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Common molecular basis of the sentence comprehension network revealed by neurotransmitter receptor fingerprints

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ABSTRACT

The language network is a well-defined large-scale neural network of anatomically and functionally interacting cortical areas. The successful language process requires the transmission of information between these areas. Since neurotransmitter receptors are key molecules of information processing, we hypothesized that cortical areas which are part of the same functional language network may show highly similar multireceptor expression pattern ("receptor fingerprint"), whereas those that are not part of this network should have different fingerprints. Here we demonstrate that the relation between the densities of 15 different excitatory, inhibitory and modulatory receptors in eight language-related areas are highly similar and differ considerably from those of 18 other brain regions not directly involved in language processing. Thus, the fingerprints of all cortical areas underlying a large-scale cognitive domain such as language is a characteristic, functionally relevant feature of this network and an important prerequisite for the underlying neuronal processes of language functions.

1. Introduction

Recent functional neuroimaging studies on language (Friederici, 2011; Vigneau et al., 2006) investigating syntactic, semantic and verbal working memory processes identified circumscribed activations located within the two classical language regions, i.e., Broca's region in the inferior frontal gyrus (IFG) and Wernicke's region in the superior temporal

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gyrus. Within Broca's area the dorsal part of the left pars opercularis (44d) processes hierarchically structured syntax (e.g., center-embedded relative clauses), whereas the left inferior frontal sulcus at the junction with the precentral sulcus (IFS1/IFJ) is involved in syntactic verbal working memory (Makuuchi, Bahlmann, Anwander, & Friederici, 2009). An involvement of 44d was also reported for the processing of complex sentences in other studies (Friederici, Fiebach, Schlesewsky, Bornkessel, & von Cramon, 2006; Grewe et al., 2005). The pars triangularis within Broca's area, which was subdivided into a more posterior part (45p) and a more anterior part (45a) (Amunts et al., 2010), is involved in processing semantic aspects both at the word (Fiez, 1997; Heim et al., 2009; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and sentence levels (Newman, Ikuta, & Burns, 2010) as well as for sentence comprehension in general (Saur et al., 2008). The posterior superior temporal gyrus and sulcus (pSTG/STS) play a significant role in sentence processing (Friederici, Makuuchi, & Bahlmann, 2009), and in the brain-based decoding of human voice and speech (Formisano, De Martino, Bonte, & Goebel, 2008). These different regions of the inferior frontal and temporal cortex are known to be structurally connected by short-range connections (Makuuchi et al., 2009; Upadhyay et al., 2008) and by long-range fiber bundles (Catani, Jones, & ffytche, 2005; Friederici et al., 2006; Saur et al., 2008). Thereby the different areas constitute a large-scale fronto-temporal language network for sentence comprehension (Friederici, 2009, 2011).

Neurotransmitters and their receptors are key molecules of neuronal function. Within a given brain region, different receptor types are expressed at largely varying densities. Thus, the balance between the densities of different receptors in a single brain region, and not the mere presence or absence of a single receptor type, results in a regional specific receptor pattern, i.e., a "receptor fingerprint" (Zilles et al., 2002). Consequently, receptor fingerprints represent the molecular default organization of the regionally specific local information processing in each cortical area. Differences between the fingerprints of unimodal sensory, motor, and multimodal association areas of the human cerebral cortex (Caspers, Schleicher, et al., 2013; Eickhoff, Rottschy, Kujovic, Palomero-Gallagher, & Zilles, 2008; Zilles, Palomero-Gallagher, & Schleicher, 2004) underlined the regional diversity of multireceptor expression levels. E.g., cortical areas belonging either to the dorsal or ventral visual streams have similar fingerprints within each of the streams, but differ between streams (Eickhoff et al., 2008). Connectionally distinct areas within inferior parietal lobule (IPL) also differ in their receptor fingerprints (Caspers, Schleicher, et al., 2013). Since the cortical areas of the dorsal or ventral streams, as well as those of the inferior parietal cortex are immediate neighbors, it could be argued, that the similarities in receptor fingerprints resulted merely from the close spatial relation of areas within each of the three regions, and not from their common affiliation to a given functional system. It is currently not known, whether widely distributed areas of the same cognitive network have similar fingerprints despite of their spatial distance. Therefore, we here investigated whether areas belonging to the large-scale fronto-temporal language network for sentence comprehension differ in their receptor fingerprints or share a common multireceptor expression, despite the fact that the areas are widely distributed between the temporal and frontal lobes. In each of these areas, multiple excitatory, inhibitory and modulatory transmitter receptors subserve the local computational processes. Here we hypothesized, that areas constituting the fronto-temporal language network may not only be characterized by similar receptor fingerprints, but also that their fingerprints differ from those of areas subserving non-language functions, i.e., different unimodal sensory, motor or multimodal functions.

2. Material and methods

Brain regions were examined in the left and right hemispheres of brains obtained from individuals (two males and two females; 77 ± 2 years of age) with no clinical records of neurological or psychiatric disorders, who participated in the body donor program of the Department of Anatomy, University of Düsseldorf. Causes of death were pulmonary edema, multi-organ failure, bronchial cancer, or sudden cardiac death.

Brains were removed from the skull within 24 h after death. Each hemisphere was dissected into five or six slabs in the coronal plane (25–30 mm thickness), frozen in isopentane at −40 °C and stored at −70 °C. Using a large-scale cryostat microtome, each slab comprising a coronal section through the complete human hemisphere was cut into continuous series of coronal sections (20 μm thickness), which were thaw-mounted onto glass slides.

2.1. *Brain regions*

Cortical areas studied here could be divided into two major groups, i.e., areas involved in language, particularly in sentence comprehension, and "non-language" related areas, which do not belong to this fronto-temporal language network.

2.1.1. *Language-related areas*

Three regions (44d, IFS1/IFJ, and pSTG/STS, Fig. 1A) were functionally (IFS1/IFJ, pSTG/STS; Friederici et al., 2006, 2009; Grewe et al., 2005; Makuuchi et al., 2009) and additionally receptor architectonically (44d; Amunts et al., 2010) defined. These three regions were found to be activated during processing of syntactically complex, embedded sentences (Friederici et al., 2009; Makuuchi et al., 2009). An involvement of 44d was also reported for the processing of non-canonical object first sentences (Friederici et al., 2006; Grewe et al., 2005). These regions were localized in the postmortem brains using their characteristic anatomical landmarks (i.e., sulci and gyri). Five further language-related regions (44v, 45a, 45p, 47 and Te2, Fig. 1A) were defined based on cyto- and receptor architectonical criteria. Area 44v is the ventral part of the left pars opercularis of Broca's region, and can be architectonically segregated from its dorsal counterpart 44d and from the rostrally adjoining area 45 (Amunts et al., 2010, 1999). Areas 45a and 45p (Amunts et al., 2010) were included as the complete region has been reported to be activated during processing of semantic aspects at both the word (Fiez, 1997; Heim et al., 2009; Thompson-Schill et al., 1997) and the