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A ventral salience network in the macaque brain

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ABSTRACT

Successful navigation of the environment requires attending and responding efficiently to objects and conspecifics with the potential to benefit or harm (i.e., that have value). In humans, this function is subserved by a distributed large-scale neural network called the "salience network". We have recently demonstrated that there are two anatomically and functionally dissociable salience networks anchored in the dorsal and ventral portions of the human anterior insula (Touroutoglou et al., 2012). In this paper, we test the hypothesis that these two subnetworks exist in rhesus macaques (*Macaca mulatta*). We provide evidence that a homologous ventral salience network exists in macaques, but that the connectivity of the dorsal anterior insula in macaques is not sufficiently developed as a dorsal salience network. The evolutionary implications of these finding are considered.

Introduction

Salience processing is crucial for survival. It enables animals to successfully navigate the detection of, attention to, and action planning for stimuli that are potentially rewarding or harmful (i.e., that are relevant for allostasis). Allostasis, as the continually adjustment of the body's internal milieu to promote survival and reproduction, is a fundamental feature of the mammalian nervous system (Sterling, 2012; Sterling and Laughlin, 2015). Affect, characterized as valence (hedonicity) and arousal (physiological activation), is a cue to the value of stimuli for allostasis (Barrett and Bliss-Moreau, 2009) and is also thought to be a general feature of the mammalian nervous system (Anderson and Adolphs, 2014). The broadly distributed neural networks that subserve salience should, then, be present, in some form, in all mammals, but the existence of such networks across mammalian species remains an open question.

A "salience network" (SN) has been identified within the intrinsic architecture of the human brain (Seeley et al., 2007) and its function linked to affect and attention (Barrett and Satpute, 2013; Touroutoglou et al., 2012). Major hubs of the salience network, including anterior insula (AI), anterior cingulate cortex (ACC), and amygdala, show spontaneous, low frequency blood oxygen level-dependent (BOLD) activity that fluctuates in a correlated manner in task independent periods (i.e., in the absence of external stimuli or tasks). We recently demonstrated (Touroutoglou et al., 2012) that the SN can be decomposed into two subnetworks that together represent salience in humans (see Fig. 1). Other neuroimaging studies have shown similar distinctive patterns of connectivity within the dorsal and ventral anterior insula (Chang et al., 2013; Deen et al., 2011; Kelly et al., 2012; Kurth et al., 2010; Taylor et al., 2009; Uddin et al., 2014). The ventral salience subnetwork, anchored in with the agranular ventral AI (vAI), is connected to visceromotor regions that regulate allostasis, as well as regions that represent interoceptive and other sensory inputs linked to affective experience. Connectivity strength variation in this subnetwork uniquely predicted affective experience intensity when viewing unpleasant images (Touroutoglou et al., 2012). In contrast, the dysgranular dorsal anterior AI (dAI) anchors the dorsal salience network; this network is similar to the so-called ventral attention network (Corbetta et al., 2008; Corbetta and Shulman, 2002). Connectivity strength variation in this subnetwork predicted attentional processing—people with greater connectivity were better at switching their attention between sets (Touroutoglou et al., 2012). Thus, the SN can be thought of as an

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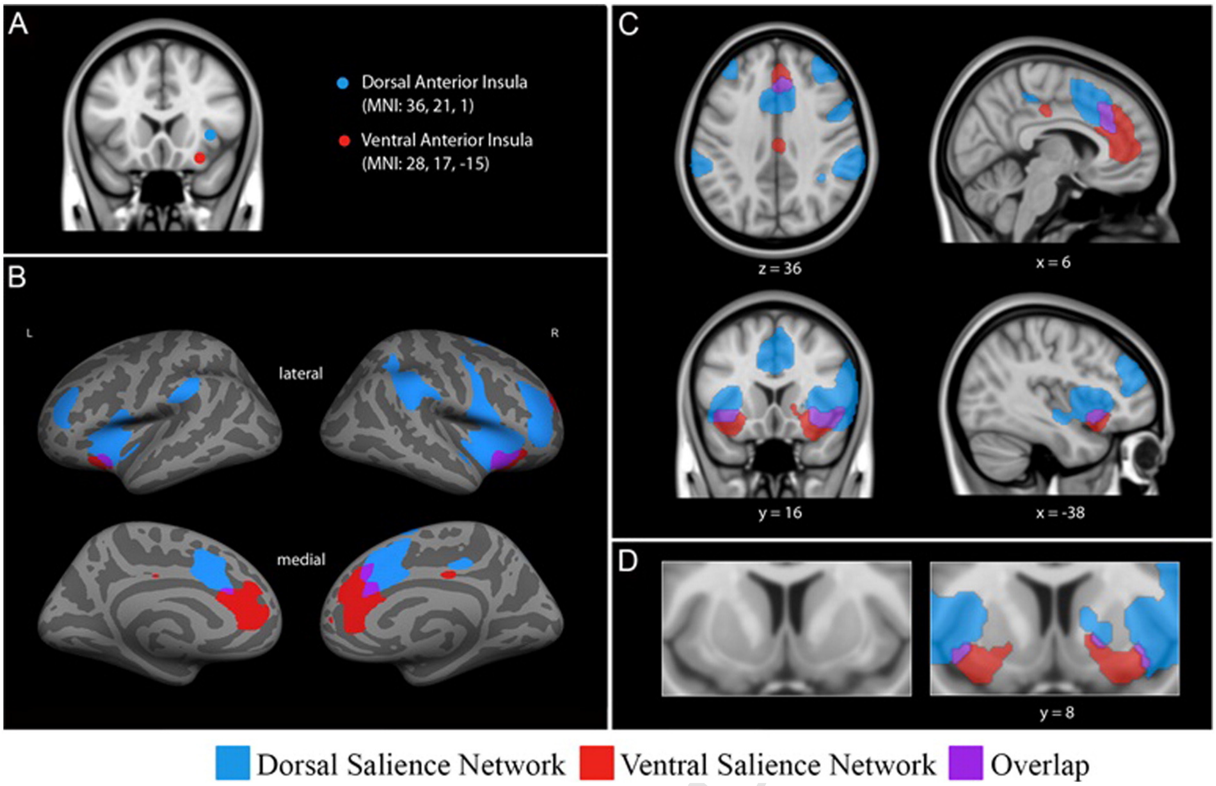

Fig. 1. Dissociable dorsal and ventral salience networks (right dorsal anterior insula seed, blue; right ventral anterior insula seed, red) in humans previously published by our laboratory (Touroutoglou et al., 2012). In B, C and D regions that preferentially correlate with the right dAI seed are shown in blue, regions that preferentially correlate with the right vAI seed are shown in red, and regions that correlate with both seeds are shown in purple. For display purposes, the binarized correlation maps, z(r) > 0.2, were overlaid on (B) the inflated cortical surfaces of the left and right hemispheres (the fsaverage template in FreeSurfer) and (C and D) the 1 mm MNI152 T1-standard template image in FSL.
Adapted figure from Touroutoglou et al., 2012.

integrated system in which affect and attention interact to encode sensory stimuli that, in the past, have had allostatic consequences.

There has been extensive study of the neurobiological systems that support attentional processing in macaques (for reviews, see Desimone and Duncan, 1995; Squire et al., 2013). Also, a good deal is known about the macaque neural systems that code for value (i.e., whether a stimulus has been disruptive to allostasis in the past) (for reviews see Wallis, 2007; Morrison and Salzman, 2010). There is still much to learn about how value signals entrain attention to incoming sensory inputs that have been important to allostasis in the past (this has been called "salience"). Some regions that regulate allostasis (i.e., active during reward processing) are also active during spatial attention, such as ventromedial prefrontal cortex, ACC (Kaping et al., 2011) and the amygdala (Peck et al., 2013). Bidirectional anatomical connections (Mesulam and Mufson, 1982a; Mufson and Mesulam, 1982) and intrinsic connections (Hutchison et al., 2011, 2012) between two major nodes of the salience network, AI and ACC, have been identified in macaques, but studies have thus far failed to identify a fully developed salience network in monkeys (Mantini et al., 2013). Failure to find any evidence of comparable SNs would call into question the use of macaques as a good model for human brain function, as well as limit their translational value for studying human diseases in which salience or the anatomy or connectivity of the SN is perturbed [e.g., multiple neuropsychiatric disorders (Menon and Uddin, 2010; Uddin, 2014)].

In this paper, we tested the hypothesis that a homologous ventral salience subnetwork exists in macaques, but that a dorsal salience subnetwork would be less in evidence. We used a "seed-based" analysis, specifying two regions in anterior insula as anchor regions (Biswal et al., 1995; Vincent et al., 2007) would reveal given the evolutionary patterns of cortical expansion in humans relative to macaques (e.g., Hill et al., 2010; Preuss, 2012; Sherwood et al., 2012) and, in particular, the cortical layers in which the expansion is thought to be focused (Finlay and Uchiyama, 2014), we reasoned that structures that constitute the ventral salience network are largely homologous across macaques and humans, while the dorsal salience network in humans included areas of frontal and parietal cortices that are substantially less developed in macaques (Orban et al., 2004; Passingham, 2009; Vanduffel et al., 2002).

Materials and methods

Subjects

Subjects were four rhesus macaques (*Macaca mulatta*, one female, 4–6 kg, 4–7 years old) who had been extensively trained and tested for other magnetic resonance imaging (MRI) studies (Mantini et al., 2012a, 2012b, 2011, 2013). Animal care standards were maintained according to all Belgian and European guidelines (European Union Directive on the Protection of Animals Used for Scientific Purposes 2010/63/EU). Experimental procedures were approved by the KU Leuven Medical School. Animals were socially housed (in pairs or small groups) and provided access to a large group socialization enclosure equipped with toys and enrichment devices. The monkeys received food ad libitum and were allowed to drink water until satiated during the experimental tests.

Resting state procedure

The current analyses used the same data as in Mantini et al. (2013). Briefly, monkeys were first trained to continuously fixate on a point (red dot centered on screen 0.3° visual angle in size) on a blank screen in a mock scanner until they reached criterion of at least 95% fixation

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