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Tackling the multifunctional nature of Broca's region meta-analytically: Co-activation-based parcellation of area 44

Mareike Clos [a,*], Katrin Amunts [a,b,c,d], Angela R. Laird [e], Peter T. Fox [f,h], Simon B. Eickhoff [a,g]

[a] Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Germany
[b] JARA-BRAIN, Jülich-Aachen Research Alliance, Germany
[c] Department of Psychiatry, Psychotherapy, and Psychosomatics, RWTH Aachen, Germany
[d] C. and O. Vogt Institute for Brain Research, Heinrich Heine University, Düsseldorf, Germany
[e] Department of Physics, Florida International University, Miami, FL, USA
[f] Research Imaging Institute, University of Texas Health Science Center at San Antonio, TX, USA
[g] Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf, Germany
[h] South Texas Administration Medical Center, San Antonio, TX, USA

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ABSTRACT

Cytoarchitectonic area 44 of Broca's region in the left inferior frontal gyrus is known to be involved in several functional domains including language, action and music processing. We investigated whether this functional heterogeneity is reflected in distinct modules within cytoarchitectonically defined left area 44 using meta-analytic connectivity-based parcellation (CBP). This method relies on identifying the whole-brain co-activation pattern for each area 44 voxel across a wide range of functional neuroimaging experiments and subsequently grouping the voxels into distinct clusters based on the similarity of their co-activation patterns. This CBP analysis revealed that five separate clusters exist within left area 44. A post-hoc functional characterization and functional connectivity analysis of these five clusters was then performed. The two posterior clusters were primarily associated with action processes, in particular with phonology and overt speech (posterior-dorsal cluster) and with rhythmic sequencing (posterior-ventral cluster). The three anterior clusters were primarily associated with language and cognition, in particular with working memory (anterior-dorsal cluster), with detection of meaning (anterior-ventral cluster) and with task switching/cognitive control (inferior frontal junction cluster). These five clusters furthermore showed specific and distinct connectivity patterns. The results demonstrate that left area 44 is heterogeneous, thus supporting anatomical data on the molecular architecture of this region, and provide a basis for more specific interpretations of activations localized in area 44.

Introduction

Area 44, as mapped cytoarchitectonically by Brodmann (1909), corresponds to the posterior part of Broca's region on the inferior frontal gyrus. More recently, the borders of this area have been redefined cytoarchitechtonically using observer-independent techniques in a series of histological sections of 10 postmortem brains (Amunts et al., 1999). Being part of Broca's speech region, left area 44 is known to be involved in both language production and comprehension although its exact contribution to language comprehension is still a matter of debate (Friederici, 2011; Hagoort, 2005). In addition to this core function, however, area 44 also plays a role in several non-language-related functions such as working memory (Buchsbaum et al., 2005; Kaan and Swaab, 2002; Rogalsky and Hickok, 2011; Smith and Jonides, 1999), execution and perception of action (as part of the mirror-neuron system; Clerget et al., 2009; Fazio et al., 2009; Heiser et al., 2003; Iacoboni et al., 1999; Rizzolatti and Craighero, 2004) and the processing of music (Koelsch, 2011; Koelsch et al., 2002; Maess et al., 2001; Platel et al., 1997). This raises the question whether this cytoarchitectonic area may indeed be regarded as a single, homogeneous functional module. Supporting the view of a structural heterogeneity within area 44, a recent postmortem, receptor-based parcellation of Broca's region indicated the presence of distinct subareas within this cytoarchitectonic region (Amunts et al., 2010). In this study left area 44 was divided into an anterior-dorsal area 44d and a posterior-ventral area 44v using multi-receptor mapping. Since transmitter receptors are key molecules for neurotransmission, it can be assumed that this heterogeneity at the molecular level corresponds to a similar differentiation at the level of function and connectivity. Evidence of such a differentiation may be achieved with connectivity-based parcellation (CBP) of functional imaging data. The rationale behind CBP is that functionally homogenous subregions show very similar connectivity patterns, which at the same time are clearly distinguished from that of other subregions. Connectivity measures employed in CBP approaches include diffusion-tensor imaging

* Corresponding author at: Forschungzentrum Jülich, INM-1, 52425 Jülich, Germany. Fax: +49 2461 61 2990.
E-mail address: m.clos@fz-juelich.de (M. Clos).

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(Johansen-Berg et al., 2004), resting state functional connectivity (Zhang and Li, 2012), and meta-analytic connectivity modeling (Cauda et al., 2012; Eickhoff et al., 2011). Previous DTI parcellations targeting Broca's region have demonstrated that areas 44 and 45 can be distinguished from each other based on their connectivity patterns (Anwander et al., 2007; Ford et al., 2010; Klein et al., 2007). However, as these studies focused mainly on the inter-area differences, no intra-area subdivisions have been identified.

In order to investigate whether functionally distinct subregions exist within the left area 44, we used a meta-analytic connectivity modeling (MACM) based parcellation (Bzdok et al., 2012a; Cieslik et al., 2012). This approach makes use of the BrainMap database (Fox and Lancaster, 2002; Laird et al., 2005, 2009a, 2011) to identify the whole-brain co-activation pattern for each voxel within area 44 across a wide range of neuroimaging experiments. The resulting individual co-activation profiles are then compared between voxels to identify clusters of voxels showing very similar co-activation patterns. Furthermore, a follow-up MACM analysis on the derived clusters was performed to reveal the overall and specific co-activation networks of these clusters. Finally, the function of the clusters in terms of behavioral domains and paradigm classes was determined from the associated BrainMap meta-data. Note that the parcellation was only based on the whole-brain co-activation pattern of the individual voxels and that the decision regarding the optimal parcellation solution was based on external stability criteria. Subsequently, only the most stable parcellation solution was functionally characterized post-hoc based on specific connectivity and BrainMap meta-data of the individual clusters (for an overview of the method see Fig. 1).

Material and methods

Meta-analytic connectivity mapping

The volume-of-interest (VOI) for the current CBP analysis was provided by representation of left area 44 in the maximum probability map (MPM) in the SPM Anatomy Toolbox (Eickhoff et al., 2005, 2006a). This MPM was derived from the cytoarchitectonic mapping of 10 postmortem human brains (Amunts et al., 1999) registered to 3D MNI space (Montreal Neurological Institute; Amunts et al., 2004; Evans et al., 2012) and specifies the likelihood that a particular cortical area is localized at each brain voxel. This whole-brain MPM thus provides a continuous, non-overlapping representation of the microanatomically defined area 44 and allows the user to define a VOI that includes only those voxels which are more likely to represent area 44 than any other cytoarchitectonic area. It should be noted that normalization into standard space (which is slightly bigger than an average brain) as well as representation of microscopical structures in $2 \times 2 \times 2$ mm^3 voxel space may result in a rather liberal definition of area 44 as compared to the stereological volume measured in postmortem data at micrometer histological resolution. Nevertheless, the MPM-based definition of the area 44 seed region has a sound biological basis (cf. Eickhoff et al., 2006a), with currently no available alternative based on in vivo imaging (but see Walters et al., 2007 for a potential future perspective). In addition, we also performed a supplementary parcellation with a more conservative definition of left area 44 based on the 50% probability map that was constrained to the surface of the pars opercularis of the inferior frontal gyrus.

The BrainMap database was used to compute whole-brain co-activation maps for each voxel within the VOI (www.brainmap.org; Fox and Lancaster, 2002; Laird et al., 2005, 2009a, 2011). BrainMap is an established database in which the activation foci of many thousand neurominaging experiments are recorded. Each experiment is furthermore coded in terms of behavioral domains and paradigm classes using a standardized taxonomy. Only fMRI and PET experiments from "normal mapping" studies (no interventions, no group comparisons) in healthy subjects that reported results as coordinates in stereotaxic space were included in the analysis. Based on these criteria, approximately 7200 functional neuroimaging experiments were available for the current analysis. The idea of the co-activation analysis is to compute

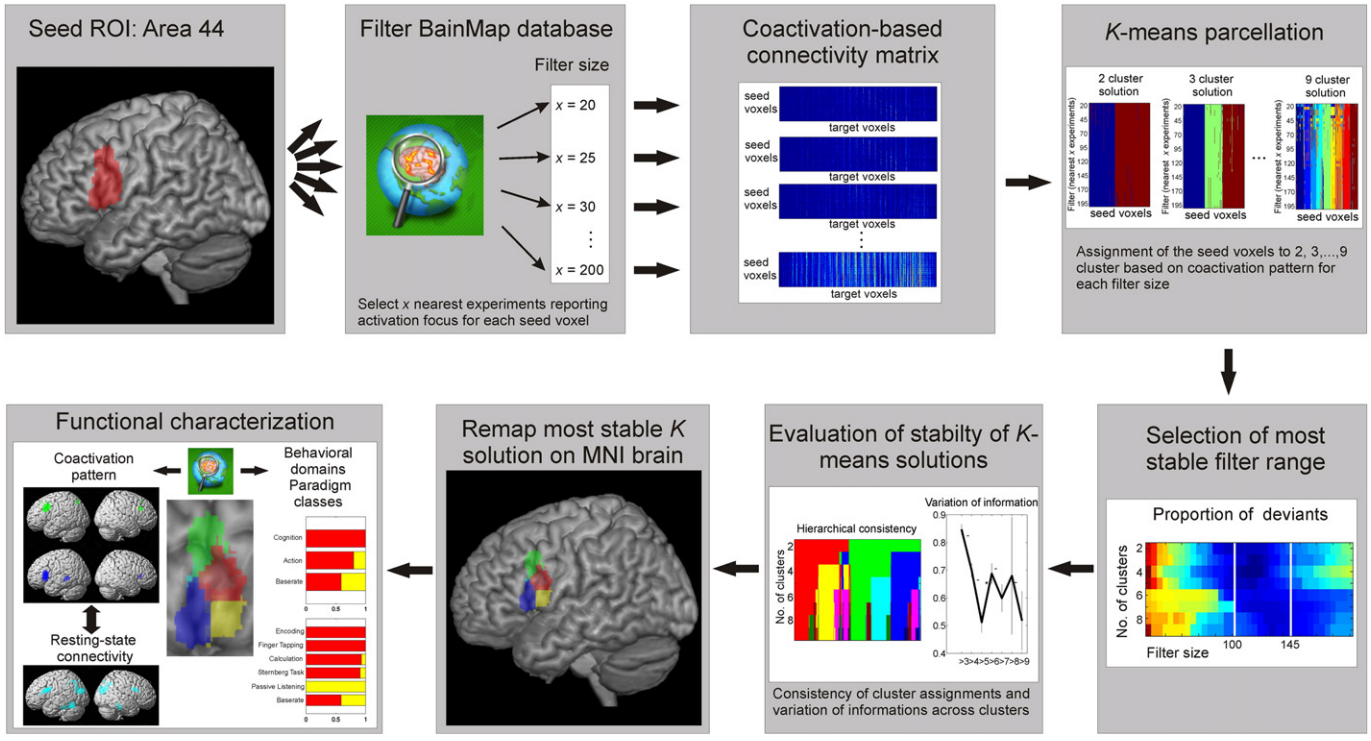

Fig. 1. Summary of analysis steps. For each voxel of area 44, activation foci from the *x* nearest experiments are selected from the BrainMap database. In the next step, the activation foci from the selected experiments are used to generate the brain-wide co-activation profile for each seed voxel and each filter size *x* based on meta-analytic co-activation modeling. Subsequent parcellation of the co-activation matrices was performed with *K*-means. Next, the optimal range of filter sizes was selected based on the consistency of the cluster assignments. The ensuing evaluation of the *K*-means solutions was limited to the optimal filter range. The most stable *K*-means solution was mapped back on the brain and the *K* clusters were functionally characterized based on their connectivity pattern and BrainMap meta-data. See methods for details.