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Individual differences in socioemotional sensitivity are an index of salience network function

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Abstract

Connectivity in intrinsically connected networks (ICN) may predict individual differences in cognition and behavior. The drastic alterations in socioemotional awareness of patients with behavioral variant frontotemporal dementia (bvFTD) are presumed to arise from changes in one such ICN, the salience network (SN). We examined how individual differences in SN connectivity are reflected in overt social behavior in healthy individuals and patients, both to provide neuroscientific insight into this key brain-behavior relationship, and to provide a practical tool to diagnose patients with early bvFTD. We measured SN functional connectivity and socioemotional sensitivity in 65 healthy older adults and 103 patients in the earliest stage (Clinical Dementia Rating Scale score ≤1) of five neurodegenerative diseases (14 bvFTD, 29 Alzheimer's disease, 20 progressive supranuclear palsy, 21 semantic variant primary progressive aphasia, and 19 non-fluent variant primary progressive aphasia). All participants underwent resting-state functional imaging and an informant described their responsiveness to subtle emotional expressions using the Revised Self-Monitoring Scale (RSMS). Higher functional connectivity in the SN, predominantly between the right anterior insula (AI) and both "hub" cortical and "interoceptive" subcortical nodes, predicted socioemotional sensitivity among healthy individuals, showing that socioemotional sensitivity is a behavioral marker of SN function, and particularly of right AI functional connectivity. The continuity of this relationship in both healthy and neurologically affected individuals highlights the role of socioemotional sensitivity as an early diagnostic marker of SN connectivity. Clinically, this is particularly important for identification of patients in the earliest stage of bvFTD, where the SN is selectively vulnerable.

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Keywords

Revised Self-Monitoring Scale; socioemotional sensitivity; resting-state functional magnetic resonance imaging; salience network; behavioral variant frontotemporal dementia

1. Introduction

A heterogeneous group of neurodegenerative disease syndromes is associated with frontoinsular and temporal degeneration, with behavioral variant frontotemporal dementia (bvFTD) syndrome accounting for up to 50% of these cases (Johnson et al., 2005; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). The earliest symptoms of bvFTD are deficits in personal and social conduct, emotion, and insight (Neary et al., 1998; Rosen et al., 2002), often in the context of otherwise preserved cognitive and motor functioning. Consequently, initial clinical diagnosis of patients with bvFTD relies entirely on the assessment of patients' social and emotional symptoms (Rascovsky et al., 2011). However, bvFTD patients are almost never identified until their disease is well past the initial stages. As a result of their emotional and behavioral symptoms, bvFTD patients often are mistaken for patients with a late onset psychiatric disorder, and may spend years under psychiatric care before receiving a correct neurodegenerative diagnosis (Khan et al., 2012; Woolley, Khan, Murthy, Miller, & Rankin, 2011). Thus, to ensure early and accurate clinical diagnosis of bvFTD patients, particularly in the stage before expensive and technically demanding brain imaging is ordered, it is necessary to identify and validate tests that not only measure characteristic patterns of bvFTD social dysfunction, but which also directly reflect changes to the specific brain circuits that degenerate in bvFTD (Shany-Ur et al., 2014; Sollberger et al., 2009). Also, because the earliest symptoms result from altered functional connectivity that precedes structural atrophy (Lee et al., 2014; Whitwell et al., 2011), tests proven to correlate with functional changes will be more diagnostically powerful.

Resting-state functional magnetic resonance imaging (rs-fMRI) studies in healthy participants have revealed a set of highly reproducible intrinsically connected functional networks (ICNs), including the salience (SN) (Seeley et al., 2007), the default-mode (DMN) (Greicius, Srivastava, Reiss, & Menon, 2004), and the sensorimotor (SMN) (Zielinski, Gennatas, Zhou, & Seeley, 2010) network. These ICNs perform specific socioemotional, cognitive, and sensorimotor functions (Yeo et al., 2011), and are affected differently by distinct neurodegenerative disease syndromes (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). The SN works to integrate and interpret interoceptive, autonomic signals, and adjust arousal and attention on the basis of perceived relevance. This network is the site of earliest dysfunction in mild and even prodromal (Dopper et al., 2013; Seeley et al., 2008; Whitwell et al., 2011) bvFTD. The key node within the SN is the right anterior insula (AI), which integrates highly processed sensory stimuli with homeostatic, affective, motivational, and hedonic information, much of which arises from subcortical SN nodes, including the dorsomedial thalamus, hypothalamus, amygdala, and midbrain periaqueductal gray (PAG) (Seeley et al., 2007). This interoceptive information provides a fundamental basis for the awareness of and sensitivity to self- and other-related emotions (Craig, 2009). Consequently, the altered socioemotional awareness of bvFTD patients likely reflects early changes in

particular connectivity patterns between the right AI and both cortical (left AI, anterior cingulate cortex [ACC]) and subcortical SN nodes, leading to a failure to integrate basic interoceptive information into a full-blown emotional experience and response (Craig, 2002; Craig, 2009).

The primary aim of the present study was to identify whether individual differences in salience network (SN) connectivity, and specific patterns of connectivity between cortical and subcortical SN nodes, predict socioemotional sensitivity and responsiveness to subtle emotional expressions. Though we predicted that this brain-behavior relationship could be observed in healthy individuals, we wished to account for the possibility of small effect sizes in this exploratory analysis. Thus, in order to ensure adequate variance to detect this relationship, we enriched our healthy control sample with individuals with very early neurodegenerative disease, who were likely to show below normal levels of SN connectivity and socioemotional sensitivity, thereby increasing variance for the regression models. We hypothesized that socioemotional sensitivity would be related to connectivity in the SN, but not to connectivity in two "control" networks, the DMN and SMN, in this enriched (controls + patients) sample. We selected the DMN and SMN as our "control" networks because DMN connectivity corresponds to efficiency of memory processing (Greicius et al., 2004), and because we assumed that the SMN is neither related to socioemotional sensitivity nor to memory. We also expected that connectivity primarily between the right AI and both cortical and subcortical SN nodes would significantly predict socioemotional sensitivity in this full sample. As secondary, exploratory analyses, taking into consideration that our subgroups were likely underpowered due to their small sample size, we investigated whether these relationships were independently detectable in any of the diagnostic subgroups, including healthy controls.

2. Material and methods

2.1. Participants

One hundred and sixty eight participants were enrolled in the study. Participants included 65 healthy older controls (NC) and 103 patients diagnosed with one of five neurodegenerative disease syndromes: 14 patients were diagnosed with behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al., 2011), 29 met NINCDS-ADRDA criteria Alzheimer's disease (AD) (McKhann et al., 2011), 20 were diagnosed with progressive supranuclear palsy (PSP) (Litvan et al., 1996), 21 had semantic variant primary progressive aphasia (svPPA) (Gorno-Tempini et al., 2011), and 19 were diagnosed with non-fluent variant primary progressive aphasia (nfvPPA) (Gorno-Tempini et al., 2011). Patients' diagnoses were determined by a multidisciplinary team of neurologists, neuropsychologists, and nurses, following thorough neurological, neuroimaging, and neuropsychological assessments. Patients were required to have Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE), Revised-Self-Monitoring Scale (RSMS) informant questionnaire, and neuropsychological scores obtained within 90 days of structural and functional imaging scanning. Only patients who were very early in disease progression (CDR score≤1) were included. All participants were required to have valid functional imaging scans, and to obtain the final number of 168 participants, 35 otherwise eligible

participants were excluded due to excessive motion during rs-fMRI scanning. Demographic and clinical characteristics of diagnostic groups are presented in Table 1. 57 of 103 patients were taking central nervous system acting medication at the time of rs-fMRI scanning (see supplementary material and methods for details). Each study participant had an informant who was a first-degree family member or friend, who had known the participant for five or more years. The study was approved by the Committee on Human Research at the University of California San Francisco and all participants and their informants gave their consent to participate. For a post-hoc analysis examining only the healthy control group, 33 young healthy controls (YNC) between the ages of 21-45 (30.4±6.5) who had appropriate test data were added to the older NC sample. These YNC were not included in any of the main analyses because they were not age matched to the dementia patients.

2.2. Behavioral measures

The Revised Self-Monitoring Scale (Lennox & Wolfe, 1984) is a thoroughly validated 13-item informant questionnaire that measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. Sample items include “In conversations, the subject is sensitive to even the slightest change in the facial expression of the other person he/she is conversing with”, and “In social situations, the subject has the ability to alter his/her behavior if he/she feels that something else is called for”. Thus, broadly speaking, the questionnaire is a measure of social alertness and responsiveness to subtle cues occurring in face-to-face interactions. The RSMS has good psychometric characteristics, including internal consistency (alpha=0.87) and re-test reliability (r=0.55) over a two-year period (Anderson, 1991; O’Cass, 2000). The questionnaire also shows construct validity as it predicts related social constructs such as social anxiety and sociability (Wolfe, Lennox, & Cutler, 1986). The RSMS was successfully used in previous studies to investigate the neuronal correlates of socioemotional sensitivity and responsiveness in both healthy and clinical populations (Hofmann, 2006; Shdo et al., 2017). Informants rated each item on a 6-point Likert scale, ranging from “certainly, always false” to “certainly, always true”. RSMS total score was the primary outcome measure of the study, and was examined in relation to SN, DMN, and SMN connectivity.

The 10-minute free delay recall of the Benson Complex Figure (BFD) (Possin, Laluz, Alcantar, Miller, & Kramer, 2011) was administered to assess the participants’ nonverbal episodic memory (Table 1). This test was used as a non-social control task to confirm that individual differences in behavioral scores would be reflected in the mean functional ICN connectivity only of specific networks. We used this measure to test our hypotheses that (1) individual differences in RSMS but not BFD would correspond to SN, and (2) individual differences in BFD but not RSMS would correspond to DMN.

2.3. Behavioral data analysis

Group differences on potentially confounding covariates (age, sex, education, MMSE) were analyzed using general linear models in SAS (SAS Proc GLM). GLMs were also used to analyze group differences in RSMS and BFD scores, controlling for age, sex, education, and MMSE score (as a proxy for disease severity). Prior to GLM analysis, RSMS and BDF scores were evaluated in order to determine the presence of outliers. Data points considered

inappropriately influential were removed after statistical examination of leverage, distance, influence, and collinearity, resulting in exclusion of one aberrant observation from the original data set. Dunnett-Hsu post-hoc tests were performed to compare each patient group's least-square mean RSMS and BFD scores to those of NCs.

2.4. Resting-state functional imaging

2.4.1. Image acquisition and preprocessing—Participants underwent functional and structural imaging using a 3T Siemens Trio scanner at the University of California San Francisco, as described in the supplementary material and methods.

Because head motion can induce systematic but spurious correlations particularly in older and clinical populations (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), only participants who fulfilled all of the following criteria were included into the study: maximum translational movement ≤ 3mm, maximum rotational movement ≤ 3 degrees, and maximum displacement ≤ 3 mm between functional volumes, and spikes (=max displacement > 1mm) occurring in less than 10% of all 240 volumes. 35 subjects (4 bvFTDs, 7 ADs, 3 PSPs, 7 svPPAs, 1 nfvPPA, and 13 NCs) who were otherwise eligible and had complete data did not meet these movement criteria thus were not included in the study. Mean root-mean-square of volume-to-volume changes in translational (in mm) and rotational (mean Euler angle) movement were calculated because these metrics can be associated with ICN strength (Van Dijk, Sabuncu, & Buckner, 2012). GLMs showed no statistical difference in translational and rotational movements between diagnostic groups (Table 2).

2.4.2. Region-of-interest-based ICN analysis—Consistent with previous approaches applied at our center (Gardner et al., 2013; Seeley et al., 2009), region-of-interest (ROI)-based ICN analysis was applied to identify the SN and the two "control" ICNs (DMN and SMN) by selecting each ICNs hub region. The MARSBAR toolbox for SPM (Brett, Anton, Valabreque, & Poline, 2002) was used to create 4mm radius spheres centered on the MNI coordinates that were chosen using a previously published gray matter atrophy peak in the right ventral AI in early bvFTD (SN) (Lee et al., 2014; Seeley et al., 2008) and ICN peak foci from healthy participants in the posterior cingulate cortex (DMN) (Laird et al., 2009), and right precentral gyrus (SMN) (Zielinski et al., 2010) (see supplementary material and methods for details). MARSBAR was also used to extract the average blood oxygen level-dependent (BOLD) signal time series of all voxels at each of the 235 volumes within each ICN's ROI. Each ROI's average BOLD signal time series were then used as covariates of interest in a whole brain regression model to derive each participant's SN, DMN, and SMN *t*-map. A CSF mask in the central portion of the lateral ventricles and a white matter (WM) mask based on the highest probability in the (FMRIB Software Library) FSL tissue probability mask were used to extract mean CSF and WM timeseries. These were included as covariates of no interest, along with each participant's 6 motion parameters, their temporal derivatives, and the squares of all previous terms. 32 total covariates of no interest were included in the design matrix. Mean ICN connectivity was calculated separately for each participant's SN, DMN, and SMN *t*-map by computing the mean beta value across all voxels within an ICN specific mask that was height and extent thresholded at $p_{FWE}<0.001$.

Each ICN's specific mask was created from an independent sample of healthy older participants (n=30) that was matched to the older NC sample with regard to age (73.1±7.6), sex (M/F: 13/17), education (17.4±2.9), and handedness (R/L: 29/1). The masks were derived by the same ROI-based ICN approach as described above, with the exception that they were created by combining the ROI-based maps seeded in the right and left hemisphere to ensure full bi-hemispheric coverage. Group differences in mean ICN connectivity were analyzed using GLMs, controlling for age, sex, education, and MMSE.

2.4.3. ICN node-pair derivation—Each participant's pairwise correlation coefficients between a set of cortical and subcortical core SN nodes were calculated, including the ventral AI, ACC, dorsomedial thalamus, hypothalamus, amygdala, and PAG (Seeley et al., 2007) (Fig. 1). MARSBAR was used to create spherical ROIs centered on MNI coordinates (see supplementary material and methods for details). In addition to the right ventral AI seed from Seeley et al. (2008), nodes were selected from two recent neuroimaging meta-analyses (Beissner, Meissner, Bar, & Napadow, 2013; Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012), and we used a left hemisphere AI seed corresponding to the right AI coordinate from Seeley et al. (2008). Each ROI's mean voxelwise BOLD signal time series was used to calculate correlations with all other node-pairs, controlling for the same 32 CSF, white matter, and motion regressors as described above. As a data reduction step intended to reduce the number of multiple comparisons required to test our between-group and brain-behavior hypotheses, we calculated regional summary scores by summing each participant's correlation coefficients between (1) all cortical (AI, ACC) nodes, (2) all subcortical (dorsomedial thalamus, hypothalamus, amygdala, PAG subregions) nodes (3), right AI and all subcortical nodes, (4) left AI and all subcortical nodes, as well as (5) ACC and all subcortical nodes. Group-differences in regional summary scores were analyzed using GLMs, controlling for age, sex, education, and MMSE. Dunnett-Hsu post-hoc tests were performed to compare each patient group's least-square mean regional summary score to that of NCs.

2.5. Brain-behavior data analysis

Mean ICN connectivity—The relationship between mean SN connectivity and RSMS was examined in the full sample (i.e. patients and NCs) and within each diagnostic subgroup by entering mean SN connectivity as a predictor of RSMS score in a GLM, controlling for age, sex, education, and MMSE (main effect analysis). In a second analysis, brain volume was added as a confounding covariate as described in the supplementary material and methods (atrophy correction analysis). As an error check to confirm that diagnostic subgroup did not disproportionately impact the main effect result, a third analysis was performed in which k-1 diagnostic groups were parametrized (0=no, 1=yes), and these binary representations of diagnosis were added as additional confounds to the main effect analysis (Rankin et al., 2009). The above series of three analyses were also performed to investigate the relationships between RSMS/DMN, RSMS/SMN, BFD/SN, BFD/DMN, and BFD/SMN.

Node-pair connectivity

Regional summary score analysis: To test our hypothesis that RSMS would correspond predominantly to functional connectivity between the right rather than the left AI, and the other cortical/subcortical SN nodes, each of the five regional summary scores was used to predict RSMS score, according to the analytic sequence described above (main effect analysis, atrophy correction analysis, and diagnostic confound analysis). Because this study is designed to detect brain-behavior relationships and no human risk is conferred by a false positive result, we accepted a $p<0.05$ threshold for significance for the resulting small number of comparisons ($n=5$) for this primary analysis (Bender & Lange, 2001; McDonald, 2009).

Node-pair analysis: Then, to perform a secondary descriptive analysis to explore the differential contribution of each node-pair within any significant regional summary scores, we correlated each individual node-pair with the RSMS, again using the main effect, atrophy correction, and diagnostic confound analytic sequence (see supplementary material and methods for details). This exploratory post-hoc analysis involved a larger number of multiple comparisons ($n=21$), thus only results exceeding the threshold of $p<0.01$ set by a Benjamini-Yekutieli multiple comparison correction were considered significant (Narum, 2006).

3. Results

3.1. Demographic and clinical features

Average age in the bvFTD (M±SD: 57.7±8.0; $p<0.05$) and AD (61.9±8.7; $p<0.05$) groups was significantly younger than in the NC group (68.0±6.8), though no other age differences were found. PSP patients (15.1±2.8 years; $p<0.05$) were significantly less educated than NCs (17.6 ±2.2). The sex distribution within each patient group did not significantly differ from NCs. No significant differences in MMSE total score were found between patient groups. Mean CDR scores were statistically different among patient groups ($p<0.01$), however the range was very small (0.5-0.8), thus was unlikely to reflect meaningful clinical differences in severity among patient groups. Age, sex, education, and MMSE were all included as confounding covariates in subsequent analyses.

3.2. Group differences in behavioral scores

Patients with bvFTD (40.3±3.3; $p<0.001$), svPPA (39.9±2.6; $p<0.001$), and PSP (48.9±2.7; $p<0.05$) had significantly lower RSMS scores than NCs (58.2±1.7) (Table 1). The other patient groups (AD, nfvPPA) did not significantly differ from NCs. Scores for the non-social control task (Benson Figure Delay) were significantly lower in patients with AD (4.5±0.7; $p<0.001$), svPPA (7.8±0.8; $p<0.001$), and PSP (8.7±0.8; $p<0.001$) than NCs (12.4±0.5), but not bvFTDs and nfvPPAs.

3.3. Mean ICN connectivity by syndrome

To confirm the validity of the mean ICN connectivity analyses, we examined whether mean SN, DMN, and SMN connectivity were decreased in predictable patterns in particular patient groups compared to NCs. As demonstrated in previous studies (Zhou et al., 2010), the bvFTD group had attenuated mean SN connectivity (0.055±0.01) compared to NCs

(0.082±0.01), though this result was only a nonsignificant trend (p=0.056), potentially due in part to the unequal sample sizes in bvFTDs (n=14) and NCs (n=65) (Table 2). Consistent with previous research (Zhou et al., 2010), mean DMN connectivity was significantly decreased in ADs (0.060±0.01; p<0.01) when compared to NCs (0.090±0.01). We predicted that patients with cortically predominant neurodegenerative syndromes would have lower connectivity in the SMN (Agosta et al., 2010; Lee et al., 2014; Seeley et al., 2009). In line with that, patients with AD (0.100±0.01; p<0.05), svPPA (0.096±0.01; p<0.05), and nfvPPA (0.096±0.01; p<0.05) had significantly lower mean SMN connectivity than NCs (0.144±0.01). Mean SMN connectivity was also lower in patients with bvFTD (0.100±0.01), though the result did not reach statistical significance (p=0.073). PSP patients did not significantly differ in mean SMN connectivity from NCs, which is in line with the predominantly non-cortical atrophy pattern found in early disease stages of PSP (Boxer et al., 2006).

3.4. Relationship of behavioral scores to mean network connectivity

To perform a proof-of-principle analysis to demonstrate that individual differences in behavioral measures can be reflected in mean functional network connectivity, and that our methods for deriving intrinsic connectivity were valid, we first tested the hypothesis that mean DMN but not mean SN or SMN connectivity would predict a score on a memory test (BFD) in the full sample. As expected, BFD score was significantly predicted by mean DMN connectivity (p<0.05, r=0.28) (Fig. 2C), with higher connectivity predicting better performance. BFD was unrelated to both mean SN (Fig. 2D) and mean SMN connectivity. Mean DMN connectivity predicted BFD even after atrophy correction analysis (p<0.05, r=0.30).

Next, to investigate whether individual differences in RSMS score corresponded directly to ICN connectivity, we examined the relationships between RSMS and mean SN, mean DMN, and mean SMN connectivity in the full sample. As hypothesized, RSMS was significantly associated with SN connectivity (main effect analysis: p<0.01, r=0.58) (Fig. 2A), with higher connectivity predicting higher score. As expected, RSMS was not associated with connectivity in the DMN (Fig. 2B) or SMN “control” networks. Mean SN connectivity predicted RSMS after atrophy correction analysis (p<0.01, r=0.55) as well as diagnostic confounding analysis (p<0.05, r=0.51; diagnostic confounding model with atrophy correction: p<0.01, r=0.49).

Our analytic models were based on the assumption that between-subject and within-group variability in ICN strength would be adequate to find significant relationships between behavioral scores and different ICNs, with greater variability increasing the likelihood of detecting such brain-behavior relationships. In our sample, mean SN, DMN, and SMN connectivity varied widely both between and within diagnostic groups (Fig. 3 and supplementary Fig. 1).

After identifying this significant relationship between RSMS and SN connectivity in the full sample, we performed a secondary, exploratory analysis to investigate whether this was detectable in any diagnostic subgroups. The relationship did not retain statistical significance within any of the patient groups, potentially due to small group sizes yielding insufficient

power (subgroup N's ranged from 14 to 29 patients). However, to increase sample size and thus statistical power to detect a relationship between SN connectivity and RSMS in the healthy control subgroup (n=65), we added 33 healthy younger controls (YNC) to the analysis who also had RSMS and compatible rs-fMRI data (age: 30.4±6.5; M/F: 15/18; education: 16.5±3.2 years; MMSE: 29.0±0.7; RSMS: 55.6±10.6). As in the full sample, we found that in this larger healthy control sample RSMS score was predicted by mean SN connectivity (main effect analysis; p<0.05, r=0.55) (Fig. 4) (atrophy correction analysis: p<0.05, r=0.55).

3.5. Relationship of behavioral scores to SN node-pairs

To identify how particular patterns of cortical and subcortical SN connectivity related to RSMS, we examined the degree to which each of the five SN regional summary scores predicted the score. The main effect analysis in the full sample showed a significant positive relationship between the RSMS score and the cortical (p<0.01, r=0.58), the right-AI-to-subcortical (p<0.05, r=0.41), and the left-AI-to-subcortical (p<0.05, r=0.40) summary scores (Fig. 5). The ACC-to-subcortical and subcortical regional summary scores did not significantly predict RSMS. The cortical and right-AI-to-subcortical summary scores remained significant after atrophy correction (cortical: p<0.01, r=0.54; right-AI-to-subcortical: p<0.05, r=0.38) and in the diagnostic confounding analysis (cortical: p<0.01, r=0.50; right-AI-to-subcortical: p<0.05, r=0.35). The left-AI-to-subcortical summary score did not retain statistical significance after atrophy correction, but remained significant in the diagnostic confounding analysis (p<0.05, r=0.33).

After observing the significant relationships between RSMS and the summary scores for cortical, right-AI-to-subcortical, and left-AI-to-subcortical, post-hoc analyses were then performed to explore the differential contributions of the individual node-pairs comprised in those summary scores. In the main effect models, the only node-pair that significantly predicted RSMS after strict multiple comparisons correction was the right AI to ACC (p<0.01, r=0.64). The left AI to ACC (p<0.05, r=0.52), right AI to right amygdala (p<0.05, r=0.36), right AI to ventrolateral PAG (vlPAG) (p=0.05, r=0.46), and left AI to left hypothalamus (p=0.05, r=0.34) node-pairs showed only a nonsignificant trend at p<0.05 (Fig. 5 and supplementary Table 1).

4. Discussion

This is the first study to find a relationship between functional SN connectivity and socioemotional sensitivity using a neurodegenerative disease model, and to provide evidence that this relationship is generalizable. Using ROI-based ICN analyses, we found that higher mean functional connectivity in the SN predicted higher socioemotional sensitivity as rated by an informant, both in a mixed sample of healthy older adults and patients with very early neurodegenerative diseases, and in healthy controls alone. This behavior prediction was specific to the SN, and was not found for either of two "control" networks, the DMN or SMN. Node-pair based ICN analysis showed that higher functional connectivity among (1) all cortical (AI, ACC), (2) all right AI and subcortical (dorsomedial thalamus, hypothalamus,

amygdala, PAG), and (3) all left AI and subcortical SN nodes, were positively related to socioemotional sensitivity.

4.1. Using functional intrinsic connectivity network analysis to reflect behavior

We chose a sample that combined healthy older controls and individuals with very early neurodegenerative disease, reflecting the wide range of normal variability of network connectivity and behavior in healthy aging, and pathological variability due to different neurodegenerative disease syndromes. This methodological approach improved our ability to identify and characterize the hypothesized brain-behavior relationship in two ways. First, the combination of healthy participants and early-disease patients broadened the variance at both the brain and behavioral levels, maximizing the likelihood of detecting a generalizable relationship between SN connectivity and socioemotional sensitivity. Second, this approach allowed us to directly examine how this brain-behavior relationship manifests in both healthy aging and clinical samples, and thus to make inferences about the clinical use of the RSMS for early disease identification of patients with bvFTD.

Several proof-of-principle analyses were designed to confirm the validity of our methodological approach. First, we examined whether the values we derived for the mean ROI-based ICNs reflected the altered patterns of connectivity previously observed in clinical samples. We found the expected mean SN connectivity reductions in early bvFTD (Farb et al., 2013; Filippi et al., 2013; Lee et al., 2014; Zhou et al., 2010) and the expected mean DMN connectivity reductions in early AD (Zhou et al., 2010). We also showed that mean SMN connectivity was reduced in neurodegenerative disease syndromes that are associated with a predominantly cortical atrophy pattern (Seeley et al., 2009), but not in PSP syndrome, which is associated with a predominantly non-cortical atrophy pattern (Boxer et al., 2006). Second, our analytic design was based on the assumption that inter-individual variability in both brain connectivity and behavior, both within and across groups, would be high enough to employ a regression approach to delineate the hypothesized relationships. We did find a high degree of variability of mean ICN connectivity in all 3 networks between and within diagnostic groups, including within the healthy aging group. This confirms that variability in ICN connectivity was not isolated to a subset of patients, and that the hypothesized brain-behavior relationships reflected a phenomenon appearing throughout the full sample. The high within-group variability in connectivity also supports the methodologic validity of further investigating brain-behavior relationships within diagnostic subgroups. Third, we sought to demonstrate that by identifying our hypothesized brain-behavior relationship between SN and socioemotional sensitivity, we were not simply reflecting overall brain connectivity or generalized cognitive function, but had isolated a specific ICN-behavior relationship. In order to test this assumption, we analyzed additional ICN-cognition relationships and showed that socioemotional sensitivity corresponded to SN but not to DMN connectivity, and that a memory task corresponded to DMN but not to SN connectivity. This double dissociation supports the specificity of our ICN-behavior results.

Thus, though we have used a fairly novel methodological approach to predict behavior from neuroimaging signatures, these proof-of-principle analyses support the validity of our results. Our data confirm that behavior and cognition, as measured by informant

questionnaires and neuropsychological testing performed outside of the scanner, are reflected in individual differences in mean ICN connectivity. This relationship is functionally and anatomically specific rather than simply a reflection of generalized brain function or overall cognitive ability, and is not merely an epiphenomenon of disease. These findings are consistent with previous studies investigating the relationship between ICNs and both socioemotional and language functions showing that individual ratings of anxiety are reflected in degree of functional SN connectivity in healthy adults (Seeley et al., 2007), and that the level of semantic knowledge relates to degree of functional connectivity in the temporal lobe-based multimodal semantic network in patients with svPPA (Guo et al., 2013).

4.2. Socioemotional sensitivity is a behavioral marker of salience network function

We found a direct relationship between socioemotional sensitivity and SN connectivity in the full sample of healthy older controls and patients with neurodegenerative diseases, and this relationship was also present in the subgroup comprised only of healthy younger and older controls. This suggests that individual differences in SN functional connectivity, reflected both by normally occurring variability across development and pathological variability due to neurodegenerative disease, were directly related to individual differences in observed socioemotional sensitivity. The relationship remained significant after including each participant's gray matter volume in the statistical model, which suggests that it is not an epiphenomenon of structural SN differences among patients or controls, but can be explained solely by individual differences in functional connectivity. Because SN functional connectivity continued to predict socioemotional sensitivity even after diagnostic confounding was accounted for, this relationship is unlikely to be a result of bias coming from a single diagnostic group, but generalizes across individuals regardless of health or disease. This direct and generalizable relationship confirms that the SN is a key network supporting socioemotional functioning (Seeley et al., 2007), and mediates sensitivity and responsiveness to subtle nonverbal social cues during face-to-face interactions.

Consistent with these results and our expectations, node-pair based ICN analysis showed that a specific pattern of cortical and subcortical SN connectivity predicted socioemotional sensitivity. The sum of (1) all cortical (AI, ACC), (2) all right-AI-to-subcortical (dorsomedial thalamus, hypothalamus, amygdala, PAG subregions), and (3) all left-AI-to-subcortical node-pairs contributed independently to behavior. The importance of interconnectivity among cortical nodes of the SN, including the insulas and ACC, for predicting socioemotional sensitivity is in line with the important role that the AI plays in human emotional awareness (Craig, 2002; Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Connectivity between both insulas and subcortical regions also made a significant contribution to socioemotional sensitivity, though only the right-AI-to-subcortical summary score survived various statistical error checks, thus it appears to be the most robust finding. We used the coordinates derived from neuropathological identification of the true SN epicenter from an independent sample of patients with bvFTD to derive mean and node-pair SN connectivity in all participants, and found this brain-behavior relationship across the entire sample of healthy older adults and patients with different neurodegenerative disease syndromes even after statistically correcting for diagnostic group membership, thus

demonstrating that this finding was not merely an artifact driven by the right ventral AI damage in the bvFTD subsample.

This reflects the important role of the autonomic nervous system (ANS) in socioemotional sensitivity, with some theories suggesting a specialization of the right hemisphere for sympathetic autonomic arousal and survival-related alertness and the left hemisphere for maintaining relaxed and receptive parasympathetic tone (Craig, 2005; Oppenheimer, Gelb, Girvin, & Hachinski, 1992). In both regional summary score and individual node-pair analyses, the interplay between the right AI and subcortical structures in the ANS was a significant predictor of socioemotional sensitivity, highlighting the importance of attention to interoceptive signals originating in the ANS for healthy social function. Right AI to right amygdala connections specifically were able to predict socioemotional behavior, highlighting the role of the amygdala in social alertness (Seeley et al., 2007). Connectivity between the right AI and vlPAG also specifically predicted socioemotional sensitivity, suggesting a mechanism by which the SN may provide interoceptive enhancement of emotional awareness in a social setting (Craig, 2002; Craig, 2009; Critchley et al., 2004; Singer, Critchley, & Preuschoff, 2009). The current model of the mammalian brain suggests that different PAG substructures evoke fundamentally opposite emotional coping strategies, with the ventrolateral column mediating passive (parasympathetic) responses, and the dorsolateral/lateral PAG mediating active (sympathetic) responses. The former is involved in quiescence, hyporeactivity (“freezing”), hypotension, and bradycardia, and the dorsolateral/lateral portion is involved in confrontational defensive flight and fight reactions, tachycardia, and hypertension (Linnman et al., 2012). Our finding that connectivity of cortical and subcortical structures in both sympathetic and parasympathetic systems predicts socioemotional sensitivity unites distinct theories about the influence of autonomic responsiveness in social behavior, suggesting that both sympathetic alertness and a calm parasympathetic state are together optimal for attunement to other-related emotions (Craig, 2005; Porges, 2007). By extension, pathologically reduced functional connectivity between the right AI and vlPAG due to neurodegenerative disease may be associated with abnormally attenuated parasympathetic responses and decreased interoceptive input into the right AI, leading to clinically significant reduction of emotional sensitivity and hyporesponsiveness to social cues. These findings also confirm a recent study showing that patients with bvFTD had reductions in both parasympathetic and sympathetic baseline tone, and that faster baseline respiration was associated with worse cognitive empathy across a mixed group of healthy controls and bvFTD patients (Sturm et al., 2015).

4.3. Clinical relevance to bvFTD and other neurodegenerative diseases

The finding that socioemotional sensitivity is a measurable behavioral marker of SN functional connectivity, even in healthy individuals with presumably normal brain structure, is an important insight from a neuroscientific perspective. However, it also suggests a practical method for early-stage identification of patients with neurodegenerative diseases like bvFTD that are characterized by SN changes. Mild and even prodromal bvFTD targets the AI and ACC, the two SN hub regions, which causes very early changes in SN functional connectivity and altered behavior (Dopper et al., 2013; Lee et al., 2014; Whitwell et al., 2011). Previous studies have shown that characteristic socioemotional symptoms of bvFTD

such as loss of empathy (Cerami et al., 2014; Rankin et al., 2006) and self-awareness (Shany-Ur et al., 2014), disrupted emotion recognition, reactivity and experience (Kumfor, Irish, Hodges, & Piguet, 2013; Omar et al., 2011; Sturm et al., 2013; Woolley et al., 2015), and changes in affiliative interpersonal traits (Sollberger et al., 2009) are directly related to atrophy in SN structures. Our finding that socioemotional sensitivity is a behavioral marker of SN function, even accounting for SN atrophy, confirms that these earlier structural brain-behavior studies were modeling a more subtle underlying functional relationship with direct clinical significance for bvFTD. Our results indicate that even in very early neurodegenerative disease patients, changes in the ability to detect and respond to subtle nonverbal social cues result from alterations in functional connectivity between cortical (AI and ACC) SN nodes, and from disconnection between particularly right AI and the subcortical (dorsomedial thalamus, hypothalamus, amygdala, PAG) nodes that provide basic interoceptive input supporting emotional awareness of other-related feelings (Craig, 2002; Craig, 2009). This provides direct evidence that early subcortical involvement may be enough to cause some of the pathognomonic socioemotional deficits of bvFTD, a finding consistent with the discovery of both cortical and subcortical subtypes of bvFTD (Ranasinghe et al., 2016). While our study only directly examined the contribution of SN function to socioemotional sensitivity, other ICNs may be responsible for additional variance in socioemotional functioning. bvFTD patients have been shown to present with variable degrees of involvement of the semantic appraisal (SAN) or limbic network (Ranasinghe et al., 2016), which involves the temporal poles, basolateral amygdala, ventral striatum, and subgenual cingulate (Yeo et al., 2011), and likely mediates semantically-driven personal evaluations (Seeley, Zhou, & Kim, 2011). svPPA patients (Gorno-Tempini et al., 2011; Hodges, Patterson, Oxbury, & Funnell, 1992), in whom the SAN is selectively vulnerable early in the disease (Seeley et al., 2009) had equally reduced RSMS scores compared to patients with bvFTD. Future studies are likely warranted to disentangle the relative contributions of SN and SAN connectivity to socioemotional sensitivity, as well as their differential impact on clinical phenotypes within and between neurodegenerative disease syndromes.

One goal of the present study was to find a behavioral test that reflects the earliest SN dysfunctions appearing in neurodegenerative disease patients, even before frank atrophy can be detected via structural MRI. By virtue of the tight relationship between socioemotional sensitivity and SN function, we suggest that the RSMS is a clinically useful tool that can be quickly administered as an informant questionnaire to measure early changes in socioemotional sensitivity, and thus improve the accuracy of clinical diagnosis at a very early stage for patients suspected to have bvFTD. The RSMS is already being collected as a clinical research measure at a national level by many NIH Alzheimer's Disease Centers as a part of the FTLD Module of the NACC UDS battery. The clinical usefulness of the RSMS for detection of patients at the earliest stages of bvFTD may be further confirmed via multi-center studies capable of pooling larger patient samples with both sporadic and early symptomatic gene-positive (MAPT, PRGN, C9) bvFTD. These larger samples would also permit investigators to determine the characteristic patterns of decline of RSMS and SN connectivity over the course of bvFTD, thereby validating the RSMS as a measure of symptom progression for bvFTD clinical trials.

Although PSP is primarily a motor disorder (Litvan et al., 1996), it is commonly associated with bvFTD-like behavioral symptoms including apathy (emotional blunting) and disinhibition (Litvan, Mega, Cummings, & Fairbanks, 1996). Our data showed that patients with PSP did have reduced socioemotional sensitivity, although in the average PSP patient this was less pronounced than in either bvFTDs or svPPAs, compared to healthy controls. Early PSP affects predominantly subcortical regions, including the midbrain and thalamus (Boxer et al., 2006), and is therefore at risk for disrupting the subcortical (interoceptive) SN input, thus changing functional SN connectivity (Gardner et al., 2013). Our findings confirm that functional disconnection between the AI and subcortical SN nodes is sufficient to cause decreased socioemotional sensitivity. Patients with PSP had the lowest right-AI-to-subcortical and left-AI-to-subcortical node-pair connectivity compared to all other patients, though only the right-sided finding reached statistical significance within our small sample of 20 PSP patients. These results strongly suggest that as patients with PSP are recruited into increasing numbers of clinical trials testing tau-modifying agents, a measure like the RSMS should be used as a secondary behavioral outcome measure to track changes in socioemotional sensitivity.

The RSMS scores of patients with AD and nfvPPA did not differ significantly from those of healthy controls, a finding that is consistent with previous studies showing that AD and nfvPPA patients typically show little socioemotional impairment in early disease stages (Rankin et al., 2006; Sollberger et al., 2009). Early AD targets the DMN and is therefore often associated with episodic memory loss and visuospatial impairment (Ossenkoppele et al., 2015; Zhou et al., 2010). This was reflected in the reduced mean DMN connectivity in our sample of early ADs, and in the significant relationship between DMN connectivity and memory scores across the full sample. Early nfvPPA targets a speech production network that involves the left frontooperculum and left dorsal AI (Gorno-Tempini et al., 2004; Mandelli et al., 2016), which is consistent with our finding of preserved integrity of SN functional connectivity and the normal levels of socioemotional sensitivity in our nfvPPA sample.

5. Limitations and conclusions

The sample sizes of our patient groups yielded insufficient power to detect significant within-group relationships between SN connectivity and socioemotional sensitivity, and thus our ability to characterize syndrome-specific relationships was limited. Also, due to the PAG's small size and its location around the cerebral aqueduct, this structure is prone to poor signal resolution and movement artifacts during rs-fMRI acquisition due to CSF pulsation and breathing (Linnman et al., 2012). Therefore, the results in the PAG must be interpreted with caution. However, none of these methodological limitations weakens the main findings of the study. Overall, we conclude that individual differences in behavioral scores, measured with informant ratings and neuropsychological tests, can reflect degree of ICN connectivity. Informant ratings on the RSMS, a behavioral measure of socioemotional sensitivity, directly reflect functional connectivity in the SN, and therefore provide a marker for early changes in functional SN connectivity in patients with neurodegenerative disease and other disorders. Because the SN is selectively vulnerable in bvFTD, the use of the

RSMS to measure changes in socioemotional sensitivity and SN function may help clinicians identify patients with bvFTD in the earliest stages of disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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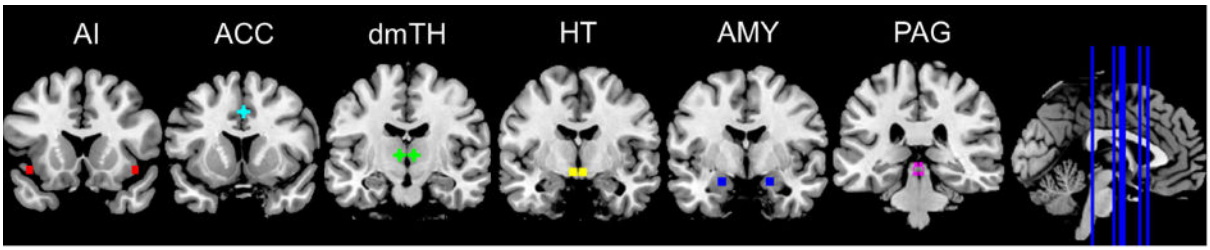

Fig. 1.

For node-pair based ICN analysis, regions-of-interest (ROIs) were centered on peak coordinates (see supplementary material and methods) in the ventral anterior insula (AI), anterior cingulate cortex (ACC), dorsomedial thalamus (dmTH), hypothalamus (HT), amygdala (AMY), and periaqueductal gray subregions (PAG).

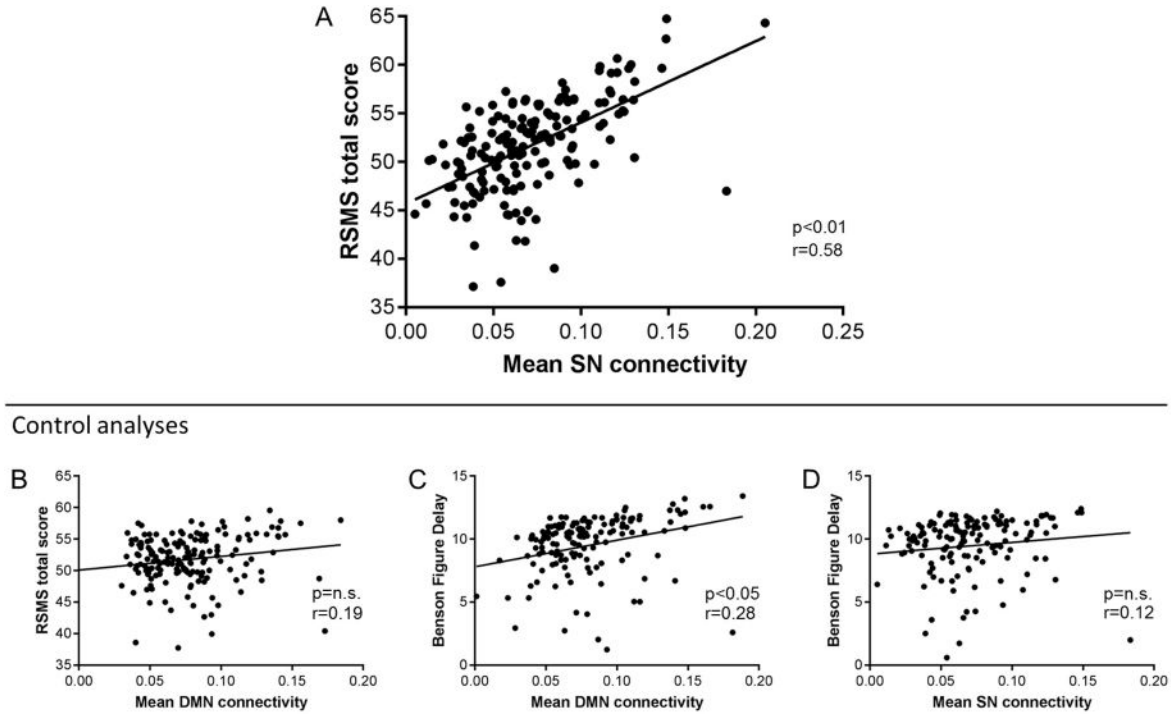

Fig. 2.

Higher mean SN connectivity was related to higher Revised Self-Monitoring Scale (RSMS) score in the full sample of healthy older controls and patients with neurodegenerative diseases (n=168). Mean salience network (SN) connectivity significantly predicted (p<0.01, r=0.58) RSMS score (A) but was unrelated to mean default-mode network (DMN) connectivity (B). By contrast, mean DMN connectivity significantly (p<0.05, r=0.28) predicted Benson Figure Delay (BFD) score (C) but was unrelated to mean SN connectivity (D). RSMS and BFD scores were adjusted for age, sex, education, and MMSE. Mean connectivity values were calculated as each participant's mean beta value across all voxels within their given ICN map, masked at the ICN as defined in an independent sample of healthy older participants (see methods).

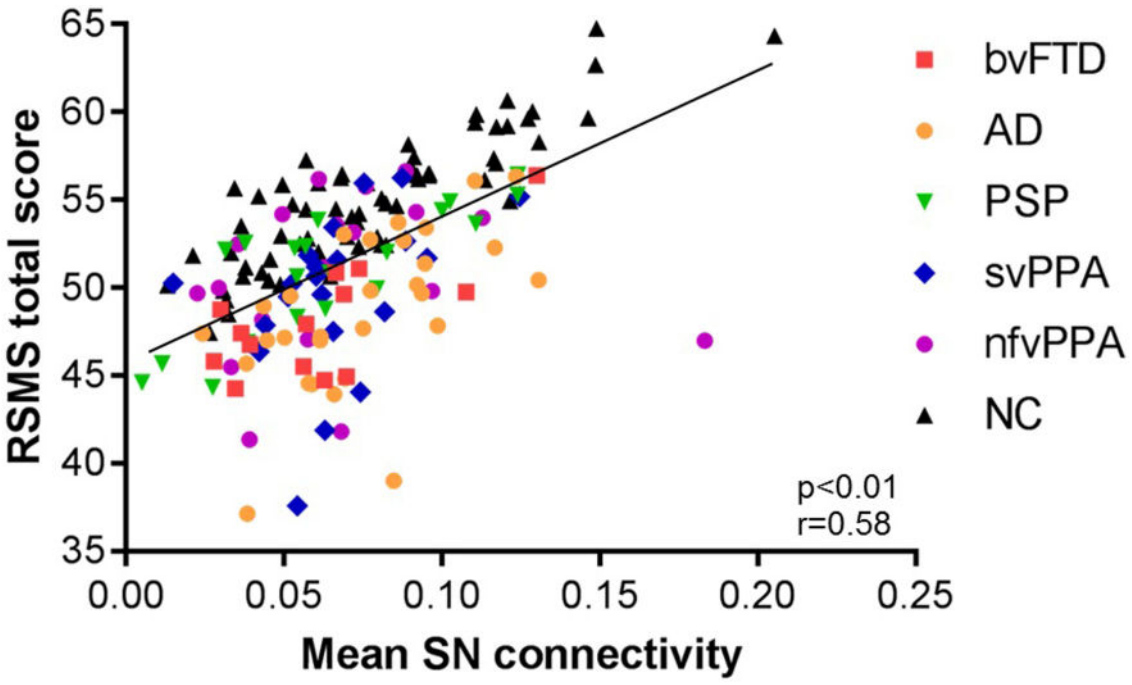

Fig. 3.

Mean salience network (SN) connectivity and Revised Self-Monitoring Scale (RSMS) scores varied widely between and within diagnostic groups (healthy older controls and patients, *n*=168). RSMS scores were adjusted for age, sex, education, and MMSE. Mean connectivity values were calculated as each participant's mean beta value across all voxels within their ICN map, masked at the ICN as defined in an independent sample of healthy older participants (see methods). bvFTD=behavioral variant frontotemporal dementia, AD=Alzheimer's disease, PSP=progressive supranuclear palsy, svPPA=semantic variant primary progressive aphasia, nfvPPA=nonfluent variant primary progressive aphasia, NC=healthy older controls.

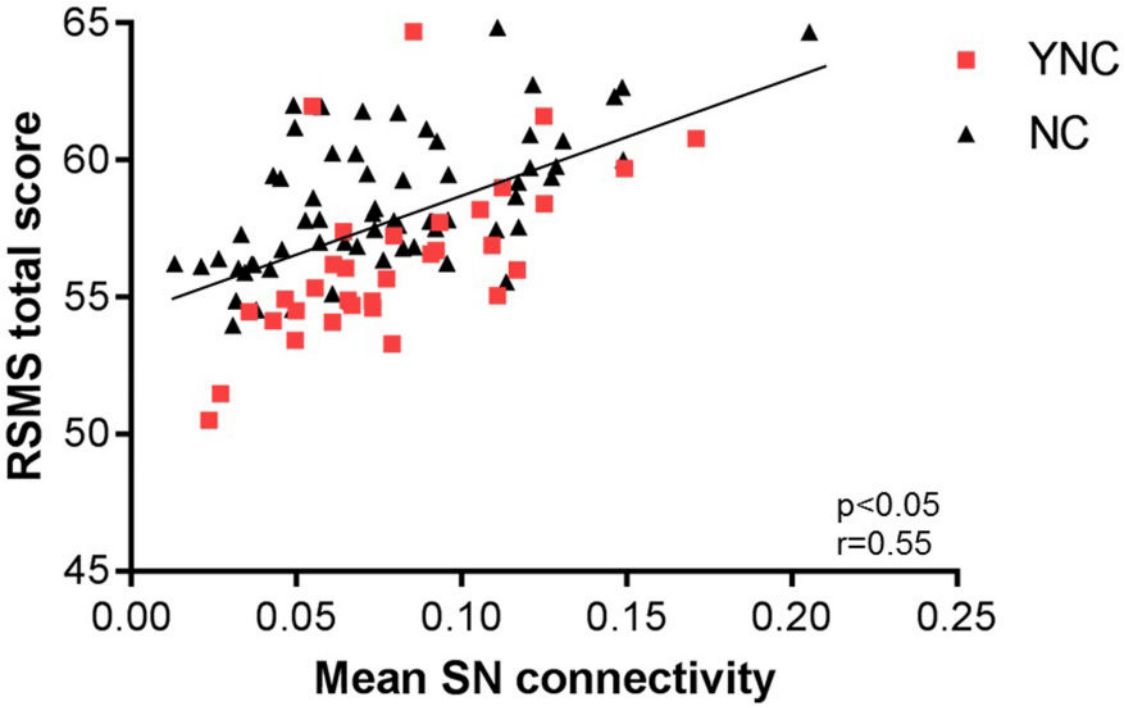

Fig. 4.

Mean salience network (SN) connectivity was positively related to Revised Self-Monitoring Scale (RSMS) score in a sample of healthy younger and older controls (n=98). Higher mean SN connectivity significantly predicted (p<0.05, r=0.55) higher RSMS score. RSMS scores were adjusted for age, sex, education, and MMSE. Mean connectivity values were calculated as each participant's mean beta value across all voxels within their ICN map, masked at the ICN as defined in an independent sample of healthy older participants (see methods). YNC=healthy younger controls, NC=healthy older controls.

Relationships between RSMS and regional summary scores.

Summary scores	Main effect	Atrophy correction	Diagnostic confound
Cortical	r=0.58, p=0.004*	r=0.54, p=0.009*	r=0.50, p=0.006*
Right-AI-to-subcortical	r=0.41, p=0.020*	r=0.38, p=0.041*	r=0.35, p=0.043*
Left-AI-to-subcortical	r=0.40, p=0.037*	r=0.27, p=n.s.	r=0.33, p=0.048*
ACC-to-subcortical	r=0.19, p=n.s.	r=0.17, p=n.s.	r=0.16, p=n.s.
Subcortical	r=0.01, p=n.s.	r=0.01, p=n.s.	r=0.01, p=n.s.

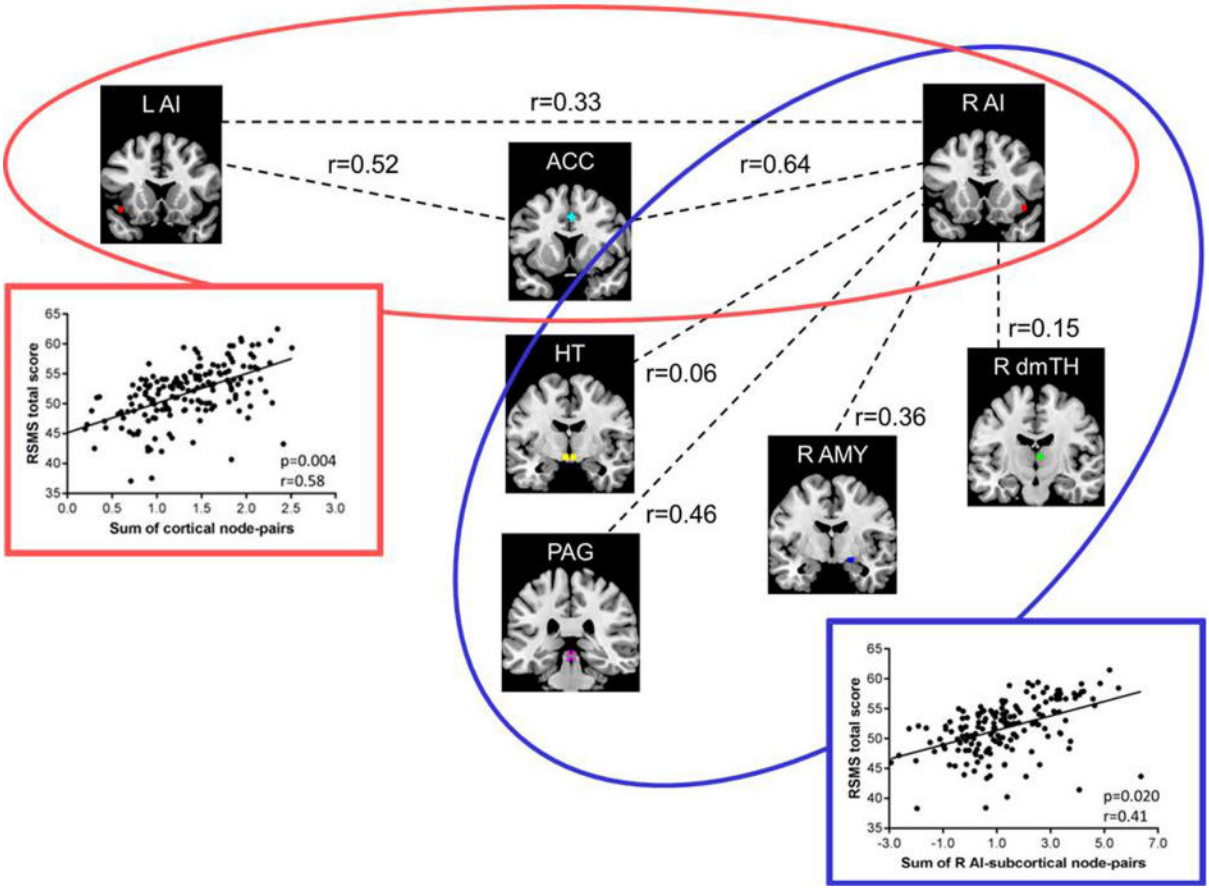

Fig. 5.

Higher functional connectivity predominantly between right ventral anterior insula (AI) and both cortical and subcortical SN nodes was positively related to higher Revised Self-Monitoring Scale (RSMS) score in the full sample (n=168). Regional summary score analysis showed that the cortical (red circle) and right-AI-to-subcortical (blue circle) regional summary scores significantly predicted RSMS score after atrophy correction and adjustment for effects of diagnostic group membership. RSMS scores were adjusted for age, sex, education, and MMSE. AI=ventral anterior insula, ACC=anterior cingulate cortex,

dmTH=dorsomedial thalamus, HT=hypothalamus, AMY=amygdala, PAG=periaqueductal gray, L=left, R=right.

Table 1

Demographic and clinical characteristics of study groups (n=168).

Mean (SD)	**NC (*n*=65)**	**bvFTD (*n*=14)**	**AD (*n*=29)**	**PSP (*n*=20)**	**svPPA (*n*=21)**	**nfvPPA (*n*=19)**	**Statistics**	***p*-value**
Age	68.0 (6.8)	57.7 (8.0)*	61.9 (8.7)*	68.9 (7.7)	62.1 (6.1)*	66.3 (8.9)	F(df)=7.44 (5)	<0.0001
Sex, M/F	30/36	10/4	14/15	10/10	11/10	9/10	χ^2(df)=3.25 (5)	n.s.
Education	17.6 (2.2)	16.7 (4.0)	17.0 (3.3)	15.1 (2.8)*	17.4 (3.1)	17.3 (3.6)	F(df)=2.31 (5)	<0.05
MMSE[a], total (max=30)	29.3 (0.7)	25.1 (3.6)	21.0 (5.9)	25.3 (3.4)	24.3 (6.5)	23.8 (6.6)	F(df)=2.46 (4)	n.s.
CDR[a], total	0	0.8 (0.5-1)	0.8 (0.5-1)	0.7 (0-1)	0.6 (0.5-1)	0.5 (0-1)	F(df)=4.67 (4)	<0.01
CDR[a], sum of boxes	0	4.8 (1.2)*	4.4 (1.9)**	4.1 (2.3)**	3.3 (1.8)	2.0 (1.6)	F(df)=6.98 (4)	<0.0001
RSMS, total (max=65)	58.2 (1.7)	40.3 (3.3)**	51.5 (2.4)	48.9 (2.7)*	39.9 (2.6)**	54.5 (2.7)	F(df)=12.84 (5)	<0.0001
BFD[b], total (max=17)	12.4 (0.5)	9.5 (1.0)	4.5 (0.7)**	8.7 (0.8)*	7.8 (0.8)**	11.1 (0.8)	F(df)=15.88 (5)	<0.0001

RSMS and BFD total scores were controlled for age, sex, education, and MMSE. Dunnett-Hsu post-hoc tests were used to compare mean least-square RSMS and BFD scores between each patient group and the control group. Group differences in age, sex, education, MMSE, and CDR were analyzed using Tukey post-hoc tests. NC=healthy older controls, bvFTD=behavioral variant frontotemporal dementia, AD=Alzheimer's disease, PSP=progressive supranuclear palsy, svPPA=semantic variant primary progressive aphasia, MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating, RSMS=Revised Self-Monitoring Scale, BFD=10-minute free delay recall of the Benson Complex Figure.

[a]Pairwise statistical comparisons only across patient groups;

[b]149 out of 168 participants had BFD scores;

*Group differs from NC at p<0.05;

**Group differs from NC at p<0.001

Table 2

Motion parameters, mean ICN connectivity, and mean regional summary scores by diagnostic group.

Mean (SD)	**NC (*n*=65)**	**bvFTD (*n*=14)**	**AD (*n*=29)**	**PSP (*n*=20)**	**svPPA (*n*=21)**	**nfvPPA (*n*=19)**	**Statistics**	***p*-value**
rs-fMRI preprocessing								
Translational motion (mRMS), mm	0.28 (0.02)	0.23 (0.04)	0.21 (0.03)	0.19 (0.04)	0.19 (0.04)	0.17 (0.04)	*F*(df)=1.81 (5)	n.s.
Rotational motion (mEuler), degrees	0.15 (0.02)	0.13 (0.03)	0.13 (0.02)	0.09 (0.03)	0.12 (0.03)	0.09 (0.03)	*F*(df)=1.01 (5)	n.s.
rs-fMRI mean ICN connectivity analysis								
Mean SN connectivity	0.082 (0.01)	0.055 (0.01)	0.070 (0.01)	0.065 (0.01)	0.063 (0.01)	0.067 (0.01)	*F*(df)=1.98 (5)	n.s.
Mean DMN connectivity	0.090 (0.01)	0.067 (0.01)	0.060 (0.01) **	0.073 (0.01)	0.074 (0.01)	0.076 (0.01)	*F*(df)=2.86 (5)	<0.05
Mean SMN connectivity	0.144 (0.01)	0.100 (0.01)	0.100 (0.01) *	0.144 (0.01)	0.096 (0.01) **	0.096 (0.01) **	*F*(df)=3.25 (5)	<0.01
rs-fMRI regional summary score analysis								
Cortical nodes (sum r)	1.49 (0.08)	0.72 (0.16) **	1.29 (0.12)	1.16 (0.13)	1.11 (0.12)	1.35 (0.13)	*F*(df)=4.26 (5)	<0.01
R AI – subcortical nodes (sum r)	2.23 (0.24)	1.80 (0.46)	1.71 (0.34)	1.06 (0.38) *	1.83 (0.37)	1.09 (0.38)	*F*(df)=2.06 (5)	=0.07
L AI – subcortical nodes (sum r)	2.24 (0.25)	1.36 (0.49)	1.44 (0.36)	1.02 (0.41)	1.64 (0.39)	1.37 (0.41)	*F*(df)=1.68 (5)	n.s.
ACC – subcortical (sum r)	2.40 (0.26)	0.93 (0.52)	1.79 (0.38)	1.43 (0.43)	2.07 (0.41)	1.43 (0.43)	*F*(df)=1.89 (5)	n.s.
Subcortical nodes (sum r)	13.69 (0.87)	10.56 (1.70)	13.47 (1.27)	11.07 (1.41)	11.97 (1.35)	12.57 (1.41)	*F*(df)=1.04 (5)	n.s.

Motion parameters, mean ICN connectivity, and mean regional summary scores were controlled for age, sex, education, and MMSE. Dunnett-Hsu post-hoc tests were used to compare mean least-square scores between each patient group and the control group. mRMS=mean root-mean-square, mEuler=mean Euler angle, NC=healthy older controls, bvFTD=behavioral variant frontotemporal dementia, AD=Alzheimer's disease, PSP=progressive supranuclear palsy, svPPA=semantic variant primary progressive aphasia, SN=salience network, DMN=default-mode network, SMN=sensorimotor network, R=right, L=left, AI=ventral anterior insula, ACC=anterior cingulate cortex.

* Group differs from NC at $p<0.05$;

** Group differs from NC at $p<0.01$