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Regional brain activity change predicts responsiveness to treatment for stuttering in adults

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ABSTRACT

Developmental stuttering is known to be associated with aberrant brain activity, but there is no evidence that this knowledge has benefited stuttering treatment. This study investigated whether brain activity could predict progress during stuttering treatment for 21 dextral adults who stutter (AWS). They received one of two treatment programs that included periodic H_2 ^{15}O PET scanning (during oral reading, monologue, and eyes-closed rest conditions). All participants successfully completed an initial treatment phase and then entered a phase designed to transfer treatment gains; 9/21 failed to complete this latter phase. The 12 pass and 9 fail participants were similar on speech and neural system variables before treatment, and similar in speech performance after the initial phase of their treatment. At the end of the initial treatment phase, however, decreased activation within a single region, L. putamen, in all 3 scanning conditions was highly predictive of successful treatment progress.

1. Introduction

Brain imaging studies conducted since the mid-1990s have consistently shown that AWS, of both genders, show aberrant patterns of neural activity during speech and even during rest when compared with normally fluent controls (Bloodstein & Ratner, 2008; Ingham, Cykowski, Ingham, & Fox, 2008; Ingham, Grafton, Bothe, & Ingham, 2012). A meta-analysis of positron emission tomography (PET) and fMRI studies of mainly dextral AWS and normally fluent controls incorporated many of these studies (Brown, Ingham, Ingham, Laird, & Fox, 2005). This meta-analysis showed that there were common activations in speech-motor brain areas for both groups, but in the AWS group there were (1) over-activations in these areas, (2) anomalous right-dominant lateralization in these areas, (3) additional areas of activation (motor and nonmotor) not seen in the controls, and (4) an absence of auditory association area activations bilaterally. However, more recent PET and fMRI studies on similar groups, while identifying aberrant activity in various brain areas for AWS, have shown decreasing agreement in regard to the particular areas that are aberrant (Ingham et al., 2012). Additional anomalous brain-related findings have appeared in recent diffusion tensor imaging (DTI) studies that have identified white matter (WM) abnormalities in adults and children who stutter (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Cykowski, Fox, Ingham, Ingham, & Robin, 2010; Sommer, Koch, Paulus, Weiller, & Büchel, 2002; Watkins, Smith, Davis, & Howell, 2008), especially within left superior longitudinal fasciculus (Chang et al., 2011; Cykowski et al., 2010).

The effects of stuttering treatments on putative abnormalities of brain activity in AWS have been the object of a number of brain mapping studies. An early study (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983) used EEG to investigate hemispheric activations before and after an intensive prolonged speech based treatment program. Signs of a shift towards more left hemisphere activation during single-word production by a group of dextral AWS ($N = 11$) were reported. Cerebral blood-flow (CBF) treatment studies of AWS began with a 2001 H_2 ^{15}O PET study (De Nil, Kroll, & Houle, 2001) that reported sustained reductions in stuttering frequency resulting from a well-established behaviorally-based treatment [Precision Fluency Shaping (PFS) (Webster, 1974)] with AWS ($N = 13$). Only activations in cerebellum were examined. The treatment

Abbreviations: AUC, area under the curve; AWS, adults who stutter; CONT, controls; E, establishment; FDR, false discovery rate; FG, fail group; MONO, monologue; MPI, modifying phonation intervals; NAT, speech naturalness; PG, pass group; %SS, percent syllables stuttered; PS, prolonged speech; PT, pretreatment; READ, oral reading; REST, eyes closed rest; ROC, receiver operating characteristics; SFSPM, stutter-free syllables spoken per minute; T, transfer; TRPI, target range phonated interval.

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resulted in reduced excessive cerebellar activations during speaking tasks when compared with normally fluent controls. Subsequent studies have involved whole brain analyses of the effects of stuttering treatment. One of these (De Nil, Kroll, Lafaille, & Houle, 2003) also used H_2 ^{15}O PET to test for rCBF changes before and after a PFS program with 13 dextral male AWS and 10 normally fluent controls. They were scanned during a single-word task that was spoken overtly and covertly before treatment and at a 12-month posttreatment follow-up. Prior to treatment there were bilateral activations in superior temporal gyrus (L > R), the pre- and post-central gyrus (L > R), insula (L > R) and cerebellum (R > L). In the right-hemisphere, activations occurred in the medial frontal gyrus, anterior cingulate and putamen – activation patterns that also differed from previous findings (see Brown et al., 2005). Improved fluency was sustained at a 1-year follow-up and activation was observed bilaterally in motor execution areas, including insula (L > R), pre-central (R > L) and post-central gyrus (L > R), and right cerebellum. Some previously unobserved activation occurred in superior temporal gyrus (R > L) and L. cingulate gyrus.

Another variant of PFS was employed in two German studies. In the first (Neumann et al., 2005) 9 AWS were scanned using event-related fMRI while reading aloud short sentences (3-s) before and after 12 weeks of treatment. Although little stuttering was recorded on the same task during a pretreatment scanning session, in the posttreatment scans during the same speaking tasks there was more activation in the frontal speech production regions (including L. anterior insula and rolandic operculum) and the temporal areas, particularly on the left. Significantly, the former occurred directly above a previously identified area of WM abnormality (Sommer et al., 2002). In the second study (Kell et al., 2009) event-related fMRI (supplemented by DTI) was also used to assess 13 male AWS before and after 3 weeks of treatment. They were compared with 13 male adults described as Recovered Stutterers (RS) because recovery was reported to have occurred either without assistance or 4–38 years after an unsuccessful treatment. It has been hypothesized that by employing a RS group it might be possible to identify the extent or type of neural change that is optimal for maximum recovery from stuttering (see Kell et al., 2009). The most prominent and surprising finding was that only one region, L. BA 12/47, distinguished between recovery and persistent stuttering; the RS group had stronger activations in L. BA 12/47, along with fewer left inferior frontal structural anomalies. At issue though is whether strong activations in L. BA 12/47 constitute a necessary condition for recovery. Unfortunately, the generality of findings to RS populations might be limited because there was a definite level of stuttering in this study's RS participants, complicating claims with respect to their brain activation data and their status as RSs.

There is, however, a broader limitation on the generality of brain imaging findings on AWS. It is important to recognize that the neural activation findings from all of the abovementioned studies have been based on group data. The variability among the findings from brain imaging studies with AWS (Ingham et al., 2012) strongly suggests that imaging studies on individual AWS may have little in common with findings from group studies. This was illustrated in a recent fMRI study (Wymbs, Ingham, Ingham, Paolini, & Grafton, 2013) with 4 AWS who were scanned while producing stuttered and nonstuttered words. The regions that differentiated between stuttered and fluent utterances for each participant were shown to be activated with high consistency across occasions when the task was repeated at least 3 weeks later. However, the differentiating regions identified for each individual showed very little in common across the 4 participants. Consequently, this finding presents a potential challenge for studies, including the present one, that aim to identify neural markers among participants in treatment studies involving groups of AWS. Such markers should, ideally, predict all AWS who succeed in treatment and who do not succeed.

The aim of the present study was to determine if it was possible to identify neural system changes that will predict AWS who succeed and AWS who fail to generalize their treatment gains. For this purpose participants were selected from an intensive stuttering treatment study that involved two different treatment programs, the effects of which were evaluated for behavioral and neurologic change at important stages of treatment. Participants within both treatment programs who failed or succeeded in advancing through their program were compared for behavioral and neural changes that might differentiate among all participants in both groups. The inconclusive brain imaging findings on stuttering and the increasing evidence of individual differences in stuttering-related neural regions necessitated testing the null hypothesis: that there would be no common neural system changes that would differentiate those AWS who succeed from those who fail to progress through treatment.

2. Method

2.1. Participants

Twenty-two AWS (17 males; age range 20–64 years; mean = 35.9 years; median 35 years) and 8 adults who do not stutter or controls (CONT) (6 males; age range 20–64 years; mean 37.8 years; median 32 years) participated in this study which was conducted at the Research Imaging Institute, University of Texas Health Science Center, San Antonio. All were healthy adult volunteers, including 17 AWS who were identified from treatment waiting lists and via advertisements in San Antonio, Austin, and Houston and five who were from UC Santa Barbara's treatment waiting list. All AWS self-reported stuttering since early childhood and displayed chronic stuttering as confirmed by the principal investigator and a certified speech-language pathologist using standard clinical assessments. All participants in both groups were right-handed [>+80 on the Edinburgh Handedness Inventory (Oldfield, 1971)]; displayed no signs of any neurologic disorder (other than stuttering-related regional differences); reported no other current speech, language, cognitive, or behavioral disorder; and passed a hearing screening.

All AWS had experienced various therapies, but no participant reported receiving treatment for stuttering during the preceding 3 years. All produced at least three percent syllables stuttered (%SS) during each of three 3-min within-clinic speaking tasks (oral reading, monologue, and a telephone conversation). All CONT participants met the same selection criteria, except that they were required to produce 0%SS during each of the three speaking tasks and not report either the presence or a history of stuttering.

2.2. Treatment procedures

The AWS were enrolled in a larger study that was designed to investigate the short- and long-term effects of two stuttering treatment programs: Modifying Phonation Intervals (MPI) (Ingham & Student, 2013; Ingham et al., 2001) and a previously described and evaluated prolonged speech (PS) program (Ingham, 1987; Onslow, Costa, Andrews, Harrison, & Packman, 1996). Both programs followed the same 5-phase format: *Pretreatment* (PT), *Establishment* (E), *Transfer* (T), *Maintenance*, and *Follow-up*. Repeated within- and beyond-clinic audio or audio-visual recordings were obtained during each phase, plus a PET scanning session (see below) occurred at the end of each phase. With the exception of the *Pretreatment* and *Follow-up* phases, each phase incorporated a schedule of speaking tasks that was partially managed by the