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Beyond production: Brain responses during speech perception in adults who stutter

Tali Halag-Milo[a,b], Nadav Stoppelman[a], Vered Kronfeld-Duenias[a], Oren Civier[a], Ofer Amir[c], Ruth Ezrati-Vinacour[c], Michal Ben-Shachar[a,d,*]

[a] The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel
[b] The Cognitive Science Program, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[c] The Department of Communication Disorders, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[d] Department of English Literature and Linguistics, Bar-Ilan University, Ramat-Gan, Israel

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ABSTRACT

Developmental stuttering is a speech disorder that disrupts the ability to produce speech fluently. While stuttering is typically diagnosed based on one's behavior during speech production, some models suggest that it involves more central representations of language, and thus may affect language perception as well. Here we tested the hypothesis that developmental stuttering implicates neural systems involved in language perception, in a task that manipulates comprehensibility without an overt speech production component. We used functional magnetic resonance imaging to measure blood oxygenation level dependent (BOLD) signals in adults who do and do not stutter, while they were engaged in an incidental speech perception task. We found that speech perception evokes stronger activation in adults who stutter (AWS) compared to controls, specifically in the right inferior frontal gyrus (RIFG) and in left Heschl's gyrus (LHG). Significant differences were additionally found in the lateralization of response in the inferior frontal cortex: AWS showed bilateral inferior frontal activity, while controls showed a left lateralized pattern of activation. These findings suggest that developmental stuttering is associated with an imbalanced neural network for speech processing, which is not limited to speech production, but also affects cortical responses during speech perception.

1. Introduction

As humans, we spend much of our day communicating with our peers through spoken language. The ability to produce speech fluently is an important component of effective oral communication, but we are often unaware of our own speech fluency, which is typically achieved automatically and effortlessly. Developmental stuttering is a speech impairment that severely affects individuals' ability to produce speech fluently. Stuttering affects many children between the ages of 3 y to 6 y, with a prevalence of about 2–5% during these ages, and an incidence of up to 8.5%–11.2% (Dworzynski et al., 2007; Reilly et al., 2009, 2013; Yairi and Ambrose, 2013). About 80% of these children regain fluency at the end of this period. The rest, nearly 1% of the adult population, will be affected by persistent developmental stuttering, manifested as involuntary speech blocks, sound/syllable repetitions, sound prolongations and fragmented words. Stuttering moments are also associated with secondary physical features such as facial grimaces, eye blinking, jaw and neck jerking (Bloodstein and Bernstein-Ratner, 2008; Riva-Posse et al., 2008). Adults who stutter (AWS) are typically painfully aware of their disfluencies, and often consider stuttering as one of their main defining features.

Although stuttering is mainly perceived as a fluency disorder, there is ample evidence that auditory deficits may be involved in this disorder as well. Behaviorally, auditory sensitivity has been shown to develop differently in young people who stutter, compared to their fluent peers (Howell and Williams, 2004). Fluency may be temporarily gained in AWS by manipulating the auditory feedback during speech production, as in delayed auditory feedback or listening to masking noise while speaking (Cherry and Sayers, 1956; Ingham et al., 2009; Kalinowski et al., 1993; Lincoln et al., 2010). The beneficial effect of such auditory manipulations suggests the existence of a sensory component in developmental stuttering. Neurally, differences were found in AWS both in motor regions and in primary and secondary auditory cortices (Beal et al., 2010, 2011; Brown et al., 2005; Chang et al., 2009; De Nil et al., 2008; Foundas et al., 2001; Kell et al., 2009; Kikuchi et al., 2011; Belyk et al., 2015; Budde et al., 2014) and in the functional interactions between motor and auditory cortices (Chang et al., 2011; Lu et al., 2010). This line of evidence supports the notion that abnormal

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[*] Corresponding author at: The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan 5290002, Israel.
E-mail address: michalb@mail.biu.ac.il (M. Ben-Shachar).

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interactions between the motor and auditory cortices are part of the etiology of developmental stuttering (Brown et al., 2005; Chang et al., 2009; Giraud et al., 2008; Ludlow and Loucks, 2004; Max et al., 2004; Neilson and Neilson, 1987). The current study examines the perceptual aspects of persistent developmental stuttering, by using an auditory language perception task to map brain activation and regional hemispheric lateralization in AWS compared to non-stuttering controls.

Several neuroimaging studies have reported anatomical and functional differences between people who stutter and non-stuttering controls. Anatomically, studies conducted with children and adults who stutter have reported abnormal gray matter volume and density in bilateral inferior frontal gyrus (IFG), precentral gyrus, supplementary motor area (SMA) and bilateral superior temporal gyrus (STG) (Beal et al., 2007; Chang et al., 2008; Kell et al., 2009; Kikuchi et al., 2011). AWS were also found to have reduced leftward asymmetry in the planum temporale (Foundas et al., 2001) and lack the standard "torque asymmetry", typically manifested as a larger volume of the right prefrontal and left occipital lobes compared to their respective homologs (Foundas et al., 2003). Differences in diffusion properties of the white matter underlying the left Rolandic Operculum were reported in both children and adults who stutter (Chang et al., 2008; Sommer et al., 2002; Watkins et al., 2008). We recently reported tract specific differences in the microstructural properties of the frontal aslant tract in AWS compared to non-stuttering controls, and a correlation between diffusivity and fluency within this tract (Kronfeld-Duenias et al., 2016). AWS were further reported to have symmetrical white matter volume underlying the auditory cortex (in contrast to a leftward asymmetry found in controls Jäncke et al., 2004) and a larger rostral half of the corpus callosum compared to controls (Choo et al., 2011). This distributed pattern of structural brain differences found in developmental stuttering is typical to many developmental impairments, in which deficient and compensatory processes mutually evolve over time. In summary, volumetric differences in gray and white matter as well as microstructural differences in white matter have been associated with developmental stuttering throughout the neural network of speech processing, with deficits affecting regions and pathways associated primarily with speech, motor and auditory functions.

Functionally, developmental stuttering has been associated with *enhanced* responses in the motor system (e.g. primary motor cortex, SMA, and cerebellum) as well as *decreased* activity in the auditory cortex when AWS are asked to produce speech during functional Magnetic Resonance Imaging (fMRI) (Brown et al., 2005; De Nil et al., 2008; Belyk et al., 2015; Budde et al., 2014). Abnormal activation has also been documented in the basal ganglia of AWS (Braun et al., 1997; Chang et al., 2009; Ingham et al., 2004; Loucks et al., 2011; Toyomura et al., 2011). Again, most of these differences were recorded during speech production conditions (but see Chang et al., 2009; Loucks et al., 2011; De Nil et al., 2008). In addition to the recurring findings mentioned above, many inconsistencies still exist in the literature, even among meta-analyses of partly overlapping pools of studies. For example, Belyk et al. (2015) found that stuttering trait was associated with deactivation of the Larynx motor cortex, but this finding was not observed in a similar meta-analysis by Budde et al. (2014). The picture is further complicated by the fact that some studies report differences within the same networks but in the opposite direction: for example, several studies report *increased* activation in the auditory cortices and *reduced* activation in speech- and motor-related brain regions of AWS (e.g. left IFG, left SMA and premotor cortex bilaterally) (Chang et al., 2009; Kell et al., 2009; Loucks et al., 2011; Toyomura et al., 2011; Watkins et al., 2008). Moreover, a recent analysis of cortical responses in individual participants during stuttering moments has shown little overlap between individuals (Wymbs et al., 2013), calling into question the relevance of group analyses and meta-analyses in individuals who stutter.

Differences have also been found in the functional lateralization patterns observed in AWS and controls during language production. In fluent speakers, speech production evokes largely left lateralized responses in inferior frontal, primary motor (M1) and premotor cortex (PMC). In contrast, AWS exhibit an activation pattern which is more bilateral and symmetrical across the two hemispheres or with right dominance, particularly in the frontal cortex (Brown et al., 2005; Kell et al., 2009; Neumann et al., 2005). These results, recorded using language production tasks in fMRI, converge nicely with the anatomical findings pointing to altered cortical asymmetry in developmental stuttering (Foundas et al., 2001, 2003).

In contrast with the abundant research available on brain activity in AWS during speech production, few studies have addressed brain responses in AWS during the perception of speech and speech-like stimuli. Most of the evidence on brain responses during speech perception in AWS comes from human electrophysiology, namely electro- or magnetoencephalography (EEG/MEG) (Biermann-Ruben et al., 2005; Corbera et al., 2005; Hampton and Weber-Fox, 2008; Kikuchi et al., 2011; Morgan et al., 1997; Weber-Fox and Hampton, 2008). Most of these studies have found that AWS were *not* different from fluent speakers in early, "perceptual" components (e.g. N100) evoked by simple, non-linguistic stimuli (Biermann-Ruben et al., 2005; Corbera et al., 2005; Hampton and Weber-Fox, 2008, but see Beal et al., 2010). The difference between AWS and non-stuttering controls emerged in later, "cognitive" components, such as the P300 (Hampton and Weber-Fox, 2008; Morgan et al., 1997), the N400 in a rhyming task (Weber-Fox et al., 2004), and when presented with more complex auditory stimuli such as speech sounds and sentences (Biermann-Ruben et al., 2005).

fMRI studies using speech perception tasks in AWS are few, and provide a mixed pattern of results. In general, such studies have identified differences in similar cortical regions as those that were found to be atypically activated during speech production. Specifically, differences were detected in right IFG (BA 44), auditory cortex, and motor regions (M1, PMC and SMA) (Chang et al., 2009; De Nil et al., 2008; Loucks et al., 2011). However, the direction of these effects is inconsistent. For example, in one study AWS showed reduced activation in auditory and motor regions (Chang et al., 2009), while in another study AWS showed over-activation in left MTG/STG including primary auditory cortex and in right insula and primary motor cortex extending into the SMA (De Nil et al., 2008). These inconsistencies may stem from different stimuli and experimental designs used in these studies. For example, De Nil et al. (2008) examined brain responses associated with auditory perception of words, while Chang et al. (2009) examined brain responses associated with perception of syllables prior to planning and execution of speech and non-speech responses that occurred in every trial. The mixed results observed in the few published fMRI studies using perception tasks in AWS preclude reaching conclusive statements about the functionality of the speech perception network in developmental stuttering.

A further gap in the literature on brain responses during language perception in AWS concerns functional lateralization. Based on the anatomical literature, one would expect differences in lateralization of responses in both frontal and temporal language regions (Foundas et al., 2001, 2003). Related findings from diffusion MRI provide independent but indirect support for the hypothesis that frontal lateralization may be different in AWS, by showing differences in the volume and diffusivity of anterior callosal connections (Cai et al., 2014; Choo et al., 2011; Civier et al., 2015; Cykowski et al., 2010; Kell et al., 2009). However, previous fMRI studies that compared cortical responses during language perception tasks in AWS against non-stuttering controls did not quantify directly the lateralization of response by measuring the relative signals in the left and right cortical homologs of specific cortical regions. This is important because functional lateralization in fMRI is not dichotomous: even when both homologs show supra-threshold activation, strong lateralization may be revealed when a quantitative lateralization index is calculated (Wilke and Lidzba, 2007). The only study to have done such an analysis in the context of an auditory processing task in AWS used near-infrared spectroscopy (NIRS) and was limited in coverage to the temporal cortex