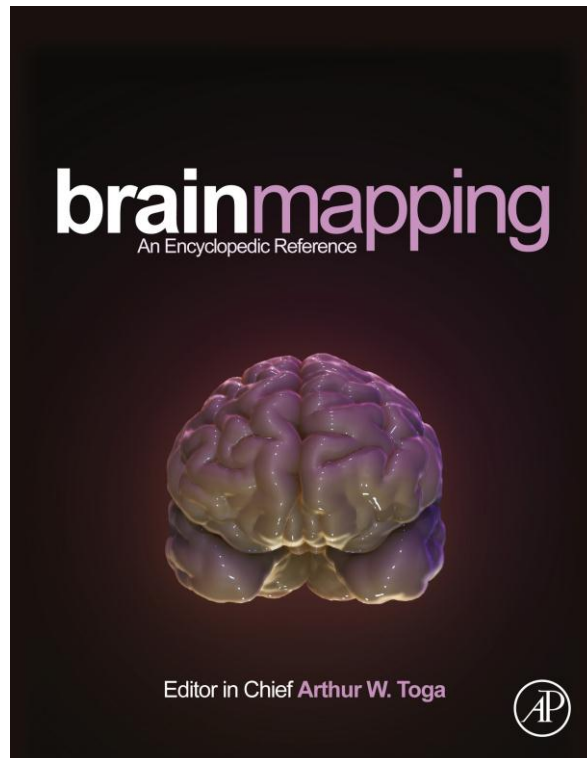


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## Saliency Network

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### Introduction and Overview

The human brain consists of multiple, distinct, and interacting networks; investigation of these networks has provided a systematic framework for understanding fundamental aspects of human brain organization and function (Bressler & Menon, 2010). In this context, identification and characterization of the saliency network (SN) have contributed greatly to our understanding of core brain systems involved in identification of biologically and cognitively relevant events to guide flexible behavior (Menon & Uddin, 2010; Seeley et al., 2007).

The SN is an intrinsically connected large-scale network anchored in the anterior insula (AI) and dorsal anterior cingulate cortex (dACC; Figure 1). The SN also includes three key subcortical structures: the amygdala, the ventral striatum, and the substantia nigra/ventral tegmental area. Crucially, a network perspective helps integrate the explosive and wide range of brain imaging studies that have implicated these regions, most notably the AI and dACC, in multiple, often disparate, cognitive and affective processes. The SN, together with its interconnected brain networks, contributes to a variety of complex brain functions, including communication, social behavior, and self-awareness through the integration of sensory, emotional, and cognitive information (Craig, 2009; Gogolla, Takesian, Feng, Fagiolini, & Hensch, 2014; Menon & Uddin, 2010).

This article summarizes recent progress in our understanding of the SN; its functional and structural organization; its role in cognition, emotion, and development; and its disruption in psychopathology. I begin with a brief outline of saliency and general saliency detection mechanisms in the brain. I then focus on identification of the SN, highlighting its key nodes and their functional and structural connectivity patterns. I describe the core functions of this network in attention and cognitive control, focusing on the AI as a dynamic hub for detection and selection of salient stimuli and for mediating interactions with other neurocognitive systems. I will then highlight its crucial role in switching between systems involved in processing exogenous and self-relevant information and briefly discuss key features of SN development from infancy to adulthood, concluding with an examination of how characterization of SN dysfunction is leading to a more thorough understanding of psychopathology.

### Saliency Detection and the Saliency Network

#### Two General Mechanisms of Saliency Detection

The nervous system dynamically selects specific stimuli for additional processing from a constant stream of incoming sensory inputs. Saliency detection mechanisms in the brain are at the core of this process and can be conceptualized into two general mechanisms. The first is a fast, automatic, bottom-up 'primitive' mechanism for filtering stimuli based on their perceptual features (Peters, Iyer, Itti, & Koch, 2005). Filtering and amplification of stimuli can, in principle, occur at multiple

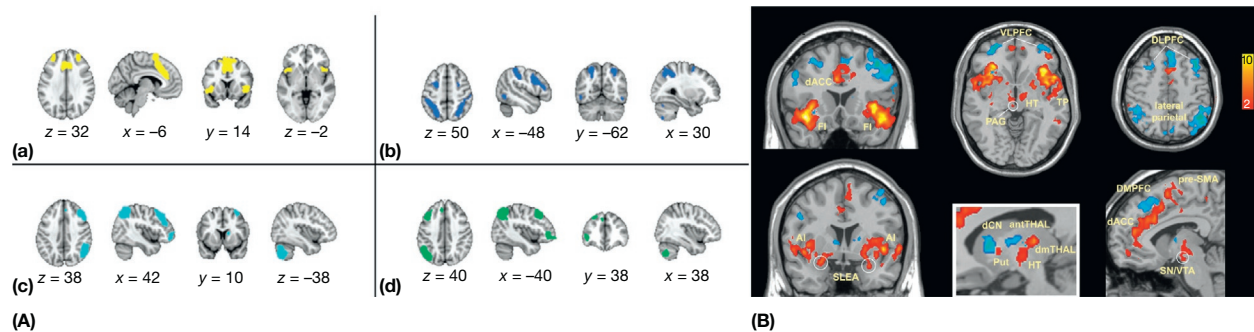
levels in the hierarchy of ascending neural pathways that bring stimuli from the external world to the sensory cortex. At each level, saliency filters enhance responses to stimuli that are infrequent in space or time or are of learned or instinctive biological importance (Knudsen, 2007). For example, neurons in the superior colliculi can amplify responses to specific visual stimuli based on stimulus-driven representations in local saliency maps (Fecteau, Bell, & Munoz, 2004). The neural mechanisms for this level of saliency detection include adaptation to repeated stimuli and center-surround properties of local circuits. The second is a higher-order system for competitive, context-specific, stimulus selection and for focusing the 'spotlight of attention' and enhancing access to resources needed for goal-directed behavior. The large-scale network described here is a core brain system that implements this latter process. The SN described here is a paralimbic–limbic network that is distinct from the dorsal spatial attention network, a system anchored in the intraparietal sulcus and frontal eye fields that helps maintain a stable 'saliency' or priority map of the visual environment (Egner et al., 2008; Fecteau & Munoz, 2006; Ptak, 2012; Szczepanski, Pinsk, Douglas, Kastner, & Saalman, 2013). Within the context of the SN, events that are likely to be perceived as salient include deviants embedded in a constant stream, surprising stimuli, and stimuli that are pleasurable and rewarding, self-relevant, or emotionally engaging.

### Conceptualizing Saliency in Psychopathology

A consideration of saliency in the context of psychopathology serves to illustrate its subjective and self-referential nature. Crucially, it helps highlight the notion that an event that is salient for one group of individuals may not be salient for another. For example, in individuals with autism, the relative saliency of social stimuli, such as face, eyes, and gaze, may be diminished, leading to poor social skills (Volkmar, 2005). On the other hand, for a hypersocial child with Williams syndrome, exactly the opposite may be true (Jabbi et al., 2012). To take a few more examples, specific drug paraphernalia may be uniquely salient to individuals with a cocaine addiction but not to individuals with anxiety or pain. In schizophrenia, misattribution of saliency to external and internal stimuli is a core feature of the disorder and may explain the genesis of psychotic symptoms such as delusions and hallucinations (Palaniyappan & Liddle, 2012). Thus, saliency has several subjective and psychopathology-specific attributes, and within the context of the SN, aberrant saliency detection has important repercussions for how exogenous and internal cues are processed and attended to (Menon, 2011), a topic that we explore further in Section 'Typical and Atypical Development of the SN.'

### Saliency Network: Identification and Anatomical Basis

The SN is most readily identified using intrinsic functional connectivity analysis of fMRI data acquired when a subject is



**Figure 1** Salience network identification using independent component analysis. (A) (a) The salience network (SN) is readily identified as an intrinsically connected large-scale network that is distinct from (b) the dorsal attention network anchored in the frontal eye field and intraparietal sulcus and (c, d) the left and right lateral frontoparietal central executive networks. (B) Cortical and subcortical nodes of the salience network (shown in red). The salience network has distinct patterns of intrinsic cortical and subcortical connectivity from the lateral frontoparietal central executive network in the anterior thalamus (antTHAL), dorsal caudate nucleus (dCN), dorsomedial thalamus (dmTHAL), hypothalamus (HT), periaqueductal gray (PAG), putamen (Put), sublenticular extended amygdala (SLEA), substantia nigra/ventral tegmental area (SN/VTA), and temporal pole (TP). Adapted from Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, *27*, 2349–2356; Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2011). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*, 158–165.

at rest (i.e., not performing any specific task). This analysis overcomes a limitation of task-based brain imaging data, in which the SN has been difficult to disentangle from other neurocognitive networks because of coactivations of the insula, dACC, dorsolateral and ventrolateral prefrontal cortices, frontal eye fields, and intraparietal sulcus across a wide range of cognitive tasks (Chang, Yarkoni, Khaw, & Sanfey, 2013; Dosenbach et al., 2006). Intrinsic functional connectivity analysis has provided evidence for a distinct paralimbic–limbic network of strongly coupled brain areas (Dosenbach et al., 2007; Seeley et al., 2007; Figure 1).

The SN is most readily identified using independent component analysis of resting-state fMRI data (Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008). This network includes prominent nodes in the AI and dACC, distinct from the central executive network anchored in the lateral frontoparietal cortex and the dorsal spatial attention network anchored in the frontal eye field and intraparietal sulcus (Seeley et al., 2007; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). The SN also includes distinct limbic areas including the amygdala, ventral striatum, dorsomedial thalamus, hypothalamus, and substantia nigra/ventral tegmental area (Seeley et al., 2007; Figure 1). Seed-based intrinsic functional connectivity analysis of its major nodes also reliably reproduces the core cortical nodes of the network, and subcortical nodes in the ventral striatum and ventral tegmental area can also be detected albeit at a weaker level (Figure 2).

Intrinsic connectivity and task-related meta-analytic investigations have consistently divided the insula into three subdivisions, encompassing its dorsal–anterior, ventral–anterior, and posterior aspects (Chang et al., 2013). The AI node of the SN corresponds most closely with the dorsal–anterior insular (Chang et al., 2013; Deen, Pitskel, & Pelphrey, 2011; Figure 3), and results from multiple methodologies have shown that the dorsal–anterior AI has particularly robust connectivity with the dACC (Brodmann area 24) node of the SN (Figure 3).

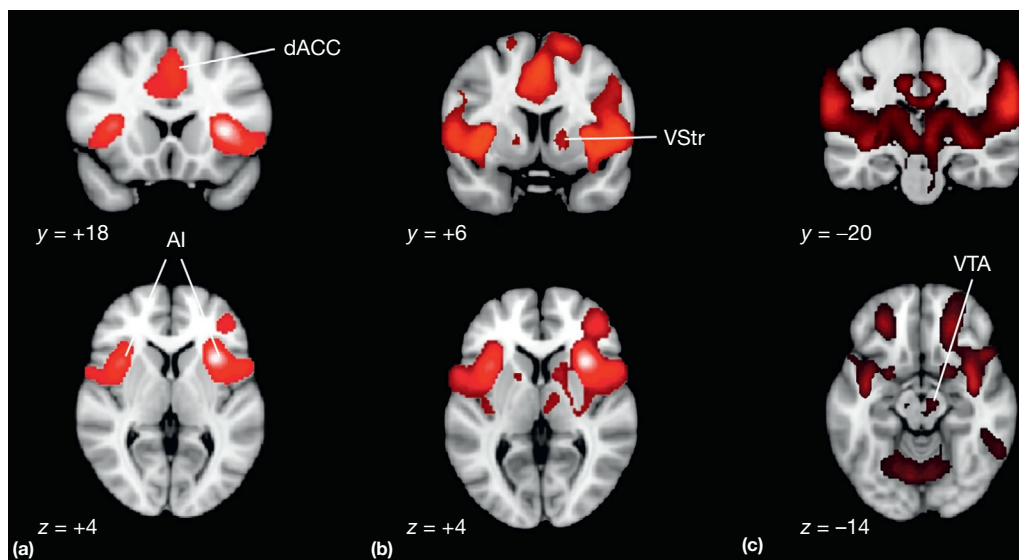
Further evidence for segregation of the SN from other networks comes from diffusion tensor imaging studies, which

have identified white matter tracts connecting the AI to dACC along the uncinate fasciculus and extending more dorsally to the medial aspects of the frontal lobe (Uddin, Supekar, Ryali, & Menon, 2011; Van Den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). These tracts are distinct from the fronto-occipital and superior longitudinal fasciculi, which connect the dorsolateral frontoparietal central executive network (Figure 4). This limbic pathway is critical for processing novel information and enabling interaction between cognition, emotion, and action (Mori, Oishi, & Faria, 2009; Schmahmann et al., 2007). The precise white matter pathways linking cortical and subcortical nodes of the SN in the human brain have yet to be delineated, but there is considerable evidence from nonhuman primates for such tracts, including other segments of the uncinate fasciculus, which link the AI with the amygdala and anterior temporal lobe (Mesulam & Mufson, 1982; Nieuwenhuys, 2012; Schmahmann & Pandya, 2009).

It is further noteworthy that the structural architecture of the AI and dACC shares unique features at the cellular level. In the human brain, the AI and dACC contain a specialized class of neurons, the von Economo neurons (VENs), with distinctive anatomical and functional properties (Allman et al., 2010; Nimchinsky et al., 1999; Figure 5). The VENs have wider axons, which can facilitate rapid relay of signals from the AI and dACC to other cortical regions (Allman, Watson, Tetreault, & Hakeem, 2005), endowing the SN with distinct mechanisms for signaling within and across the SN.

### The Salience Network Modes Are Commonly Coactivated Across a Wide Range of Cognitive and Affective Tasks

The AI and dACC are among the most frequently activated regions in all of functional neuroimaging research (Buchsbaum, Greer, Chang, & Berman, 2005; Dosenbach et al., 2006; Nelson et al., 2010; Smith et al., 2009; Supekar & Menon, 2012; Wager et al., 2005; Yarkoni, Poldrack, Nichols,



**Figure 2** Saliency network identified using right anterior insula (AI) connectivity. (a) The AI shows high levels of correlation ( $r > 0.3$ ) with the right anterior insula (AI) seed (MNI coordinates: 36, 18, 4) ( $y = 18$  and  $z = 4$ ). (b) At lower thresholds ( $r < 0.2$ ), AI connectivity is also evident in the ventral striatum (VStr;  $y = 6$  and  $z = 4$ ) and (c) ventral tegmental area (VTA;  $z = -20$  and  $z = -14$ ). Image generated from a sample of 1000 subjects using Neurosynth.org, based on Yeo et al. (2011).

Van Essen, & Wager, 2011). To illustrate this, I used the Neurosynth database to conduct a search using the right AI node of the SN (MNI coordinate:  $x = 36$ ,  $y = 18$ ,  $z = 4$ ). The search revealed significant AI activation across a wide range of tasks, with over 400 descriptive features ranging from pain to go-no-go, number, letter, counting, and anticipation (Figure 6). Crucially, the AI and dACC show strong functional covariance across a wide range of tasks (Cauda et al., 2011; Chang et al., 2013; Deen et al., 2011). Consistent with these findings, meta-analytic coactivation analysis of the AI also revealed prominent overlap in cortical and subcortical nodes of the SN (Figure 7).

### Integrated Salience Network Function in Cognition, Action, and Emotion

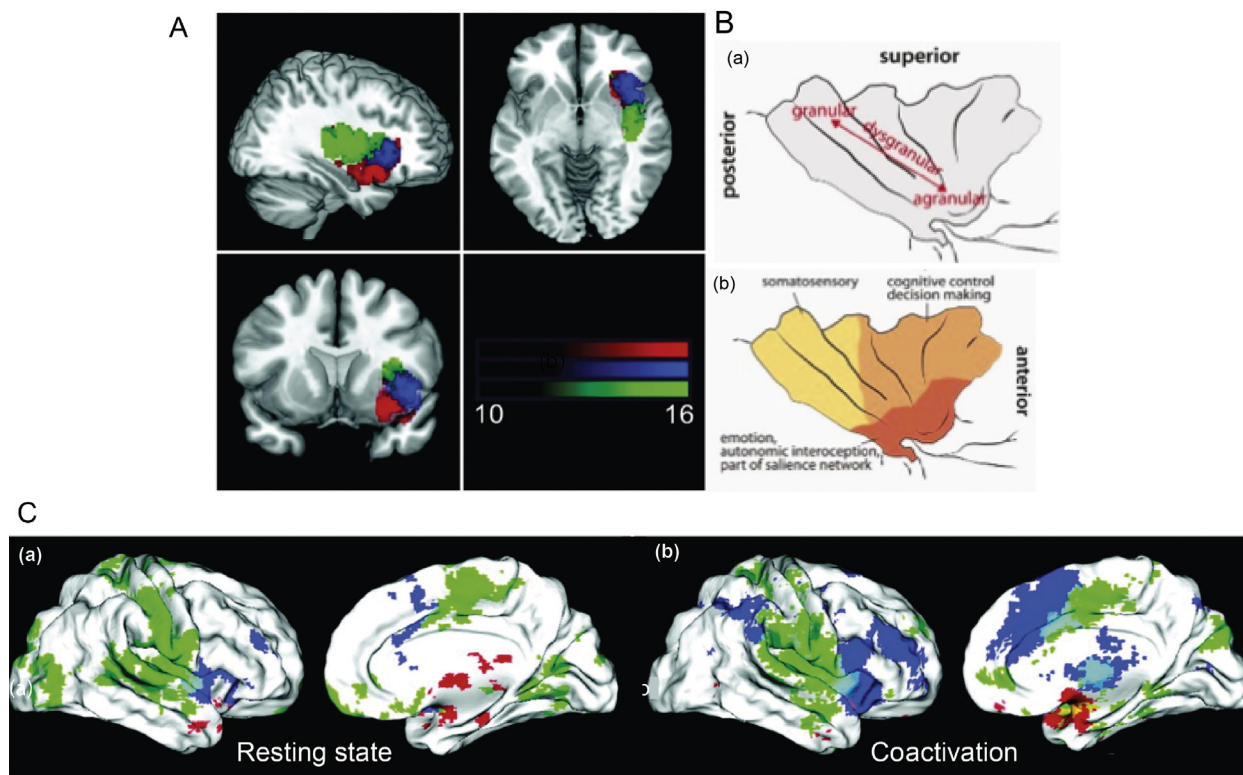
SN responses show close correspondence between intrinsic connectivity and task-related coactivation patterns (Figures 1, 2, and 7). This correspondence allows intrinsic and task-related fMRI activations associated with the SN to be identified and studied in a common framework (Bonnelle et al., 2012; Ham, Leff, De Boissezon, Joffe, & Sharp, 2013; Sridharan et al., 2008; Supekar & Menon, 2012). Despite this similarity and their largely common pattern of activation, until recently, the AI and dACC were thought to be part of different functional systems. The AI was typically associated with social and affective tasks involving pain, empathy, disgust, and introspective processes (Craig, 2009; Singer, Critchley, & Preusschoff, 2009), whereas the dACC was most closely associated with response selection, conflict resolution, and cognitive control (Botvinick, Cohen, & Carter, 2004). Identification of the AI and dACC as core nodes of the SN in the intrinsic state and their concurrent activation across a wide range of tasks has led to a more integrated view of the function of these regions. This section describes an integrative model of SN function predicated on

the conjoint activations, but differential inputs, outputs, and putative roles, of its major nodes in cognition, action, and emotion (Figure 8).

### Detection and Integration of Salient Sensory Cues: Differential Role of the AI

The two main cortical nodes of the SN serve distinct functions by virtue of their differential inputs and outputs. The AI receives convergent input from multiple sensory modalities including auditory and visual systems (Augustine, 1996; Bamiou, Musiek, & Luxon, 2003; Butti & Hof, 2010; Mesulam & Mufson, 1982; Nieuwenhuys, 2012), and there is converging evidence from human neuroimaging studies for its involvement in simultaneous attention to multisensory stimuli (Bushara, Grafman, & Hallett, 2001; Bushara et al., 2003). Other major sources of input include the amygdala, ventral striatum, and the ventral tegmental nuclei, constituting the key subcortical nodes of the SN, which provide access to the emotional and reward saliency of stimuli. Crucially, in addition to its response to external stimuli, the insula is also sensitive to internal signals associated with autonomic processes such as heartbeat, skin conductance, and respiration (Critchley, Eccles, & Garfinkel, 2013; Singer et al., 2009). These autonomic processes have been linked to interoceptive awareness of salient events and likely involve interactions of the SN with the posterior insula (Figure 9).

A major function of the AI node of the SN is the detection of behaviorally relevant stimuli. Influential models of attention have long postulated a key role for the right fronto-opercular cortex in orienting attention (Corbetta, Patel, & Shulman, 2008), but recent studies have more directly associated the AI subdivision with saliency detection (Crottaz-Herbette & Menon, 2006; Eckert et al., 2009; Seeley et al., 2007; Sridharan et al., 2008; Sterzer & Kleinschmidt, 2010). Detection of



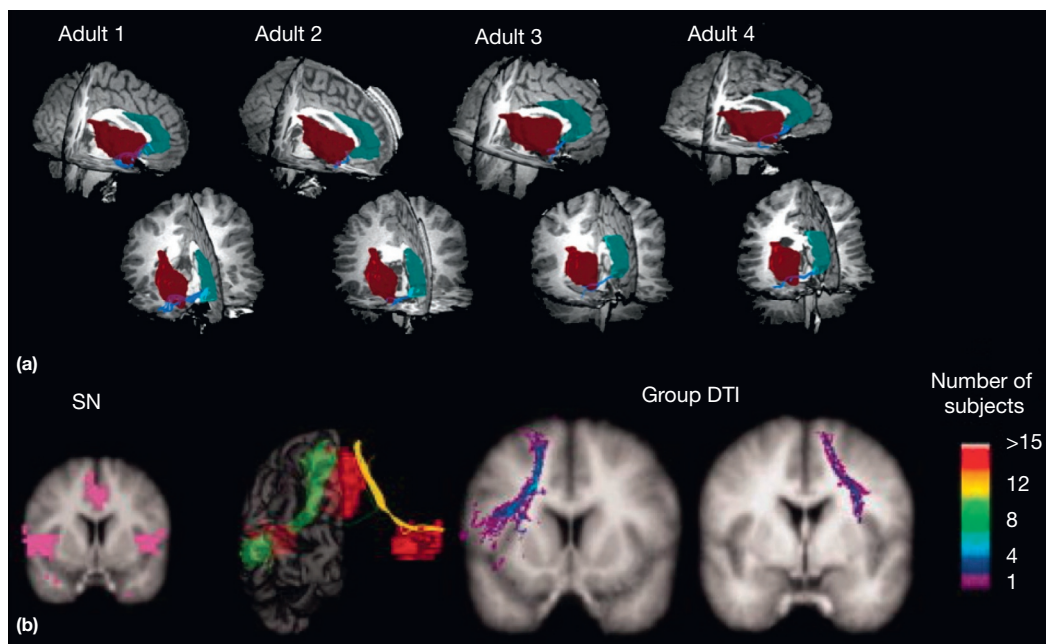
**Figure 3** Anatomical localization and connectivity of the anterior insula node of the salience network. (a) Three major functional subdivisions of the insular cortex identified using intrinsic connectivity analysis: dorsal–anterior insula (blue), ventral–anterior insula (red), and posterior insula (green). The dorsal–anterior insula corresponds most closely to the AI node of the SN. (b) (A) Cytoarchitectonic gradient from the agranular cortex in the anterior inferior insula via the dysgranular cortex to the granular cortex in the posterior insula. (B) Approximate boundaries and putative functions of the three insula subdivisions. Adapted from Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral Cortex*, *21*, 1498–1506; Chang, L. J., Yarkoni, T., Khaw, M. W., & Sanfey, A. G. (2012). Decoding the role of the insula in human cognition: Functional parcellation and large-scale reverse inference. *Cerebral Cortex*, *23*, 739–749; Klein, T. A., Ullsperger, M., & Danielmeier, C. (2013). Assessing error awareness without relying on introspective judgment? *Frontiers in Neuroscience*, *7*, 113. (c) (A) Intrinsic functional connectivity of the three insula subdivisions illustrating largely segregated systems associated with the AI node of the salience network (shown in blue). Networks associated with the three insula subdivisions are largely segregated in the resting state. (B) Similar profiles are observed in meta-analytic coactivation analysis of task-based fMRI data. Although networks associated with the three insula subdivisions are largely segregated during active tasks, they show prominent overlap in the posterior insula, basal ganglia, and thalamus. Adapted from Chang, L. J., Yarkoni, T., Khaw, M. W., & Sanfey, A. G. (2012). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cerebral Cortex*, *23*, 739–749.

behaviorally salient relevant stimuli is an essential component of almost all cognitive tasks. Consistent with this view, meta-analysis of a wide range of attention tasks, including the canonical ‘oddball’ task, which involves detection of deviant stimuli embedded in a stream of standard stimuli (Crottaz-Herbette & Menon, 2006; Debener, Kranczioch, Herrmann, & Engel, 2002; Kiehl & Liddle, 2003; Yago, Duarte, Wong, Barcelo, & Knight, 2004), and cognitive control tasks, such as the stop signal and go-no-go tasks, have revealed that the AI and dACC are consistently coactivated across many different cognitive paradigms (Swick, Ashley, & Turken, 2011).

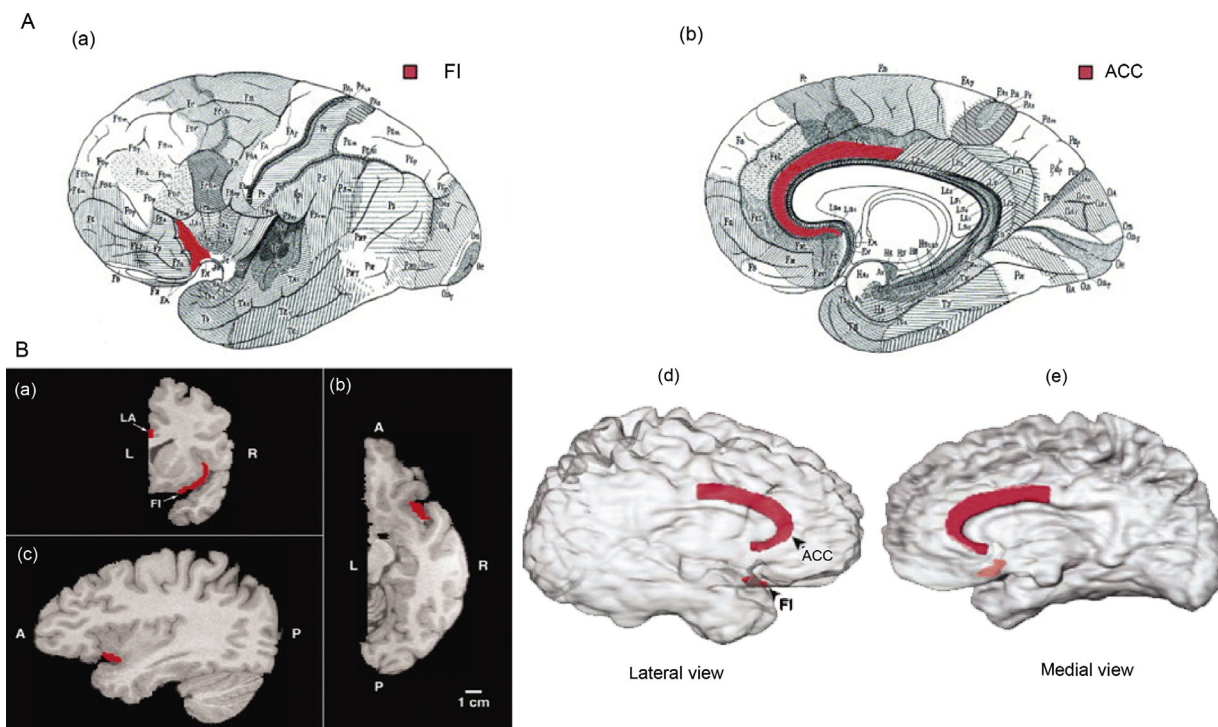
### Response Selection and Monitoring: Differential Role of the dACC

In contrast to the AI, the dACC node of the SN is more directly involved in response selection and conflict monitoring (Ide,

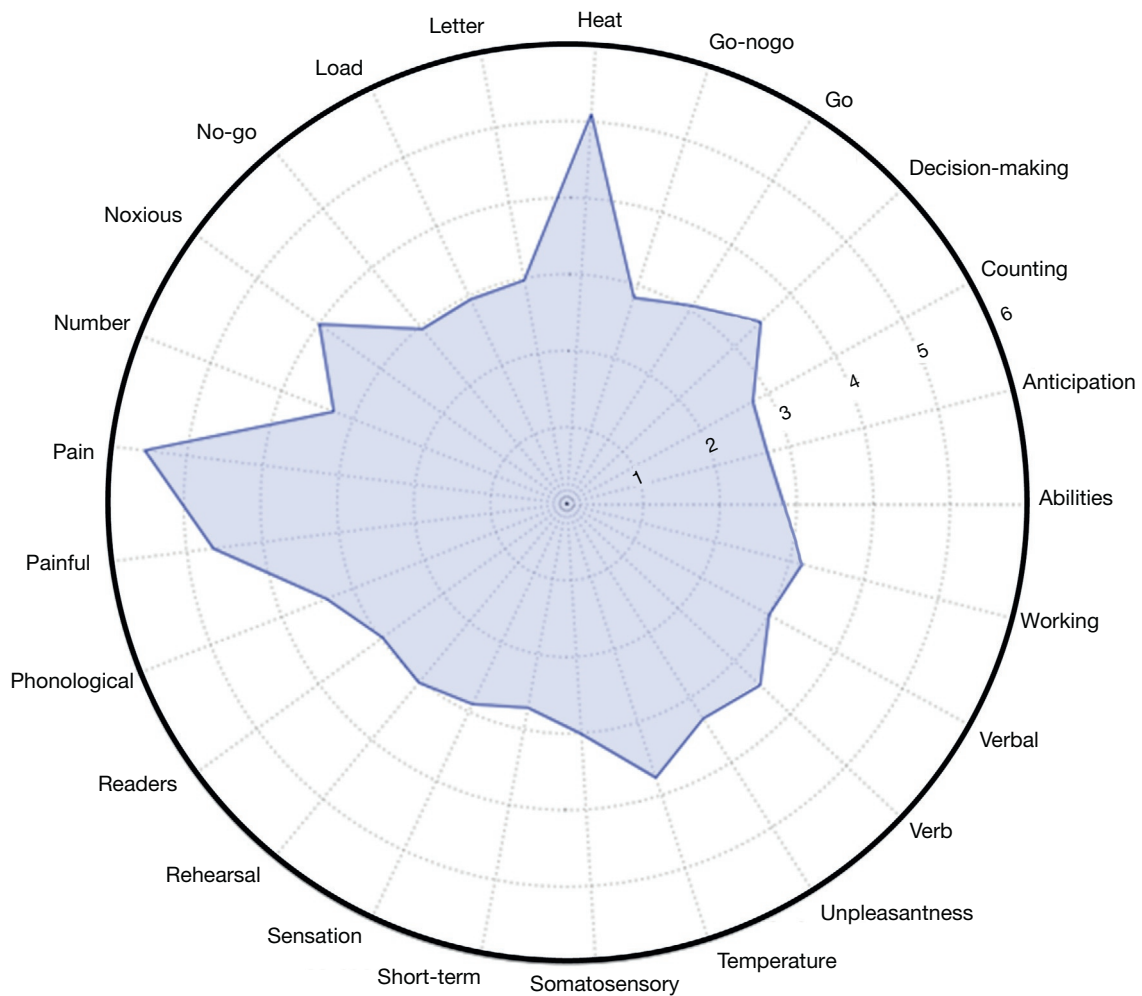
Shenoy, Yu, & Li, 2013). A wide range of functional imaging studies and theoretical models have suggested that the ACC plays a prominent role in action selection (Rushworth, 2008). An examination of the pattern of input–output connectivity of the AI and the ACC provides further insights into the differential functions of the AI and dACC. While the AI receives multimodal sensory input, the dACC and associated dorsomedial prefrontal cortex receive very little such inputs (Averbeck & Seo, 2008; Vogt & Pandya, 1987). Conversely, while the ACC and associated dorsomedial prefrontal cortex send strong motor output, there is relatively little direct motor output from the AI. Furthermore, the ACC and dorsomedial prefrontal cortex have direct connections to the spinal cord and subcortical oculomotor areas (Fries, 1984), giving them direct control over action. With these differential anatomical pathways and von Economo neurons that facilitate rapid signaling between the AI and the ACC, the SN is well positioned to



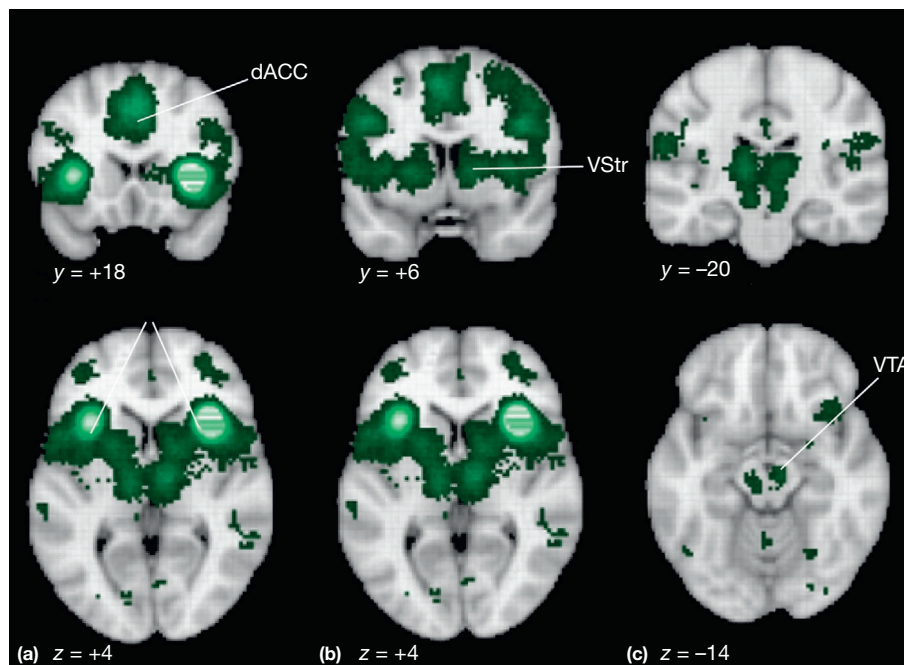
**Figure 4** Structural connectivity between salience network nodes. (a) White matter pathways between the extended frontoinsula, including the AI node of the SN, and ACC, including the dACC node of the SN. DTI tractography reliably identified ventral white matter tracts overlapping with the uncinate fasciculus. Fibers (blue) connecting the frontoinsula cortex (red) and ACC (green) in representative adults. The first row shows sagittal slices viewed from the right, and the second row shows coronal slices viewed anteriorly. These tracts were detected in 11 of 15 adults (73%). Adapted from Uddin, L. Q., Supekar, K. S., Ryali, S., & Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *The Journal of Neuroscience*, *31*, 18578–18589. (b) Dorsal tracts linking the frontoinsula cortex and ACC. Adapted from Van Den Heuvel, M. P., Mandl, R. C., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*, *30*, 3127–3141.



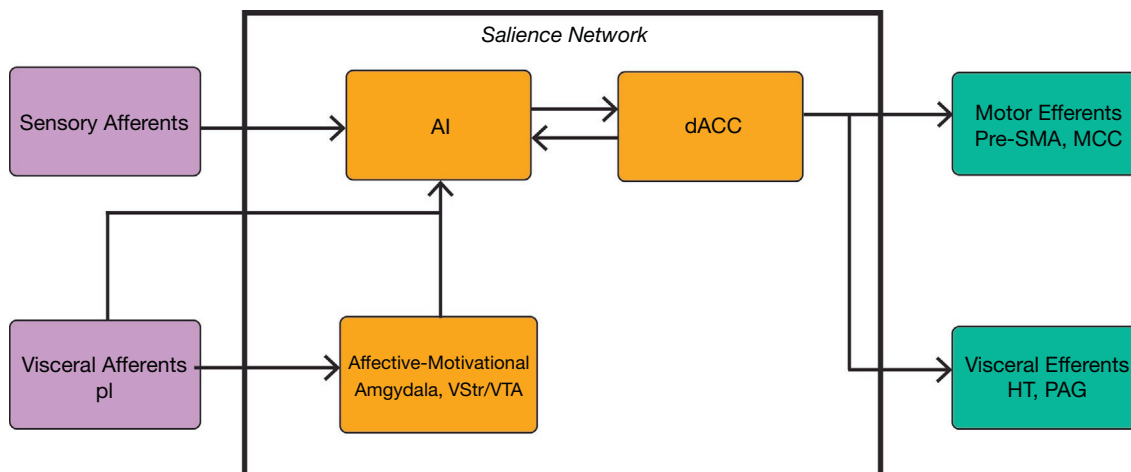
**Figure 5** Specialized neurons in the AI and dACC nodes of the salience network. (a) Regions of the brain containing von Economo neurons (VENs). (A) Lateral view with the frontoinsula (FI) shown in red. (B) Medial view with the anterior cingulate cortex (ACC) shown in red. Adapted from Allman, J. M., Watson, K. K., Tetreault, N. A., & Hakeem, A. Y. (2005). Intuition and autism: A possible role for Von Economo neurons. *Trends in Cognitive Sciences*, *9*, 367–373. (b) MRI cross sections showing the location of the VEN-containing AI and dACC areas in the right hemisphere of a young adult human female. (A–C) MRI sections are frontal, horizontal, and parasagittal sections that intersect in the AI. (D, E) Three-dimensional reconstructions of the left hemisphere. Adapted from Allman, J. M., Tetreault, N. A., Hakeem, A. Y., Manaye, K. F., Semendeferi, K., Erwin, J. M., et al. (2010). The von Economo neurons in frontoinsula and anterior cingulate cortex in great apes and humans. *Brain Structure and Function*, *214*, 495–517.



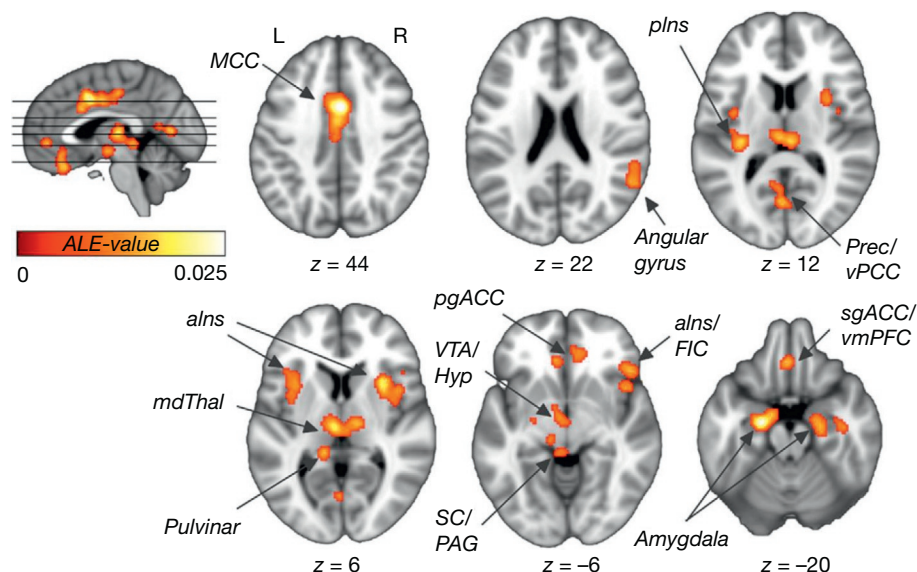
**Figure 6** Polar plot illustrating the wide range of cognitive and affective tasks that engage the salience network. Data based on meta-analysis of the same right AI seed (MNI coordinates: 36, 18, 4) as in [Figure 2](#). Z-scores correspond to likelihood of specific task-based terms in the Neurosynth database.



**Figure 7** Task-related coactivation of salience network nodes. (a) Cortical nodes in the AI and dACC show high levels of task-related coactivation ( $y=18$  and  $x=4$ ). At lower thresholds, coactivation is also evident in (b) the ventral striatum (VStr;  $y=6$  and  $z=4$ ) and (c) ventral tegmental area (VTA;  $z=-20$  and  $z=-4$ ). Slice locations are the same as in [Figure 2](#). Image generated using Neurosynth.org.



**Figure 8** Summary of salience network organization in relation to its major afferents and efferents. The AI receives convergent multisensory inputs, affective and motivational signals, and visceral afferents, reflecting biological saliency and cognitive demands. In contrast, the dACC plays a more dominant role in response selection, guiding overt behavior and modulating autonomic reactivity. AI, anterior insula; dACC, dorsal anterior cingulate cortex; HT, hypothalamus; PAG, periaqueductal gray; pl, posterior insula; VStr, ventral striatum; VTA, ventral tegmental area. Adapted from Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, 214, 655–667; Zhou, J., & Seeley, W. W. (2014). Network dysfunction in Alzheimer's disease and frontotemporal dementia: Implications for psychiatry. *Biological Psychiatry*, 75, 565–573.



**Figure 9** Cortical and subcortical regions associated with autonomic processing overlap with the salience network. Meta-analyses of studies showing general brain regions involved in autonomic processing. Prec, precuneus; vPCC, ventral posterior cingulate cortex; mdThal, mediadorsal thalamus; pgACC, pregenual ACC; VTA, ventral tegmental area; Hyp, hypothalamus; SC, superior colliculus; PAG, periaqueductal gray; FIC, frontoinsula cortex; L, left; R, right. Adapted from Beissner, F., Meissner, K., Bar, K. J., & Napadow, V. (2013). The autonomic brain: An activation likelihood estimation meta-analysis for central processing of autonomic function. *The Journal of Neuroscience*, 33, 10503–10511.

influence not only attention but also motor responses to salient sensory stimuli.

#### Integration of Salient Affective Cues: Inputs from Subcortical Nuclei

The major subcortical nodes of the SN – the amygdala, ventral striatum, and ventral tegmental area – provide preferential context-specific access to affective and reward cues. These

cues include biasing signals from the amygdala associated with negatively valenced stimuli and the nucleus accumbens and ventral tegmental area signals associated with reward (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). A more general view of this organization is that emotional and motivational signals can be embedded into the SN through multiple channels (Pessoa, 2014), allowing preferential access to affective cues within the cognition–action mechanisms subserved by the AI and dACC, the two major cortical nodes of the



SN. Comparatively, little is known, however, about the integrative role of the subcortical nuclei in the context of SN function, and this remains an important area for future research, especially with respect to social and affective processes.

### Dynamic Interaction of the SN with Other Brain Networks: Evidence for Switching Networks

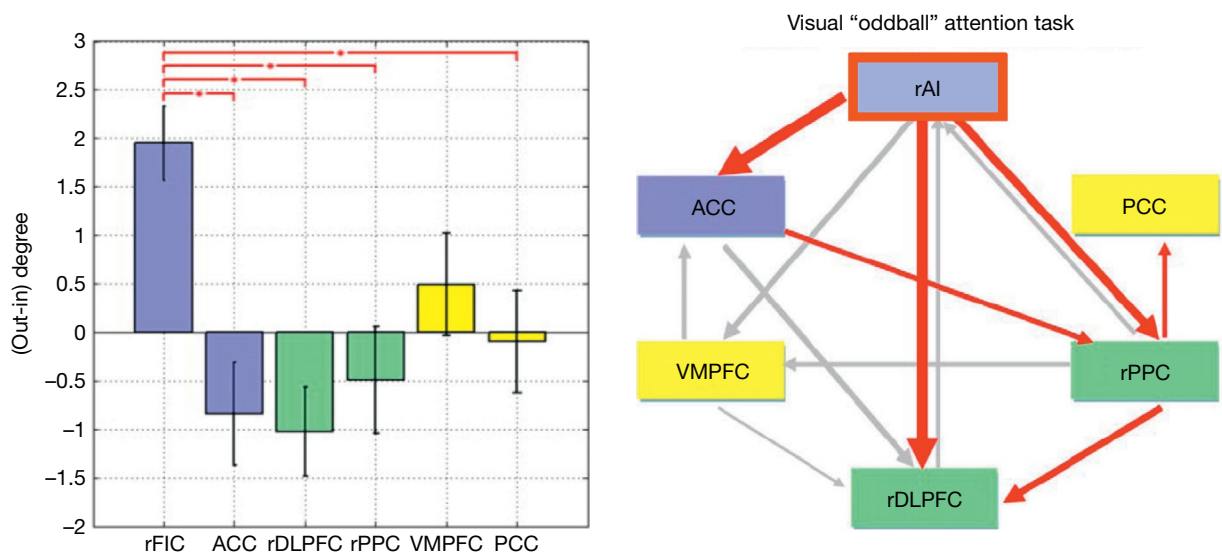
The SN not only plays an important role in saliency detection and reactivity but also facilitates access to attention and working memory resources once a salient event has been detected. Emerging evidence suggests that the SN plays a crucial role in switching between large-scale brain networks involved in externally oriented attention and internally oriented mental processes (Sridharan et al., 2008). During the performance of many cognitively demanding tasks, the SN, together with the lateral frontoparietal central executive network, typically shows increase in activation, whereas the default-mode network shows consistent decrease in activation below the resting baseline (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Raichle et al., 2001). Importantly, brain responses within these regions increase and decrease proportionately and often antagonistically, in relation to specific cognitive demands and subjective task difficulty. Once a salient event is detected, the AI facilitates sustained processing by initiating appropriate transient control signals that engage cognitive and task control systems while suppressing the default-mode network (Sridharan et al., 2008). The right AI node of the SN, in particular, has been shown to be a causal hub for signaling the dorsal frontoparietal 'central executive' network (Figure 10), a system important for maintaining and manipulating information in working

memory (D'Esposito, 2007; Fuster, 2000; Goldmanrakic, 1995; Miller & Cohen, 2001; Smith & Jonides, 1998).

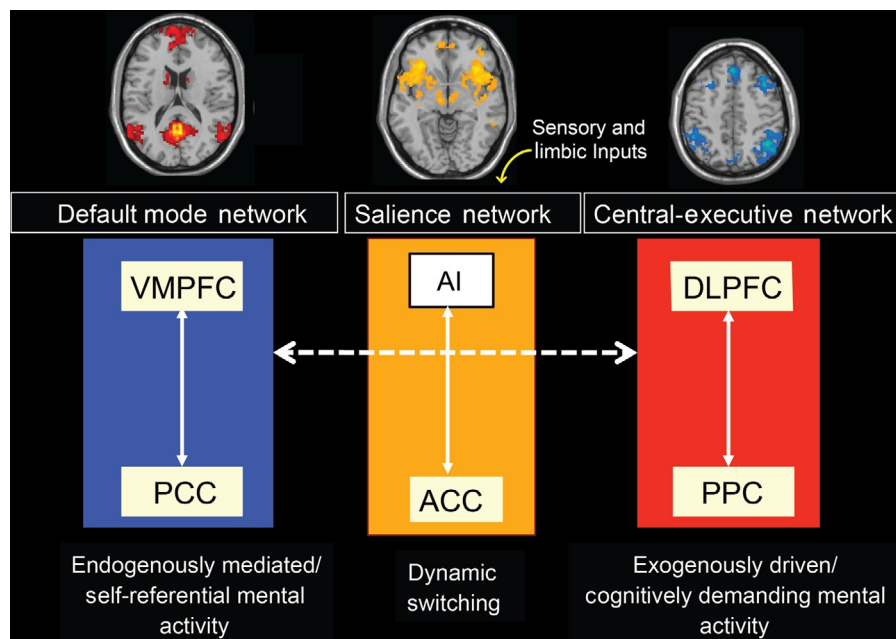
The most dramatic evidence for the role of the SN in mediating the dynamic interaction between networks comes from studies of patients with traumatic brain injury. Bonnelle and colleagues found that abnormal default-mode network function was specifically predicted by the amount of white matter damage in the SN tract connecting the right AI to the dACC and presupplementary motor area (Bonnelle et al., 2012). These results provide evidences that structural integrity of the SN is necessary for the efficient regulation of activity in the default-mode network and that a failure of this regulation leads to inefficient cognitive control and weaker performance on cognitive control tasks. Critically, these switching mechanisms help focus attention on task-relevant stimuli and goals, and as a result, they take on added significance or saliency (Menon & Uddin, 2010; Figure 11).

### Typical and Atypical Development of the SN

A thorough understanding of the SN requires critical consideration of the developmental pathways by which plasticity and learning lead to the construction of this dedicated large-scale brain system. Although the study of brain network development is still in its infancy, new studies are beginning to shed light on the typical and atypical developmental trajectories of this network. The SN can be readily identified by age 2, but it undergoes protracted changes in connection strength throughout childhood (Gao et al., 2013). Between the ages 7 and 20, the SN undergoes further developmental changes that span both within- and across-network links (Uddin et al., 2011). Analysis of these links provides unique insights into the



**Figure 10** Net causal outflow of major nodes of the salience, central executive, and default-mode networks. (a) Dynamical systems analysis reveals that the right anterior insula (AI) has a significantly higher net causal outflow than any of the nodes of the central executive or default-mode networks. (b) Granger causal analysis of connectivity showed significant causal outflow from the right AI to major nodes of the two other networks. These results, together with latency analyses, suggest that the rAI functions as a causal outflow hub for salient events. Adapted from Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 12569–12574.



**Figure 11** Dynamic salience network-mediated switching of large-scale brain networks. The salience network (SN) plays a crucial role in dynamic switching between the central executive and default-mode networks. The SN recruits the central executive and task control regions to maintain cognitive set and manipulate information in working memory while suppressing the default-mode network to keep attention focused on task-relevant goals. Adapted from Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, 14, 277–290.

maturation of core neurocognitive systems. Compared with adults, children show significantly weaker functional connectivity between the AI and dACC (within the SN) and the AI and dorsolateral prefrontal cortex and posterior cingulate cortex (between the SN and other networks). Notably, the AI is the only node that shows significant age-related differences in functional connectivity between the SN and other networks, suggesting that this region is a locus of weak signaling in children. Consistent with this view, the right AI also shows weaker causal influences on the dorsolateral frontoparietal areas involved in problem solving and weaker signaling, a phenomenon associated with lower levels of overall behavioral performance in children (Supekar & Menon, 2012; Figure 12). These observations suggest that the functional maturation of AI pathways is a critical process by which human brain networks reconfigure and mature during development to support more flexible cognitive control processes in adulthood (Uddin et al., 2011).

Deficits in SN function and its interaction with other neurocognitive networks also play a significant role in many neurodevelopmental disorders (Menon, 2011). For example, characterization of the SN has turned out to be particularly promising for identifying atypical development in children with autism (Di Martino et al., 2009; Uddin et al., 2013), a disorder with early-life onset and variable developmental trajectory (Stefanatos, 2008). The SN shows significant hyperconnectivity in children with autism, and critically, connectivity in these networks can be used to reliably distinguish children with autism from typically developing children (Uddin et al., 2013). Notably, among all networks examined, connectivity patterns of the SN show the highest classification accuracy between children with autism and typically

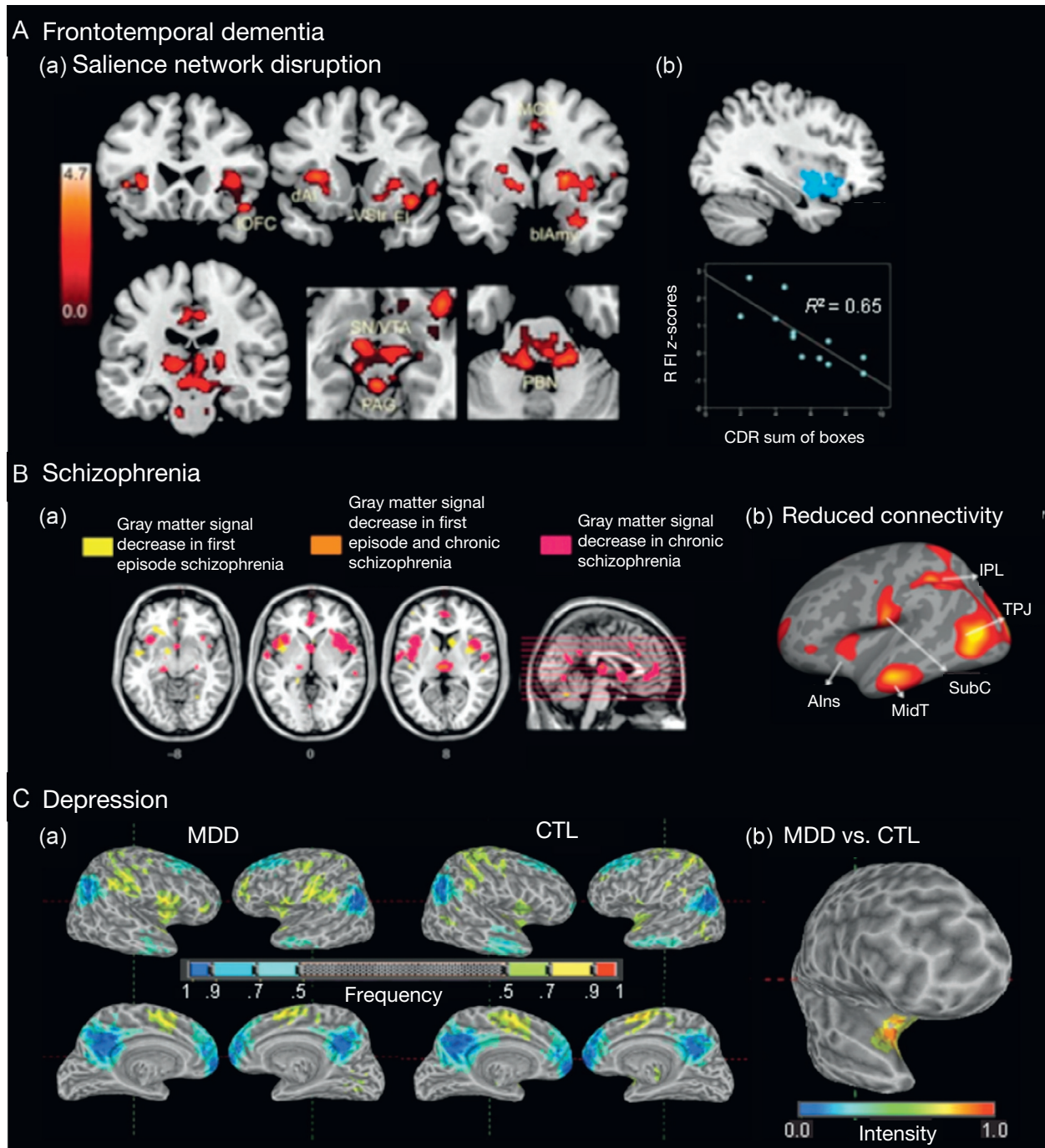
developing children. The SN's functional organization also predicts restricted and repetitive behavior scores – one of the core symptoms of childhood autism (Di Martino et al., 2009; Uddin et al., 2013). Identification of the SN as a particular locus of aberrant connectivity in autism is consistent with the hypothesis that inappropriate assignment of saliency to external stimuli or internal mental events by this network plays a prominent role in developmental disorders (Menon & Uddin, 2010).

More generally, aberrant detection of saliency linked to weak development of signaling from the AI to key nodes of the SN and default-mode network may be a particular source of vulnerability for psychopathology in the developing brain (Fair et al., 2012; Menon, 2011; Uddin & Menon, 2009). The application of a SN-based model holds great promise for the principled investigation of psychopathology in both the developing and adult brains, as elaborated in the next section.

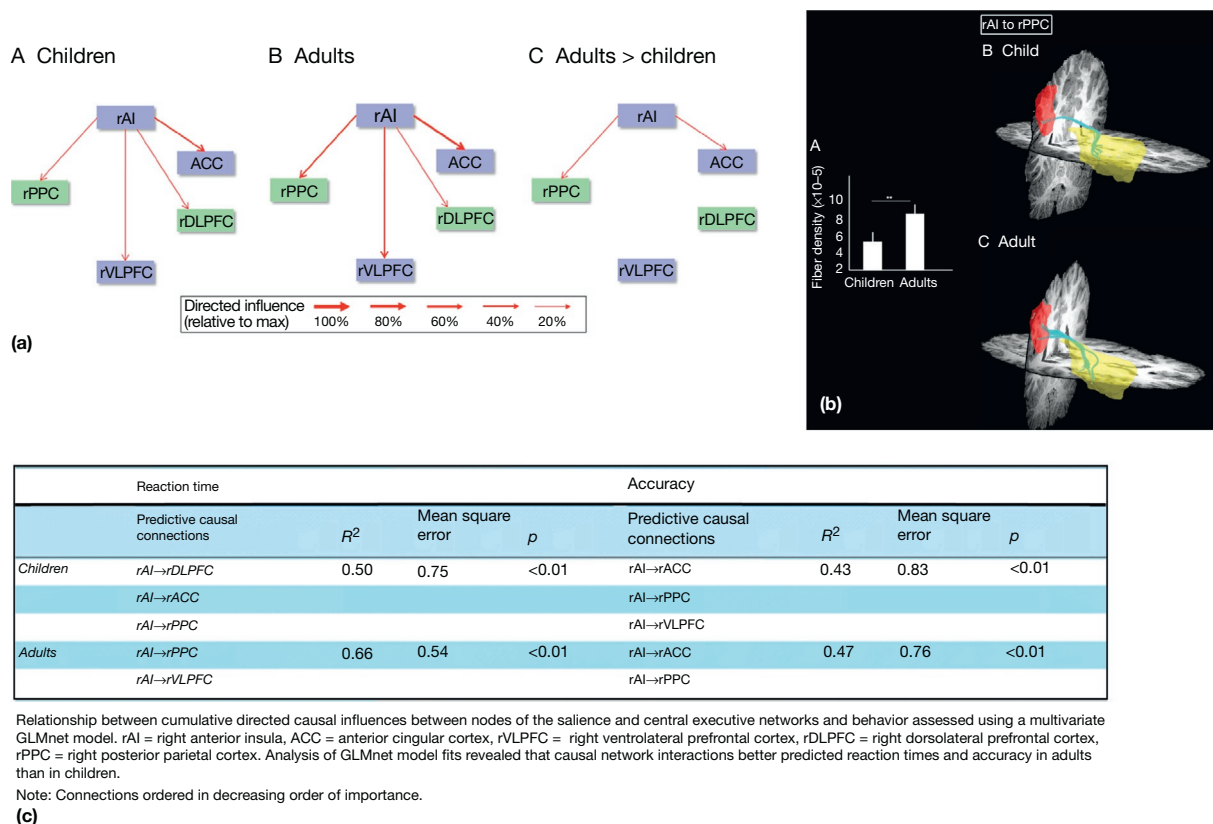
## The SN in Psychopathology

### SN Deficits Are Prominent in Psychopathology

Network models are now being widely used to characterize deficits in a wide range of psychiatric and neurological disorders (Menon, 2011). These studies have provided evidence for prominent SN dysfunction in many psychopathologies, including frontotemporal dementia, mood and anxiety disorders, schizophrenia, drug addiction, and pain (Figure 13). In addition, isolated lesions to the insula have been associated with dysfunction in autonomic function; gustatory, olfactory, auditory, somatosensory, and multimodal perception; body



**Figure 12** SN dysfunction in major psychopathology. (A) Frontotemporal dementia: (a) SN connectivity disruption in patients with bvFTD. Multiple nodes of the SN, including the FIC, lateral orbitofrontal cortex (IOFC), dorsal AI (dAI), midcingulate cortex (MCC), VStr, basolateral amygdala (blAmy), thalamus, SuN/VTA, PAG, and dorsal pons and parabrachial nuclei (PBN), showed deficits in the patient group. (b) Of these regions, only the right FIC responses were associated with functional severity, as measured by the Clinical Dementia Rating (CDR) scale, sum of boxes score. Adapted from Zhou, J., Greicius, M. D., Gennatas, E. D., Growdon, M. E., Jang, J. Y., Rabinovici, G. D., et al. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain: A Journal of Neurology*, 133, 1352–1367. (B) Schizophrenia: (a) Both functional and anatomical deficits are prominent in patients with schizophrenia. SN structural deficits in the insula and ACC are prominent in both the early and late stages of schizophrenia, with progressive increase in gray matter deficits in chronic schizophrenia. Adapted from Ellison-Wright, I., Glahn, D. C., Laird, A. R., Thelen, S. M., & Bullmore, E. (2008). The anatomy of first-episode and chronic schizophrenia: An anatomical likelihood estimation meta-analysis. *The American Journal of Psychiatry*, 165, 1015–1023. (b) Significantly reduced functional connectivity in patients compared with controls both within the SN (between AI and ACC) and with other networks (AI and vmPFC). Alns, anterior insula; IPL, inferior parietal lobule; MidT, middle temporal; SubC, subcentral; TPJ, temporoparietal junction. Adapted from White, T. P., Joseph, V., Francis, S. T., & Liddle, P. F. (2010). Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophrenia Research*, 123, 105–115. (C) Depression: (a) SN and CEN activation (yellow-red) and DMN deactivation (blue-cyan) in patients with major depressive disorder (MDD) and control (CTL) participants. (b) Chi-square statistic map showing increased frequency of inclusion of right FIC in the SN and CEN in the MDD group. Adapted from Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. *Biological Psychiatry*, 2, 2.



**Figure 13** Developmental changes in salience network organization and links to cognition. (A) Dynamic causal interactions network analysis using state-space multivariate dynamical systems (MDS) model in (a) children and (b) adults. (c) Weaker causal interactions in children, compared with adults. (B) Developmental changes in white matter tracts linking the AI and posterior parietal cortex. (a) Fiber density, the number of fibers per unit area, between the rAI (yellow) and rPPC (red) is significantly lower in children, compared to adults (\*\* $p < 0.01$ ). Tracts connecting the rAI to the rPPC (cyan tracts) are shown in (b) children and (c) adults. (C) SN causal network interactions predict behavior differently in children and adults. Adapted from Supekar, K., & Menon, V. (2012). Developmental maturation of dynamic causal control signals in higher-order cognition: A neurocognitive network model. *PLoS Computational Biology*, 8, e1002374.

awareness; the emotion of disgust; mood and willed action; and addiction (Ibanez, Gleichgerricht, & Manes, 2010). I discuss a few examples here from recent advances in network modeling of the dementias, schizophrenia, and mood disorders.

Systematic investigation of the SN has provided better differentiation of neurodegenerative disorders including frontotemporal dementia (Zhou et al., 2010). Of particular note is behavioral variant frontotemporal dementia, which leaves patients unable to model the emotional impact of their own actions or inactions and involves progressive breakdown of the SN arising from an initial core of fronto-insular degeneration (Seeley, 2010). Crucially, this pattern of degeneration shows a divergent pattern of changes from Alzheimer's disease, which has its primary origins in default-mode network dysfunction (Zhou & Seeley, 2014).

In schizophrenia, both functional and structural studies have pointed to dysfunctional organization of the SN. Bilateral volume reduction in the AI and dACC nodes of the SN has been detected in individuals with schizophrenia (White, Joseph, Francis, & Liddle, 2010), and this reduction has been linked to the severity of reality distortion (Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2010). Aberrant intrinsic functional connectivity of the SN and its interactions with

other networks has been found in patients with schizophrenia (Manoliu et al., 2014) and younger adults at risk for psychosis (Wotruba et al., 2013). Notably, conceptualization of psychosis as aberrant signaling of salient events (Kapur, 2003) has led researchers to propose that abnormalities in the attribution of salience to external and internal stimuli are a core feature of schizophrenia and may explain the genesis of psychotic symptoms such as delusions and hallucinations (Palaniyappan & Liddle, 2012).

SN abnormalities are also prominent in mood and anxiety disorders. Depressed subjects with high apathy show decreased intrinsic connectivity of the SN, which suggests an important role for the network in motivated behavior (Yuen et al., 2014). The role of the SN in mood disorders is further highlighted by findings that all the major nodes of the SN are affected in patients with major depression, leading to the suggestion that the occurrence of repetitive, preservative, negative thinking and biases in attention to negative events may underlie aberrant SN response and connectivity in the disorder (Hamilton, Chen, & Gotlib, 2013). In anxiety disorders, hyperactivity of the AI node of the SN has been consistently detected in patients (Paulus & Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007), and intrinsic functional connectivity analyses have

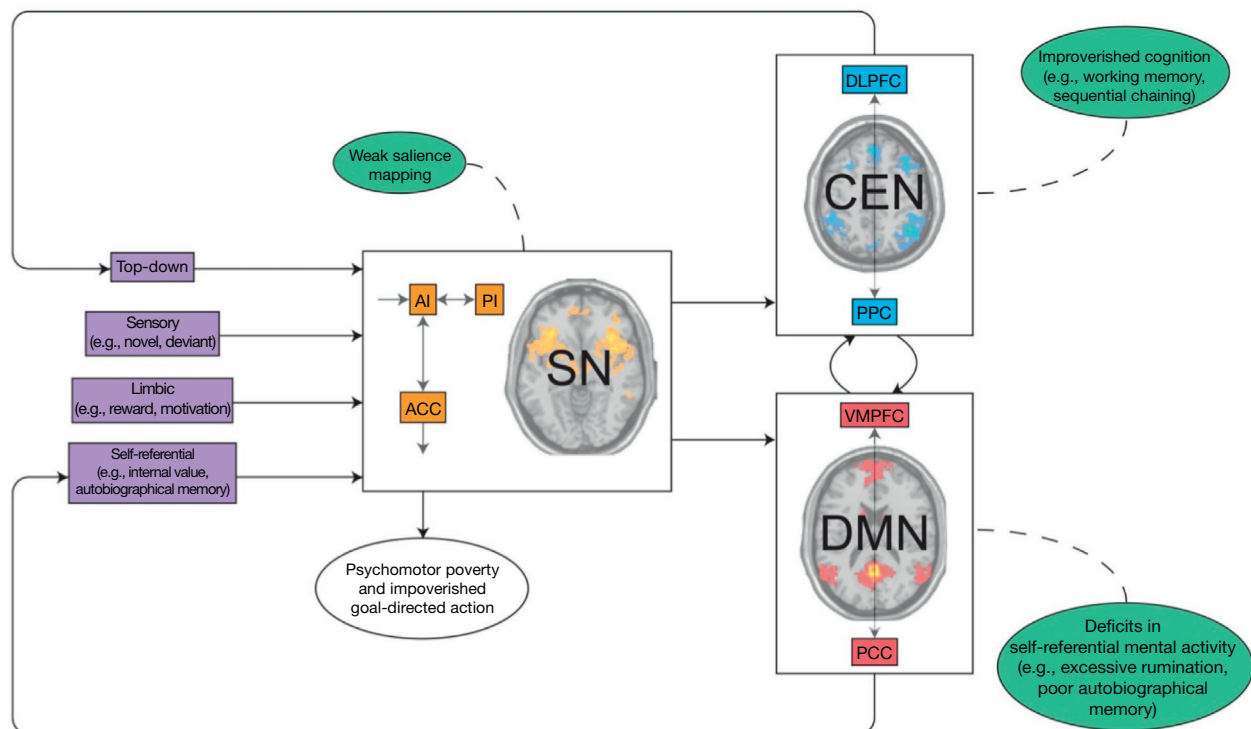
demonstrated alterations within the SN in patients with generalized anxiety disorder (GAD) and social anxiety disorder and posttraumatic stress disorder (Peterson, Thome, Frewen, & Lanius, 2014). These findings are important because anxiety disorders are a common comorbid feature of many psychiatric disorders, including depression, phobia, and posttraumatic stress disorder (Antony & Stein, 2009).

Taken together, these findings suggest that SN dysfunction is a prominent feature of many psychiatric and neurological disorders. In particular, the SN appears to be closely associated with disorders in which attribution of saliency to biologically and cognitively relevant stimuli are disrupted.

### Saliency Mapping Deficits as an Integrative Model for Psychopathology

The identification of SN dysfunction across multiple disorders suggests basic network-level mechanisms by which aberrations in this system can contribute to cognitive and affective dysfunction. Specifically, the characterization of the AI as a dynamic causal hub for initiating network switching has provided novel insights into mechanisms underlying deficits in cognitive

functioning in which (1) SN integrity and/or connectivity is compromised as in frontotemporal dementia or (2) stimulus/event saliency is (a) weakly mapped as in autism or (b) erroneously mapped as in addiction, anxiety, or pain (Figure 14). Signaling deficits can arise from aberrant filtering and mapping of salient stimulus cues into the SN and weak signaling mechanisms from the SN to other networks such as the lateral frontoparietal central executive network. These signaling mechanisms together with poor integrity of network nodes and their anatomical connectivity (e.g., the posterior cingulate cortex and medial temporal lobe nodes of the default-mode network in Alzheimer's disease or the ventromedial prefrontal cortex in depression) can compromise interactions between these core networks. Diminished outflow from the cingulate cortex results in psychomotor poverty and impoverished goal-directed action. Weak interactions along the anterior–posterior axis of the insular cortex contribute to altered introspective awareness and physiological monitoring of the internal milieu. The consequence of abnormalities at any of these levels is deficient, context-dependent engagement and disengagement of cognitive systems important for attending to salient external stimuli or internal mental events.



**Figure 14** Saliency network-based model of major psychopathology. Aberrant intrinsic organization and interconnectivity of the salience network (SN), central executive network (CEN), and default-mode network (DMN) are characteristic of many psychiatric and neurological disorders. The model proposes that weak salience detection and mapping of goal-relevant external stimuli and internal mental events from, and into, the SN play a major role in psychopathology. Weak mapping from the insular–cingulate SN gives rise to aberrant engagement of the frontoparietal CEN, compromising cognition and goal-relevant adaptive behavior. Aberrant DMN organization and weak engagement or disengagement of the DMN by salient events are associated with altered self-referential mental activity (e.g., excessive rumination in patients with depression). Weak salience mapping can arise from at least three input factors: (i) aberrant stimulus mapping, such as weak or enhanced cue signaling and novelty detection; (ii) aberrant limbic reward and motivational signals; and (iii) aberrant self-referential mental processes representing internal value and autobiographical memory. Key nodes of the SN: AI and ACC; key nodes of the CEN: dLPFC and the PPC; key nodes of the DMN: vmPFC and PCC. Adapted from Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15, 483–506.

## Conclusions

The SN is situated at the interface of the cognitive, homeostatic, motivational, and affective systems of the human brain. It plays a crucial role in identifying the most biologically and cognitive relevant endogenous and external stimuli in order to adaptively guide behavior (Beissner, Meissner, Bar, & Napadow, 2013; Lovero, Simmons, Aron, & Paulus, 2009; Menon & Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008). With the AI as its dynamic hub, the SN contributes to a variety of complex brain functions through the integration of sensory, emotional, and cognitive information. The mechanisms by which the SN contributes to cognitive and affective function can be summarized as follows:

1. Detection of salient events by the AI via differential sensory input and links with subcortical nodes involved in signaling reward, motivation, and affective saliency
2. Functional coupling of the AI with the dACC to facilitate rapid access to the motor system
3. Interaction of the AI with other insula subdivisions to mediate physiological reactivity to, and interoceptive awareness of, salient stimuli
4. Control signals to other large-scale networks that facilitate access to working memory resources
5. Switching between the lateral frontoparietal central executive network and the medial frontoparietal default-mode network to keep attention focused on task-relevant goals.

Together, these processes allow the SN to function collectively as a key brain system for integrating cognition, action, and feelings.

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**See also:** **INTRODUCTION TO ACQUISITION METHODS:** Functional MRI Dynamics; **INTRODUCTION TO ANATOMY AND PHYSIOLOGY:** Insular Cortex; **INTRODUCTION TO CLINICAL BRAIN MAPPING:** Frontotemporal Dementias; Functional Studies of Parkinson's Disease; The Anatomy of Parkinsonian Disorders; **INTRODUCTION TO COGNITIVE NEUROSCIENCE:** Attentional Capacity and Limitations; Response Inhibition; Reward Processing; Salience/Bottom-Up Attention; Task Switching Processes; Top-Down Suppression; **INTRODUCTION TO METHODS AND MODELING:** Resting-State Functional Connectivity; **INTRODUCTION TO SOCIAL COGNITIVE NEUROSCIENCE:** Empathy; Neural Correlates of Social Cognition Deficits in Autism Spectrum Disorders; **INTRODUCTION TO SYSTEMS:** Autonomic Control; Emotion; Hubs and Pathways; Large-Scale Functional Brain Organization; Neural Networks Underlying Novelty Processing.

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