

The background of the cover is a dark blue field filled with a complex, interconnected network of small, glowing orange and yellow nodes. These nodes are connected by thin, light-colored lines, creating a web-like structure that resembles a neural network or a data visualization. The pattern is dense and covers the entire surface of the book cover.

SALIENCE NETWORK OF THE HUMAN BRAIN

Lucina Q. Uddin



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Salience Network of the Human Brain

DEDICATION

For my parents

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CHAPTER 1

What Is Salience?

At any given moment, our senses are bombarded with information from a variety of sources. We know that flashing lights and sirens signal emergencies, that the presence of dangerous predators can keep us vigilant, and emotional memories might arise at the slightest provocation. Our brains must continuously parse this abundance of information to allow us to successfully navigate the environment. In order to do this, our nervous system must somehow determine what is critical to direct attention to, and what can safely be ignored. Things that are more salient naturally attract more attention. But what exactly do we mean by “salience”?

When we use the term “salience” in daily life, we often mean to convey the Merriam-Webster dictionary definition of the term: “the quality or state of being salient,” where salient is “very important or noticeable.” Objects, ideas, or events that are “very important or noticeable” have a privileged status in that they attract significant attention and can occupy a disproportionate amount of space in our imaginations. The term salience has been used in multiple domains of psychology and neuroscience to convey this concept of importance and noticeability.

In perception research, and specifically in studies of the visual system, the term salience is typically used to describe aspects of an item that make it stand out relative to its neighbors. For example, the well-known “pop out” effect during visual search (Treisman, 1998) describes the phenomenon that it is easier to identify a target that differs from distractors on one feature than on several features. Certain stimuli are salient by virtue of ease of discrimination from the surroundings (Fig. 1). This type of automatic and effortless salience detection enables rapid direction of visual attention.

The concept of a “saliency map” (Koch & Ullman, 1985), derived from empirical work in visual search, is the idea that a two-dimensional map encodes the saliency of objects in the visual environment.

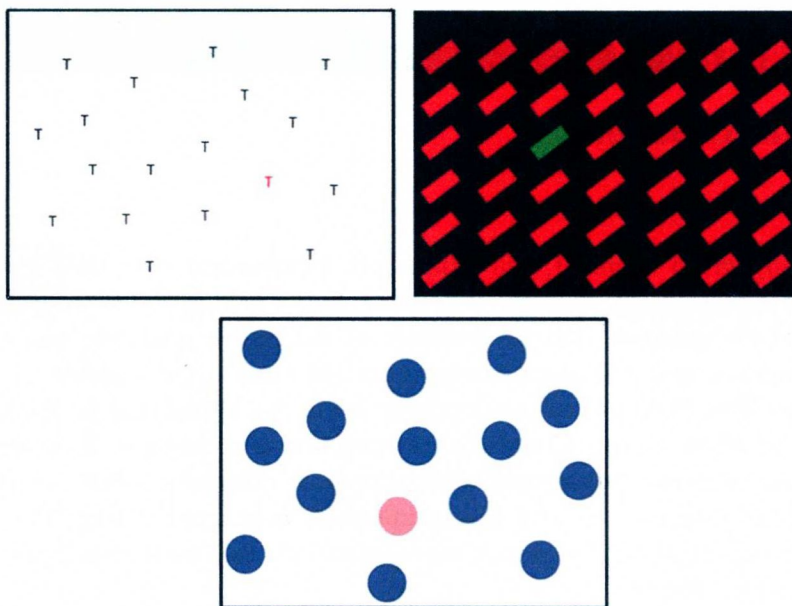


Figure 1 Saliency in visual search. Some stimuli are salient by virtue of the “pop out” effect (Treisman, 1998). It is easier to identify a target that differs from distractors on one feature (e.g., color) than on several features. Certain stimuli—the red T, the green bar, and the pink circle—are salient by virtue of ease of discrimination from their surroundings.

Computational models of this process are based on the idea that early visual features such as color and intensity are computed based on retinal input and activity from these feature maps is combined at each location, giving rise to a topographic saliency map. The “winner-take-all” system subsequently detects the most salient location and directs attention toward it (Itti & Koch, 2000). This type of model is limited to the bottom-up, stimulus-driven control of attention. However, contextual factors and previous experience can also contribute to perceptions of what is salient.

Most theories of saliency detection and attention adopt a two-component framework incorporating both bottom-up processes such as the ones just described, as well as top-down contextual influences (Itti & Koch, 2001). In an influential model of attention, Corbetta and colleagues describe two partially segregated networks: a ventral-attention network responding to external environmental stimuli, and a dorsal-attention network responsible for goal-directed, top-down processing (Corbetta & Shulman, 2002). Chapters 2 and 3, Anatomy of

the Saliency Network and Functions of the Saliency Network, will further elaborate on the anatomy and function of these networks as they relate to saliency processing.

In areas outside of vision research and computational modeling of attention, saliency is often described using a different emphasis, namely that of personal relevance. In such cases, stimuli and/or events that are meaningful or emotionally provocative are termed as salient. This conceptualization of saliency as a relatively high-level cognitive process can be seen, e.g., in the literature on emotional learning (Dunsmoor, Murty, Davachi, & Phelps, 2015). In the area of memory research, saliency is thought to influence the likelihood that an event or object will be remembered; objects can be salient because of their meaning or semantic relationship with other objects. Some have proposed that perceptual- (based on low-level sensory features) and semantics-related (based on prior knowledge) saliency affect encoding and memory representation in different ways, acting through dorsal and ventral neural systems, respectively (Santangelo, 2015).

In the addiction literature, the term incentive saliency or motivational saliency refers to the “wanting” that accompanies most addictions, and is thought to be modulated by dopamine (Tibboel, De Houwer, & Van Bockstaele, 2015). As with the definitions of saliency we have discussed, the term saliency again highlights the property of standing out or being attention-grabbing, in this case to the point of pathology.

As we will review throughout the next several chapters, the concept of saliency is ubiquitous in psychology and neuroscience; thus a great deal of research has been devoted to understanding the mechanisms by which saliency detection occurs in the brain and the anatomical structures that support it.

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CHAPTER 2

Anatomy of the Salience Network

The view that the brain functions as a vast, interconnected network currently dominates the cognitive neuroscience landscape (Pessoa, 2014). The older idea that the brain comprises discrete “modules” for performance of specific functions has given way to more recent models that emphasize dynamics, connectivity, and large-scale brain networks underlying cognition (Barrett & Satpute, 2013; Bressler & Menon, 2010). Resting state functional magnetic resonance imaging (rsfMRI), first used by Biswal and colleagues to examine functional connectivity within the motor system in the absence of task performance (Biswal, Yetkin, Haughton, & Hyde, 1995), has emerged as a powerful tool for discovering the intrinsic architecture and network structure of the human brain.

Brain areas that exhibit strong functional connectivity (e.g., temporal correlations in signal) (Friston, 1994) are thought to form large-scale brain networks that are reproducible across individuals (Damoiseaux et al., 2006) and relatively stable (Shehzad et al., 2009). The most well studied of these brain networks is the default mode network (Greicius, Krasnow, Reiss, & Menon, 2003), first noted for its high metabolic activity during baseline resting states (Raichle et al., 2001) and subsequently linked with prospective memory (Buckner & Carroll, 2007), self-related, and social cognitive processes (Uddin, Iacoboni, Lange, & Keenan, 2007). Large-scale brain networks corresponding to attention (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006) and numerous other cognitive processes have also been identified using rsfMRI. These networks bear strong resemblance to those actively engaged during a variety of cognitive paradigms (Smith et al., 2009).

In the context of modern functional neuroimaging, the first use of the term “salience network” in the literature can be traced to a seminal paper by Seeley and colleagues, in which the now widely used nomenclature of “intrinsic connectivity networks” (ICNs) was also introduced. Using both

region-of-interest (ROI) and independent-component analysis, Seeley and colleagues demonstrated the existence of an ICN including frontoinsula (FIC)/anterior insular (AI) cortices, dorsal anterior cingulate cortex (dACC), dorsomedial thalamus, hypothalamus, periaqueductal gray, sub-lenticular extended amygdala, substantia nigra/ventral tegmental area, and temporal pole (Seeley et al., 2007). Prior to this work, the term “salience network” did not appear in descriptions of human neuroimaging studies examining the neural basis of salience processing, although networks with some overlapping nodes had been previously described.

Subsequent studies delineated the anatomy of the salience network in greater detail. As reviewed in Seeley et al. (2012) and Uddin (2015), salience network communication with subcortical regions enables integration of interoceptive and visceromotor signals, which can be used to guide behavior. Ascending inputs from visceromotor sensors are integrated in the FIC within the salience network. Interoceptive signals travel via the vagus nerve, through autonomic afferent nuclei and the thalamus, and via the dorsal posterior insular cortex and mid-insula (midINS) to the FIC. The cortical nodes of the salience network integrate these ascending signals to coordinate other large-scale networks in the cortex. The salience network also sends information to visceromotor central pattern generators, which send signals to autonomic efferent nuclei such as the nucleus of the solitary tract and the dorsal motor nucleus of the vagus nerve. These signals then travel to the intermediolateral cell column of the spinal cord, which drives visceromotor responses to salient stimuli (Fig. 2).

The anatomy of the insular cortex is of particular importance in enabling salience network function. Located deep within the lateral sulcus of the brain, the insula has traditionally been described as paralimbic or limbic integration cortex (Augustine, 1996). Structural connections delineated in the macaque suggest that the insula communicates with amygdala, orbitofrontal cortex, olfactory cortex, anterior cingulate cortex (ACC), and superior temporal sulcus (Mufson & Mesulam, 1982), thus positioning it at the crossroads of affective, homeostatic, and cognitive systems in the brain.

The ACC comprises subareas with distinct anatomical and functional properties. The observation that dense interconnections exist between the ACC and motor cortices, lateral prefrontal regions, and thalamic and brainstem nuclei led to the suggestion that the region

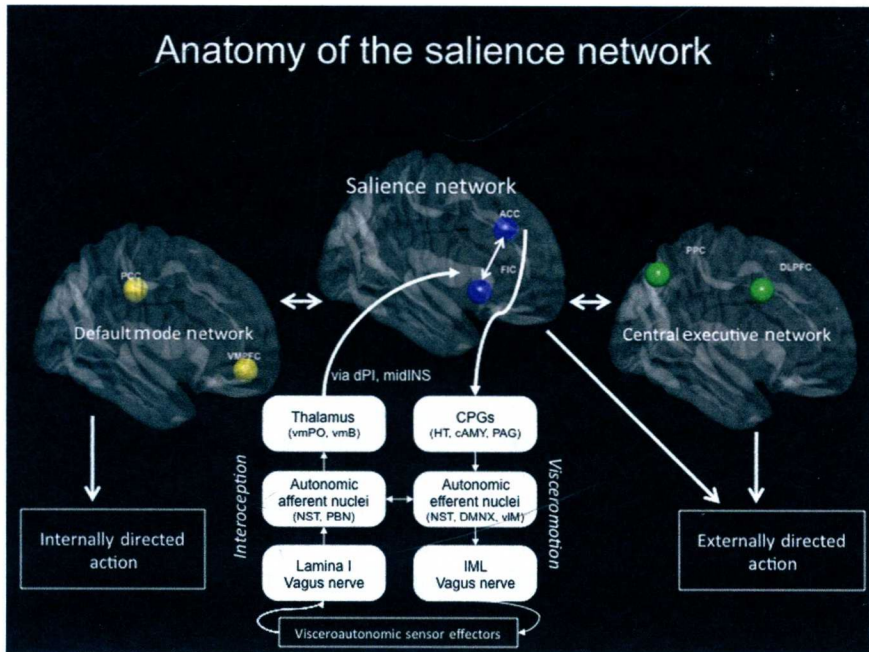


Figure 2 Anatomy of the salience network. Ascending inputs communicating information about the condition of the body are integrated in the frontoinsula cortices (FIC) within the salience network. Interoceptive signals travel through the vagus nerve through autonomic afferent nuclei (NST, nucleus of the solitary tract; PBN, parabrachial nucleus) and the thalamus (vmPO, ventromedial nucleus of the thalamus, posterior; vmB, ventromedial nucleus of the thalamus, basal) onto the FIC via dorsal posterior insula (dPI) and mid-insula (midINS). The salience network communicates with visceromotor central pattern generators (CPGs: HT, hypothalamus; cAMY, central nucleus of the amygdala; PAG, periaqueductal gray) that convey signals to autonomic efferent nuclei (NST: DMNX, dorsal motor nucleus of the vagus nerve) and the vagus nerve (IML, intermediolateral cell column). Salient signals are integrated in the anterior insular cortices. Signals from the anterior insula causally influence the default mode network (DMN, yellow; key nodes in PCC, posterior cingulate cortex; VMPFC, ventromedial prefrontal cortex) and central executive network (CEN, green; key nodes in PPC, posterior parietal cortex; DLPFC, dorsolateral prefrontal cortex). These pathways for communication between the insula and brain regions for interoception and visceromotion allow integration of salient signals to guide behavior (Uddin, 2015).

may serve an integrative function to translate intentions to actions (Paus, Castro-Alamancos, & Petrides, 2001). The dACC is considered to be a major cortical node of the salience network. Based on structural connectivity-based parcellation, the dACC can be subdivided into three distinct regions (Beckmann, Johansen-Berg, & Rushworth, 2009). As functional connectivity studies demonstrate strong connections between anterior insula and anterior and posterior mid-cingulate cortex (Taylor, Seminowicz, & Davis, 2009), the most likely ACC subdivision to participate in the salience network is one that is centered midway along the cingulate gyrus.

An interesting structural feature of a salience network is that its two prominent cortical nodes, the AI and ACC, contain a special type of neuron not found in any other cortical region. Spindle cells, or Von Economo neurons (VENs), are large cells with distinct morphology (Seeley et al., 2012) that have only been found to exist in the brains of humans (Nimchinsky et al., 1999), great apes, and a select few other species (Butti, Sherwood, Hakeem, Allman, & Hof, 2009). The fact that VENs appear to be unique, from both phylogenetic and ontogenetic standpoints, has led to some interesting speculation regarding their function. For example, it has been posited that the function of these cells is to relay outputs of the AI and ACC to association cortices to aid rapid intuitive assessments of complex situations, as is necessary during social cognitive processes (Allman, Watson, Tetreault, & Hakeem, 2005).

As network neuroscience is a rapidly evolving field, we have yet to reach consensus on questions such as: How many brain networks are there? How stable and reproducible are brain networks? How do brain networks interact? and How do they change over the course of development? One of the key nodes of the salience network, the AI, appears to also participate in networks that go by other names. For example, a cinguloopercular network comprising the AI, anterior prefrontal cortex, dorsal ACC, and thalamus has been posited to perform set-maintenance activities to maintain control in the service of task goals (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Clearly the salience and cinguloopercular networks overlap anatomically, and it has not yet been resolved whether they constitute separate or entities or are merely different descriptions of the same network. The AI also participates in the ventral attention network comprising this region along with the right temporoparietal junction, middle frontal gyrus, and ventral frontal cortex. The ventral attention network is thought to mediate stimulus-driven control of attention, detecting salient environmental events and reorienting (Corbetta, Patel, & Shulman, 2008). Again, the ventral attention network appears to overlap to some degree both anatomically and functionally with the salience network. However, the ventral attention network is right lateralized, whereas the salience network is bilateral. An important direction for future research will be to characterize the extent to which each of the networks discussed here represent unique entities. This will have implications for understanding their relative functional independence and potential interactions among them.