



# Reduced fractional anisotropy in the anterior corpus callosum is associated with reduced speech fluency in persistent developmental stuttering



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## ABSTRACT

Developmental stuttering is a speech disorder that severely limits one's ability to communicate. White matter anomalies were reported in stuttering, but their functional significance is unclear. We analyzed the relation between white matter properties and speech fluency in adults who stutter (AWS). We used diffusion tensor imaging with tract-based spatial statistics, and examined group differences as well as correlations with behavioral fluency measures. We detected a region in the anterior corpus callosum with significantly lower fractional anisotropy in AWS relative to controls. Within the AWS group, reduced anisotropy in that region is associated with reduced fluency. A statistically significant interaction was found between group and age in two additional regions: the left Rolandic operculum and the left posterior corpus callosum. Our findings suggest that anterior callosal anomaly in stuttering may represent a maladaptive reduction in interhemispheric inhibition, possibly leading to a disadvantageous recruitment of right frontal cortex in speech production.

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## 1. Introduction

Developmental stuttering is a disorder of speech fluency, primarily characterized by prolongations, blocks and repetitions of sounds and/or syllables. The etiology of stuttering is not fully understood to date. One of the earliest theories on stuttering relates the disorder to atypical cerebral dominance (Moore, 1984; Travis, 1978; Travis & Johnson, 1934; Webster, 1997). Although initial attempts to provide evidence for this theory were mostly unsuccessful (see Kushner, 2012), modern functional brain imaging studies have established that adults-who-stutter (AWS) indeed exhibit different functional lateralization when compared to fluent speakers (Braun et al., 1997; De Nil, Kroll, & Houle, 2001; De Nil, Kroll, Kapur, & Houle, 2000; Kell et al., 2009; Neumann et al., 2005; Pool, Devous, Freeman, Watson, & Finitzo, 1991). These studies, as a whole, demonstrate that regions in the

right hemisphere, particularly in the frontal cortex, are over-activated in AWS (see Brown, Ingham, Ingham, Laird, & Fox, 2005).

There is an ongoing debate on the functional significance of the right frontal over-activation observed in developmental stuttering. Some authors suggest that the greater recruitment of the right hemisphere is beneficial (Braun et al., 1997; Kell et al., 2009; Neef et al., 2011; Preibisch et al., 2003), whereas others suggest it is not (Brown et al., 2005; Chang, Synnestvedt, Ostuni, & Ludlow, 2010; Fox et al., 2000; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2014; Moore, 1984). There are also suggestions that the right hemisphere recruitment is maladaptive (Andrews, Quinn, & Sorby, 1972; Webster, 1997), that it is an outcome of negative emotions (Forster, 1995; Webster, 1993), or causally related to overt stuttering behavior (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Fox et al., 1996; Wood, Stump, McKeehan, Sheldon, & Proctor, 1980). In fact, some combination of the above explanations could be true, given that over-activations were detected in several distinct right frontal regions. As the debate is still open after more than two decades of functional imaging studies on stuttering, alternative methodological approaches may be necessary.

The right frontal over-activation observed in AWS could be better understood in the context of the underlying structural

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properties of their brains. Several studies conducted over the last decade have detected structural anomalies in stuttering individuals, frequently in the form of reduced fractional anisotropy (FA) in white matter regions (see Cai et al., 2014; Cykowski, Fox, Ingham, Ingham, & Robin, 2010). The majority of FA reductions are in the left hemisphere, most notably in the left Rolandic Operculum (RO) (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Connally, Ward, Howell, & Watkins, 2014; Kell et al., 2009; Sommer, Koch, Paulus, Weiller, & Buchel, 2002; Watkins, Smith, Davis, & Howell, 2008). This is commonly attributed to white matter tracts involved in speech motor control (Civier, Bullock, Max, & Guenther, 2013; Cykowski et al., 2010). Previous studies suggest that these left hemisphere anomalies are most likely related to the origin of the disorder (Chang et al., 2008; Kell et al., 2009), and that the right frontal cortex is recruited to cope with the deficiency (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Chang et al., 2008, 2010; Kell et al., 2009; Neef et al., 2011; Preibisch et al., 2003; Sowman, Crain, Harrison, & Johnson, 2014; Tourville & Guenther, 2011; Tourville, Reilly, & Guenther, 2008). Following such an interhemispheric reorganization, the right hemisphere may carry tasks usually carried out by the left hemisphere (e.g., Karbe et al., 1998).

We propose that interhemispheric reorganization in developmental stuttering may involve changes in the main highway connecting the hemispheres, namely, the corpus callosum. Indeed, several callosal anomalies were reported in stuttering individuals, with most studies pointing to the forceps minor (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Choo et al., 2011; Cykowski et al., 2010; Kell et al., 2009). This interhemispheric pathway connects the lateral and medial frontal cortices and crosses the midline via the genu of the corpus callosum (Abe et al., 2004). As the corpus callosum regulates the division of labor between the hemispheres (Geschwind & Galaburda, 1985), callosal differences observed in AWS might reflect subcortical plasticity that shifts control of speech production from the dysfunctional left hemisphere to the intact right hemisphere. But plasticity is not always beneficial: in acquired disorders, such as aphasia, interhemispheric reorganization is often deleterious (Hamilton, Chrysikou, & Coslett, 2011). Similarly, we hypothesize that reorganization-related callosal differences may intensify stuttering, possibly due to recruitment of brain regions not well adapted for speech production.

The goal of this study was to examine the relation between micro-structural properties of callosal connections and the level of speech fluency in adults who stutter. For the purpose of this paper, speech fluency is defined as the ability to speak without stuttering (note that fluency here does not concern articulatory rate, language proficiency, normal interruptions in speech flow, etc.). We first established reliable group difference in FA in the corpus callosum of AWS versus matched controls. We then conducted a focused correlation analysis within the AWS group, and examined the relation between speech fluency and FA in the implicated corpus callosum region. We were interested not only in the identification of a significant correlation, but more importantly, in the direction of the relation. We reasoned that if the least fluent individuals showed the most extreme anomaly in the callosal tracts, this would be considered evidence against beneficial plasticity. Finally, we also examined the contribution of age and its interaction with stuttering, in explaining white matter variability in the callosum and in other white matter regions.

## 2. Methods

### 2.1. Participants

We recruited fourteen adults who stutter (M:F = 11:3; mean age 32.14, standard deviation (SD) 10.17, range 19–52) and

fourteen fluent controls (M:F = 11:3; mean age of 31.36, SD 8.95, range 19–47). The participants were right handed according to the Edinburgh inventory (Oldfield, 1971), and all were native Hebrew speakers, with no prior history of neurological or psychiatric disorders. All participants in the AWS group had a history of stuttering since childhood. In addition, two independent speech-language pathologist (SLP) experts confirmed the diagnoses of stuttering based on audiovisual recordings of each individual's experimental session (for details, see Section 2.2). The two SLP experts also assessed stuttering severity using the Stuttering Severity Instrument (SSI-3, Riley, 1994). An average SSI-3 score of 24.36 (SD: 7.62; range [9.5–41.5]) was measured in the AWS participants, ranging from very mild to very severe stuttering. We were able to collect therapy history from 12 out of 14 AWS. All twelve underwent treatments of various kinds and durations at one or more points in their life. However, no participant was receiving speech therapy at the time of the study, or had received treatment within the two preceding years. Fluent participants were assigned to the control group based on their self-report of having no history of stuttering, and were pair-matched with the AWS on the basis of age and gender (see Table 1). The two groups did not differ significantly on handedness, age or education. The study was approved by the institutional ethics committee of Bar Ilan University and by the Helsinki committee at Tel Aviv Sourasky Medical Center. Written informed consent was obtained from each participant prior to the study.

### 2.2. Data acquisition: Behavioral

Each participant went through an unstructured interview. The participant was seated in a quiet room together with the experimenter, and was asked to talk for 10 min about a neutral topic, such as a recent travel experience, a movie or a book. The experimenter was instructed to refrain from interrupting the speaker, and to ask questions only when the participant was having difficulties finding a topic to talk about. In addition to the interview, participants performed other behavioral tasks not reported in this study. The sessions were recorded with a digital video camera (Sony DCR-DVD 106E, Sony Corporation of America, New York, NY) and with a high-quality microphone (Sennheiser PC21, Sennheiser Electronic Corporation, Berlin, Germany).

### 2.3. Data acquisition: MRI

Magnetic Resonance Imaging (MRI) data were collected using a 3T scanner (Signa Excite, General Electric Medical Systems, Milwaukee, WI, USA) located at the Tel Aviv Sourasky Medical Center. Scanning was conducted with an eight-channel head coil for parallel imaging. Head motion was minimized by padding the head with cushions, and participants were asked to lie still during the scan.

A standard diffusion tensor imaging (DTI) protocol was applied by means of a single-shot spin-echo diffusion-weighted echo-planar imaging sequence (FOV = 240 mm; 128 × 128 matrix; 68 ± 5 2-mm thick axial slices covering the entire cerebrum; voxel size: ~2 × 2 × 2 mm). 19 diffusion-weighted volumes ( $b = 1000$  s/mm<sup>2</sup>) and one reference volume ( $b = 0$  s/mm<sup>2</sup>) were acquired using a standard direction matrix (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). This protocol was repeated twice without averaging, such that tensors were fit to the entire dataset from both scans (see Section 2.5). Scanning 19 directions twice was motivated by the fact that all our participants (study and control groups) are inexperienced and are likely to move as the scan gets longer. Short scan time (350 s per scan) reduces the chances of within-scan motion which is hard to correct, while maintaining robust anisotropy measurements (Jones, 2004). An added benefit of the

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