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Reflections of word processing in the insular cortex: A sub-regional parcellation based functional assessment

Emiliano Zaccarella *, Angela D. Friederici

Max Planck Institute for Human Cognitive and Brain Sciences, Department of Neuropsychology, Stephanstraße 1a, 04103 Leipzig, Germany
Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Unter den Linden 6, 10099 Berlin, Germany

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ABSTRACT

Knowledge about the neuroanatomy of the human brain has exponentially grown in the last decades leading to finer-grained sub-regional parcellations. The goal of this functional Magnetic Resonance Imaging (fMRI) study was to specify the involvement of the insula during visual word processing using a sub-regional parcellation approach. Specifically, we assessed: (1) the number of active voxels falling in each sub-insular cluster; (2) the signal intensity difference between word and letter strings within clusters; (3) the subject-specific cluster selectivity; (4) the lateralization between left and right clusters. We found that word compared to letter string processing was strongly sub-regional sensitive within the anterior-dorsal cluster only, and was left-lateralized. Interestingly, this sensitivity held at both group level and individual level. This study demonstrates that integrating hemodynamic activity with sub-topographic architecture can generate an enriched understanding of sub-regional functional specializations in the human brain.

1. Introduction

Since first pioneering subdivisions of the cerebral cortex around one hundred and fifty years ago (Brodmann, 1909; Meynert, 1865), a number of whole-brain atlases based on diverse parcellation approaches have been produced during the last decades. Among others, there are the Automated Anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and the Harvard-Oxford Cortical (HOC) atlas (Desikan et al., 2006) which are derived from cortical landmarks (sulci and gyral), or the Eickhoff-Zilles (EZ) atlas (Eickhoff et al., 2005) and the Talairach and Tournoux (TT) atlas (Lancaster et al., 2000; Talairach & Tournoux, 1988) based on post-mortem cyto- and myelo-architectonics. More recently, novel parcellation approaches which took functional or structural connectivity-based profiles into account have shown that a single anatomical region can be further subdivided into more fundamental sub-areas, thereby producing more fine grained cluster-oriented topographical maps (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Long, Goltz, Margulies, Nierhaus, & Villringer, 2014; Margulies et al., 2007; Solano-Castiella et al., 2011). The existence of such functional sub-regional clusters suggests that neural activity measurable in the region during a certain task might be sensitive to specific locations internal to the area, according to the function under analysis. These maps can therefore potentially allow inferring structure-function sensitivity at a more fine-grained resolution. In the present study we use this sub-cluster based approach to describe the involvement of the insular cortex during word processing as indicated by functional Magnetic Resonance Imaging (fMRI).

The human insular region comprises an entirely hidden portion of cerebral cortex, located in the depth of the sulcus lateralis, below the Sylvian fissure. The insula—also known as the island of Reil—forms a large triangle within the limbus, with a more extended anterior portion and a more restricted posterior one divided by the sulcus lateralis insulae, and enfolded during embryonic maturation by the adjacent orbitofrontal, frontoparietal, and temporal opercula (Flynn, Benson, & Ardila, 1999). According to in-vivo gross morphological subdivisions, the insula covers a surface area of approximately 17 cm^2 on average, representing about the 2% of the total cortex (Tramo et al., 1995). First investigations on the laminar architecture separated the region into a posterior granular isocortical zone and into an anterior agranular allocortical zone, in which layer IV was completely missing (Brodmann, 1909). Enriched sub-regional partitions, which also considered the arrangement of cortical fibers (Brockhaus, 1940; Rose, 1935; Vogt & Vogt, 1919), additionally described a third dysgranular region running dorsally to the anterior zone, with sparse granule

* Corresponding author at: Max Planck Institute for Human Cognitive and Brain Sciences, Department of Neuropsychology, Stephanstraße 1a, 04103 Leipzig, Germany.

E-mail address: zaccarella@cbs.mpg.de (E. Zaccarella).

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elements visible between layers III and V (Rose, 1928; von Economo & Koskinas, 1925). This tripartite subdivision was found to occur in monkeys, and in other primate species as well (Bauernfeind et al., 2013; Mesulam & Mufson, 1982). Histochemical and autoradiographic studies have revealed a massive number of efferent and afferent connections linking the insula to several loci on the cerebral cortex, and to different subcortical regions of the basal ganglia, the amygdala, and the thalamus (Augustine, 1996). Because of the interconnected nature and the impressive activation rate across experiments, the region has been associated to a wide variety of cognitive and autonomous functions, including heart beat, breathing, somatosensory processes, awareness, goal-directed cognition, and other higher cognitive processing including language (Craig, 2010; Nieuwenhuys, 2012). This has been confirmed by a recent foci density map with more than forty thousand reported foci from more than one thousand studies, which has shown that the left and right insula are among the most active regions found across all those studies (http://brainvis.wustl.edu).

The question of whether specific parts in the insula should be ascribed to different functions is still a matter of debate (Singer, Critchley, & Preuschoff, 2009). Converging evidence in favor of the existence of sub-insular functional components—in which cognitive, affective and somatosensory processing are attributed to different areas within the region—is now being proposed in recent literature, also considering data from patient studies and meta-analytical investigations (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Mutschler et al., 2009; Stephani, Fernandez-Baca Vaca, Maciunas, Koubeissi & Luders, 2011). A recent meta-analysis comprising about two thousand activation seeds from about eight hundred papers found that sensorimotor tasks and olfacto-gustatory stimuli corresponded to increased activity in the mid-posterior and central insula; personal emotions and social-emotional tasks triggered activity in the antero-ventral insula; finally cognitive tasks—such as attention, language processing, active speech and memory retrieval—rather activated the antero-dorsal insular region (Kurth, Zilles et al., 2010). Concurrently, different modern parcellation methodologies have shown quite a higher sub-regional consistency, suggesting some convergence with this internal functional distribution. Probabilistic maps, for example, have confirmed the existence of distinct cytoarchitectonic clusters in the posterior insula through observer-independent algorithms (Kurth et al., 2010). Tractography has found different white matter pathways isolating sub-areas within the region, which neatly resemble previous topographical demarcations (Nanetti, Cerliani, Gazzola, Renken, & Keysers, 2009). Resting-state functional connectivity and task-related fMRI have coherently demonstrated similar sub-regional subdivisions within the insula either when combined together, or when each used in isolation (Kurth, Zilles et al., 2010; Nelson et al., 2010). Finally, a cross-modal study including task-evoked co-activation, task-independent functional connectivity, and gray matter structural covariance, has lead to highly detailed parcellation maps, ranging from two up to fifteen sub-regional clusters, which can be potentially used as diagnostic tool, to describe the precise anatomical distribution of individual cognitive, affective or somato-sensory processes within the insular complex, and therefore to relate structure-to-function mapping at a finer-grained resolution (Kelly et al., 2012).

Concerning cognitive processes, it has been argued that the anterior insula plays a very basic role in human cognition, such as domain-general attentional/task-level control, supporting for example object/item recognition during visual stimulation (Nelson et al., 2010), attention-shift to selective features (Wager, Jonides, & Reading, 2004), or feature-selection during evaluation (Wager & Barrett, 2004). These findings suggest that this part of the insula subscribes essential operational processes common to goal-oriented behavior in general, thereby justifying the enormous functional activation span found in this region across different tasks and cognitive domains (Dosenbach et al., 2006, 2007).

However, with respect to the specific case of language and speech, the anterior insula has been long reported to be involved in speech and auditory processing (Dronkers, Ogar, Willock, & Wilkins, 2004; Saygin, Dick, Wilson, Dronkers, & Bates, 2003), and to support the integration of auditory stimuli with other associative functions (Bamioua, Musiekb, & Luxona, 2003). Insular activation was found both at the word level (Price, 2000) and the phrasal level (Stowe et al., 1998). However, an artificial grammar study indicates that the insula does not increase activation specifically as a function of grammaticality, but rather as a function of increasing processing demands (Bahlmann, Schubotz, & Friederici, 2008). Wager and Barrett (2004), indeed, suggest an involvement of the anterior insula when mental efforts of a cognitive task are high. As recent meta-analysis focusing on linguistic and emotion-regulation processing in the anterior insula alone, reported a quite selective response to auditory and linguistic tasks in a more restricted area of the antero-dorsal insula (Mutschler et al., 2009).

In the present report, we use the available cross-modal parcellation map of the insula (Kelly et al., 2012), to investigate which parts of the insula are involved in language processes at the word and phrasal level. Based on previous findings (Mutschler et al., 2009) we hypothesize that the antero-dorsal part of the insula might be of particular relevance for these processes. In an fMRI study we systematically varied the number of words in a sequence (1 vs 2 words) and the type of word sequence (phrase vs word list) and localized the respective insular activation. The available cross-modal parcellation map with three different subclusters (Kelly et al., 2012) in each hemisphere allows measurements of: (1) the quantitative relation between active voxels and overlapping clusters; (2) the relative difference in the signal intensity per cluster between conditions; (3) the subject-specific cluster selectivity; (4) the activity lateralization between left and right hemispheric clusters.

The visual fMRI study consisted of a 2x2 design with number of WORDS (1- vs. 2-words) and type of SEQUENCE (phrase: PH vs. list: LS) serving as factors (Fig. 1). Crucially, to allow to answer the question of whether the insula is differentially or equally involved in processes at the phrase and at the word level we varied the type two-word sequences. The phrasal stimuli (2-PH) consisted of two words (determiner *plus* pseudo-noun: DIESE FLIRK), allowing the build up of a basic syntactic phrase; the control stimuli (2-LS) consisted of two-word lists (noun *plus* noun: APFEL FLIRK) with no syntactic processing possible. In order to see whether function word processing and content word processing resulted in differential insula involvement, different one-word sequences were used: 1-PH containing a determiner and 1-LS containing a noun. Both 1-PH and 1-LS conditions were identical to their corresponding two-word counterparts, except for the fact that the second word was replaced with a string of X letters of equal length (DIESE XXXXX; APFEL XXXXX) thereby allowing lexical access for the first part of the sequence, but disallowing any lexical access for the

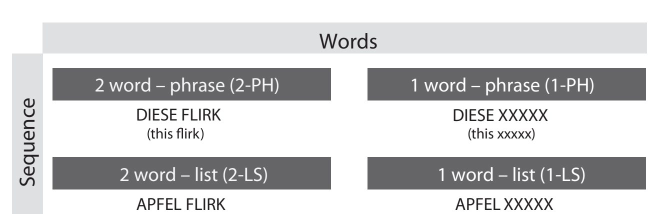

Fig. 1. Experimental design: factors WORDS (1- vs. 2-word) and SEQUENCE (phrase vs. list).