Current Behavioral Neuroscience Reports (2020) 7:203–211
https://doi.org/10.1007/s40473-020-00224-3

SOCIAL COGNITION (J BEADLE, SECTION EDITOR)

Brain Networks Supporting Social Cognition in Dementia

Katherine P. Rankin [1,2]

Accepted: 27 October 2020 / Published online: 11 November 2020
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Abstract

Purpose of Review This review examines the literature during the past 5 years (2015–2020) as it describes the contribution of three key intrinsically connected networks (ICN) to the social cognition changes that occur in various dementia syndromes.

Recent Findings The salience network (SN) is selectively vulnerable in behavioral variant frontotemporal dementia (bvFTD), and underpins changes in socioemotional sensitivity, attention, and engagement, with specific symptoms resulting from altered connectivity with the insula, amygdala, and medial pulvinar of the thalamus. Personalized hedonic evaluations of social and emotional experiences and concepts are made via the anterior temporofrontal semantic appraisal network (SAN), selectively vulnerable in semantic variant primary progressive aphasia (svPPA). Recent research supports this network's role in engendering empathic accuracy by providing precision to socioemotional concepts via hedonic tuning. The default mode network (DMN), focally affected in Alzheimer's disease syndrome (AD), supports social cognition by providing context from learned experiences to generate more accurate inferences about others' thoughts, emotions, and intentions.

Summary The focal breakdown of these normal canonical intrinsically connected brain networks during neurodegeneration sheds light on disease processes as well as on important mechanisms involved in healthy socioemotional functioning, thus contributing important insights to the larger field of social affective neuroscience.

Keywords Social cognition · Emotion · Frontotemporal dementia · Alzheimer's disease · Semantic variant primary progressive aphasia · Brain networks · Functional connectivity

Introduction

It has been over 10 years since the breakthrough discovery that the major neurodegenerative dementia syndromes each result from focal, selective vulnerability of the brain's intrinsically connected networks (ICNs) [1]. In the time since, clinical research investigations have increasingly moved from single-structure explanations for dementia patients' cognitive and behavioral changes to a more holistic network-based view. This shift in interpretive approach has been particularly fruitful as the field develops a richer understanding of the neural etiologies of socioemotional symptoms in neurodegenerative disease. A key example has been the recognition that the focal degeneration of the previously understudied "salience network" (SN) ICN [2] is the primary driver of the drastic socioemotional impairments seen in behavioral variant frontotemporal dementia [3–6]. The breakdown of these normally occurring brain networks during disease sheds light on important mechanisms supporting healthy socioemotional functioning, and thus contributes to the larger field of social affective neuroscience.

This review examines the literature during the past 5 years (2015–2020) as it describes the contribution of three key ICNs to the social cognition changes that occur in various dementia syndromes. While some of these papers do use functional brain imaging to directly examine these important brain-behavior relationships, the majority of studies in the dementia field continue to use atrophy-based models in which scores on behavior measures are correlated with regional brain volume, either on a voxel-wise or region-of-interest level. Though only an indirect relationship between these structural results and the functional ICNs can be presumed, these papers with important

This article is part of the Topical Collection on *Social Cognition*

✉ Katherine P. Rankin
kate.rankin@ucsf.edu

[1] Department of Neurology, University of California San Francisco, San Francisco, CA, USA

[2] The Memory and Aging Center, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94143, USA

findings related to regions of interest within the known distribution of the ICNs will still be reviewed. The normally occurring ICNs in the brain with the most explanatory relevance for social cognition in the neurodegenerative syndromes include the SN, involved in socioemotional sensitivity, attention, and engagement; the semantic appraisal network (SAN), which supports personalized hedonic evaluations of social and emotional experiences and concepts; and the default mode network (DMN), which provides context from learned experiences to generate more accurate inferences about others' thoughts, emotions, and intentions. For each network, its overarching function, specific relevance to social cognition, and findings related to the neurodegenerative disease syndromes will be discussed (Fig. 1).

The Salience Network: Socioemotional Attention and Engagement

One brain network that is central to understanding socioemotional deficits in dementia is the cinguloinsular or "salience" ICN. It was first identified in healthy individuals in 2007 [2] by dementia researchers who recognized that the hubs of this functional network overlap with the key foci of neurodegeneration in the behavioral variant frontotemporal dementia (bvFTD) syndrome [1]. Since then, it has become clear that SN degeneration is necessary and sufficient to engender the core socioemotional symptoms of bvFTD [6, 7], which has raised important neuroscientific questions about how this network supports healthy social cognition.

The SN includes two key cortical hubs in the ventral anterior insula and the anterior cingulate (ACC), as well as a number of subcortical nodes including the dorsomedial thalamus, hypothalamus, amygdala, and periaqueductal gray (PAG) [2, 8]. A central function of the SN is to alert the individual to exogenous or endogenous stimuli that are personally salient, i.e., that have homeostatic relevance to safety, survival, or flourishing. Through the insula, the SN provides interoceptive awareness, including emotionally relevant signals such as visceral emotional experiences, hedonic reward evaluations, and negative reinforcers such as punishment cues. As a corollary to its importance for awareness, it is also involved in alertness and arousal, with growing evidence that the SN plays a role in modulating both the sympathetic and parasympathetic branches of the autonomic nervous system [9••]. When these core SN functions are considered in terms of social cognition, this network might best be understood to convey the capacity for socioemotional sensitivity, i.e., the capacity to spontaneously and appropriately alert to social signals, and social engagement, i.e., the ability to maintain social attention.

Using a functional connectivity magnetic resonance imaging (fcMRI) approach, Toller and colleagues [3••] showed that informant ratings of socioemotional sensitivity directly predicted the individual's mean intrinsic connectivity in the SN,

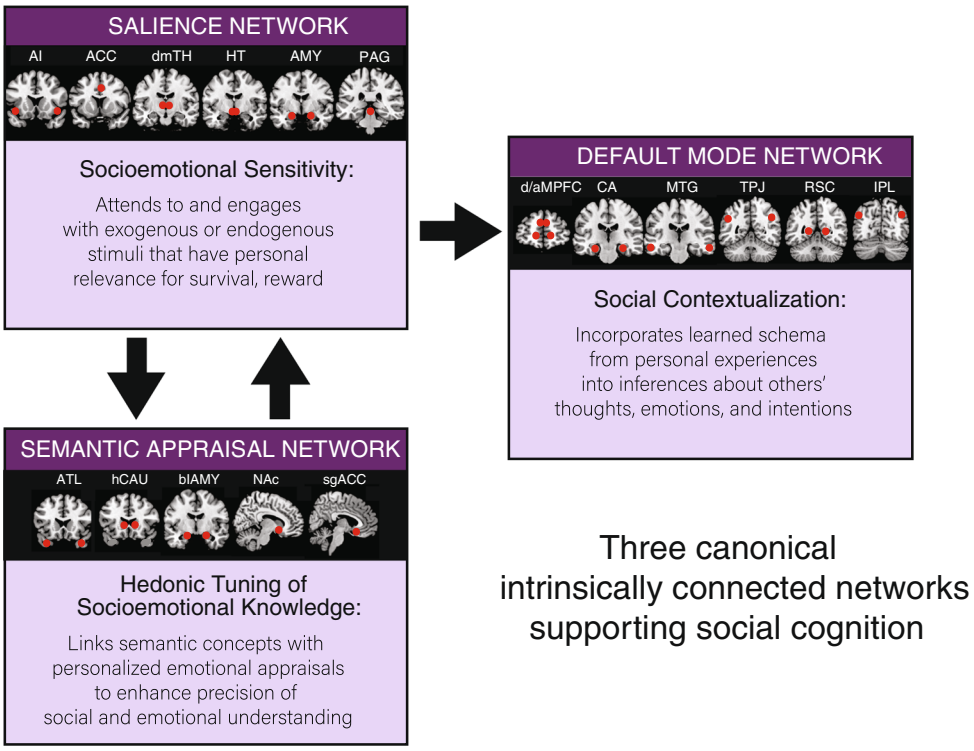

Fig. 1 The three primary intrinsically connected networks that support social cognition. Functional nodes, brain structures, socioemotional relevance, and inter-network information flow among the salience network, the semantic appraisal network, and the default mode network ICNs. AI anterior insula, ACC anterior cingulate cortex, dmTH dorsomedial thalamus, HT hypothalamus, AMY amygdala, PAG periaqueductal gray, ATL anterior temporal lobe, hCAU caudate head, blAMY basolateral amygdala, NAc nucleus accumbens, sgACC subgenual anterior cingulate cortex, d/aMPFC dorsal/anterior medial prefrontal cortex, CA hippocampus, MTG middle temporal gyrus, RSC retrosplenial cortex, IPL intraparietal lobule

both in neurologically healthy adults across the lifespan and in patients with neurodegenerative disease syndromes. A node pair connectivity analysis showed that this interpersonal sensitivity was mediated partly by connectivity in the cortical nodes of the SN, i.e., the right insula and ACC, and partly by the connectivity between the right insula and the subcortical nodes of the SN, including central pattern generators such as the periaqueductal gray PAG, right amygdala, and hypothalamus, as well as the right dorsomedial thalamus. This group later showed that these changes in socioemotional sensitivity in bvFTD patients over the disease course directly tracked with longitudinal volume loss in the right anterior insula node of the SN [10]. This corresponding loss of empathy and SN degeneration throughout medial frontal, insular, and thalamic regions in bvFTD has been found to correspond directly with the loss of large layer 5 projection cells, called Von Economo neurons (VENs), in the insula [4•]. VENs are located only in the SN (insula and ACC), and only humans and other highly gregarious animals including higher primates, elephants, and cetaceans have them. While their function is still being defined, VENs are generally understood to play an important role in the kinds of rapid neuronal communication required for social cognition, and are directly targeted in bvFTD.

Prosocial behaviors often occur as a result of spontaneous attentional engagement during a social interaction. One's level of social interest and responsiveness is observable to others in one's milieu, and is associated with personality traits such as agreeableness and interpersonal warmth. A recent study has shown that informant ratings of dementia patients' degree of warmth were directly predicted by functional connectivity in the SN [11•]. Importantly, SN connectivity was a stronger predictor of patients' loss of warmth than any structural brain changes, highlighting the additional precision gained by examining these brain-behavior relationships using functional network approaches rather than relying solely on atrophy-based structural models. Another key finding this study was that there was a wide divergence both between and within dementia syndrome groups in the degree to which SN connectivity, and interpersonal warmth, dropped from estimated premorbid levels. While bvFTD and semantic variant primary progressive aphasia (svPPA) patients were more likely than Alzheimer's (AD) or non-fluent variant PPA (nfvPPA) patients to show clinically significant drops in SN connectivity and warmth, only about a third of those patients showed drastic changes.

In the past 5 years, there have also been numerous structural brain-behavior studies with dementia patients that solidify this mechanistic link between SN function and level of spontaneous engagement with socioemotional stimuli. The insula is a key SN structure for which dysfunction relates to diminished or disorganized attentional engagement during social cognition. Among bvFTD and svPPA patients, Kumfor et al. [12] showed a direct relationship between insula damage and reduced EMG-recorded facial expressiveness in response to positive emotional films. In another study of bvFTD patients' responses to films, left insula volume corresponded with patients' tendency to report subjectively experiencing "non-target emotions," i.e., emotions that did not fit the situation being depicted [13]. Using a task-based fMRI paradigm with bvFTD patients, Marshall and colleagues [14••] found that insula activity while viewing emotional faces predicted patients' ability to correctly identify emotions in a post-scan testing session. This same link between insula damage and loss of emotional engagement has been seen in studies of bvFTD patients' diminished disgust reactivity, as well as their failure to correctly identify disgust in others [15, 16]. Furthermore, Muhtadie et al.[17] showed that volume loss in the insula also predicts dementia patients' impairments in appropriately suppressing emotions. Together, these results suggest that the insula may play a role in both attention to and organization of interoceptive information in response to socioemotional stimuli, and functional disruptions of the insula may result in heterogeneous emotion deficits in different patients.

The amygdala has also been found to be important for emotional attention in bvFTD, with evidence that amygdala volume loss mediates patients' deficits in reading facial emotions [18], potentially via its failure to functionally facilitate the fusiform face area (FFA) in the context of emotion [19]. In a recent review of facial emotion reading across the FTD syndromes, Hutchings and colleagues [20••] suggest that, in part because bvFTD patients' emotion reading performance improves when emotions are exaggerated and declines with more subtle expressions [21, 22], with the amygdala repeatedly associated with impairment across studies, the fundamental deficit in bvFTD may be attentional rather than a loss of emotional semantics. While another study from the same group unexpectedly showed that bvFTD patients had *increased* fixations to the eyes of emotional faces, despite reading the emotions inaccurately [23], this does not rule out the possibility that emotion reading deficits in bvFTD are at least in part due to breakdown of the attentional salience system. Rather than being interpreted as reflecting normal attention, these patients' hyper-fixation behavior may be a compensation for the reduced activation of the FFA by the amygdala in response to emotional faces, a pattern known to occur in bvFTD patients [19]. Marshall and colleagues also found reduced FFA activation in bvFTD patients in response to emotional faces, but in their study this was associated with hypoactivation of the left insula and caudate [14••] rather than amygdala.

The medial pulvinar nucleus of the thalamus is highly connected with SN structures including the insula and anterior cingulate cortex [24], and damage to the pulvinar has been shown to reduce functional connectivity in the SN in bvFTD

patients [25]. Recent work with dementia patients has demonstrated that this key relay plays an important role in the loss of prosocial engagement. Sturm and colleagues [26] studied the relationships among resting parasympathetic activity, brain structure, and helping behaviors in bvFTD and AD patients using an empathy challenge paradigm. Volume in the medial pulvinar directly related to whether patients were likely to display consolation behaviors toward an examiner who pretended to struggle to reach a dropped key. They also found that left insula atrophy was associated with loss of parasympathetic control, reflected in lower respiratory sinus arrhythmia (RSA), as well as greater disengagement and less consolation behavior. This group also showed that medial pulvinar atrophy predicted lower levels of generosity during a prosocial game paradigm [27].

Finally, while the majority of recent studies of SN connectivity in dementia are focused on how loss of network function produces socioemotional deficits in bvFTD and related disorders, one investigation highlighted the effects of paradoxical facilitation in the SN. Fredericks and colleagues [28••] measured SN function in patients with AD, and showed that not only do AD patients have increased mean SN connectivity, but that this directly predicted higher levels of anxiety.

The Semantic Appraisal Network: Emotional Precision and Empathic Accuracy

While the SN has been the most widely studied ICN with respect to social cognition in dementia, a second ICN called the "semantic appraisal" (SAN) [7, 11] or "limbic" [29] network has been gaining recognition for playing an important role in socioemotional dysfunction, particularly with respect to emotion reading. The SAN is selectively vulnerable in svPPA syndrome [1], and while the SN is the core selectively vulnerable ICN in bvFTD, the SAN is still substantially impacted in a subset of patients with bvFTD, and is more important than any other non-SN network in determining inter-individual differences in bvFTD patients' atrophy patterns [30]. The SAN has been mapped in a number of studies of healthy individuals [29, 31–33], and is defined as having a hub in the dorsomedial anterior temporal lobe (ATL), and nodes in the subgenual cingulate area of the ventromedial orbitofrontal cortex, the head of the caudate and nucleus accumbens, and the amygdala, along with cerebellar nodes. Importantly, for almost two decades, studies of social cognition have repeatedly conflated the medial frontal regions of the SAN with the earlier-identified default mode network (DMN), though they are now clearly understood to be two distinct ICNs in neurologically healthy adults [29]. As a result, many socioemotional functions previously attributed to the DMN are more correctly understood as being performed by the SAN.

While studies of socioemotional deficits in bvFTD and svPPA repeatedly emphasize the importance of structures in the SAN using primarily atrophy-based methods, there are as of yet only a few direct studies correlating SAN network functional connectivity to behavior in healthy individuals. The SAN has been referred to as the "prejudice network" [34, 35] because of its role in automated evaluations and bias, and others have called it the "affiliation network" [36], in acknowledgment of its importance for socioemotional functioning. Combining its roles in prejudice and affiliation, more accurately the SAN provides a range of hedonic evaluations of positive and negative valence in response to both socioemotional and non-social stimuli. While the ATL hub plays a key role in semantic conceptual knowledge about the world, the subgenual cingulate, caudate, and nucleus accumbens regions are involved in making personalized hedonic evaluations of those concepts [7]. Social and emotional concepts in particular are more likely to incorporate hedonic evaluations as a part of their semantic structure [37], and these evaluations appear to be critical for enabling precise emotion reading, both of self and others, and provide a foundation for empathic accuracy in response to ambiguous or complex socioemotional cues. Baez et al. [38] extended this link between the amygdala and emotion beyond the face, by showing that amygdala volume was the primary predictor of performance when FTD patients were asked to attribute degree of intentionality to harmful actions involving video characters whose faces were obscured.

In part due to their interrelated functions supporting social cognition, mean functional connectivity in the SN and SAN are highly correlated in both healthy individuals and in dementia patients [11•], and the network dynamics involved in the interaction between these two ICNs have not yet been well-characterized experimentally. However, given what we know about the flow of information among the component structures in these networks, current models suggest that at times stimuli are first assigned meaning and valence by the SAN before the SN is able to recognize the personal salience of those stimuli in order to redeploy attentional resources to them, thus information flow may at times start with the SAN and flow to the SN[7]. Currently, studies are rare [11•] that directly examine the interplay of SN and SAN functional network dynamics in health or dementia, representing an important gap in this literature.

Despite this, there is substantial evidence for how degeneration and dysfunction in the SAN leads to an array of emotion deficits in patients with dementia. These studies can be categorized as reflecting two highly related emotional functions mediated by the SAN: understanding socioemotional experiences and concepts at a nuanced level, and providing hedonic valence to emotional and social concepts.

Recent work has emphasized the importance of connections between the subgenual cingulate OFC regions, involved

in hedonic evaluation, with anterior temporal regions mediating semantic knowledge, to explain dementia patients' impairments decoding the nuances of socioemotional material. Precision in both emotional and social concepts appears to rely on linking personalized hedonic evaluations from the OFC with anterior temporal lobe semantic knowledge, and dementia-related damage to this connection results in inaccurate emotion reading and loss of richness for social conceptual information. Particularly in svPPA patients, who more uniformly exhibit dysfunction in the SAN, reduced temporal-OFC connection has been found to predict poor conceptualization of subcategories of emotion, such as distinguishing among emotions with the same valence like sadness and fear [20]. Using functional connectivity analyses in svPPA patients, Bejanin and colleagues [39] showed that disconnection between medial temporal and rostromedial frontal regions predicted poor affective cognitive inferences. Reduced integrity of the uncinate fasciculus (UF), an important white matter tract in the SAN that connects ventromedial OFC and anterior temporal regions, was found to explain inaccurate emotion attribution in a study of cognitively unimpaired patients with amyotrophic lateral sclerosis [40]. UF frontotemporal connectivity was the main etiology of deficits in bvFTD patients who had difficulty naming emotions depicted in videos [41•].

Studies in dementia patients have recently highlighted the role of the anterior temporal (ATL) node of the SAN in placing emotions in a more precise socioemotional semantic context that improves empathic accuracy. This is evident in studies using simple emotion identification, such as in a task-based fMRI study by Marshall and colleagues'[14••] showing that anterior temporal functional activation during passive emotional face viewing was the best predictor of how well svPPA patients named emotions outside of the scanner. But it is also notable in studies of more complex socioemotional constructs. In two studies of bvFTD patients, ATL volume [42] and inferior ATL connectivity [41••] were the primary predictors of patients' ability to understand social normative rules. Structural studies of the neural correlates of interpreting complex paralinguistic social signals like sarcasm [43] and facial signals with incongruent contexts [44•] have emphasized the importance of the ATL, particularly in patients with svPPA disproportionately affecting the SAN. Additionally, a recent study of humor processing showed that volume loss in a network including the ATL predicted bvFTD and svPPA patients' inability to detect humor from non-verbal cartoons, particularly with novel scenarios that required additional contextual processing [45].

A number of studies in the past 5 years have elucidated how dysfunction in the ventromedial frontal-subcortical nodes of the SAN disrupt patients' ability to derive accurate hedonic evaluations of emotions in both self and other. Normally, humans covertly simulate emotions, an involuntary behavior which is not merely a form of emotional contagion, but which functions to provide an internal interoceptive representation of the other's emotion that allows more accurate decoding of that emotion [46, 47]. A study by Marshall and colleagues [47] found that accuracy of facial emotional mimicry has been found to directly predict accuracy of emotion naming across a sample of bvFTD, svPPA, and nfvPPA patients. While bvFTD patients showed overall reduction of both facial mimicry and emotion reading, svPPA patients mimicked emotions but did not correctly identify them, suggesting that a disruption not in the interoceptive signaling, but in the patients' interpretation of these signals' emotional meaning, was responsible for their emotion naming deficits. Hua and colleagues [48] also performed facial EMG with bvFTD patients, and found that patients had inappropriately positive facial reactions while viewing negative emotional faces, which corresponded with lack of real-world empathy as quantified by informants. This dysregulated, stereotyped positive emotion corresponded to a network including inferior frontal and temporal SAN regions, potentially reflecting patients' inability to assign a correctly nuanced range of hedonic valences to internally experienced or observed emotions. BvFTD patients have been documented to have insensitivity to punishment cues, finding normally aversive stimuli such as bad smells rewarding [49]. A study examining the neural correlates of empathy in bvFTD and svPPA patients found that volume in the nucleus accumbens, a node in the anterior SAN that plays a pivotal role in reward processing, directly predicted patients' degree of real life prosocial motivation [50]. Together these results suggest that disruption of patients' hedonic evaluations uncouples their internal experience from the external emotional context, contributing to loss of empathic accuracy.

The Default Mode Network: Situational Contextualization of Emotional Experience

The last ICN of particular importance for understanding social cognition in dementia is the DMN, one of the first intrinsic brain networks to be identified; it was initially thought to be active only while the brain was at rest (i.e., not engaged in a specific cognitive task). However, it has since become clear that this task-free DMN activity was actually occurring because research participants were spontaneously engaging in memory rumination and mind-wandering between cognitive tasks. The DMN is now understood to function predominantly as a memory network 51, 52, and has since been found to be selectively vulnerable in typical Alzheimer's disease syndrome [1, 53]. It can be divided into at least two functionally distinct units [54]: (1) a ventral subsystem, incorporating the hippocampus, ventral posterior cingulate, and posterior inferior parietal lobule, which is involved in retrieving and re-experiencing episodic memories, and (2) a dorsal

subsystem incorporating the antero-dorsal medial prefrontal cortex, the temporoparietal junction, the posterior cingulate cortex, and the precuneus, which is involved in top-down selection and comparison of memories and is more directly relevant to social cognition.

The primary function of the DMN in social cognition is to provide contextualized interpretations of one's own and others' behavior, in the form of self-referential processing and social perspective taking based on previous experience. Specifically, this system uses memories to model future predictions about ambiguous or unknown interpersonal information, such as others' beliefs, emotions, and intentions [55, 56]. This makes the dorsal/anterior nodes of the DMN particularly important for complex social reasoning, including theory of mind and moral reasoning, because these regions support the capacity to reason about others' goals, and to determine the potential socioemotional impact of one's choices on others [56].

There have been a set of interesting studies during the past 5 years that clarify the contribution of the DMN to complex, context-driven aspects of social cognition in dementia patients. Caminiti and colleagues [57] analyzed resting functional connectivity in patients with bvFTD and correlated it with their performance on a story-based empathy task that required them to make inferences about characters thoughts and feelings based on non-verbal contextual cues. Patients' ability to correctly attribute emotions to the characters corresponded directly with network connectivity in the dorsal anterior nodes of the DMN, emphasizing the importance of this region in decoding contextual cues in order to perform empathic perspective taking. In a study where bvFTD patients were asked to read the emotions on faces that were combined with misleading non-facial contextual cues, they were found to make errors because they attended too much to the context and failed to adequately consider facial emotions [58]. This highlights the relative preservation of the DMN's social contextualization function in bvFTD, particularly in contrast to their loss of the SN and SAN functions that more directly support emotion reading.

Other studies of the DMN and bvFTD have more explicitly focused on memory for social features. Wilson and colleagues have done a series of studies of social scene construction, first demonstrating that the neuroanatomic substrate of scene construction in FTD involves the DMN [59], and then performing a study showing that when bvFTD patients are asked to simulate scenes, the level of detail they are able to generate for social scenes is impoverished compared to non-social scenes, and was significantly worse than AD patients [60•]. Finally, additional studies have extended this area of "social memory." Wong and colleagues [61] had AD and bvFTD patients play a social "trust game" and engage in a non-social lottery, and found that for both groups, memory for the social condition was better than for the non-social condition, and corresponded with a network of structures that included medial frontal (for bvFTD) and hippocampal (for AD) nodes of the DMN.

Summary and Conclusions

One of the most important trends occurring during the past 5 years in this area has been the shift from simple atrophy-based modeling of brain-behavior relationships toward more sophisticated multimodal analyses that incorporate resting- or task-based functional connectivity and structural connectivity of white matter tracts. While structural analyses of social behavior are valuable, future studies clarifying how neurodegeneration impacts the functional dynamics of these interconnected ICNs will likely provide important new insights into behavior that have previously been missed. Beyond functional studies, the role of white matter structural connectivity in dementia patients' social cognition is also likely important but remains understudied [62, 63]. The role of the cerebellum in social cognition is another area in which there has not yet been adequate study [64, 65], despite substantial evidence that the cortical ICNs are recapitulated in the cerebellum [32], that cerebellar change can produce social cognitive symptoms [66•], and that cerebellar disconnection if not frank atrophy is common in a number of neurodegenerative diseases, including those with significant behavioral symptoms [67–69]. Ideally, in the next 5 years, more precise and creative social cognitive phenotyping of these patients will increasingly be combined with multimodal, computational brain analytic approaches, which will significantly clarify the network underpinnings of socioemotional behavior not only in neurodegenerative disease but also in healthy development as well.

Compliance with Ethical Standards

Conflict of Interest Katherine P. Rankin has received research funding through grants from the National Institutes of Health (NIH), Marcus Foundation, Rainwater Charitable Foundation, and Quest Diagnostics.

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