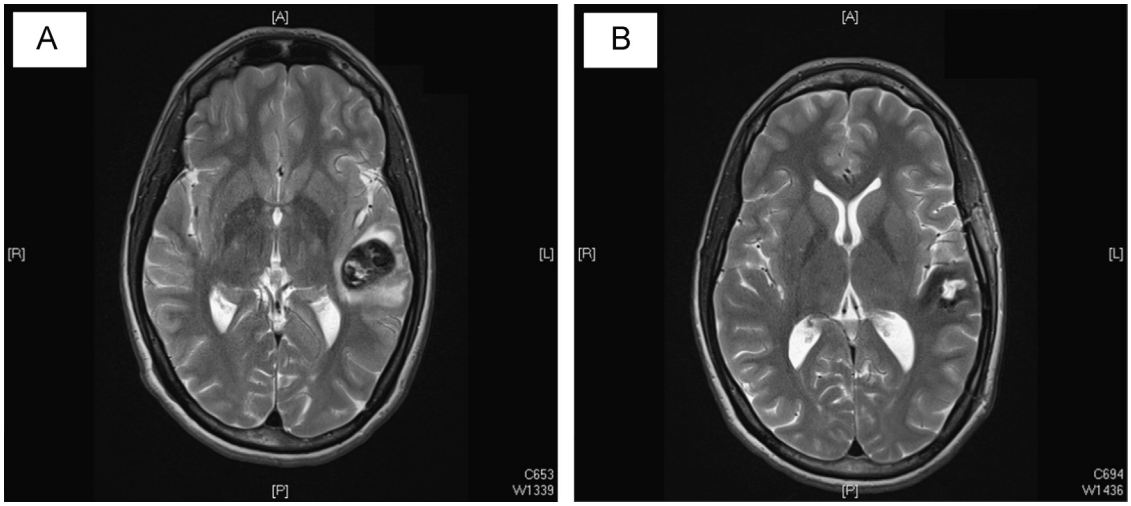

Fig. 2. MRI scan, T2-axial, after the third stroke (A) and 2 months after surgery (B).

considerably over the course of a conversation, long speech samples are recommended to obtain a reliable representation of the stuttering pattern (Sawyer and Yairi, 2006). This holds especially true for a single case study. Since the shortest conversation sample consisted of 735 syllables, the first 735 syllables of each sample were evaluated.

All samples were scored independently by two speech language pathologists (SLP) specialized in stuttering. One of the raters was blind to the sequence of the test sessions. Inter-rater reliability was assessed by calculating the intraclass correlation coefficient (ICC). All ICC's were high which ensured good to even excellent agreement. Any points of disagreement were discussed to reach consensus (Table 1).

Stuttering severity was also perceptually judged by three other speech language therapists specialized in stuttering using the scale from the Camperdown Program (O'Brian et al., 2004; Karimi et al., 2014). The latter is a nine point scale in which 1=no stuttering, 2=extremely mild stuttering, and 9=extremely severe stuttering. Conversation and reading samples were judged separately. Samples were presented in a randomized order and scored independently by the judges. The severity of each sample was then determined by calculating the mean of the severity scores assigned (Table 1).

2.2.2. EEG data acquisition

EEG data were collected with Neuron-Spectrum-5 (4EPM) registration software (Neurosoft, Moscow, Russia). By use of an universal EEG cap (Haube S2), 21 Ag/AgCl electrodes (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2) were placed on the scalp according to the international 10/20 system. Two more electrodes were placed above the right side of the upper lip and underneath the left side of the under lip to register the EMG of the orbicularis oris muscle. An additional electrode on the forehead was used as ground. Neurophysiological data were recorded against a linked ears reference at a sampling rate of 500 Hz (0.01–75 Hz band-pass filter). Impedance of each electrode was kept below 5 kΩ. During all tasks, MH was encouraged to avoid orofacial movements and to reduce eye-blinks as much as possible. MH's performances were also videotaped using a Canon ACV HD (1920 × 1080) camera.

2.2.3. CNV paradigm

A self-composed picture naming task was administered in which S1 consisted of a picture that was shown for 1 s. The S2, in the form of a short, black line, appeared 2 s after S1 onset (the foreperiod duration was 2 s) indicating that MH should name the picture as quickly as possible. S2, shown for 2 s, was followed by a black screen for another 2 s. If MH continued to stutter on a word once this black screen appeared, she was instructed to stop speaking in order not to contaminate the next trial with muscular artifacts (for a diagram of the CNV task, see Fig. 3A). One hundred and ten black and white pictures were shown on a white background in the middle of a computer screen that was placed 1 m in front of MH. She was instructed to name only one word or to say 'pass' if she did not know the noun.

The pictures were selected from a picture naming norms database, provided by the Department of Experimental Psychology from the Ghent University, Belgium (Severens et al., 2005). For further analysis, speech onset had to be determined. Articulatory movements were shown to precede vocalization during a Bereitschaft-spotential paradigm. Depending on the initial phoneme, the lips or the tongue were the first source (McArdle et al., 2009). Lip movements are easier to detect than tongue movements with electromyography (EMG). Therefore, pictures were chosen that referred to a noun that had a bilabial (/m/, /w/, /b/, /p/) or labiodental (/f/, /v/) initial phoneme. For the 4 session, MH correctly identified 106, 107, 106, and 107 pictures respectively. Some responses were additionally excluded from further analyses because (1) the word was produced before S2 was shown (2) the produced word did not have a labiodental or bilabial initial phoneme, (3) MH swallowed or made an inappropriate lip movement within 1500 ms preceding S2 which was judged based on the videotape recordings and visual inspection of the EMG signal. Stuttered responses would have been analyzed separately. However, no stutters occurred. This was judged on-line by the first SLP and off-line based on the videotape recordings by the second SLP. In this way, the following number of trials was preserved for further off-line EEG analyses: 100, 104, 101, 102 for the 4 sessions respectively.

These off-line analyses were performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). After additional filtering (0.01–30 Hz band-pass filter, Notch filter 50 Hz), eye artefacts were removed by Independent Component Analysis (Mennes et al., 2010). Two components (eye blinks; left-right eye movements) were excluded based on inspection of the components' spatial distribution. It is recommended to analyze language related brain activities not only time-locked to stimulus onset, but also time locked to response onset. Activities linked to response execution emerge time-locked to the response and might consequently be reduced in analyses time-locked to stimulus presentation (Riès et al., 2013). Therefore, data were analyzed with respect to S2 and lip movement onset, from here on referred to as stimulus and response locked respectively. For the stimulus locked analyses, the continuous EEG data were segmented into epochs of 4200 ms, starting 2200 ms prior to S2, and baseline corrected to the first 200 ms of the

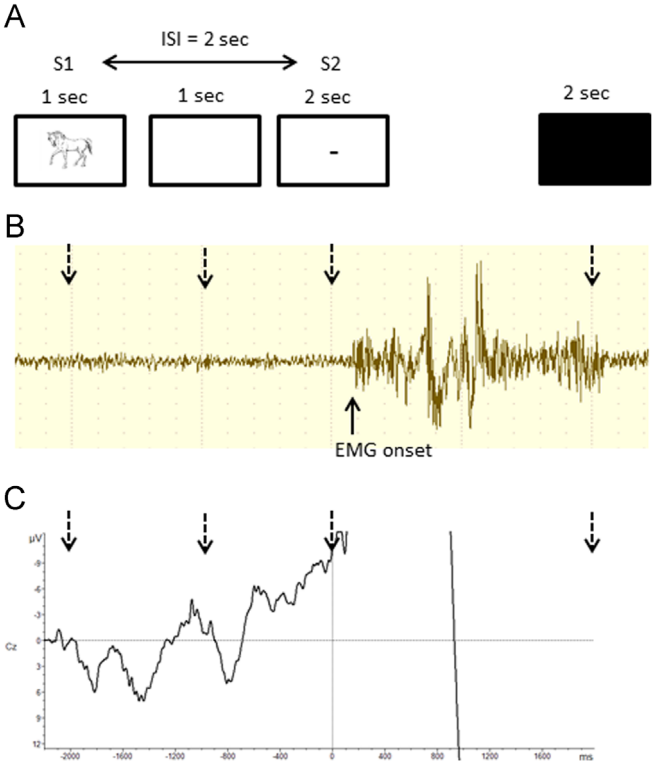

Fig. 3. (A) Diagram of the picture naming CNV task. The warning stimulus (S1) consists of a picture, the imperative stimulus (S2) of a short, black line that prompts the participant to name the picture as quickly as possible. Interstimulus interval (ISI) is 2 s. (B) EMG signal of the orbicularis oris muscle of one response. The dotted arrows represent the onset of the corresponding image in (A). The full arrow represents the onset of the EMG signal. Reaction time is the time between S2 onset and EMG onset. (C) Stimulus locked average at Cz at the first test session. Latency (*x*-axis) is represented in milliseconds (ms) and amplitude (*y*-axis) in microvolts (μV). Negative is plotted upwards. Baseline is the first 200 ms op the epoch i.e. 200 ms before S1 onset. The 0 ms point is S2 onset. Again, dotted arrows represent the onset of the corresponding image in (A).

Table 1
Results of the SSI-4 (Riley, 2008) obtained after consensus, the corresponding ICC's and the mean severity rating score obtained from 3 clinicians.

	Stuttering Severity Instrument (SSI-4)									Severity rating	
	Reading		Conversation		Duration		Physical concomitants	Total score	Severity label	Reading	Conversation
	%SS	Score	%SS	Score	Average	Score					
Pre-surgery	0	0	0.8	2	0.6	4	1	7	Not stuttering	1.0	1.7
1 month post-surgery	0.5	2	1.4	2	1.2	6	2	12	Very mild	2.0	2.3
3 months post-surgery	0	0	7.3	6	1.2	6	4	16	Very mild	1.0	5.0
4 months post-surgery	0	0	2.5	3	0.6	4	6	13	Very mild	1.0	2.5
ICC	80		98		82		88	90			

epochs (Luck, 2005), which is the 200 ms time window before S1 onset. For the response locked analyses, lip movement onset was visually determined based on the EMG data. Therefore, the EMG data were separately band-pass filtered from 15 Hz to 100 Hz to reduce the contamination by motion artefacts and non-myogenic potentials (Van Boxtel, 2001). The continuous EEG data were also segmented into epochs of 4200 ms, starting 2300 ms prior to lip EMG onset, and baseline corrected to the first 200 ms of the epochs (Luck, 2005). The starting point of the segmentation was somewhat different than in the stimulus locked analyses due to a reaction time delay. Reaction time was determined as the time between S2 and lip EMG onset (see Fig. 3B). For the 4 test sessions respectively, 55%, 65%, 40% and 40% of the responses had an EMG onset occurring after S2. If the segmented epochs started 2200 ms before lip movement onset and were baseline corrected to the first 200 ms, on average 50% of the responses would have a baseline that contained a part of the visual evoked potentials elicited by S1. This would have added a serious amount of noise to the data since baselines should be as neutral as possible and are not allowed to contain any kind of potentials. Therefore, the starting point of the segmentation was put 100 ms earlier and thus started 2300 ms prior to lip movement onset. For all test sessions, more than 90% of all responses had a reaction time $\leq$100 ms. All trials containing artefacts were manually excluded (Cui et al., 2000; Bares et al., 2007; Mock et al., 2011). By averaging over corresponding epochs, the CNV potential could be computed for each test moment. For the 4 test sessions, the average was based on 92, 96, 91, 99 and 89, 95, 91, 102 trials for the stimulus locked and response locked analyses respectively.

For both stimulus and response locked analysis, mean amplitude was calculated from −500 to 0 ms since this time window contained the maximal variation of the CNV potential. This was done for all frontal (F7, F3, Fz, F4, F8), central (C3, Cz, C4) and 2 temporal (T3, T4) electrodes. The latter electrodes were situated above the lesion site and its contralateral homolog. The other electrodes were located near regions important for speech preparation and execution.

2.2.4. Phonological assessment

As mentioned above, a detailed analysis of phonological processing skills was recommended due to the localization of the lesion. As behavioral tests may not be sensitive enough to detect very mild language problems, an additional neurophysiological examination was performed at the first three test sessions. Tests for this additional examination were selected from Aerts et al. (2013) in which a detailed description of the tasks and their analyses can be found. All tasks were auditory oddball paradigms in which the proportion of standard vs deviant stimuli was 4/1. Phoneme discrimination was evaluated under an attended (P300) and unattended (Mismatch Negativity – MMN) condition. Both contained [bə] as standard and [gə] as deviant phonemes. An unattended MMN paradigm was used as word recognition task in which real words were presented as standard and pseudowords as deviant stimuli. During the P300, MH had to press a button when hearing the deviant stimulus. During the MMN tasks, MH was instructed to ignore the stimuli and focus on a silent movie. All stimuli were presented binaurally with Apple Inc. earphones, placed directly into the external ear, at a comfortable listening level of ca. 70 dB.

Peak latency and amplitude were measured at Fz/Cz for the MMN wave and at Pz for the P300 wave in the unattended and attended phoneme discrimination task respectively. In the word recognition task, both real and pseudowords evoked the successive peaks N100, P200 and N400. Peak latency and amplitude were calculated at F3/Fz/F4 for P200 and at Cz for N100 and N400. These values were compared to the norms obtained in Aerts et al. (2013). Although scores that fall within 2 SD from the mean are usually considered normal, scores falling between 1.5 and 2 SD are already borderline (Lezak et al., 2004). Therefore, only latency and amplitude values falling within 1.5 SD from the averages obtained in Aerts et al. (2013) were considered normal.

3. Results

3.1. Speech samples

In Table 1, an overview of all stutter related scores is given. According to the SSI-4 (Riley, 2008), no stuttering could be diagnosed pre-surgery and a very mild stuttering severity occurred post-surgery. Although all post-surgery test sessions showed only minor differences in total score, a large variation in %SS during conversation occurred. Based on these scores, MH stuttered moderately during the 3rd and mildly during the other test sessions (Onslow, 2000). Conversely, no such variation was observed in non-propositional speech. MH rarely stuttered during reading. Moreover, no stutters were noted during automatic speech and during repetition of words and sentences at the 3rd testing. The severity rating by the three judges mirrored the results of %SS for both reading and conversation. Only at the 2nd test session, extremely mild stuttering was perceived during reading. For conversation, test sessions 1, 2, and 4 gave comparable results, while test session 3 obtained a much higher score.

MH exclusively stuttered at word initial phonemes. No stutters involving entire syllables or longer linguistic units were noted. These stutters were mainly blocks and prolongations. Additionally, a slight increase in amount of physical concomitants seemed to appear over time. MH sometimes nodded her head and frowned. At the 4th evaluation, a glottal fry could be heard occasionally. All these behaviors were transient and mostly scored as 'barely noticeable for a casual observer'.

Concerning avoidance and escape related secondary behaviors, MH was observed to look for synonyms and to break off sentences when a stutter appeared or was anticipated. Remarkably, she was scarcely aware of this behavior herself. When asked whether she applied some tricks to avoid/escape a stutter, she mentioned not to do so. MH also underestimated her stuttering severity. Both at the 2nd and 4th testing, she said that the stuttering was almost gone, while both speech therapists could clearly distinguish several stutters during the conversation. Overall, MH was concerned about her stuttering, especially in the beginning, when the stuttering appeared, and at the 3rd testing, when the sudden increase had occurred.

3.2. CNV paradigm

A typical CNV wave was evoked, as can be seen in Figs. 3C and 4. After visual and linguistic processing of the pictures (S1), a clear increase in negativity occurred between 700 and 1000 ms following S1. This early CNV was seen over (pre)frontal, central and parietal electrodes. At 1000 ms, the early CNV was interrupted by a new phase of visual processing because at this point in time the picture disappeared from the screen. Shortly hereafter, a steep increase in negativity could be observed, peaking around the presentation of S2. This negativity is the late CNV and has a wide scalp distribution. The largest CNV was elicited in the pre-surgery test session (Figs. 5, 6 and 7).

Two different activity patterns could be discerned which were most clearly seen in the EMG averaged data. Over bilateral and midline central (C3, Cz, C4) and left and midline frontal (F7, F3, Fz) electrodes, CNV amplitude was inversely proportional to stuttering severity and frequency during conversation. The more MH stuttered, the lower the CNV amplitude became. The remaining 4 electrodes (T3, F4, F8, T4) showed a different pattern that was particularly observed in the response locked analyses. While the CNV amplitude at the 1st, 2nd and 4th test session did show the inverse association with stuttering symptoms, the CNV amplitude measured at the 3rd testing did not. Although MH stuttered more at the 3rd than at the 4th testing, the CNV was much higher at the 3rd test session. Note that at the 1st, 2nd and 4th testing, 3 out of these 4 electrodes were amongst the lowest amplitudes of all electrodes. However at the 3rd testing, T3, F4 and F8 had the highest amplitude of all (see Fig. 5). Thus, the CNV at these electrodes showed a *relative increase* compared to the CNV over central and left frontal areas.

3.3. Phonological evaluation

All neurophysiological tests evoked clear event-related potentials in which all peaks could be distinguished (see Fig. 8). Only minor deviations were seen in latency measures (Table 2). These deviations solely encompassed faster latencies than average. All amplitude measures were within normal limits (Table 3).

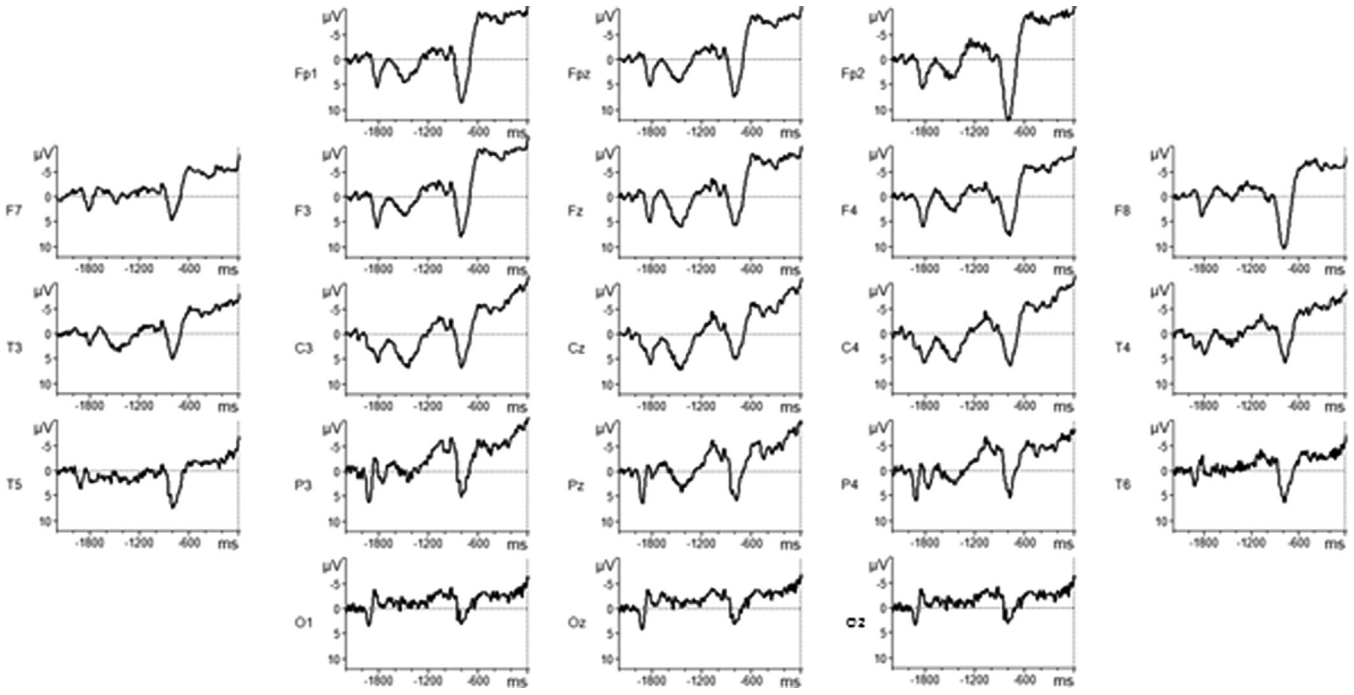

Fig. 4. Stimulus locked analysis of all electrodes at the first test session. Latency (*x*-axis) is represented in milliseconds (ms) and amplitude (*y*-axis) in microvolts (μV). Negative is plotted upwards. Baseline is the first 200 ms op the epoch i.e. 200 ms before S1 onset. The 0 ms point is S2 onset.

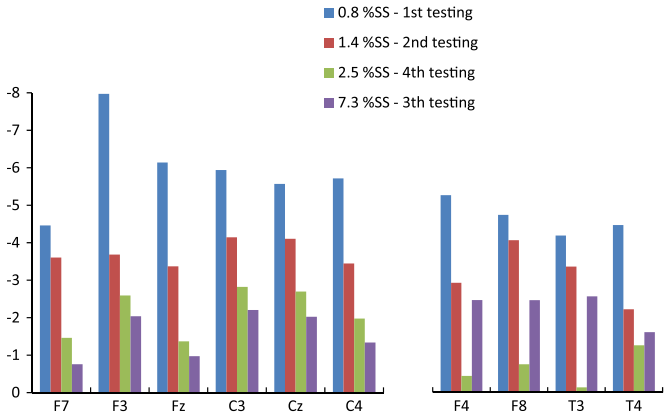

Fig. 5. Mean CNV amplitude (μV) of the response locked analysis at all test sessions. Bars are colored corresponding to % SS during conversation.

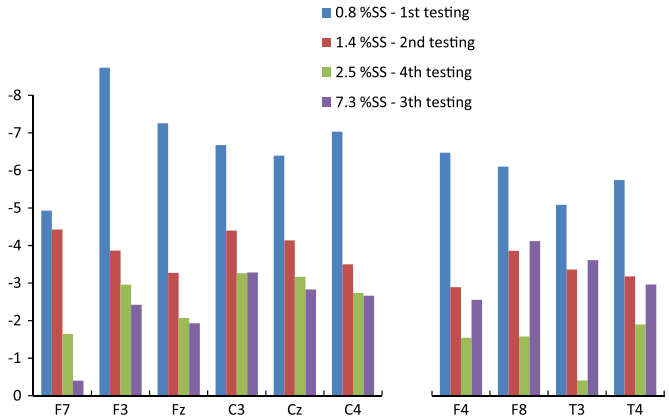

Fig. 6. Mean CNV amplitude (μV) of the stimulus locked analysis at all test sessions. Bars are colored corresponding to % SS during conversation.

4. Discussion

In the present case report, motor preparation was evaluated by a CNV task at several points in time with differences in stuttering severity and frequency. A typical CNV wave was evoked by a picture naming task. Besides an early CNV at 700–1000 ms following S1, S2 was preceded by a second and larger negativity over (pre)frontal, central, parietal and temporal areas. The latter wave is the late CNV related to motor preparation.

4.1. CNV amplitude related to motor preparation

Surprisingly, a reversed association appeared between late CNV amplitude and stuttering frequency during conversation. The higher the stuttering frequency, the smaller the CNV amplitude. This observation was mainly seen in the response locked analysis which highlights the importance of taking reaction time into account in stuttering (Smits-Bandstra and Gracco, 2013). As outlined in the method section, activities linked to response execution might be reduced in stimulus locked analyses (Riès et al., 2013). The reduction in CNV amplitude was observed over bilateral and midline central, and over left and midline frontal electrodes. These electrode sites approximate bilateral (pre)motor, somatosensory areas and left IFG, which are known to be responsible for motor preparation and execution (Price, 2012). The present study suggests that articulatory preparation has an important role in stuttering. The amount of reduction in motor programming activation seems to be related to the amount of stutters that will occur during conversation.

This observation is opposite to the hypothesis put forward in Section 1. Neuroimaging research mostly described positive correlations between stuttering severity/frequency and several (sub) cortical brain structures that are part of the cortico-basal ganglia–thalamic–cortical loop (Braun et al., 1997; Fox et al., 2000; Giraud et al., 2008; Chang et al., 2009; Kell et al., 2009; Ingham et al., 2012). As the amount of activity in this loop is known to be positively associated with the CNV amplitude (Fan et al., 2007), an increased amplitude was expected. Indeed, some old CNV reports

Fig. 7. The late CNV at Cz for all test sessions, the 700 ms preceding the averaging point are shown. On the left, the stimulus locked analysis is displayed in which 0 ms represents S2 onset. On the right, response locked analysis is depicted in which 0 ms represents EMG onset. Negative is plotted upwards.

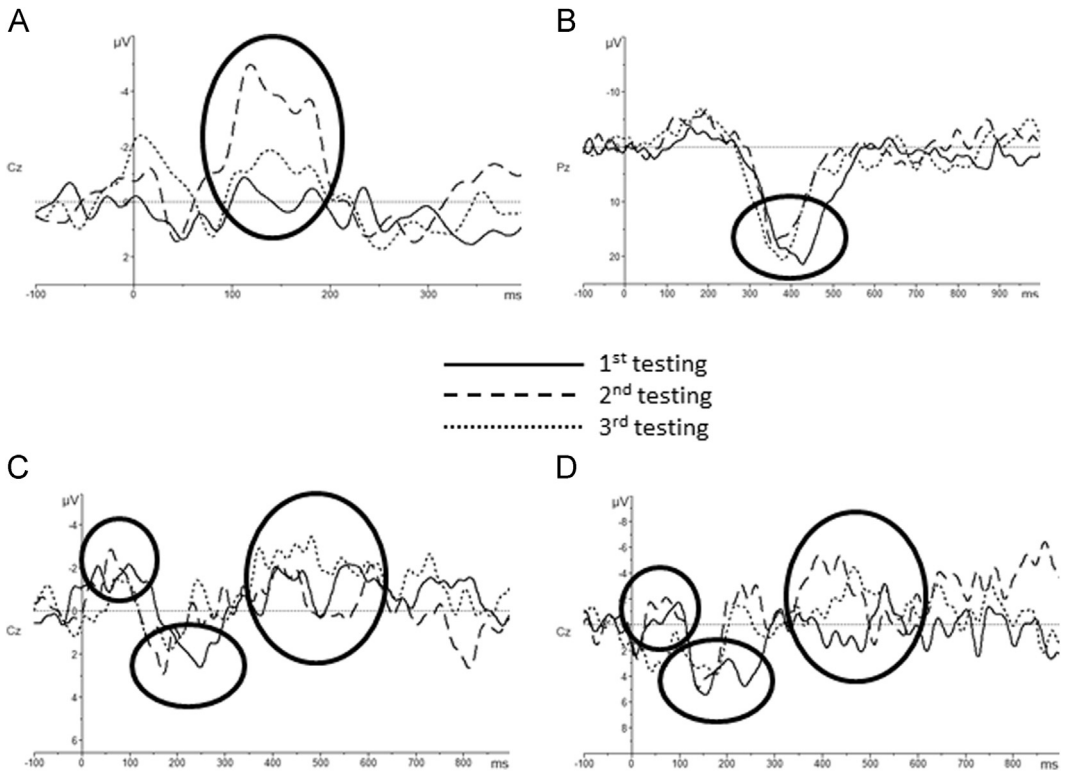

Fig. 8. Event-related potentials (ERP) evoked by the phonological tasks. Latency (*x*-axis) is represented in milliseconds (ms) and amplitude (*y*-axis) in microvolts (μV). Negative is plotted upwards. Top: the unattended and attended phoneme discrimination tasks: (A) MMN at Cz (B) P300 at Pz. Bottom: the word recognition tasks evoked the successive peaks N100, P200 and N400: (C) real words at Cz (D) pseudowords at Cz.

in stuttering found an enlarged CNV amplitude (Prescott and Andrews, 1984; Prescott, 1988). However, all these studies concern developmental stuttering. Although neurogenic and developmental stuttering are suggested to share common neural substrates (Theys et al., 2012), its translation in CNV amplitude seems to be different. The neural network involved in fluent (and stuttered) speech is suggested to be differently interrupted causing the opposite observation in MH.

According to the DIVA (Directions into Velocities of Articulators) speech model, two systems are necessary for fluent speech: a feedforward and a feedback system. Motor preparation is provided by the so called Speech Sound Map situated in the caudoventral portion of the precentral gyrus. The initiation and sequencing of different speech motor programs would depend on activity in the basal ganglia and the thalamus. Both are part of the feedforward system (Guenther, 2006). As the CNV is related to motor programming and the cortico-basal ganglia–thalamic–cortical loop, this potential would reflect activity in the feedforward loop. Left STG on the other hand, MH's lesion site is situated in the feedback system. In this system, the expected and the actual sensory speech output are compared and corrected if necessary (Guenther, 2006; Golfinopoulus et al., 2010). Thus, MH's lesion site is primarily affecting another subsystem than the one that is measured by the CNV.

Moreover, developmental stuttering is suggested to have its primary lesion in the proximity of the left IFG (Sommer et al., 2002; Chang et al., 2008, 2011; Watkins et al., 2008; Kell et al., 2009; Cykowski et al., 2010) which is located in the feedforward

Table 2
Latency (ms) values of the neurophysiological assessment of auditory phonological processing.

	Phoneme discrimination		Auditory word recognition					
			Words			Pseudowords		
	MMN	P300	N100	P200	N400	N100	P200	N400
Pre-surgery	***115***	426	98	205	406	98	159	530
1 month post-surgery	***120***	372	***68***	168	416	72	153	***392***
3 months post-surgery	140	378	***70***	181	544	90	155	464
Norms: M (SD)	171 (28.17)	409 (37.71)	92 (8.41)	182 (18.74)	494 (60.02)	94 (16.39)	170 (19.40)	507 (54.51)

Latencies not falling within M ± 1.5 SD are italicized and displayed in bold. Norm scores are obtained from Aerts et al. (2013).

Table 3
Amplitude (μV) values of the neurophysiological assessment of auditory phonological processing.

	Phoneme discrimination		Auditory word recognition					
			Words			Pseudowords		
	MMN	P300	N100	P200	N400	N100	P200	N400
Pre-surgery	−1.37	21.41	−2.15	3.17	−2.05	−1.70	4.67	−3.18
1 month post-surgery	−5.32	16.56	−2.55	3.27	−2.14	−2.06	5.15	−5.33
3 months post-surgery	−1.86	20.67	−1.55	1.44	−2.47	0.55	4.06	−4.40
Norms: M (SD)	−4.48 (2.12)	13.03 (5.65)	−2.03 (1.12)	1.67 (1.34)	−3.26 (1.26)	−3.16 (2.35)	3.52 (3.26)	−4.37 (2.83)

All amplitudes fall within M ± 1.5 SD. Norm scores are obtained from Aerts et al. (2013).

system. This lesion will affect auditory-motor integration and provide aberrant input to the basal ganglia (Giraud et al., 2008). In the presented case, auditory-motor integration will probably be disturbed as well due to the lesion in the feedback system. However, since MH's lesion is located in a different region, and in a different subsystem of the DIVA model, than the hypothesized lesion in developmental stuttering, its impact on auditory-motor integration, on left IFG activation and consequently on the cortico-basal ganglia–thalamic–cortical loop, might be different as well. Hence, the direction of the CNV amplitude alteration might be reversed.

Since the present study concerns a case description, no correlation analysis could be performed. Future group studies may clarify whether a correlation between CNV amplitude and stuttering severity/frequency exists. Moreover, these group studies are recommended to involve developmental stuttering to see whether the hypothesized positive correlation based on the literature and the alternative explanation for the reversed association found in MH hold true. But taken together, late CNV amplitude elicited by a relatively simple speech task is hypothesized to provide an objective, neural correlate of stuttering frequency.

Note that MH did not stutter during the CNV task. Isolated word production usually evokes no or very little stuttering (Brown, 1938; Adams et al., 1973) probably because it requires relatively little effort by the neural speech motor system (Bloodstein and Ratner, 2008). So, even without stuttered speech during task performance, a substantial motor programming dysfunction may be present. This observation suggests that when a limited load is put on the speech motor system, motor programming disturbances are either not enough to evoke stuttering or are surmountable by compensation strategies.

In the response-locked analysis, the reversed activity pattern was not observed over F4, F8, T3 and T4. Late CNV was larger at the 3rd compared to the 4th test session though %SS was larger at the 3rd session. At the 1st, 2nd and 4th testing, 3 out of these 4 electrodes were amongst the lowest amplitudes of all electrodes. Conversely, 3 out of these 4 (T3, F4 and F8) had the highest amplitude of all at the 3rd evaluation. Thus, at the 3rd evaluation, the CNV over these electrodes showed a relative increase compared to the CNV over central and left frontal sites. It is tempting to suggest that this relative increase at the right sided electrodes is related to compensation strategies and at T3 to the cause of the stuttering worsening since T3 is closely located to left STG, MH's lesion site. This suggestion concurs with a traditional divergence made between left and right hemisphere in developmental stuttering. While left hemisphere observations would reflect the primary deficit (Sommer et al., 2002; Chang et al., 2008, 2011), right sided activations would result from compensatory processes. Especially right frontal regions are reported in this respect (Braun et al., 1997; Preibisch et al., 2003). RFO is the most frequently reported brain region to show anomalous right activation in AWS (for a meta-analysis, see Brown et al., 2005). Its overactivation is suggested to compensate for a deficient signal transmission in left hemisphere areas for motor preparation and execution (Sommer et al., 2002; Watkins et al., 2008; Chang et al., 2011). As F4, F8 and T3 are closely located to RFO and to the contralateral homolog of MH's lesion site, these electrodes might have registered this overactivation. However, to substantiate this hypothesis, source reconstruction techniques should be applied on the data. Unfortunately, source localization would not provide reliable results because the present manuscript concerns a case report in which data is collected with 21 electrodes. In sum, right sided increases in CNV amplitude observed at the 3rd evaluation are cautiously suggested to reflect an attempt to deal with the increase in stuttering frequency.

4.2. Stuttering frequency, not severity

CNV amplitude was inversely proportional to both %SS during conversation and overall stuttering severity as measured by the SSI-4 (Riley, 2008). However, the latter measure only showed small differences between the post-surgery evaluations. Such small differences are very unlikely to have caused such obvious changes in neural activity. Therefore, the pattern in CNV amplitude observed over central and left frontal sites is assumed to be related

to stuttering frequency during conversation rather than to overall stuttering severity. Similarly, previous studies documenting associations between neural findings and stutter related variables, mostly found this correlation with a measure related to stuttering frequency (Braun et al., 1997; Fox et al., 2000; Giraud et al., 2008; Chang et al., 2009; Kell et al., 2009; Ingham et al., 2012). The severity measure differs from stuttering frequency in that it also includes 'physical concomitants'. These secondary behaviors do not belong to the primary speech characteristics of stuttering. They are, at least partly, not the result of neural disturbances, but rather of the coping behavior by the speaker to his/her stuttering. Also the severity ratings provided by the judges, mirror the %SS scores. This is in line with previous research reporting high correlations between %SS and clinician severity rating (O'Brian et al., 2004; Karimi et al., 2014).

4.3. Other influencing factors

Although influences from attention deficits cannot be excluded, the present data provide several arguments for stuttering frequency to be the main contributor to CNV changes. First, the reversed association pattern is observed over brain regions that are well-known to be primarily involved in motor functions (Price, 2012). Secondly, the relative increase during the 3rd testing at right frontal areas is a typical compensation strategy for motor difficulties in stuttering (Preibisch et al., 2003). Also a retest-effect is very unlikely to have occurred since CNV amplitude measures are shown to be reliable and stable (Kropp et al., 2000). Moreover, if there had been a retest-effect, all electrodes should have shown a similar, decreasing pattern over consecutive test sessions. Finally, although MH's neurological condition was not entirely stable over time (after the pre-surgery test session, MH experienced one more stroke and the surgery in itself), no variance in neurological condition between all three post-surgery sessions was present. Therefore, its influence on the present results will be limited to even absent.

As the left STG is a key area for auditory and phonological processing (Salmelin, 2007; Vigneau et al., 2006), problems in these domains may arise. However, MH was flawless at behavioral auditory language testing. Also neurophysiological examination revealed no particular auditory or language deficits. The only observed deviations concerned faster latencies than average which can but be seen as an alteration, not as a dysfunction. Even more so because the amplitudes of all peaks were within normal limits at all test sessions. Early sensory-perceptual processes and intermediate stages of auditory feature analyses are reflected by N100 and P200 (Cooper et al., 2006; Näätänen et al., 2011). The latter peak also reflects some phonological processing (Zhang et al., 2009). In addition, phonological processing was specifically evaluated by the MMN and P300 task which required phoneme discrimination (Aerts et al., 2013). As all these peaks were within normal limits, MH can be concluded to have normal auditory and phonological processing skills. Finally, following the N400 results, also lexical processing (pseudo word processing) and semantic integration (real word processing) seems to be unaffected (Kutas and Federmeier, 2000; Giaquinto et al., 2007; Hauk et al., 2012). In conclusion, both behavioral and neurophysiological evaluation revealed no remarkable deficits in auditory, phonological and lexico-semantic processing that might have had a modifying role in CNV amplitude variation.

4.4. Acquired stuttering

Stuttering following brain damage may not always be 'neurogenic' stuttering. Psychogenic stuttering has been described as well and the differential diagnosis may be complex. One of the reasons is that literature on their stuttering pattern is characterized by conflicting observations. Even attempts to find correspondences between patients with a similar neurogenic etiology resulted in contradictory results (Theys et al., 2008; De Nil et al., 2009). The present case report is no exception to this. MH stutters were mainly blocks and prolongations which contradicts the general finding that repetitions are the predominant speech characteristic in most neurogenic and psychogenic stuttering patients (Theys et al., 2008; Van Borsel, 2011). For the following reasons however, MH was concluded to suffer neurogenic and not psychogenic stuttering. Psychogenic stuttering patients (1) typically stutter during all speech modalities (2) are generally found to be indifferent to their stuttering and (3) often had earlier psychosomatic disorders (Van Borsel, 2011). In contrast, MH only stutters during conversation, is clearly concerned about her stuttering, and had no previous psychogenic related complaints. Moreover, stuttering onset is clearly linked with a neurological event. Although stuttering occurred a few days after a stroke with no observed increase in bleeding, neurologists suggested the increase in edema would be the cause of the somewhat delayed appearance. Finally, MH's lesion site, left STG, is well known to have a crucial role in fluent and stuttered speech (Brown et al., 2005; Guenther, 2006).

As mentioned before, no uniformity can be found among neurogenic stuttering patients. This accounts for MH as well. Neurogenic AWS would be more likely to stutter during non-propositional speech than developmental AWS (Helm-Estabrooks et al., 1986; Helm-Estabrooks, 1993). However, MH rarely stuttered during reading, automatic speech and repetition. Her %SS during conversation on the other hand, increased to a moderate level. This opposite pattern has been described in some cases with neurogenic stuttering following stroke, traumatic brain injury and brain surgery (Theys et al., 2008). It is even a recurrent finding after thalamic stroke (Abe et al., 1993; Van Borsel et al., 2003).

Overall, MH's stutters occurred exclusively in word initial position, which is a typical finding in both developmental and neurogenic stuttering (Bloodstein and Ratner, 2008; De Nil et al., 2009). MH' stuttering solely involved sounds, not syllables or longer units. MH displayed only limited secondary behaviors that were less elaborate and more transient than typically seen in developmental stuttering. Indeed, secondary behavior is suggested to occur less frequently or to be absent in neurogenic AWS because they stutter mostly for a relatively short period of time. Full blown secondary behavior may, as is the case in developmental stuttering, appear after stuttering for a significant period of time (De Nil et al., 2009). Note that in line with this suggestion, a slight increasing trend in physical concomitants was observed in MH, despite a decrease in stuttering frequency at the 4th session.

One last form of acquired stuttering is pharmacogenic stuttering. Several medicines have been described to influence fluency/stuttering (for a review, see Brady, 1998; and Boyd et al., 2011). At all test sessions, MH only took levetiracetam, an antiepileptic medicine. Several antiepileptic drugs have been found to affect fluency (Sechi et al., 1997; Brady, 1998; Mula et al., 2003). However, levetiracetam is consistently described to reduce stuttering (Canevini et al., 2002; Sechi et al., 2006). Therefore, MH's stuttering is very unlikely to have a pharmacogenic origin.

5. Conclusion

For the case described, CNV amplitude is shown to be inversely related to stuttering frequency during conversation. The larger the stuttering frequency, the smaller the CNV amplitude. Thus, the amount of disturbance in articulatory preparation seems to be related to the amount of stutters that will occur during

conversation. During task performance, no stuttering appeared. This observation suggests that when only a limited load is put on the speech motor system, motor programming disturbances are either not enough to evoke stuttering or are surmountable by compensation strategies. At the test session with most severe stuttering, such a cortical compensatory mechanism was cautiously suggested to be triggered at right frontal electrodes.

Overall, motor preparation is suggested to have an important role in stuttering. Late CNV amplitude elicited by a relatively simple speech task seems to be able to provide an objective, neural correlate of stuttering frequency.

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References

Abe, K., Yokomay, R., Yorifuji, S., 1993. Repetitive speech disorder resulting from infarcts in the paramedian thalami and midbrain. J. Neurol. Neurosurg. Psychiatry 56, 1024–1026.
Adams, M., Lewis, J., Besozzi, T., 1973. The effect of reduced reading rate on stuttering frequency. J. Speech Hear. Res. 16, 671–675.
Aerts, A., van Mierlo, P., Hartsuiker, R., Hallez, H., Santens, P., De Letter, M., 2013. Neurophysiological investigation of phonological input: aging effects and development of normative data. Brain Lang. 125, 253–263.
American Speech-Language-Hearing Association. (1999). Terminology pertaining to fluency and fluency disorders: guidelines. Opgehaald van. www.asha.org/policy.
Bares, M., Nestrasil, I., Rektor, I., 2007. The effect of response type (motor output versus mental counting) on the intracerebral distribution of the slow cortical potentials in an externally cured (CNV) paradigm. Brain Res. Bull. 7, 428–435.
Bastiaanse, R., Bosje, M., Visch-Brink, E., 1995. Psycholinguïstische Testbatterij voor Onderzoek naar de Taalverwerking van Afasiepatiënten (PALPA). Psychology Press, Hove, East Sussex.
Bender, S., Resch, F., Weisbrod, M., Oelkers-Ax, R., 2004. Specific task anticipation versus unspecific orienting reaction during early contingent negative variation. Clin. Neurophysiol. 115, 1836–1845.
Bezemer, M., Bouwen, J., Winkelman, K., Embrechts, M., 2010. Stotteren: Van Theorie Naar Therapie. Coutinho, Bussum.
Bloodstein, O., Ratner, N., 2008. A Handbook on Stuttering. Cengage Learning, Delmar.
Boey, R., Wuyts, F., Van De Heyning, P., Heylen, L., De Bodt, M., 2009. Characteristics of stuttering in Duth-speaking individuals. Clin. Linguist. Phon. 23, 241–254.
Boyd, A., Dworzynski, K., Howell, P., 2011. Pharmacological agents for developmental stuttering in children and adolescents: a systematic review. J. Clin. Psychopharmacol. 31, 740–744.
Brady, J., 1998. Drug-induced stuttering: a review of the literature. J. Clin. Psychopharmacol. 18, 50–54.
Braun, A., Varga, M., Stager, S., Schulz, G., Selbie, S., Maisog, J., Ludlow, C., 1997. Altered patterns of cerebral activity during speech and language production in developmental stuttering: a H2 15O positron emission tomography study. Brain 120, 761–784.
Brown, S., 1938. A further study of stuttering in relation to various speech sounds. Q. J. Speech 24, 390–397.
Brown, S., Ingham, R., Ingham, J., Laird, A., Fox, P., 2005. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. Hum. Brain Mapp. 25, 105–117.
Canevini, M., Chifferi, R., Piazzino, A., 2002. Improvement of a patient with stuttering on levetiracetam. Neurology 59, 1288.
Chang, S.-E., Erickson, K., Ambrose, N., Hasegawa-Johnson, M., Ludlow, C., 2008. Brain anatomy differences in childhood stuttering. NeuroImage 39, 1333–1344.
Chang, S.-E., Horwitz, B., Ostuni, J., Reynolds, R., Ludlow, C., 2011. Evidence of left inferior frontal-premotor structural and functional connectivity deficits in adults who stutter. Cereb. Cortex 21, 2507–2518.
Chang, S.-E., Kenney, M., Loucks, T., Ludlow, C., 2009. Brain activation abnormalities during speech and non-speech in stuttering speakers. NeuroImage 46, 201–212.
Cooper, R., Todd, J., McGill, K., Michie, P., 2006. Auditory sensory memory and the aging brain: a Mismatch Negativity study. Neurobiol. Aging 27, 752–762.
Cui, R., Egkher, A., Huter, D., Lang, W., Lindinger, G., Deecke, L., 2000. High resolution spatiotemporal analysis of the contingent negative variation in simple or complex motor tasks and a non-motor task. Clin. Neurophysiol. 111, 1847–1859.
Cykowski, M., Fox, P., Ingham, R., Ingham, J., Robin, D., 2010. A study of the reproducibility and etiology of diffusion anisotrophy differences in developmental stuttering: a potential role for imparied myelination. NeuroImage 52, 1495–1504.
De Nil, L., Kroll, R., Kapur, S., Houle, S., 2000. A positron emission tomography study of silent and oral single word reading in stuttering and nonstuttering adults. J. Speech Lang. Hear. Res. 43, 1038–1053.
De Nil, L., Kroll, R., Lafaille, S., Houle, S., 2003. A positron emission tomography study of short- and long-term effects on functional brain activation in adults who stutter. J. Fluency Disord. 28, 357–380.
De Nil, L., Rochon, E., Jokel, R., 2009. Adult-onset neurogenic stuttering. In: McNeil, M. (Ed.), Clinical Management of Sensorimotor Speech Disorders, 2nd ed. Thieme, New York, pp. 235–248.
Duffy, J., 2013. Motor Speech Disorders. Substrates, Differential Diagnosis, and Management, 3rd edition. Elsevier Mosby, St. Louis, Missouri.
Einarsdottir, J., Ingham, R., 2005. Have disfluency tipe measures contributed to the understanding and treatment of developmental stuttering? Am. J. Speech-Lang. Pathol. 14, 260–273.
Fan, J., Kolster, R., Ghajar, J., Suh, M., Knight, R., Sarkar, R., McCandliss, B., 2007. Response anticipation and response conflict: an event-related potential and functional magnetic resonance imaging study. J. Neurosci. 28, 2272–2282.
Fox, P., Ingham, R., Ingham, J., Hirsch, T., Downs, J., Martin, C., 1996. A PET study of the neural systems of stuttering. Nature 382, 158–162.
Fox, P., Ingham, R., Ingham, J., Zamarripa, F., Xiong, J.-H., Lancaste, J., 2000. Bran correlates of stuttering and syllable production: a PET performance-correlation analysis. Brain 123, 1985–2004.
Giaquinto, S., Ranghi, F., Butler, S., 2007. Stability of word comprehension with age: an electrophysiological study. Mech. Aging Dev. 128, 628–638.
Giraud, A.-L., Neumann, K., Bachoud-Levi, A.-C., von Gudenberg, A., Euler, H., Lanfermann, H., Preibisch, C., 2008. Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. Brain Lang. 104, 190–199.
Golfinopoulus, E., Tourville, J., Guenther, F., 2010. The integration of large-scale neural network modeling and functional brain imaging in speech motor control. NeuroImage 52, 862–874.
Golob, E., Ovasapyan, V., Starr, A., 2005. Event-related potentials accompanying motor preparation and stimulus expectancy in the young, young-old and oldest-old. Neurobiol. Aging 26, 531–542.
Gomez, C., Marco, J., Grau, C., 2003. Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density. NeuroImage 20, 216–224.
Graetz, P., de Bleser, R., Willmes, K., 1991. Akense Afasie Test, Nederlandstalige versie. Swets & Zeitlinger, Lisse.
Gregory, H., 1993. A clinician's perspective: comments on identification of stuttering, prevention, and early intervention. J. Fluency Disord. 18, 389–402.
Guenther, F., 2006. Cortical interactions underlying the production of speech sounds. J. Commun. Disord. 39, 350–365.
Guitar, B., 2006. Stuttering: An Integrated Approach to its Nature and Treatment, third edition Lippincott Williams & Wilkins, Baltimore – Philadelphia.
Hamano, T., Lüders, H., Ikeda, A., Collura, T., Comair, Y., Shibasaki, H., 1997. The cortical generators of the contingent negative variation in humans: a study with subdural electrodes. Electroencephalogr. Clin. Neurophysiol. 104, 257–268.
Hauk, O., Coutout, C., Holden, A., Chen, Y., 2012. The time-course of single-word reading: evidence from fast behavioral and brain responses. NeuroImage 60, 1462–1477.
Helm-Estabrooks, N., 1993. Stuttering associated with acquired neurological disorders. In: Curlee, R. (Ed.), Stuttering and Related Disorders of Fluency. Thieme, New York, pp. 205–218.
Helm-Estabrooks, N., Yeo, R., Geschwind, N., Freedman, M., 1986. Stuttering: disappearance and reappearance with acquired brain lesions. Neurology 36, 1109–1112.
Ingham, J., & Ingham, R. (2011). ⟨http://sms.id.ucsb.edu/downloads/SMS_Manual.pdf⟩. Opgehaald van The Stuttering Measurement System.
Ingham, R., Grafton, S., Bothe, A., Ingham, J., 2012. Brain activity in adults who stutter: similarities across speaking tasks and correlations with stuttering frequency and speaking rate. Brain and Language 122, 11–24.
International Phonetic Association, 1974. The Principles of the International Phonetic Association. International Phonetic Association, London.
Karimi, H., Jones, M., O'Brian, S., Onslow, M., 2014. Clinician percent syllables stuttered, clinician severity ratings and speaker severity ratings: are they interchangeable? Int. J. Lang. Commun. Disord. 49, 364–368.
Kay, J., Lesser, R., Coltheart, M., 1992. PALPA: Psycholinguistic Assessments of Language Processing in Aphasia. Psychology Press, Hove, East Sussex.
Kell, C., Neumann, K., von Kriegstein, K., Posenenske, C., von Gudenberg, A., Euler, H., Giraud, A.-L., 2009. How the brain repairs stuttering. Brain 132, 2747–2760.
Kropp, P., Kiewitt, A., Göbel, H., Vetter, P., Gerber, W.-D., 2000. Reliability and stability of contingent negative variation. Appl. Psychophysiol. Biofeedback 25, 33–41.
Kutas, M., Federmeier, K., 2000. Electrophysiology reveals semantic memory use in language comprehension. Trends Cogn. Sci. 4, 463–470.
Lamarche, M., Louvel, J., Buser, P., Rektor, I., 1995. Intracerebral recordings of slow potentials in a contingent negative variation paradigm: an exploration in epileptic patients. Electroencephalogr. Clin. Neurophysiol. 95, 268–276.
Lezak, M., Howieson, D., Loring, D., 2004. Neurophychological Assessment, fourth edition Oxford Univerisity Press, New York.
Loveless, N., Sanford, A., 1974. Slow potential correlates of preparatory set. Biol. Psychol. 1, 303–314.

Lu, C., Chen, C., Ning, N., Ding, G., Guo, T., Peng, D., Lin, C., 2010. The neural substrates for atypical planning and execution of word production in stuttering. Exp. Neurol. 221, 146–156.
Luck, S., 2005. An Introduction to the Event-Related Potential Technique. The MIT Press, Massachusetts, USA.
McArdle, J., Mari, Z., Pursley, R., Schulz, G., Braun, A., 2009. Electrophysiological evidence of functional integration between the language and motor systems in the brain: a study of the speech Bereitschaftspotential. Clin. Neurophysiol. 120 (2), 275–284.
McCallum, W., 1988. Potentials related to expectancy, preparation and motor activity. In: Picton, T. (Ed.), Handbook of Electroencephalography and Clinical Neurophysiology: Revised series, vol.3: Human Event-related Potentials. Elsevier, New York, pp. 427–534.
McClelland, J., Elman, J., 1986. The TRACE model of speech perception. Cognit. Psychol. 18, 1–86.
Michalewski, H., Weinberg, H., 1977. The contingent negative variation (CNV) and speech production: slow potentials and the area of Broca. Biol. Psychol. 5, 83–96.
Mock, J., Foundas, A., Golob, E., 2011. Modulation of sensory and motor cortex activity during speech preparation. Eur. J. Neurosci. 33, 1001–1011.
Mula, M., Trimble, M., Thompson, P., Sander, J., 2003. Topiramate and word-finding difficulties in patients with epilepsy. Neurology 60, 1104–1107.
Näätänen, R., Kujala, T., Winkler, I., 2011. Auditory processing that leads to conscous perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. Psychophysiology 48, 4–22.
O'Brian, S., Packman, A., Onslow, M., O'Brian, N., 2004. Measurement of stuttering in adults: comparison of stuttering-rate and severity-scaling methods. J Speech Lang. Hear. Res. 47, 1081–1087.
Onslow, M., 2000. Stuttering: treatment for adults, Current therapeutics 41, 73–76.
Pinsky, S., McAdam, D., 1980. Electroencephalographic and dichotic indices of cerebral laterality in stutterers. Brain Lang. 11, 374–397.
Poeppel, D., Idsardi, W., van Wassenhove, V., 2008. Speech perception at the interface of neurobiology and linguistics. Philos. Trans. R. Soc. London Ser. B. Biol. Sci. 363, 1071–1086.
Preibisch, C., Neumann, K., Raab, P., Euler, H., von Gudenberg, A., Lanfermann, H., Giraud, A.-L., 2003. Evidence for compensation for stuttering by the right frontal operculum. NeuroImage 20, 1356–1364.
Prescott, J., 1988. Event-related potential indices of speech motor programming in stutterers and non-stutterers. Biol. Psychol. 27, 259–273.
Prescott, J., Andrews, G., 1984. Early and late components of the contingent negative variation prior to manual and speech responses in stutterers and non-stutterers. Int. J. Psychophysiol. 2, 121–130.
Price, C., 2012. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. NeuroImage 62, 816–847.
Regan, D., 1989. Electrical activity that precedes motor action. In: Regan, D. (Ed.), Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fiels in Science and Medicine. Elsevier, New York, pp. 217–227.
Riès, S., Janssen, N., Burle, B., Alario, F., 2013. Response-locked brain dynamics in word production. PLoS One 8, 1–14.
Riley, G., 2008. Stuttering Severity Instrument for Children and Adults (SSI-4), fourth edition Pro-Ed, Austin.
Rohrbaugh, J., Gaillard, A., 1983. Sensory and motor aspects of the contingent negative variation. In: Gaillard, A., Ritter, W. (Eds.), Tutorials in Event-related Potential Research: Endogenous Components. North-Holland, Amsterdam, pp. 269–310.
Salmelin, R., 2007. Clinical neurophysiology of language: the MEG approach. Clin. Neurophysiol. 118, 237–254.
Salmelin, R., Schnitzler, A., Schmitz, F., Freund, H.-J., 2000. Single word reading in developmental stutterers and fluent speakers. Brain 123, 1184–1202.
Sawyer, J., Yairi, E., 2006. The effect of sample size on the assessment of stuttering severity. Am. J. Speech-Lang. Pathol. 15, 36–44.
Sechi, G., Cocco, G., D'Onofrio, M., Deriu, M., Rosati, G., 2006. Disfluent speech in patients with partial epilepsy: beneficial effect of levetiracetam. Epilepsy Behav. 9, 521–523.
Sechi, G., Correddu, P., Deiana, G., Zucca, G., Rosati, G., 1997. Expressive aphasia exacerbated by lamotrigine and gabapentin. Epilepsia 38 (Suppl. 3), A73.
Severens, E., Van Lommel, S., Ratinckx, E., Hartsuiker, R., 2005. Tiimed picture naming norms for 590 pictures in Dutch. Acta Psychol. 119, 159–187.
Smits-Bandstra, S., Gracco, V., 2013. Verbal implicit sequence learning in persons who stutter and persons with Parkinson's Disease. J. Mot. Behav. 45, 381–393.
Sommer, M., Koch, M., Paulus, W., Weiller, C., Büchel, C., 2002. Disconnection of speech-relevant brain areas in persistent developmental stuttering. Lancet 360, 380–383.
Theys, C., De Nil, L., Thijs, V., van Wieringen, A., Sunaert, S., 2012. A crucial role for the cortico-striato-cortical loop in the pathogenesis of stroke-related neurogenic stuttering. Hum. Brain Mapp. 34, 2103–2112.
Theys, C., van Wieringen, A., De Nil, L., 2008. A clinician survey of speech and non-speech characteristics of neurogenic stuttering. J. Fluency Disord. 33, 1–23.
Van Borsel, J., 2011. Basisbegrippen Logopedie. Deel 2: communicatiestoornissen. Stotteren en broddelen. Acco, Leuven, Belgium.
Van Borsel, J., 1997. Neurogenic stuttering: a review. J. Clin. Speech Lang. Stud. 7, 16–33.
Van Borsel, J., Van Der Made, S., Santens, P., 2003. Thalamic stuttering: a distinct clinical entity? Brain Lang. 85, 185–189.
Van Boxtel, A., 2001. Optimal signal bandwidth for the recording of surface EMG activity of facial, jaw, oral, and neck muscles. Psychophysiology 38, 22–34.
Van Zaalen, Y., Winkelman, C., 2009. Broddelen: een (on)begrepen stoornis. Coutinho, Bossum.
Vigneau, M., Beaucousin, V., Hervé, P., Duffau, H., Crivello, F., Houdé, O., Tzourio-Mazoyer, N., 2006. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. NeuroImage 30, 1414–1432.
Walter, W., Cooper, R., Aldridge, V., McCallum, C., Winter, A., 1964. Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. Nature 203, 380–384.
Watkins, K., Klein, D., 2011. Brain structure and function in developmental stuttering and bilingualism. In: Howell, P., Van Borsel, J. (Eds.), Mulitlingual Aspects of Fluency Disorders. Multilingual Matters, Bristol, England, pp. 63–89.
Watkins, K., Smith, S., Davis, S., Howell, P., 2008. Structural and functional abnormalities of the motor system in developmental stuttering. Brain 131, 50–59.
Xuan, Y., Meng, C., Yang, Y., Zhu, C., Wang, L., Yan, Q., Yu, C., 2012. Resting-state brain activity in adult males who stutter. PLoS One 2012, 1–11.
Yaruss, J. (1997). Clinical measurement of stuttering behaviors. Opgehaald van www.asha.org.
Zhang, Q., Zhang, J., Kong, L., 2009. An ERP study on the time course of phonological and semantic activation in Chinese word recognition. Int. J. Psychophysiol. 73, 235–245.
Zimmerman, G., Knott, J., 1974. Slow potentials of the brain related to speech processing in normal speakers and stutters. Electroencephalogr. Clin. Neurophysiol. 37, 599–607.