Neuropsychologia 64 (2014) 349–359

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

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

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ARTICLE INFO

Article history:
Received 7 May 2014
Received in revised form
17 September 2014
Accepted 18 September 2014
Available online 2 October 2014

Keywords:
Contingent negative variation
Stuttering
Stuttering severity
%SS
Motor preparation

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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http://dx.doi.org/10.1016/j.neuropsychologia.2014.09.036
0028-3932/

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