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Spatiotemporal signatures of an abnormal auditory system in stuttering

Yoshikazu Kikuchi [a,b], Katsuya Ogata [b,*], Toshirou Umesaki [a], Takashi Yoshiura [c], Masamutsu Kenjo [f], Yoji Hirano [d], Tsuyoshi Okamoto [e], Shizuo Komune [a], Shozo Tobimatsu [b]

[a] Department of Otolaryngology, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[b] Department of Clinical Neurophysiology, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[c] Department of Clinical Radiology, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[d] Department of Neuropsychiatry, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[e] Department of Digital Medicine Initiative, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[f] Department of Special Education, Fukuoka University of Education, Fukuoka, Japan

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ABSTRACT

People who stutter (PWS) can reduce their stuttering rates under masking noise and altered auditory feedback; such a response can be attributed to altered auditory input, which suggests that abnormal speech processing in PWS results from abnormal processing of auditory input. However, the details of this abnormal processing of basic auditory information remain unclear. In order to characterize such abnormalities, we examined the functional and structural changes in the auditory cortices of PWS by using a 306-channel magnetoencephalography system to assess auditory sensory gating (P50m suppression) and tonotopic organization. Additionally, we employed voxel-based morphometry to compare cortical gray matter (GM) volumes on structural MR images. PWS exhibited impaired left auditory sensory gating. The tonotopic organization in the right hemisphere of PWS is expanded compared with that of the controls. Furthermore, PWS showed a significant increase in the GM volume of the right superior temporal gyrus, consistent with the right tonotopic expansion. Accordingly, we suggest that PWS have impaired left auditory sensory gating during basic auditory input processing and that some error signals in the auditory cortex could result in abnormal speech processing. Functional and structural reorganization of the right auditory cortex appears to be a compensatory mechanism for impaired left auditory cortex function in PWS.

Introduction

Stuttering is a developmental disorder that affects speech fluency. This disorder is observed in 5% of children aged between 2 and 4 years (Månsson, 2000). The mechanism of stuttering is still a matter of debate. People who stutter (PWS) decrease their stuttering rates temporarily under masking noise and altered auditory feedback, which is not only because of the resulting slower speech rate but also because of altered auditory input (Altrows and Bryden, 1977; Kalinowski et al., 1993; Lincoln et al., 2006; Hampton and Weber-Fox, 2008). This suggests that auditory input processing could be different in PWS compared with non-stuttering subjects. Postma and Kolk (1992) proposed "auditory feedback defect theories in PWS," in which PWS have deviant error monitoring of speech production, namely, PWS detect errors more than people who do not stutter. Postma and Kolk (1993) and Postma (2000) also proposed "the covert repair hypothesis," in which stuttering derives from the need to repeatedly repair errors before and after speech motor movement. Thereafter, Max et al. (2004) proposed "internal models and feedback-biased motor control theory". In this hypothesis, a motor plan is constructed and executed by a feedforward controller, and execution is adjusted by a feedback controller that integrates in real time both afferent (auditory) and efferent (motor) signals. They speculated that stuttering resulted from a mismatch between predicted (feedforward) and actual (feedback) consequences of the executed movements. Overall, stuttering could be related to impaired auditory–motor integration.

Fox et al. (1996) performed neuroimaging studies and reported that stuttering is a disorder of integration within the speech system and not of a single area. Subsequently, stutter-typical networks are not only involved in an extended right-hemispheric network, including the frontal operculum, the temporo-parietal junction, and the dorsolateral prefrontal cortex (Kell et al., 2009), but also in the impaired left-hemispheric network, including the arcuate fasciculus

Abbreviations: AEF, auditory event-related field; BA, Brodmann area; DTI, diffusion tensor imaging; ECD, equivalent current dipole; fMRI, functional magnetic resonance imaging; GM, gray matter; ISI, interstimulus interval; MEG, magnetoencephalography; PWS, people who stutter; PET, positron emission tomography; Q1, dipole moment strength of P50m evoked by S1; Q2, dipole moment strength of P50m evoked by S1; RMS, root mean square; S1, first auditory click stimulus; S2, second auditory click stimulus; STG, superior temporal gyrus; VBM, voxel-based morphometry.

* Corresponding author. Department of Clinical Neurophysiology, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Fax: +81 92 642 5545.
E-mail address: katuya@med.kyushu-u.ac.jp (K. Ogata).

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(Sommer et al., 2002; Chang et al., 2008; Watkins et al., 2008; Cykowski et al., 2010), which connects temporal regions with frontal speech motor-planning (including Broca's area) and motor regions, as well as the striato-thalamico-cortico-striatal loop, which has important connections to the auditory regions (Giraud et al., 2008). Additionally, Chang et al. (2008) identified bilaterally abnormal fractional anisotropy in the corticospinal/corticobulbar tract (which is involved in speech motor control) and in a posterior-lateral region underlying the supramarginal gyrus (rostral portion of the inferior parietal lobe that is connected to the classic frontotemporal language areas) in stuttering children. Watkins et al. (2008) also found disturbed integrity of the white matter underlying the functional underactive areas in the ventral premotor cortex (a connection with posterior-superior temporal and inferior parietal cortex), which provides a substrate for the integration of articulatory planning and sensory feedback. Fluency-shaping therapies reduce right hemispheric over-activation, normalize basal ganglia activity and reactivate left-hemispheric cortex (De Nil et al., 2003; Neumann et al., 2005; Giraud et al., 2008; Kell et al., 2009). Taken together, abnormal auditory–motor integration can be the neural basis of stuttering.

Auditory–motor integration has been investigated in 2 magnetoencephalographic (MEG) studies (Salmelin et al., 1998; Beal et al., 2010). Salmelin et al. (1998) recorded auditory evoked magnetic fields to a single pure tone during the performance of 4 language-related tasks (reading silently, mouth movements only, reading aloud, and reading in chorus with another person). They found that the interhemispheric balance of the N100m responses of PWS was affected more severely by the tasks involving speech than by the 2 non-verbal tasks. Beal et al. (2010) reported the phenomenon of speech-induced suppression of the auditory N100m for vowel stimuli and showed that both the P50m and N100m were suppressed for word stimuli. They also revealed that the P50m and N100m latencies in PWS were significantly longer than those in the controls, which suggested that the timing of cortical auditory processing in PWS was slower than that in controls under various stimuli. These findings support the altered auditory–motor integration in PWS.

Therefore, we hypothesized that PWS have an abnormal auditory–motor integration system. We tested our hypothesis by using auditory sensory gating that modulates auditory inputs and tonotopic organization that corresponds to auditory inputs. PWS do not have abnormal auditory inputs to brainstem responses (Decker et al., 1982; Newman et al., 1985; Stager, 1990). To validate our hypothesis, we conducted 3 experiments. First, we examined auditory sensory gating by MEG using a P50m (or P50 in EEG) suppression standard paradigm, as has been used in studies on schizophrenia and Alzheimer's disease (Adler et al., 1982; Jessen et al., 2001; Thoma et al., 2003; Hirano et al., 2010). We presented 2 successive click sounds to the subjects monaurally, and the lack of P50m suppression in response to the second sound suggested an inability to filter unnecessary auditory information. Second, we measured the most frequently used N100m in response to 3 tonal stimuli at 250, 1000, and 4000 Hz to elucidate the expansion of the tonotopic map (Pantev et al., 1998b; Naka et al., 1999). MEG has both high spatial and temporal resolution and can be used to evaluate the differences in tonotopic organization in both auditory cortices of PWS and controls. Third, we performed three-dimensional voxel-based morphometry (VBM) to assess structural changes in the auditory cortex. Using the results of these studies, we have provided electrophysiological and structural evidence for abnormal auditory processing in PWS.

Methods

Experiment 1: Auditory sensory gating

Subjects

Seventeen men who stutter (mean age, 30.2 ± 5.7 years; range, 21–41 years) and 18 control male subjects (mean age, 30.6 ± 6.2 years; range, 22–43 years) participated in the present study. PWS were recruited from a self-help group as volunteers and were diagnosed as having developmental stuttering according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV). All subjects gave their written informed consent for participation in the study, and the study was approved by the Ethics Committee of Kyushu University. None of the participants had a history of otological or neurological disorders, and all were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Unfortunately, we were unable to enroll the same participants across all experiments.

The severity of stuttering was assessed by a speech-language-hearing therapist as the percentage of stuttered syllables of at least 300 analyzable syllables averaged over 3 different speaking contexts (reading a short story, describing pictures, and asking questions) and rated as 8.4% (range, 0.8%–36.7%) for PWS and 0.22% (range, 0%–0.55%) for the control group. We excluded 1 subject because of a low dysfluency of less than 1% (Jones et al., 2005; Kell et al., 2009). The stuttered syllables included only the instances of unambiguous stuttering (Jones et al., 2000) and incorporated syllable repetitions and audible and inaudible sound prolongations (Conture, 2001), except normal dysfluencies such as interjections, whole-word repetitions, revisions, and phrase-repetitions.

Stimulus setting

Auditory stimuli were 3-ms monaural clicks presented in pairs with a 500-ms interstimulus interval (ISI) and an intertrial interval that randomly varied between 8 and 12 s (Thoma et al., 2003). The hearing threshold was determined for each subject, and the stimuli were delivered at an intensity of 30 dB above the threshold so as not to induce cross-hearing. The subjects received the stimuli from a Tone Burst Generator (Kyushu Keisokuki, Japan) passed through a plastic tube (length, 6 m; inner diameter, 8 mm) into sponge ear pieces fitted in the subjects' ears. The subjects were in supine position.

MEG recording

Auditory evoked magnetic fields were measured using a whole-head 306-channel biomagnetometer system (Elekta-Neuromag, Helsinki, Finland) in a quiet, magnetically shielded room. The detector array comprised 102 identical triple sensor elements, with each sensor element comprising 2 orthogonally oriented planar-type gradiometers and 1 magnetometer. Planar gradiometers pick up the strongest signals just above the local current, and consequently, the locations of the sensors detecting the strongest signals could be readily used as the first guesses of the activated brain areas (Hämäläinen et al., 1993). Prior to the recording, four head position indicator (HPI) coils were attached to the scalp, and a 3D digitizer was used to measure anatomical landmarks of the head with respect to the HPI coils. During data acquisition, the HPI coils were continuously active and the head position was continuously measured. The magnetic responses were digitally sampled at a rate of 1000 Hz. In order to keep subjects alert and to prevent them from paying attention to the auditory stimuli, we instructed them to watch a silent cartoon movie during the recordings (Thoma et al., 2008; Weisser et al., 2001).

After a recording, the movement compensation realized by the temporal extension signal space separation (MC-tSSS) with Maxfilter 2.0 software (Elekta Neuromag®) was applied off-line to the recorded raw data to reduce artifact signals arising from outside the sensor array and to correct the head position as well as the associated movement-related artifacts (Taulu et al., 2004, 2005; Medvedovsky et al., 2007). Off-line averaging of the auditory event-related field (AEF) was performed using the MC-tSSS-reconstructed raw data, and 150 responses were averaged for each ear. A −100 to −10 ms baseline adjustment and a 5–55 Hz bandpass filter (Thoma et al., 2003; Lu et al., 2007) were then applied to the AEF. Of the 306 channels recorded, 70 channels, including the P50m signal