Progressions

The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands

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The term "salience network" refers to a suite of brain regions whose cortical hubs are the anterior cingulate and ventral anterior insular (i.e., frontoinsular) cortices. This network, which also includes nodes in the amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei, coactivates in response to diverse experimental tasks and conditions, suggesting a domain-general function. In the 12 years since its initial description, the salience network has been extensively studied, using diverse methods, concepts, and mammalian species, including healthy and diseased humans across the lifespan. Despite this large and growing body of research, the essential functions of the salience network remain uncertain. In this paper, which makes no attempt to comprehensively review this literature, I describe the circumstances surrounding the initial discovery, conceptualization, and naming of the salience network, highlighting aspects that may be unfamiliar to many readers. I then discuss some of the key advances provided by subsequent research and conclude by posing a few of the questions that remain to be explored.

In 2003, when my University of California, San Francisco (UCSF) behavioral neurology fellowship began, the human brain mapping community was just beginning to recognize that regional low-frequency BOLD signal fluctuations were correlated, within functional-anatomical systems, even while subjects lay quietly awake in the MRI scanner (Biswal et al., 1995; Greicius et al., 2003). To some, this seemed like nonsense (most likely "noise"), to others it was magic (something closer to voodoo), and to still others it was a revelation. To me, a neurologist and aspiring neuroanatomist, the results were breathtaking. Here was an opportunity to study large-scale brain networks and bridge the gap from axonal tracer studies, performed in nonhuman primates, to humans. The potential of the advance was clear, but I needed some convincing about the methods. I learned what I could and sought guidance from another early-career behavioral neurologist, Michael Greicius, who, with Vinod Menon and his team at Stanford, had just published the seminal paper identifying the "default mode network" (DMN) using "resting state fMRI" (Greicius et al., 2003). For Greicius, whose foresight was remarkable, the motivation to study the DMN arose, at least in part, from a clinical interest in Alzheimer's disease (AD), which targets many of the structures that compose the DMN.

I too had a specific agenda. My clinical training had exposed me to patients with a little-known disorder called frontotemporal dementia (FTD), which would become my major research interest. My mentor, Bruce Miller, was one of the few American neurologists who had been writing about FTD over the preceding decade. Patients with the behavioral variant (bvFTD) were known to slowly lose specialized social-emotional capacities, such as grace, tact, drive, and empathy, but new research had begun to suggest additional deficits in nociceptive and autonomic processing (Snowden et al., 2001). Fascinated by this phenomenology, I wondered whether there might be a unifying functional deficit that could help to explain the syndrome's diverse manifestations. Coworkers at UCSF had just revealed, using voxel-based morphometry, that bvFTD was associated with prominent atrophy in the ACC and anterior insular cortex (aINS) (Rosen et al., 2002). Their observations led me to read across a range of unfamiliar fields. I learned that the ACC and aINS contain subregions featuring cytoarchitecturally related agranular cortices (lacking a visible layer 4) that provide a transition from peri-allocortex to pro-isocortex (Mesulam and Mufson, 1982a; Ongür et al., 2003; Heimer and Van Hoesen, 2006). In rodents and monkeys, homologous regions are interconnected with limbic, subcortical, and brainstem sites involved in autonomic processing and emotion (Carmichael and Price, 1996; Saper, 2002). Task-based fMRI studies from the preceding ~5 years had shown, collectively, that ACC and aINS coactivate in the context of diverse tasks and conditions, ranging from those designed to induce thirst, hunger, pain, bladder distention, embarrassment, and uncertainty to those eliciting amusement, compassion, tenderness, and humor (Craig, 2002; Critchley, 2005). Many authors in their respective fields had begun to write about the ACC and aINS as key hubs of a [fill-in-the-blank] network, where the blank could be filled by almost anything a human might care about. Other authors, particularly those from a more anatomical tradition, were beginning to write about the ACC and aINS as domain-general regions that participate in emotion, autonomic functions, or self-awareness (Craig, 2002; Saper, 2002; Critchley, 2005; Heimer and Van Hoesen, 2006).

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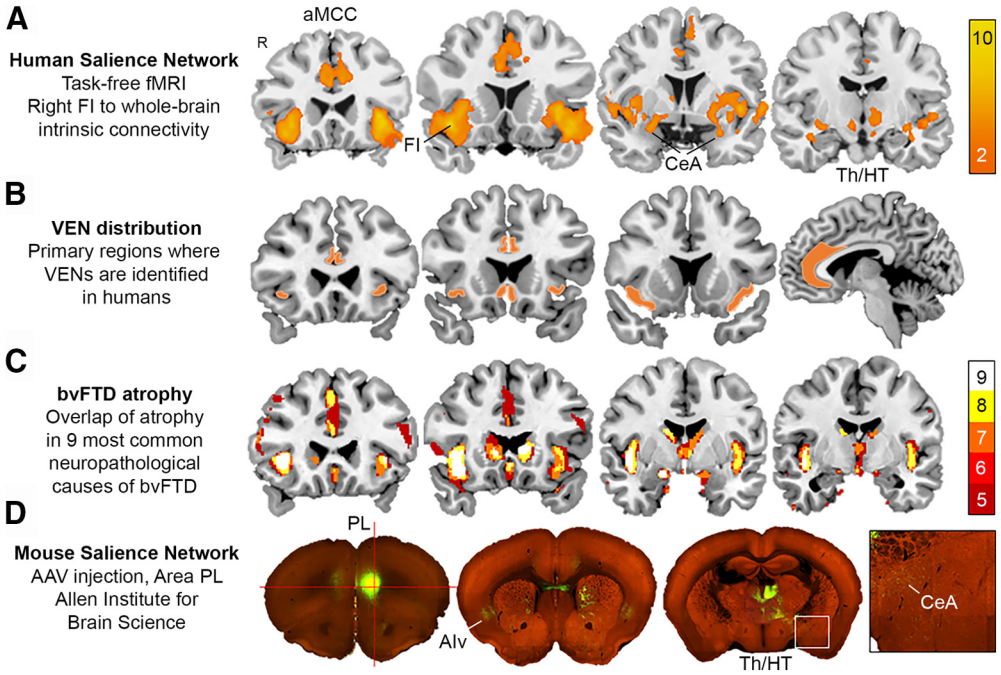

Figure 1. The human salience network (***A***), topography of the VENs (***B***), and the atrophy pattern in bvFTD (***C***) strongly overlap. ***D***, A homologous network is elicited by injecting adeno-associated virus (AAV) into mouse prelimbic area (area PL), which produces layer 5 labeling in area ventral anterior insula area (AIv), as well as in the ventral striatum, dorsomedial thalamus (TH), hypothalamus (HT), and central amygdala (CeA). ***A***, Map adapted with permission from Seeley et al. (2007b). ***B***, Map is rendered by the author. ***C***, Map adapted with permission from Perry et al. (2017). ***D***, Map assembled using the Allen Mouse Brain Connectivity Atlas.

Patients with bvFTD have limited insight into their deficits, but their family members taught me that bvFTD-related "personality change" takes many forms. Work and household duties lapse or require constant encouragement. Patients show little interest in their spouse's feelings, even if the spouse has been injured or diagnosed with a serious illness. Social boundaries and conventions lose their influence on behavior, resulting in myriad transgressions. Patients may become difficult to embarrass, humorless, and insensitive to satiety, eating as long as food is present. In later stages, even immediate-impact stressors, such as thirst, ambient temperature extremes, or ongoing tissue damage, elicit muted or absent responses. Together, the stories I heard evoked a patient whose usual cares, including their own social errors, could elicit neither an internal sense of concern nor the usual corrective actions. In essence, nothing important mattered anymore, yet both restraint (the brakes) and drive (the gas pedal) were broken. Why? What lesion could explain this deficit?

The next step along the path was the least expected. In 2004, I attended a lecture by John Allman, an evolutionary biologist who was visiting UCSF. He presented recent work on a curious population of large layer 5 projection neurons, called von Economo neurons (VENs), which, he proposed, had become specialized to support social functioning (Allman et al., 2001). What captured my attention, however, was the topographic distribution of these cells: virtually all of them, Allman explained, were concentrated in the domes of the ACC (agranular subareas 24a and b) and ventral (agranular) aINS, also known (and henceforward referred to) as the frontoinsular cortex (Fig. 1*B*) (von Economo, 1926; Nimchinsky et al., 1995). On the day of Allman's lecture, three related hypotheses began to take shape. First, I imagined that bvFTD might begin in the VENs, whose specialized nature might somehow confer vulnerability to disease. Second, I wondered whether the VENs and their home regions might anchor a large-scale network that could (now) be mapped in living humans (with "resting-state fMRI"). Third, I hypothesized that degeneration of this VEN-related network might drive the core symptoms seen in bvFTD.

Within days of Allman's lecture, he and I were on airplanes bound for Washington, DC, where we would spend a week exploring the idea that bvFTD might target the VENs. The Yakovlev-Halleem Collection, an extraordinary archive of whole-mounted human brain sections capturing a broad range of diseases, contained a few patients with FTD (diagnosed decades earlier as "Pick's disease"). We spent the week poring over the materials, trying to find what few VENs may have remained in those FTD sections, mostly without success (Seeley et al., 2007a). I returned to California, energized, and asked Greicius: what would happen if we mapped the regions whose BOLD signals correlate with those of the (VEN-rich) frontoinsular cortex? We designed a study in healthy young adults, the results came in, and the "salience network" was born (Fig. 1*A*) (Seeley et al., 2007b). Born with it, a sort of fraternal twin, was a more familiar "executive-control network," a lateral frontoparietal system made up of regions known to support working memory, executive function, and cognitive control processes. The strength of these networks, we showed, could be linked to emotional and cognitive data obtained outside the scanner. The salience network showed stronger intranetwork regional BOLD correlations in subjects with high prescan anxiety (but had no relationship to executive functioning). Executive-control network regions showed tighter coupling in patients with better executive task performance (but no relationship to anxiety). This double dissociation raised the possibility that networks measured in this way might have a significant "trait component." The final manuscript made only passing reference to bvFTD and VENs despite the outsized roles they played in motivating the study. It was a systems neuroscience experiment performed with a clinical goal in mind. It also convinced me, Greicius, and others that these so-called resting-state networks contained important neurobio-

logical information. Likewise, the presence of a human, VEN-enriched network intensified my interest in whether VENs were targeted in bvFTD, a hunch that has been confirmed (Seeley et al., 2006; Kim et al., 2012; Nana et al., 2019) and replicated by other laboratories (Santillo et al., 2013; Santillo and Englund, 2014; Yang et al., 2017). Subsequent work also confirmed the consistency of salience network involvement across the diverse neuropathological causes of bvFTD (Fig. 1*C*) (Perry et al., 2017).

A brief aside on terms. At the time of the paper, we named the salience network based on our impressions of what the ACC, aINS, and their interacting partners might collectively do. The concept then, as it remains for me now, was that the frontoinsula was a major afferent cortical hub for perceiving viscero-autonomic feedback, whereas the ACC was the efferent hub responsible for generating relevant visceral, autonomic, behavioral, and cognitive responses. Through interactions with each other, these regions could form a sort of information processing loop for representing and responding to homeostatically relevant internal or external stimuli and imbuing these stimuli with emotional weight. These ideas represented a synthesis of many related prior notions put forth by thought leaders in the field (Mesulam and Mufson, 1982b; Craig, 2002, 2003; Saper, 2002; Critchley, 2005; Heimer and Van Hoesen, 2006). We chose "salience" as a substitute for "homeostatic relevance" because "homeostatic relevance network" seemed a bit of a mouthful and salience captured the essence of the concept. Other terms introduced in the paper (in addition to the name of the fraternal twin) included "intrinsic connectivity network," as an alternative to "resting state network," and "task-free fMRI," as an alternative to "resting-state fMRI." Our hope was to push the field away from the idea that mental inactivity (i.e., "rest") was the key to identifying networks in this way.

The salience network paper was published shortly after Nico Dosenbach, Steve Petersen, and their colleagues had identified a topographically similar pattern of brain regions using a different approach (Dosenbach et al., 2006). These regions, which make up a more dorsal and opercular frontal and anterior parietal pattern that nonetheless includes the anterior mid-cingulate and aINS cortices, were identified based on their activation during specific phases of 10 diverse task-based fMRI studies. For years, many researchers understood their work and ours to be describing the same system. Slowly, the distinction between the two networks became clearer (Power et al., 2011; Touroutoglou et al., 2012; Nomi et al., 2016). The network identified by Dosenbach et al. (2006), now often referred to as the "cingulo-opercular task-control network," is anchored by the dorsal aINS (a nearly VEN-free aINS subregion) and the adjacent frontal operculum and appears critical for task set initiation and maintenance, perhaps by providing the sustained vigilance or "tonic alertness" (Sadaghiani et al., 2010) required to enter and stay in a behavioral or cognitive set. In contrast, the nearby salience network is anchored by the more ventral frontoinsula (where VENs are abundantly found), and represents, in my way of thinking, the homeostatic system whose job is, in part, to engage the task-control network so it can (1) maintain the most relevant task set for as long as the salient stimulus complex remains or (2) orchestrate switching to a new task set (and relevant network configuration) in response to shifts in the salience landscape (Menon and Uddin, 2010). Looking back at the Dosenbach et al. (2006) study, one can already see the importance of the frontoinsula in salience processing; across their several analyses, the frontoinsula appears only in the map derived from behavioral errors, one major form of salience that the network must represent to support the guidance and tuning of behavior.

What has research performed since 2007 taught us about the salience network, its functions, and the consequences of its dysfunction? The volume of relevant studies is overwhelming, so I have selected a few favorites, each representing a different method. An important meta-analysis, performed in 2013, showed that the ACC and aINS respond to salience independent of value (Bartra et al., 2013). This observation, made by aggregating fMRI data from >206 studies, confirmed a key premise of the salience network concept: that the network should respond to homeostatically relevant stimuli and outcomes whether their valence is negative (penalizing) or positive (reinforcing). Another key question concerns whether the network operates under substantial influence of major ascending neuromodulatory systems. Of these, the most natural allies are the following: (1) the noradrenergic system, anchored by the locus ceruleus and thought to increase signal-to-noise within cortical networks in response to salience; and (2) the mesocorticolimbic dopamine system, anchored by the ventral tegmental area and thought to provide signals related to error, reward, and novelty. Regarding the noradrenergic system, one inventive study exposed healthy subjects to an emotion-eliciting video clip (of a violent bar brawl) after treatment with propranolol (a beta-adrenergic receptor blocker) or placebo (Hermans et al., 2011). They found that beta-receptor blockade significantly attenuated the salience network synchrony normally induced by the film. Regarding the dopamine system, a recent experiment evaluated large-scale network connectivity after dopamine depletion via acute phenylalanine and tyrosine depletion (Shafiei et al., 2019), which produced a conspicuous reduction in connectivity between the salience network and other parts of the brain. Optogenetic experiments in mice suggest that dopaminergic neurons in the dorsal raphe nucleus may also play a role in behavioral responses to salience (Cho et al., 2017). Related studies of salience network function have focused on the network's proposed role in awareness and even consciousness. For example, one study identified a dorsal pontine region commonly injured across a broad sample of neurological lesion patients who presented with coma (i.e., disruptions in conscious wakefulness) (Fischer et al., 2016). They went on to show that this region, near the locus ceruleus and adjacent medial parabrachial nucleus (both key nodes for autonomic integration), featured the ACC and frontoinsula as its major cortical functional connections. Many groups, including ours, have highlighted the role of the salience network in autonomic processing (Critchley et al., 2011; Beissner et al., 2013; Guo et al., 2016; Sturm et al., 2018), but it has proved challenging to disentangle representations related to homeostatic salience from those that drive autonomic responses to that salience. Indeed, in a remarkable study of awake, behaving patients with epilepsy who underwent presurgical monitoring and electrophysiological mapping, direct stimulation of the ACC elicited not only an internal sense of a looming challenge but also heart rate acceleration and, perhaps most strikingly, the will to act and persevere in response to the perceived challenge (Parvizi et al., 2013). Overall, the studies reviewed here support the idea that the salience network hubs, whatever else they may be doing, are intimate partners for conscious integration of autonomic feedback and responses with internal goals and environmental demands.

One could argue that no ecological niche places more demands on the salience network, as conceived here, than a complex social environment. In the thick of social living, short- and long-term goals and actions compete against a backdrop of *N*

dynamic, interacting, multidimensional agents (i.e., *N* other humans), where *N* ranges from 1 to 100s or even 1000s now (through social media) in a given moment. Add the need to integrate learned social rules, hierarchies, and contingencies, and you have a daunting challenge for any system. In this light, it has been intriguing that the most convincing clinical examples of salience network dysfunction are disorders of social-emotional function. bvFTD is perhaps the best-documented example, but schizophrenia, bipolar disorder, major depression, attention-deficit/hyperactivity, anxiety states, autism spectrum, and substance abuse disorders have now all been linked to volume loss or altered connectivity in salience network regions (Goodkind et al., 2015; Sha et al., 2019). These findings add support to the notion that salience network hubs play a domain-general function that can somehow be disrupted to produce diverse clinical manifestations. The specific manifestations may depend on the following: (1) the micro-anatomical targets (neuron types and circuit elements), (2) physiological details (affected channels or modulatory neurotransmitters), or (3) the other brain areas involved. Conversely, some neuropsychiatric diseases, most notably AD and Williams' syndrome, appear to involve a gain of social-emotional sensitivity that relates to intensification of salience network connectivity, structure, or function (Zhou et al., 2010; Jabbi et al., 2012; Zhou and Seeley, 2014). Clearly, there is more to learn about the healthy salience network by studying the salience network-opathies and other disorders in which the salience network is perturbed, even when another network remains the primary locus of dysfunction.

After Greicius and his colleagues published the 2003 DMN paper (Greicius et al., 2003), they and now many others went on to show that Alzheimer-type dementia is indeed associated with DMN-localized atrophy, hypometabolism, and disrupted intrinsic connectivity (Greicius et al., 2004; Buckner et al., 2005). Following suit, we showed similar findings for bvFTD and the salience network (Zhou et al., 2010). By around that time, it seemed most parsimonious to think that the pairing of a neurodegenerative syndrome to a large-scale network would not be limited to AD and bvFTD. In the behavioral neurology clinic at UCSF, we routinely see patients with a diversity of clinical syndromes, including AD-type dementia and bvFTD, but also other FTD syndromes that affect language or movement. In a series of subsequent studies, we showed that each of these syndromes is associated with atrophy that mirrors a specific large-scale network, with associated connectivity disruption (Seeley et al., 2009; Gardner et al., 2013; Guo et al., 2013). Later work revealed that a region's connectivity to a likely region-of-onset, or "epicenter," was a strong predictor of that region's vulnerability to disease, suggesting that trans-synaptic spreading may account, at least in part, for the network-based atrophy observed (Zhou et al., 2012). Ongoing research continues to advance this frontier (Iturria-Medina et al., 2014; Raj et al., 2015; Torok et al., 2018; Brown et al., 2019).

Where should salience network research go from here? Fundamental questions remain about what core domain-general function or functions the salience network performs. Sorting through these questions may require human neuroscience techniques that afford millisecond temporal resolution in combination with more sophisticated behavioral paradigms and continuous multichannel recordings of autonomic and other emotion-relevant data (facial expression, vocalization, etc.). Framed by this knowledge, modern circuit dissection tools could be used to tease apart some of the network's most basic functions, leaning on the overall conservation of the salience network in laboratory mammals (Fig. 1*D*) and the opportunities for causal manipulation and microscale *in vivo* resolution. The knowledge gained from these convergent approaches may facilitate differentiation of salience network-related clinical disorders based on their distinct pathophysiological profiles and mechanisms. This deeper understanding may, in turn, lead to a more precise understanding of the microanatomy and neurochemistry of these disorders. Now, with the advent of single-cell sequencing approaches, researchers can begin to explore disease-specific links between salience network deficits and changes in the number, states, or functioning of specific human neuronal and glial cell types. The road ahead promises to teach us a great deal about ourselves and how our brains handle the moments that matter most in our lives. More importantly, we can hope to learn enough to help those who lack or lose this fundamental human capacity.

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