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Left posterior-dorsal area 44 couples with parietal areas to promote speech fluency, while right area 44 activity promotes the stopping of motor responses

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ABSTRACT

Area 44 is a cytoarchitectonically distinct portion of Broca's region. Parallel and overlapping large-scale networks couple with this region thereby orchestrating heterogeneous language, cognitive, and motor functions. In the context of stuttering, area 44 frequently comes into focus because structural and physiological irregularities affect developmental trajectories, stuttering severity, persistency, and etiology. A remarkable phenomenon accompanying stuttering is the preserved ability to sing. Speaking and singing are connatural behaviours recruiting largely overlapping brain networks including left and right area 44. Analysing which potential subregions of area 44 are malfunctioning in adults who stutter, and what effectively suppresses stuttering during singing, may provide a better understanding of the coordination and reorganization of large-scale brain networks dedicated to speaking and singing in general. We used fMRI to investigate functionally distinct subregions of area 44 during imagery of speaking and imaginary of humming a melody in 15 dextral males who stutter and 17 matched control participants. Our results are fourfold. First, stuttering was specifically linked to a reduced activation of left posterior-dorsal area 44, a subregion that is involved in speech production, including phonological word processing, pitch processing, working memory processes, sequencing, motor planning, pseudoword learning, and action inhibition. Second, functional coupling between left posterior area 44 and left inferior parietal lobule was deficient in stuttering. Third, despite the preserved ability to sing, males who stutter showed bilaterally a reduced activation of area 44 when imagine humming a melody, suggesting that this fluency-enhancing condition seems to bypass posterior-dorsal area 44 to achieve fluency. Fourth, time courses of the posterior subregions in area 44 showed delayed peak activations in the right hemisphere in both groups, possibly signaling the offset response. Because these offset response-related activations in the right hemisphere were comparably large in males who stutter, our data suggest a hyperactive mechanism to stop speech motor responses and thus possibly reflect a pathomechanism, which, until now, has been neglected. Overall, the current results confirmed a recently described co-activation based parcellation supporting the idea of functionally distinct subregions of left area 44.

1. Introduction

In 1861, Broca assigned a region in the human left frontal lobe to a designated function – articulated language. More than 150 years later, it is still an open question, how the human brain generates well-organized, fluent speech. The most famous functions of Broca's area consider operations of speech production, ranging from semantic, to syntactic, and phonologic processing (Amunts et al., 2004; Eickhoff et al., 2009; Flinker et al., 2015; Friederici, 2011; Heim et al., 2008; Heim et al., 2010; Price, 2010; Sahin et al., 2009). Besides, this region is engaged in domain-general functions including hierarchical structure building (Sakai and Passingham, 2006), aspects of action processing (Nishitani and Hari, 2000), rhythm and music processing (Platel et al., 1997), working memory processing (Buchsbaum et al., 2005; Fiebach et al., 2005; Ranganath et al., 2003), or cognitive control (Koechlin and Summerfield, 2007). Recent theories postulate a rostral-to-caudal gradient for structured sequence processing (Uddén and Bahlmann, 2012) and degree of automaticity (Jeon and Friederici, 2015) stretching from orbital area 47, to area 45 and 44 over the whole left inferior

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frontal gyrus (IFG). Across cognitive domains including language, music and action, it has been suggested that more abstract control demanding components of action are supported by anterior prefrontal regions, whereas, with increasing degree of automaticity, concreteness, and, thus, temporally proximity more posterior regions are likely to be involved (Badre, 2008; Jeon and Friederici, 2013).

Growing evidence consolidates morphological and physiological subdivisions of Broca's area. Cytoarchitectonically, anatomists distinguish anterior area 45 and posterior area 44 (Aboitiz and García, 1997; Amunts et al., 1999; Brodmann, 1909). Macroanatomic landmarks give a coarse estimation of where these areas are settled. However, real locations vary between subjects. The anatomical organization of Broca's region has been detailed in the seminal works by Amunts and colleagues (Amunts et al., 1999, 2010). Area 45 occupies the pars triangularis of the IFG with a rostral border to area 47 occupying the orbital part of the IFG. Dorsally area 45 and area 44 border on areas in the inferior frontal sulcus, ventrally opercular areas adjoin area 45 and area 44 at varying positions at the entrance of the Sylvian fissure. The border between area 45 and area 44 has been described within the ascending branch of the lateral fissure or between the diagonal sulcus and ascending branch on the cortical surface of the IFG. Area 44 is settled in the pars opercularis of the posterior IFG, anterior to area 6 on the precentral gyrus. These areas differ with respect to size and laminar distribution of neurons (cytoarchitectonics) suggesting different attributions to brain function. Results from diffusion-weighted magnetic resonance imaging are complementary to this. Based on probabilistic tractography, Broca's area was segregated into three cortical areas with mutually distinct and internally coherent connectivity reminiscent of the cytoarchitectonic parcellation (Anwander et al., 2007). Receptorarchitectonically, area 45 can be further subdivided into an anterior (area 45a) and posterior (area 45p) part; area 44 can be further subdivided into a dorsal (area 44d) and a ventral (area 44v) part (Amunts et al., 2010), because neurotransmitter receptors are expressed at largely varying density across these parts.

An additional operative segmentation was suggested by a recent functional connectivity analysis reporting five functionally different subdivisions of left area 44 (Fig. 1) (Clos et al., 2013). Theses subdivisions build the regions of interest (ROI) of the current work. Clos and colleagues obtained this segmentation by a connectivity-based parcellation as a way of meta-analytic connectivity modelling (Laird et al., 2009). Thereby, area 44 was used as a seed region in a brain template (Amunts et al., 1999, 2004; Evans et al., 2012). Co-activation patterns of area 44 were subsequently extracted from a large data base, the BrainMap database (https://www.brainmap.org/), considering several thousand imaging experiments from pure mapping studies in healthy subjects. To delineate the brain networks that are co-active across many different experimental tasks, an algorithm computed the convergence across all reported foci of all BrainMap experiments, where the seed region in question was reported to be active. Eventually, the seed region was clustered into different subdivisions based on similarities and differences in the co-activation profile (Cieslik et al., 2013; Laird et al., 2009). Due to the co-activation based parcellation analysis the region specific information processing of area 44 can be roughly described as following. Three anterior clusters (Fig. 1, C2, C3, and C5) were primarily associated with language and cognition, and two posterior clusters (Fig. 1, C1 and C4) were primarily associated with action processes such as imagined movements, articulation of speech, and rhythmic sequencing (Clos et al., 2013). In the following, area 44pd refers to the posterior-dorsal cluster 1 and area 44pv refers to posterior-ventral area 44.

Stuttering is associated with various neuronal changes throughout cortical and subcortical networks. For a recent review see (Neef et al., 2015a). The left prefrontal cortex is a brain region often associated with stuttering as well as its remediation (Belyk et al., 2015; Kell et al., 2009; Neumann et al., 2005) and has been considered as the region with an etiologic role for stuttering (Lu et al., 2012). In particular, left area 44 is a neural correlate of stuttering. Grey matter probability matures irregularly (Beal et al., 2015; Beal et al., 2013; Chang et al., 2008), which is still evident in adulthood (Kell et al., 2009; Lu et al., 2012). Various speech tasks elicit aberrant activation patterns (Braun et al., 1997; Ingham et al., 2012; Lu et al., 2012; Salmelin et al., 2000; Toyomura et al., 2011; Wymbs et al., 2013), resting state functional connectivity is diminished (Lu et al., 2012), and functional connectivity between left area 44 and the adjacent premotor cortex is reduced during speech tasks (Chang et al., 2011). Here we investigated whether the trait of stuttering can be associated with a particular subdivision of area 44. To achieve this aim, we conducted a functional magnetic
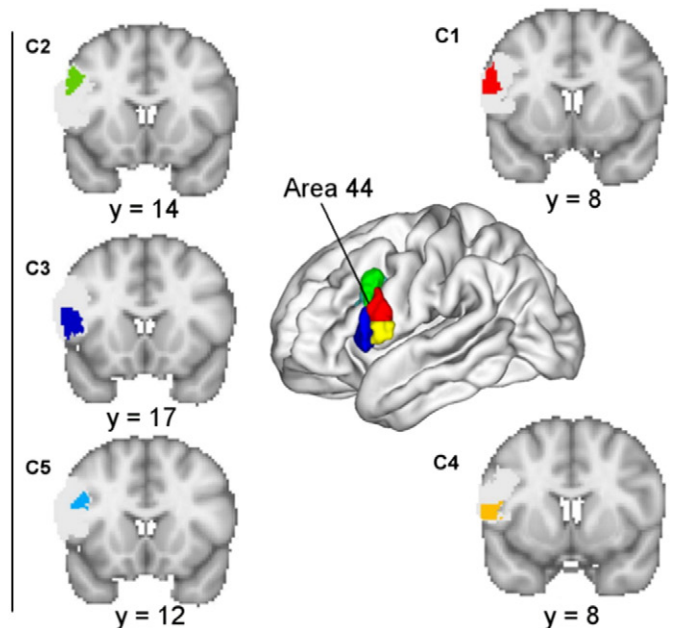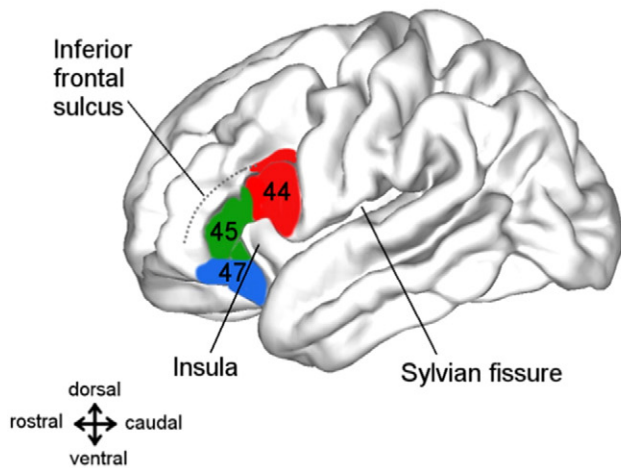

Fig. 1. Area 44 parcels. The surface mesh of the left hemisphere of the MNI standard brain on the left shows the inferior frontal gyrus and the approximate location of Brodmann areas 44, 45, and 47. Coronal slices on the right display the Juelich probability map of area 44 (Amunts et al., 1999, 2004) in light-grey. Functionally distinctive area 44 clusters that resulted from a co-activation based parcellation (Clos et al., 2013) are displayed separately on these coronal slices posterior (y = 8) to anterior (y = 17). The surface mesh of the left hemisphere of the MNI standard brain shows the collocation of all clusters in left area 44 in the middle.