Nature Reviews Neuroscience | AOP, published online 19 November 2014; doi:10.1038/nrn3857

OPINION

Salience processing and insular cortical function and dysfunction

Lucina Q. Uddin

Abstract | The brain is constantly bombarded by stimuli, and the relative salience of these inputs determines which are more likely to capture attention. A brain system known as the 'salience network', with key nodes in the insular cortices, has a central role in the detection of behaviourally relevant stimuli and the coordination of neural resources. Emerging evidence suggests that atypical engagement of specific subdivisions of the insula within the salience network is a feature of many neuropsychiatric disorders.

We make sense of the multiple internal and external inputs that compete for attention by determining which ones are salient. In psychology and neuroscience, the term 'salient' is used to describe a stimulus or an aspect of a stimulus that stands out or that is set apart from others[1]. What is perceived as salient can be influenced by previous experiences and memories, current psychological state, goals and drives[2,3]. Salience processing is not necessarily accessible to conscious awareness; the integration of visceral and autonomic stimuli, and homeostatic functions of the brain can influence what is perceived to be salient[4]. In other instances, salience processing can be dependent on top-down attention and cognitive control processes that are focused on the execution of goal-directed behaviours[5].

Recent empirical evidence suggests that dysregulation of salience-processing systems can occur in many brain conditions, including neurodevelopmental disorders[6], psychosis[7] and dementia[8]. Interestingly, dysfunction of the insular cortex — a brain structure that has many diverse functions — has been implicated in several of these neural pathologies.

Meta-analyses of task-based functional MRI (fMRI) studies[9–11] and parcellation studies using resting-state fMRI data[12–14] have revealed that the human insula can be subdivided into 2–4 distinct regions, each with their own partially distinct functional connectivity profiles and functional repertoires[15]. Given that the insula is the first cortical target of ascending interoceptive[16] and viscerosensory[4] inputs, it has long been considered to be important in the generation of subjective feelings that guide decision making[17]. In this Opinion article, I aim to build on previous influential models of insular function by describing the functional organization of the human insular cortex in the context of a recently described 'salience network' (REF. 18) and by outlining the interactions of this network with other large-scale neurocognitive networks, such as the default-mode network (DMN) and central executive network (CEN). I also review recent evidence that suggests that altered salience processing in subdivisions of the insula contributes to different aspects of several prevalent brain disorders.

Salience detection in the brain

The neuroscience of salience processing has been most well studied in the context of visual attention[19]. Electrophysiologists have identified a set of cortical and subcortical structures that support the detection of visually salient stimuli. In monkeys, the activity of neurons in the lateral intraparietal area (LIP) is associated with attending to specific locations in visual space and is thought to provide a topological salience map that is used by the oculomotor and visual systems, which have been extensively studied in non-human primates[3,20–22]. However, there are other external and internal sources and modalities of information besides visually salient stimuli that also compete for neural resources. Moreover, the systems that mediate the detection of salience have been studied more extensively in non-human primates than in humans, primarily owing to the use of electrophysiological approaches in animal models.

A prevailing neurobiological model of attention systems in the human brain posits that a dorsal frontoparietal network that includes the intraparietal sulcus, superior parietal lobule and frontal eye fields mediates goal-directed, top-down attention, whereas a ventral frontoparietal network that comprises the temporoparietal junction, middle frontal gyrus and anterior insular cortex (AIC) mediates stimulus-driven, bottom-up control of attention[5,23]. Empirical findings demonstrate that the ventral frontoparietal network responds to behaviourally relevant salient stimuli[24], including pain[25].

Recent research has examined a broader set of brain regions that contribute inputs that can influence the detection and processing of salient stimuli. Ascending inputs that communicate information, via interoceptive and visceromotor signals, about the moment-by-moment condition of the body converge in the insular cortices[8] (FIG. 1). The AIC is thought to be a key node of a salience network that also includes the dorsal anterior cingulate cortex (dACC) and other subcortical and limbic structures, and that integrates external sensory information with internal emotional and bodily state signals[18]. The ventral frontoparietal attention network and the salience network both have nodes that are located in the AIC, but whereas the ventral attention network is lateralized to the right hemisphere[5], the salience network is bilateral[18,26,27]. Although some investigators see the high degree of functional and anatomical overlap between the ventral frontoparietal network and the salience network as evidence that they are part of the same network[28], others conceptualize these two neural systems as distinct entities[29,30].

The right dorsal AIC (dAIC) node of the salience network is thought to be involved in coordinating brain network dynamics[31]. In the first study to demonstrate this role, chronometric techniques and Granger causal analysis (GCA) revealed that across auditory tasks, visual tasks and task-free conditions, the right dAIC acts as a 'causal outflow hub' at the junction of large-scale neurocognitive networks, including the CEN (which is involved in the maintenance and manipulation of information, as well as in decision making) and the DMN (the function of which is associated with self-oriented and social cognition)[32]. In networks, hubs allow increased levels of information flow between distant nodes[33], and a causal outflow hub is a highly influential brain region that exhibits a high number of causal outflow connections and a low number of causal inflow connections[26]. A key study by Sridharan and colleagues, as well as subsequent work, showed that the right dAIC generates control signals that causally influence the DMN and CEN[26,32,34] (FIG. 2). The ability of the right dAIC to cause changes in activation levels in the CEN and DMN has now been demonstrated using transcranial magnetic stimulation[35] and through dynamic causal modelling of fMRI data[36]. The structural

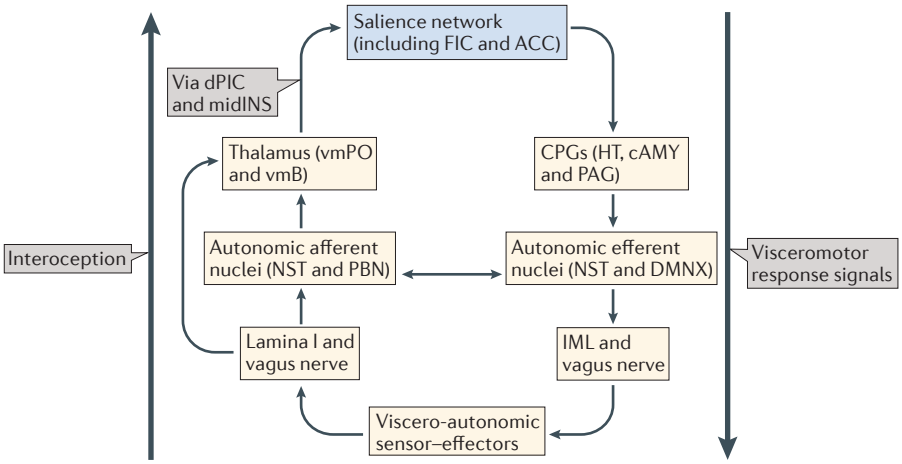

Figure 1 | **Salience network communication with subcortical structures.** Communication pathways between the insula and the brain regions that are involved in interoception and visceromotor responses enable the integration of signals of salience, which are used to guide behaviour. Ascending inputs communicating information about the moment-by-moment condition of the body from viscero-autonomic sensors are integrated in the frontoinsular cortex (FIC) within the salience network, which also includes the anterior cingulate cortex (ACC). Interoceptive signals travel through the vagus nerve, then through autonomic afferent nuclei and the thalamus, and via the dorsal posterior insular cortex (dPIC) and mid-insula (midINS) to the FIC. Direct connections also exist between lamina I of the spinal cord and the thalamus. The salience network integrates these ascending signals to coordinate large-scale networks in the cortex. In turn, the salience network sends information to visceromotor central pattern generators (CPGs), which send signals to autonomic efferent nuclei (including the nucleus of the solitary tract (NST) and the dorsal motor nucleus of the vagus nerve (DMNX)). These signals then travel to the intermediolateral cell column (IML) of the spinal cord, which drives viscero-autonomic responses to salient stimuli. cAMY, central nucleus of the amygdala; HT, hypothalamus; PAG, periaqueductal grey; PBN, parabrachial nucleus; vmB, basal ventromedial nucleus of the thalamus; vmPO, posterior ventromedial nucleus of the thalamus. Modified, with permission, from Seeley W. W., Zhou J., Kim E. J., *Neuroscientist* (**18** (4)) pp. 373–385, copyright © 2012 by SAGE Publications. Reprinted by Permission of SAGE Publications.

integrity of white-matter tracts that are associated with the insula and that form connections within the salience network is necessary for efficient regulation of the DMN: patients who have sustained traumatic brain injuries that affect white-matter tracts associated with the insula show deficits in inhibition of motor responses[37]. The central role of the insula in a global salience-detection system is further discussed below.

Salience and the insula

Emerging evidence indicates that the insular cortex is a centre of salience processing across multiple sensory and cognitive domains. Here, I provide a brief overview of the structural connectivity of the insula to illustrate that the region occupies a unique anatomical position that is crucial for its function. I then summarize new insights from functional neuroimaging studies of the insula that highlight its participation in the processing of salient stimuli.

The insula, which is located deep within the lateral sulcus of the brain, has traditionally been described as paralimbic[38] or as being the 'limbic integration cortex' (REF. 39) owing to its extensive structural connections with the amygdala, orbitofrontal cortex, olfactory cortex, ACC and superior temporal sulcus[38,40]. The insula was recognized in early anatomical studies to be a multifaceted brain region. Indeed, the insula participates in visceral and somatic sensory processing, contributes to autonomic regulation of the gastrointestinal tract and heart, and is a motor association area[39].

The past decades of functional neuroimaging research have shown that the AIC tracks emotions (for example, disgust) and perceptions (for example, pain and temperature) that are associated with bodily states[16,41–43], and that the roles of the AIC and the posterior insular cortex (PIC) differ. For example, whereas PIC activity correlates with actual changes in the thermal intensity of a stimulus, activity of the right AIC correlates with perceived thermal intensity[44]. Moreover, whereas the PIC is involved in innocuous-temperature perception, the AIC is active during perception of pain[45]. The right AIC is active when individuals experience an illusory heat stimulus — that is, even when their skin temperature is cool or neutral[46] — suggesting that the more evaluative aspects of sensation are represented in the AIC. By contrast, stimulus intensity is linearly coded by activity in the PIC[44]. These studies were among the first to demonstrate an anterior–posterior functional dissociation within the insula.

Pain — whether it is chronic or acute, physical or psychological — activates the AIC and mid-cingulate cortex[25,47–49]. The cortical network that responds to nociceptive stimuli is the so-called 'pain matrix', and it includes somatosensory, insular and mid-cingulate cortices. Recently, the pain matrix has been reconceptualized as a system that is involved in detecting, orienting attention towards and reacting to salient sensory stimuli, regardless of their modality[50,51]. Salient signals, whether they come from, for example, the experience of pain or disgust, all seem to activate the AIC.

The insula has long been thought to have a role in the experience of emotions that derive from information about bodily states[4]. Pure autonomic failure (PAF) is a disorder in which peripheral denervation disrupts autonomic responses. Critchley *et al.*[52] used positron emission tomography (PET) to demonstrate that, compared with controls, individuals with PAF exhibited reduced activity in the right insula when they performed stressor tasks such as mental arithmetic. Individuals with PAF also had subtly impaired emotional responses, reporting their agreement with statements such as "I can no longer feel sad" and "I have lost my ability to feel emotional". The volume of grey matter in the AIC correlates with the accuracy of individuals' interoception and their subjective ratings of visceral awareness[42] as measured by the 'Body Perception Questionnaire', which assesses awareness of, for instance, stomach pains, muscle tension, itch and breathing speed[53]. Taken together, these studies implicate the right insula as a substrate in which physiological arousal may be integrated with conscious appraisal[4].

Neuroimaging studies implicate the insular cortices in the representation of autonomic responses and changes in visceral state[4,16]. In particular, the right AIC mediates the incorporation of autonomic nervous signals with conscious thought processing[16,54,55]. The activity of the insula, often together with amygdala activity, represents an individual's subjective and conscious emotional state, as well as the emotive value of external stimuli[55,56]. Various signals from the body, including interoceptive states, which are communicated to the brain via

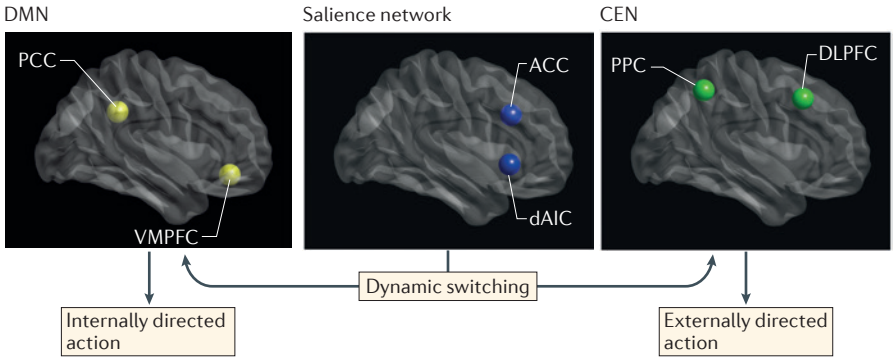

Figure 2 | **Salience-network-induced coordination between the default-mode network and the central executive network.** Salience signals are integrated in the salience network (blue), which includes the dorsal anterior insular cortex (dAIC) and the anterior cingulate cortex (ACC). Signals from the dAIC then causally influence signals in the default-mode network (DMN; yellow) — which has key nodes in the posterior cingulate cortex (PCC) and the ventromedial prefrontal cortex (VMPFC) — and in the central executive network (CEN; green), which has key nodes in the posterior parietal cortex (PPC) and the dorsolateral prefrontal cortex (DLPFC). The DMN and CEN support self-related (or internally directed) and goal-oriented (or externally directed) cognition, respectively[26,32]. The salience network mediates the 'switching' between activation of the DMN and of the CEN to guide appropriate responses to salient stimuli[31]. In light of recent work that suggests the existence of distinct functional subdivisions within the insular cortex[12,13], the right dAIC is now thought to be the specific brain region that assists in switching between networks. Modified and reprinted from *Neurosci. Biobehav. Rev.*, **33** (8), Uddin L. Q. & Menon V., The anterior insula in autism: under-connected and under-examined, 1198–1203, Copyright (2009), with permission from Elsevier.

spinothalamocortical pathways, are represented in posterior subregions of the insula[16] and induce dissociable emotional states such as disgust[4,57].

However, insular function is not limited to affective and interoceptive processes[11,31]. The insula responds consistently during cognitive 'oddball' paradigms[58–60] in which, for example, a participant views a series of items (such as blue circles) interspersed with relatively few oddballs (such as green circles) at unpredictable intervals. The insula consistently shows greater activation in response to the oddball stimulus[58] across both visual and auditory modalities[61], implying that the insula plays an important part in the detection of novel salient stimuli across multiple modalities.

Thus, converging evidence from a number of brain imaging studies across several task domains suggests that activity in the insula correlates with the degree of subjective salience, whether it is influenced by homeostatic, emotional or cognitive factors[16,62].

Insular functional connectivity

The functional role of any brain region depends on its pattern of connectivity with other regions[63]. The existence of multiple subdivisions within the insular cortex and the functional connectivity profiles of these subdivisions shed light on how the insula participates in so many diverse processes. Recent studies of the functional parcellation[12–14], co-activation[9,15] and intrinsic connectivity[64,65] of the human insular cortex suggest a more fine-grained functional organization of this region than was previously appreciated.

Novel insights into the functional organization and specialization of the insula have been obtained from meta-analyses of neuroimaging data from large databases[66,67]. In these meta-analyses, 'functional connectivity' is defined as the tendency of different brain regions to be simultaneously active during a given experimental condition or task[68,69]. One co-activation meta-analysis reported that the insula can be subdivided into three parts, such that the dorsal anterior portion is more involved in high-level cognitive processes (such as task switching, inhibition or error processing), the ventral AIC is associated with affective processes (for example, the perception of others' emotions) and the PIC is associated with sensorimotor processes (for instance, the perception of tactile stimuli)[13].

In line with this study, additional assessments of intrinsic functional connectivity[12,70] and meta-analytic studies[11] indicate that the insula can be divided into dorsal and ventral[9,11], as well as anterior and posterior[10], subregions. However, these subdivisions are not independent, and it has been shown that each subdivision participates to varying degrees in nearly every task domain that has been investigated, including those involving language, memory, sensory and emotional processing[15]. Functional co-activation maps that pinpoint the brain regions in which activity tends to covary with that of each insular subdivision have recently been published (FIG. 3). Overall, the evidence presented so far suggests a central role for the insula in salience processing[11,15].

One insular subdivision that seems to serve a unique function is the dAIC. The dAIC seems to be the only insular subdivision that is consistently activated across all task domains that have been investigated, which has led some to propose that it plays a part in multimodal functional integration[11]. One measure of the ability of a brain region to participate in different task domains is 'functional diversity' (REF. 68). The right dAIC is a particularly functionally diverse brain region compared with other insular subdivisions; it shows co-activation with association cortices, including the lateral prefrontal regions, superior parietal cortices and mid-cingulate gyrus[15]. These findings further support the idea that the dAIC might have a role in salience detection across multiple domains. As mentioned above, it is also the right dAIC that seems to function as a hub, as it exerts direct influences on the CEN and DMN[26,71]. The right dAIC, with its high level of functional diversity and its hub properties, is thus uniquely able to facilitate salience processing in the brain.

Insula and salience dysfunction

Given the extent of the evidence supporting a role of the insular cortex in salience processing, it is perhaps not surprising that atypical connectivity patterns and responses of this brain region have been posited to contribute to the aberrant salience processing that is observed in individuals with certain neuropsychiatric disorders.

Functional activation studies reveal atypical insular cortical responses to salient stimuli in autism[72], schizophrenia[73] and frontotemporal dementia (FTD)[74], and the intrinsic functional connectivity patterns of subdivisions of the insular cortex are increased or decreased differentially in these disorders[75–77]. In addition, neural signals from the insula can be used to determine diagnostic classification (with 78% classification accuracy, 75% sensitivity and 80% specificity in autism[27]) and to predict disease progression (for example, in FTD[78]). These findings can now be interpreted with greater anatomical precision in light of recent work showing that the right dAIC subdivision has a key role in coordinating brain network dynamics[26,32].

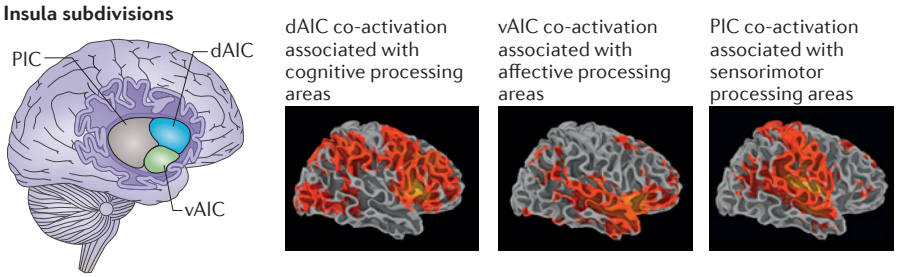

Figure 3 | **Co-activation profiles of insula subdivisions.** The NeuroSynth Database catalogues functional activations that are associated with different task domains, including working memory, language, vision, attention and emotion[67]. Co-activation analyses determine which brain regions are statistically likely to be active at the same time (for instance, during the same task). Functional subdivisions of the insula[12] exhibit partially distinct patterns of co-activation across all of the different tasks that were used. The dorsal anterior insular cortex (dAIC) tends to co-activate with the fronto-parietal association cortex (which is thought to mediate cognitive processes); the ventral anterior insular cortex (vAIC) with limbic cortices (which mediate affective processes); and the posterior insular cortex (PIC) with the somatosensory cortex (which mediates sensorimotor processes). Areas in which functional co-activation is observed are indicated in colour, from low (red) to high (yellow) levels of co-activation. Figure adapted from REF. 15, The MIT Press.

This evidence suggests that atypical engagement of the insula by subjectively salient stimuli — together with anomalous patterns of functional connectivity that hinder interactions between the right dAIC subdivision and other large-scale brain networks — could result in misappropriated salience detection and altered attentional processes that are characteristic of several psychiatric conditions. Below, I describe three distinct clinical profiles in which, among other symptoms, dysfunction of salience processing is often observed, and relate this to new insights into the functional differences associated with atypical insular cortical engagement.

Autism. Autism spectrum disorder (ASD) is typically diagnosed at around 3 years of age[79] and is characterized by atypicalities in the development of affective, sensory and motor systems, as well as by social deficits, such as impairments in social communication, that are thought to result from abnormal social attention and motivation[80,79]. Compared with typically developing individuals, individuals with ASD often exhibit reduced attention towards social stimuli such as human faces[81] and have concomitantly restricted interests[82] — symptoms that could be due to altered perceptions of what is salient.

Functions that depend on an intact salience network — including social cognition[83], self-oriented cognition[84] and high-level cognitive control[85] — all seem to be compromised to some extent in individuals with ASD. A meta-analysis of functional neuroimaging studies demonstrated that, among other brain regions, the right AIC of individuals with ASD consistently shows hypoactivity during social processing tasks such as face recognition and mentalizing[72]. Moreover, following subsequent hypotheses that insular connectivity might be altered in individuals with ASD[86], several studies found that the functional connectivity of the insula indeed differs in individuals with ASD. In the largest study so far, data that were collected at multiple sites from a total of 539 individuals with ASD and 573 age-matched typical controls demonstrated that there is a hypoconnectivity of the mid and posterior insula in autism[75], a finding that had also been reported in earlier, smaller studies in adolescents and adults[87,88]. A recent study found that in children with ASD (aged 7–12 years old) there was a hyperconnectivity of the insula-based salience network[27]. The shift from the hyperconnectivity seen in younger children to hypoconnectivity seen in adolescents and adults in these studies suggests that developmental changes in insular functional connectivity might accompany the disorder[89,90].

Using machine learning, several studies have demonstrated that the pattern of functional connectivity of the insular cortex can be used to discriminate individuals with ASD from typically developing individuals[27,91,92]. In addition, salience-network connectivity has recently been linked with the severity of symptoms in ASD: multivariate sparse regression analyses demonstrated that the level of activity that was measured in voxels within the salience network is predictive of the severity of restricted and repetitive behaviours of children with ASD[27]. The severity of ASD symptoms also correlates with changes in the pattern of functional connections among the dAIC, DMN and CEN[71].

In several earlier neurobiological theories of ASD based on fMRI data, the disorder was associated with different response patterns in brain regions, including the amygdala[93] and the ACC[94], within the salience network. In other theoretical work, the 'intense-world' theory of ASD was put forth[95] on the basis of empirical findings of hyper-reactivity, hyperconnectivity and hyperplasticity of local neural microcircuits in a rodent model of autism[96]. This theory is a potential cellular explanation for why the autistic brain might be overly responsive to sensory stimuli, perhaps experiencing sights and sounds as aberrantly salient and painfully intense. Thus, although the focus on the insula in autism is relatively recent[86], there is precedence for conceptualizing the core deficits of the disorder as abnormalities in salience processing.

Taken together, the emerging picture is that both the activation levels and the functional connectivity patterns of the insular cortex are informative with regards to the clinical profile of ASD. It remains to be seen whether the observed pattern of hyperconnectivity in children and hypoconnectivity in adults with ASD might be related to the amelioration of symptoms across the lifespan. In addition, it will be interesting to see whether behavioural therapies in which children with ASD are taught to detect salient social cues can result in the normalization of insular cortical activity.

Schizophrenia. Schizophrenia is another disorder of brain connectivity[97,98] that, in contrast to autism, typically emerges during adolescence or young adulthood. Schizophrenia is characterized by positive symptoms, including delusions and hallucinations, and negative symptoms, such as blunted affect[99], and it has a long history of being associated with aberrations in frontal lobe function[100]. One influential hypothesis[7] posits that psychosis in schizophrenia can be attributed to a dysregulated, hyperdopaminergic brain state that leads to the aberrant assignment of salience to one's own experience. According to this model, delusions are the result of cognitive efforts to make sense of aberrantly salient experiences, and hallucinations are direct experiences of the aberrant salience of internal representations[7].

A reduction in the volume of bilateral insular cortex grey matter in patients with schizophrenia is one of the most consistently observed findings in the structural neuroimaging literature[101–104]. Reduced activation of the insular cortex, particularly during emotion-regulation tasks, is also commonly observed in individuals with schizophrenia[105]. It has been suggested that insular

dysfunction might contribute to hallucinations by diminishing the capacity of the brain to discriminate between self-generated and external information[106].

A whole-brain functional connectivity study found that individuals with schizophrenia had reduced strength of regional connectivity in the left insula[107]. On the basis of recent structural and functional neuroimaging research, it has been proposed that the salience network might be an appropriate target for a combined pharmacological and cognitive-training treatment approach[108]. The most compelling evidence for salience-network dysfunction in schizophrenia comes from three studies that used GCA. These neuroimaging studies collectively provide evidence that individuals with schizophrenia exhibit a reduction in the strength of the causal influences from the right AIC on the CEN and DMN[76,109,110].

Together, this research suggests that, along with the well-documented hyperconnectivity of the DMN in schizophrenia[111,112], structural and functional abnormalities of the insula are components of the neuropathology of schizophrenia. As suggested in earlier theories of the disorder[7], inappropriate detection of salience may contribute to the positive and negative symptoms that are experienced by individuals with schizophrenia.

Frontotemporal dementia. FTD is characterized by social–emotional dysfunction and primary progressive aphasia, and is associated with neurodegeneration of the frontoinsular cortices and pregenual ACC, which spreads over time to adjacent orbitofrontal and dorsolateral frontal regions[8,113]. Individuals with FTD exhibit poor judgement (for instance, during organizational or problem-solving activities)[114], loss of initiative, deficiencies in self-control and a profound loss of interpersonal warmth, tact and empathy[115]. Unlike autism and schizophrenia, the symptoms of FTD typically emerge in the sixth decade of life; however, the social, affective and attentional deficits that are observed in patients with FTD are remarkably similar to those observed in the neurodevelopmental disorders discussed above.

A unique population of cells known as von Economo neurons, which are found only in the ventral AIC[116] and the ACC[117] (BOX 1), seems to be selectively vulnerable in FTD, as demonstrated in post-mortem quantitative neuroanatomical studies[118–121]. A meta-analysis of PET studies (examining glucose utilization) and MRI studies (examining atrophy) identified the right AIC as the most consistently affected structure in FTD[74]. Individuals with FTD exhibit reduced intrinsic functional connectivity of the salience network, and advancing FTD severity correlates with reduction in the functional connectivity of the right AIC[77]. Changes in resting-state fMRI signals from the salience network were also found to predict FTD disease progression (as reflected by increases in apathy)[78].

Although AIC pathology can be observed in FTD[113], there is still work to be done to understand the specific contributions made by particular insular subdivisions to the cognitive and behavioural symptoms of FTD and other disorders. The initial findings described here demonstrate the utility of delineating the functional contributions of specific insular subdivisions. In future research it will be of interest to investigate how the cognitive profiles of individuals with early-life insular damage differ from those of individuals with later-life disorders such as FTD to establish the importance of the function of subdivisions of the insula during different stages of development. The evidence reviewed here suggests that damage to different insular subdivisions at various time points during development can produce different cognitive and behavioural phenotypes[27,104,113].

Summary and future directions

Identifying and responding to salient inputs requires the integration of sensory, visceral, autonomic and attention systems throughout the brain[4,16]. The evidence reviewed here suggests that salience processing in the human brain is mediated by a network of regions (including the AIC and ACC) that initiates appropriate responses to stimuli that are important to an individual[18]. Moreover, the evidence indicates that compromises to the integrity of the salience network can contribute to deficits in social, affective, attention and cognitive control processing in certain neurodevelopmental and neurodegenerative disorders[27,78,109].

One of the challenges for future research will be to establish and differentiate the nuanced activation profiles and patterns of functional connectivity of particular subdivisions of the insula. For example, the recent findings that the right dAIC is functionally unique in the brain[11,15] are in line with studies demonstrating that this subdivision acts as a 'causal hub' of the salience network that influences key nodes of other large-scale brain networks, including the CEN and DMN[26,32]. Recent co-activation meta-analyses that take insular subdivisions into account also demonstrate the consistency of the activation of specific insular subdivisions across cognitive, affective and sensorimotor tasks[9,10,13]. These studies provide a framework for interpreting the hypoactivity or hyperactivity within these subdivisions that can accompany neuropsychiatric conditions such as autism, psychosis and FTD.

The identification of these insular subdivisions suggests that more-precise structure–function mappings that may be useful

Box 1 | von Economo neurons in the ventral anterior insula

A curiosity specific to the human insula and anterior cingulate is that these regions contain a type of neuron that is not seen in any other cortical region. These spindle cells[117], or von Economo neurons (VENs), are large, recently evolved bipolar cells that develop late in ontogeny[126]. Owing to their large size and anatomical location, it has been proposed that a function of these unique cells is to relay the outputs of insular and anterior cingulate cortices to frontal and temporal regions to aid rapid intuitive assessments of complex situations — for instance, during social cognition[126].

First noted for their distinctive morphology[116], VENs have since been found only in humans, great apes[117], elephants and cetaceans[127]. The restriction of VENs to specific cortical regions and their unique phylogeny led to the hypothesis that these neurons support evolutionarily new functions, particularly those related to the ability to make adaptive responses to changing environmental conditions[128].

Interestingly, in the human brain only 15% of the eventual maximum numbers of VENs are present at birth; the adult number, which is still remarkably low, is apparent by approximately 4 years of age. Moreover, there are 30% more VENs in the right hemisphere of the brain than in the left hemisphere. Although it is not known precisely to which locations VENs project, the frontoinsular and anterior cingulate cortices — the regions in which these cells reside — are connected to the amygdala, as well as to prefrontal, orbitofrontal and temporal cortices[126].

Now, much more is known about the functional subdivisions of the human insular cortex[9,10,12,13,15] than was known at the time of the discovery of VENs. VENs are specifically found in the ventral anterior portion of the insula[116] and are affected in frontotemporal dementia (FTD)[118] but not in autism[129]. Thus, knowing the specific anatomical location and laterality of these neurons helps to discriminate the insular pathologies that are associated with autism and schizophrenia from the insular pathologies that underlie FTD and other disorders.

for understanding the pathophysiology of these disorders are on the horizon. Future research should be able to identify precisely which subdivisions of the insula are selectively disrupted in autism, schizophrenia or FTD, and thereby provide more-specific targets for pharmacological and behavioural treatments. Studies that use a high level of anatomical specificity will continue to clarify how distinct clinical outcomes are associated with insular pathology. This functional-subdivision framework will be useful in understanding other disorders that are associated with insular dysfunction, including anxiety[122], depression[123] and chronic pain[47].

Understanding salience processing within a framework that acknowledges the complexity of the organization of the human insular cortex would have widespread implications. In neuropsychiatry, neuroimaging data could be used to discriminate disorders with high levels of comorbidity, such as ASD and attention-deficit hyperactivity disorder (ADHD)[124]. In the case of neurodevelopmental disorders, there might be insula-based signatures of ASD that discriminate it from ADHD[125]. As for neurodegenerative disorders, there is already evidence to suggest that differences in salience-network functional connectivity distinguish FTD from Alzheimer's disease[77]. The challenge of incorporating recent findings from cognitive neuroscience into the study of salience processing and insular dysfunction will require multimodal, multidisciplinary approaches, but the potential for novel clinical insights clearly exists.

Lucina Q. Uddin is at the Department of Psychology, University of Miami, PO Box 248185–0751, Coral Gables, Florida 33124, USA, and the Neuroscience Program, University of Miami Miller School of Medicine, Miami, Florida 33136, USA.
e-mail: l.uddin@miami.edu

doi:10.1038/nrn3857
Published online 19 November 2014

1. Yantis, S. & Hillstrom, A. P. Stimulus-driven attentional capture: evidence from equiluminant visual objects. *J. Exp. Psychol. Hum. Percept. Perform.* **20**, 95–107 (1994).
2. Puglisi-Allegra, S. & Ventura, R. Prefrontal/accumbal catecholamine system processes emotionally driven attribution of motivational salience. *Rev. Neurosci.* **23**, 509–526 (2012).
3. Goldberg, M. E., Bisley, J. W., Powell, K. D. & Gottlieb, J. Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. *Prog. Brain Res.* **155**, 157–175 (2006).
4. Critchley, H. D. & Harrison, N. A. Visceral influences on brain and behavior. *Neuron* **77**, 624–638 (2013).
5. Corbetta, M., Patel, G. & Shulman, G. L. The reorienting system of the human brain: from environment to theory of mind. *Neuron* **58**, 306–324 (2008).
6. Klin, A., Jones, W., Schultz, R. & Volkmar, F. The enactive mind, or from actions to cognition: lessons from autism. *Phil. Trans. R. Soc. Lond. B* **358**, 345–360 (2003).
7. Kapur, S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* **160**, 13–23 (2003).
8. Seeley, W. W., Zhou, J. & Kim, E. J. Frontotemporal dementia: what can the behavioral variant teach us about human brain organization? *Neuroscientist* **18**, 373–385 (2012).
9. Kelly, C. *et al.* A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage* **61**, 1129–1142 (2012).
10. Cauda, F. *et al.* Meta-analytic clustering of the insular cortex: characterizing the meta-analytic connectivity of the insula when involved in active tasks. *Neuroimage* **62**, 343–355 (2012).
11. Kurth, F., Zilles, K., Fox, P. T., Laird, A. R. & Eickhoff, S. B. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct. Funct.* **214**, 519–534 (2010).
12. Deen, B., Pitskel, N. B. & Pelphrey, K. A. Three systems of insular functional connectivity identified with cluster analysis. *Cereb. Cortex* **21**, 1498–1506 (2011).
13. Chang, L. J., Yarkoni, T., Khaw, M. W. & Sanfey, A. G. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb. Cortex* **23**, 739–749 (2012).
14. Ryali, S., Chen, T., Supekar, K. & Menon, V. A parcellation scheme based on von Mises–Fisher distributions and Markov random fields for segmenting brain regions using resting-state fMRI. *Neuroimage* **65**, 83–96 (2012).
15. Uddin, L. Q., Kinnison, J., Pessoa, L. & Anderson, M. L. Beyond the tripartite cognition–emotion–interoception model of the human insular cortex. *J. Cogn. Neurosci.* **26**, 16–27 (2014).
16. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Rev. Neurosci.* **3**, 655–666 (2002).
17. Singer, T., Critchley, H. D. & Preuschoff, K. A common role of insula in feelings, empathy and uncertainty. *Trends Cogn. Sci.* **13**, 334–340 (2009).
18. Seeley, W. W. *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* **27**, 2349–2356 (2007).
19. Robinson, D. L. & Petersen, S. E. The pulvinar and visual salience. *Trends Neurosci.* **15**, 127–132 (1992).
20. Fecteau, J. H. & Munoz, D. P. Salience, relevance, and firing: a priority map for target selection. *Trends Cogn. Sci.* **10**, 382–390 (2006).
21. Treue, S. Visual attention: the where, what, how and why of saliency. *Curr. Opin. Neurobiol.* **13**, 428–432 (2003).
22. Gottlieb, J., Balan, P., Oristaglio, J. & Suzuki, M. Parietal control of attentional guidance: the significance of sensory, motivational and motor factors. *Neurobiol. Learn. Mem.* **91**, 121–128 (2009).
23. Corbetta, M., Kincade, J. M. & Shulman, G. L. Neural systems for visual orienting and their relationships to spatial working memory. *J. Cogn. Neurosci.* **14**, 508–523 (2002).
24. Downar, J., Crawley, A. P., Mikulis, D. J. & Davis, K. D. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J. Neurophysiol.* **87**, 615–620 (2002).
25. Downar, J., Mikulis, D. J. & Davis, K. D. Neural correlates of the prolonged salience of painful stimulation. *Neuroimage* **20**, 1540–1551 (2003).
26. Uddin, L. Q., Supekar, K. S., Ryali, S. & Menon, V. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *J. Neurosci.* **31**, 18578–18589 (2011).
27. Uddin, L. Q. *et al.* Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry* **70**, 869–879 (2013).
28. Kucyi, A., Hodaie, M. & Davis, K. D. Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks. *J. Neurophysiol.* **108**, 3382–3392 (2012).
29. Cole, M. W. *et al.* Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neurosci.* **16**, 1348–1355 (2013).
30. Power, J. D. *et al.* Functional network organization of the human brain. *Neuron* **72**, 665–678 (2011).
31. Menon, V. & Uddin, L. Q. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* **214**, 655–667 (2010).
32. Sridharan, D., Levitin, D. J. & Menon, V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl Acad. Sci. USA* **105**, 12569–12574 (2008).
33. Honey, C. J., Kotter, R., Breakspear, M. & Sporns, O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc. Natl Acad. Sci. USA* **104**, 10240–10245 (2007).
34. Supekar, K. & Menon, V. Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. *PLoS Comput. Biol.* **8**, e1002374 (2012).
35. Chen, A. C. *et al.* Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc. Natl Acad. Sci. USA* **110**, 19944–19949 (2013).
36. Goulden, N. *et al.* The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage* **99**, 180–190 (2014).
37. Bonnelle, V. *et al.* Salience network integrity predicts default mode network function after traumatic brain injury. *Proc. Natl Acad. Sci. USA* **109**, 4690–4695 (2012).
38. Mesulam, M. M. & Mufson, E. J. Insula of the old world monkey. III: Efferent cortical output and comments on function. *J. Comp. Neurol.* **212**, 38–52 (1982).
39. Augustine, J. R. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res. Brain Res. Rev.* **22**, 229–244 (1996).
40. Mufson, E. J. & Mesulam, M. M. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *J. Comp. Neurol.* **212**, 23–37 (1982).
41. Zaki, J., Davis, J. I. & Ochsner, K. N. Overlapping activity in anterior insula during interoception and emotional experience. *Neuroimage* **62**, 493–499 (2012).
42. Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A. & Dolan, R. J. Neural systems supporting interoceptive awareness. *Nature Neurosci.* **7**, 189–195 (2004).
43. Wicker, B. *et al.* Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron* **40**, 655–664 (2003).
44. Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. Thermosensory activation of insular cortex. *Nature Neurosci.* **3**, 184–190 (2000).
45. Davis, K. D., Kwan, C. L., Crawley, A. P. & Mikulis, D. J. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J. Neurophysiol.* **80**, 1533–1546 (1998).
46. Davis, K. D., Pope, G. E., Crawley, A. P. & Mikulis, D. J. Perceptual illusion of "paradoxical heat" engages the insular cortex. *J. Neurophysiol.* **92**, 1248–1251 (2004).
47. Simons, L. E., Elman, I. & Borsook, D. Psychological processing in chronic pain: a neural systems approach. *Neurosci. Biobehav. Rev.* **39**, 61–78 (2014).
48. Eisenberger, N. I. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nature Rev. Neurosci.* **13**, 421–434 (2012).
49. Wager, T. D. *et al.* An fMRI-based neurologic signature of physical pain. *N. Engl. J. Med.* **368**, 1388–1397 (2013).
50. Legrain, V., Iannetti, G. D., Plaghki, L. & Mouraux, A. The pain matrix reloaded: a salience detection system for the body. *Prog. Neurobiol.* **93**, 111–124 (2011).
51. Iannetti, G. D., Salomons, T. V., Moayedi, M., Mouraux, A. & Davis, K. D. Beyond metaphor: contrasting mechanisms of social and physical pain. *Trends Cogn. Sci.* **17**, 371–378 (2013).
52. Critchley, H. D., Mathias, C. J. & Dolan, R. J. Neuroanatomical basis for first- and second-order representations of bodily states. *Nature Neurosci.* **4**, 207–212 (2001).
53. Porges, S. Body Perception Questionnaire. Laboratory of Developmental Assessment, Univ. of Maryland [online], http://stephenporges.com/index.php/publicationss/21-body-perception-questionnaires (1993).
54. Critchley, H. D., Melmed, R. N., Featherstone, E., Mathias, C. J. & Dolan, R. J. Volitional control of autonomic arousal: a functional magnetic resonance study. *Neuroimage* **16**, 909–919 (2002).
55. Critchley, H. D. The human cortex responds to an interoceptive challenge. *Proc. Natl Acad. Sci. USA* **101**, 6333–6334 (2004).
56. Gray, M. A. & Critchley, H. D. Interoceptive basis to craving. *Neuron* **54**, 183–186 (2007).
57. Harrison, N. A., Gray, M. A., Gianaros, P. J. & Critchley, H. D. The embodiment of emotional feelings in the brain. *J. Neurosci.* **30**, 12878–12884 (2010).
58. Crottaz-Herbette, S. & Menon, V. Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. *J. Cogn. Neurosci.* **18**, 766–780 (2006).

59. Downar, J., Crawley, A. P., Mikulis, D. J. & Davis, K. D. A multimodal cortical network for the detection of changes in the sensory environment. *Nature Neurosci.* **3**, 277–283 (2000).
60. Linden, D. E. *et al.* The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. *Cereb. Cortex* **9**, 815–823 (1999).
61. Kim, H. Involvement of the dorsal and ventral attention networks in oddball stimulus processing: a meta-analysis. *Hum. Brain Mapp.* **35**, 2265–2284 (2014).
62. Bud Craig, A. D. How do you feel — now? The anterior insula and human awareness. *Nature Rev. Neurosci.* **10**, 59–70 (2009).
63. Passingham, R. E., Stephan, K. E. & Kotter, R. The anatomical basis of functional localization in the cortex. *Nature Rev. Neurosci.* **3**, 606–616 (2002).
64. Cauda, F. *et al.* Functional connectivity of the insula in the resting brain. *Neuroimage* **55**, 8–23 (2011).
65. Taylor, K. S., Seminowicz, D. A. & Davis, K. D. Two systems of resting state connectivity between the insula and cingulate cortex. *Hum. Brain Mapp.* **30**, 2731–2745 (2009).
66. Laird, A. R., Lancaster, J. L. & Fox, P. T. BrainMap: the social evolution of a human brain mapping database. *Neuroinformatics* **3**, 65–78 (2005).
67. Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C. & Wager, T. D. Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods* **8**, 665–670 (2011).
68. Anderson, M. L., Kinnison, J. & Pessoa, L. Describing functional diversity of brain regions and brain networks. *Neuroimage* **73**, 50–58 (2013).
69. Toro, R., Fox, P. T. & Paus, T. Functional coactivation map of the human brain. *Cereb. Cortex* **18**, 2553–2559 (2008).
70. Ryali, S., Chen, T., Supekar, K. & Menon, V. A parcellation scheme based on von Mises-Fisher distributions and Markov random fields for segmenting brain regions using resting-state fMRI. *Neuroimage* **65**, 83–96 (2013).
71. Uddin, L. Q. *et al.* Brain state differentiation and behavioral inflexibility in autism. *Cereb. Cortex* http://dx.doi.org/10.1093/cercor/bhu161 (2014).
72. Di Martino, A. *et al.* Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol. Psychiatry* **65**, 63–74 (2009).
73. Li, H., Chan, R. C., McAlonan, G. M. & Gong, Q. Y. Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. *Schizophr. Bull.* **36**, 1029–1039 (2010).
74. Schroeter, M. L., Raczka, K., Neumann, J. & von Cramon, D. Y. Neural networks in frontotemporal dementia — a meta-analysis. *Neurobiol. Aging* **29**, 418–426 (2008).
75. Di Martino, A. *et al.* The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol. Psychiatry* **19**, 659–667 (2014).
76. Moran, L. V. *et al.* Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biol. Psychiatry* **74**, 467–474 (2013).
77. Zhou, J. *et al.* Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* **133**, 1352–1367 (2010).
78. Day, G. S. *et al.* Salience network resting-state activity: prediction of frontotemporal dementia progression. *JAMA Neurol.* **70**, 1249–1253 (2013).
79. Lord, C. *et al.* The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J. Autism Dev. Disord.* **30**, 205–223 (2000).
80. Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S. & Schultz, R. T. The social motivation theory of autism. *Trends Cogn. Sci.* **16**, 231–239 (2012).
81. Carver, L. J. & Dawson, G. Development and neural bases of face recognition in autism. *Mol. Psychiatry* **7** (Suppl. 2), S18–S20 (2002).
82. Happe, F. & Ronald, A. The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychol. Rev.* **18**, 287–304 (2008).
83. Baron-Cohen, S. Autism: the empathizing-systemizing (E-S.) theory. *Ann. NY Acad. Sci.* **1156**, 68–80 (2009).
84. Uddin, L. Q. The self in autism: an emerging view from neuroimaging. *Neurocase* **17**, 201–208 (2011).
85. Hill, E. L. Executive dysfunction in autism. *Trends Cogn. Sci.* **8**, 26–32 (2004).
86. Uddin, L. Q. & Menon, V. The anterior insula in autism: under-connected and under-examined. *Neurosci. Biobehav. Rev.* **33**, 1198–1203 (2009).
87. von dem Hagen, E. A., Stoyanova, R. S., Baron-Cohen, S. & Calder, A. J. Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions. *Soc. Cogn. Affect Neurosci.* **8**, 694–670 (2012).
88. Ebisch, S. J. *et al.* Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum. Brain Mapp.* **32**, 1013–1028 (2010).
89. Dickstein, D. P. *et al.* Developmental meta-analysis of the functional neural correlates of autism spectrum disorders. *J. Am. Acad. Child Adolesc. Psychiatry* **52**, 279–289 (2013).
90. Uddin, L. Q., Supekar, K. & Menon, V. Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front. Hum. Neurosci.* **7**, 458 (2013).
91. Nielsen, J. A. *et al.* Multisite functional connectivity MRI classification of autism: ABIDE results. *Front. Hum. Neurosci.* **7**, 599 (2013).
92. Anderson, J. S. *et al.* Functional connectivity magnetic resonance imaging classification of autism. *Brain* **134**, 3742–3754 (2011).
93. Baron-Cohen, S. *et al.* The amygdala theory of autism. *Neurosci. Biobehav. Rev.* **24**, 355–364 (2000).
94. Mundy, P. Annotation: the neural basis of social impairments in autism: the role of the dorsal medial-frontal cortex and anterior cingulate system. *J. Child Psychol. Psychiatry* **44**, 793–809 (2003).
95. Markram, K. & Markram, H. The intense world theory — a unifying theory of the neurobiology of autism. *Front. Hum. Neurosci.* **4**, 224 (2010).
96. Markram, H., Rinaldi, T. & Markram, K. The intense world syndrome — an alternative hypothesis for autism. *Front. Neurosci.* **1**, 77–96 (2007).
97. Fitzsimmons, J., Kubicki, M. & Shenton, M. E. Review of functional and anatomical brain connectivity findings in schizophrenia. *Curr. Opin. Psychiatry* **26**, 172–187 (2013).
98. van den Heuvel, M. P. & Fornito, A. Brain networks in schizophrenia. *Neuropsychol. Rev.* **24**, 32–48 (2014).
99. Andreasen, N. C. Schizophrenia: the fundamental questions. *Brain Res. Brain Res. Rev.* **31**, 106–112 (2000).
100. Weinberger, D. R. & Berman, K. F. Prefrontal function in schizophrenia: confounds and controversies. *Phil. Trans. R. Soc. Lond. B* **351**, 1495–1503 (1996).
101. Kasai, K. *et al.* Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. *Arch. Gen. Psychiatry* **60**, 1069–1077 (2003).
102. Glahn, D. C. *et al.* Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol. Psychiatry* **64**, 774–781 (2008).
103. Fornito, A., Yucel, M., Patti, J., Wood, S. J. & Pantelis, C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr. Res.* **108**, 104–113 (2009).
104. Shepherd, A. M., Matheson, S. L., Laurens, K. R., Carr, V. J. & Green, M. J. Systematic meta-analysis of insula volume in schizophrenia. *Biol. Psychiatry* **72**, 775–784 (2012).
105. van der Meer, L. *et al.* Neural correlates of emotion regulation in patients with schizophrenia and non-affected siblings. *PLoS ONE* **9**, e99667 (2014).
106. Wylie, K. P. & Tregellas, J. R. The role of the insula in schizophrenia. *Schizophr. Res.* **123**, 93–104 (2010).
107. Wang, X. *et al.* Disrupted resting-state functional connectivity in minimally treated chronic schizophrenia. *Schizophr. Res.* **156**, 150–156 (2014).
108. Palaniyappan, L., White, T. P. & Liddle, P. F. The concept of salience network dysfunction in schizophrenia: from neuroimaging observations to therapeutic opportunities. *Curr. Top. Med. Chem.* **12**, 2324–2338 (2012).
109. Palaniyappan, L., Simmonite, M., White, T. P., Liddle, E. B. & Liddle, P. F. Neural primacy of the salience processing system in schizophrenia. *Neuron* **79**, 814–828 (2013).
110. Manoliu, A. *et al.* Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophr. Bull.* **40**, 428–437 (2014).
111. Karbasforoushan, H. & Woodward, N. D. Resting-state networks in schizophrenia. *Curr. Top. Med. Chem.* **12**, 2404–2414 (2012).
112. Whitfield-Gabrieli, S. & Ford, J. M. Default mode network activity and connectivity in psychopathology. *Annu. Rev. Clin. Psychol.* **8**, 49–76 (2012).
113. Seeley, W. W. Anterior insula degeneration in frontotemporal dementia. *Brain Struct. Funct.* **214**, 465–475 (2010).
114. Hu, W. T. *et al.* Clinical features of pathologic subtypes of behavioral — variant frontotemporal dementia. *Arch. Neurol.* **64**, 1611–1616 (2007).
115. Miller, B. L., Chang, L., Mena, I., Boone, K. & Lesser, I. M. Progressive right frontotemporal degeneration: clinical, neuropsychological and SPECT characteristics. *Dementia* **4**, 204–213 (1993).
116. Seeley, W. W. *et al.* Distinctive neurons of the anterior cingulate and frontoinsular cortex: a historical perspective. *Cereb. Cortex* **22**, 245–250 (2012).
117. Nimchinsky, E. A. *et al.* A neuronal morphologic type unique to humans and great apes. *Proc. Natl Acad. Sci. USA* **96**, 5268–5273 (1999).
118. Kim, E. J. *et al.* Selective frontoinsular von Economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. *Cereb. Cortex* **22**, 251–259 (2012).
119. Seeley, W. W. *et al.* Early frontotemporal dementia targets neurons unique to apes and humans. *Ann. Neurol.* **60**, 660–667 (2006).
120. Santillo, A. F., Nilsson, C. & Englund, E. von Economo neurones are selectively targeted in frontotemporal dementia. *Neuropathol. Appl. Neurobiol.* **39**, 572–579 (2013).
121. Allman, J. M. *et al.* The von Economo neurons in the frontoinsular and anterior cingulate cortex. *Ann. NY Acad. Sci.* **1225**, 59–71 (2011).
122. Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V. & Greicius, M. D. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Arch. Gen. Psychiatry* **66**, 1361–1372 (2009).
123. Hamilton, J. P. *et al.* Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *Am. J. Psychiatry* **169**, 693–703 (2012).
124. Taurines, R. *et al.* ADHD and autism: differential diagnosis or overlapping traits? A selective review. *Atten. Defic. Hyperact. Disord.* **4**, 115–139 (2012).
125. Di Martino, A. *et al.* Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **74**, 623–632 (2013).
126. Allman, J. M., Watson, K. K., Tetreault, N. A. & Hakeem, A. Y. Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn. Sci.* **9**, 367–373 (2005).
127. Butti, C., Sherwood, C. C., Hakeem, A. Y., Allman, J. M. & Hof, P. R. Total number and volume of Von Economo neurons in the cerebral cortex of cetaceans. *J. Comp. Neurol.* **515**, 243–259 (2009).
128. Allman, J., Hakeem, A. & Watson, K. Two phylogenetic specializations in the human brain. *Neuroscientist* **8**, 335–346 (2002).
129. Kennedy, D. P., Semendeferi, K. & Courchesne, E. No reduction of spindle neuron number in frontoinsular cortex in autism. *Brain Cogn.* **64**, 124–129 (2007).

Acknowledgements
This work was supported by a US National Institute of Mental Health (NIMH) Career Development Award (K01MH092288) and a Slifka/Ritvo Innovation in Autism Research Award from the International Society for Autism Research. The content is solely the responsibility of the author and does not necessarily represent the official views of the NIMH or the US National Institutes of Health.

Competing interests statement
The author declares no competing interests.

DATABASES
Brainmap: http://www.brainmap.org/
BrainNet Viewer: http://www.nitrc.org/projects/bnv/
NeuroSynth Database: http://neurosynth.org/
Pathway Interaction Database: http://pid.nci.nih.gov

ALL LINKS ARE ACTIVE IN THE ONLINE PDF