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Divergent patterns of loss of interpersonal warmth in frontotemporal dementia syndromes are predicted by altered intrinsic network connectivity

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ABSTRACT

Loss of warmth is well-documented in behavioral variant frontotemporal dementia (bvFTD) and semantic variant primary progressive aphasia (svPPA) at a group level, and has been linked to salience (SN) and semantic-appraisal (SAN) network atrophy. However, clinical observations of individual patients show much greater heterogeneity, thus measuring this clinical variability and identifying the underlying neurologic mechanisms is a critical step for understanding the symptom profile of any one patient. We used reliable change indexes with premorbid and current informant-based evaluations to characterize patterns of change on the warmth subscale of the Interpersonal Adjective Scale (IAS) questionnaire in 132 patients (21 bvFTD, 19 svPPA, 22 nonfluent variant primary progressive aphasia [nfvPPA], 37 Alzheimer's disease [AD]) and 33 healthy older adults. We investigated whether individual differences in warmth change were reflected in SN or SAN functional connectivity, or structural volume of individual brain regions in these two networks. Though one subset of patients showed significant drop in warmth to abnormally low levels (bvFTD: 38%; svPPA: 21%; nfvPPA: 5%; AD: 11%), a second subset significantly dropped but remained within the clinically normal range (bvFTD: 33%; svPPA: 21%; nfvPPA: 9%; AD: 5%), and a third subset did not drop and stayed in the clinically normal range (bvFTD: 29%; svPPA: 58%; nfvPPA: 86%; AD: 84%). Furthermore, interpersonal warmth score was strongly predicted by SN functional connectivity ($p < .01$), but not by SAN functional connectivity or by structural volume in these networks. Our results extend earlier group-level findings by showing wide individual variability in degree of disease-related reduction of interpersonal warmth and SN functional connectivity in bvFTD and svPPA, and highlight new approaches to revealing how brain connectivity predicts behavior on an individual patient level. Our findings suggest that measures of interpersonal warmth can provide important clinical information about changes in underlying brain networks, and help clinicians and clinical researchers better identify which bvFTD and svPPA patients are at greater risk for interpersonal disruption.

1. Introduction

Dramatic changes in personality are a hallmark of behavioral variant frontotemporal dementia (bvFTD), a clinically and anatomically heterogeneous neurodegenerative syndrome that is selectively vulnerable to changes to cingulo-insular networks (Ranasinghe et al., 2016; Seeley et al., 2009). Loss of empathy is one of the key early socio-emotional symptoms and a core diagnostic feature of bvFTD (Rascovsky et al., 2011), which can be accompanied by progressive loss of interpersonal warmth (Rankin et al., 2003; Sollberger et al., 2009; Sollberger et al., 2011). Although semantic variant primary progressive aphasia (svPPA) is primarily a language disorder that is characterized by pronounced semantic loss (Gorno-Tempini et al., 2011), patients with svPPA who have right temporal lobe involvement show many of the same socioemotional symptoms seen in patients with bvFTD, including loss of empathy and interpersonal warmth (Binney et al., 2016; Gorno-Tempini et al., 2004; Gregory et al., 2002; Multani et al., 2017; Perry et al., 2001; Rosen et al., 2004; Sollberger et al., 2009; Sollberger et al., 2011).

Though these group-level changes in patients with bvFTD and

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svPPA are well-documented, clinical observations of individual patients show much greater heterogeneity, with some patients maintaining near-normal levels of warmth throughout the disease course (Ranasinghe et al., 2016; Rankin et al., 2003). Clarifying the frequency with which these clinical exceptions occur, and identifying the neurologic mechanisms underlying these individual differences, is a critical step for understanding the clinical symptom profile in any one patient. Without this knowledge, it is more difficult to consistently identify patients at the earliest stage of disease, correctly phenotype them for enrollment into clinical trials for FTD that are currently proliferating, and assess symptom progression in such trials.

Consistent with the frontotemporal regions affected in both early bvFTD and svPPA, previous studies suggest that loss of warmth in neurodegenerative diseases corresponds to atrophy in structures associated with the salience (SN) (Seeley et al., 2007) and semantic-appraisal (SAN) (Yeo et al., 2011) intrinsically connected networks (ICNs). The SN consists of fronto-insular (anterior insula [AI], dorsal anterior cingulate cortex [ACC]) and subcortical (thalamus, hypothalamus, amygdala, periaqueductal gray) regions (Seeley et al., 2007) and is closely linked to the SAN, which includes the temporal poles, orbitofrontal cortex (OFC), subgenual ACC, nucleus accumbens, and caudate. SN structures are selectively vulnerable in presymptomatic and mild bvFTD (Dopper et al., 2013; Seeley et al., 2008; Whitwell et al., 2011), and structures in the SAN are affected early in svPPA (Gorno-Tempini et al., 2004; Guo et al., 2013) and some subtypes of bvFTD (Ranasinghe et al., 2016). There is emerging evidence that functional connectivity in the SN and SAN mediate complex socioemotional behaviors like socioemotional sensitivity (Toller et al., 2018). Thus, further investigation is warranted to determine if these networks mediate socioemotional behaviors, such as interpersonal warmth, that reflect functions like visceral emotional reactivity and semantic appraisal of person-specific information.

The first aim of the present study was to characterize the differential patterns of change in interpersonal warmth in patients with bvFTD and svPPA syndromes on an individual basis, compared to patients in dementia “control” groups who are less likely to show loss of warmth (i.e., nonfluent variant primary progressive aphasia [nfvPPA] and Alzheimer's disease syndrome [AD]). Because of the heterogeneity of regional degeneration among patients with bvFTD (Ranasinghe et al., 2016) and the divergent hemispheric lateralization of degeneration in patients with early svPPA (Binney et al., 2016; Woollams and Patterson, 2017), we hypothesized that even though on a group level, bvFTD and svPPA patients would show greater loss of warmth than patients with nfvPPA or AD, a subset of individual bvFTD and svPPA patients would be resilient to loss of warmth, i.e., their levels of interpersonal warmth would not show clinically meaningful change from their premorbid personalities. Second, based on earlier findings relating socioemotional functions to network connectivity, we theorized that individual differences in early loss of interpersonal warmth might result from early functional connectivity changes in the SN and SAN networks, even before atrophy to structures in those networks is observed. Thus, our second aim was to identify whether (a) individual differences in current warmth would correspond predominantly to SN or SAN functional connectivity, or to the interaction between the two networks, and (b) whether individual differences in loss of warmth would be better reflected in the functional connectivity or the structure of the brain regions in these networks. We specifically hypothesized that individual differences in current warmth would correspond more closely to functional connectivity than structural volume, and that loss of warmth from premorbid levels would be more accurately reflected by functional connectivity in the SN than the SAN.

2. Material and methods

2.1. Participants

One hundred and thirty-two subjects participated in the study, including 33 healthy older adults (NC) and 99 patients with four neurodegenerative disease syndromes, including 21 patients with bvFTD (Rascovsky et al., 2011), 19 were diagnosed with svPPA (Gorno-Tempini et al., 2011), 22 with nfvPPA (Gorno-Tempini et al., 2011), and 37 with AD (McKhann et al., 2011). The rationale for including both NC and individuals with different neurodegenerative disease syndromes was to reflect (a) the wide range of normal variability in warmth scores and functional network connectivity in healthy aging and (b) the wide range of pathological variability occurring early in individuals with different neurodegenerative disease syndromes. This approach also maximizes the variability in our key measures, increasing the likelihood of detecting a statistically significant relationship between behavior and ICNs that can be considered generalizable across both health and disease (Toller et al., 2018). Patients were diagnosed by a multidisciplinary team of neurologists, neuropsychologists, and nurses, following thorough neurological, neuroimaging, and neuropsychological assessments. Each participant had an informant who was a first-degree family member or friend, who had known the participant for five or more years. Informants were study partners who were willing to participate in this study and who were identified as having the cognitive and psychological resources to provide adequately reliable ratings. The large majority of informants were spouses (77%), followed by children (11%), siblings (6%), close friends (5%), and parents (1%). Patients were required to have Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE), and Interpersonal Adjectives Scales (IAS) informant questionnaire scores obtained within 90 days of functional and structural imaging scanning. Only patients who had a CDR score ≤ 1 (= very mild symptoms, i.e. early in disease progression) were included. Demographic and clinical characteristics of NC and patients are presented in Table 1. Sixty-two out of 99 patients were taking central nervous system-acting medication at the time of resting-state functional MRI (rs-fMRI) scanning (see supplementary material for details). 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.

2.2. Behavioral measures

The Interpersonal Adjective Scales (IAS) is a thoroughly validated questionnaire that consists of 64 adjectives, each characterizing one of eight personality traits, including warmth, coldness, dominance, submissiveness, extraversion, introversion, arrogance, and ingenuousness. Informants were asked to rate participants' *premorbid* and *current* personality by assessing how well each adjective described the participant on an 8-point Likert scale, ranging from extremely inaccurate to extremely accurate. Informants were asked to complete their premorbid (retrospective) evaluations describing patients' personality “before they became ill”, and healthy control participants' personality “5 years ago”. Each participant's raw subscale scores were *t*-transformed based on a gender-matched, community-based normative sample dataset collected by the IAS developers (Wiggins, 1995). The *t*-transformed warmth and coldness subscale scores were used to create premorbid ([IAS premorbid warmth-50]-[IAS premorbid coldness-50]/2 + 50) and current ([IAS current warmth-50]-[IAS current coldness-50]/2 + 50) trait warmth composite *t*-scores.

We used the Reliable Change Index (RCI) (Jacobson and Truax, 1991), which is a standardized z-score of change relative to the NC group, to identify what degree of change from premorbid to current warmth in individual patients could be considered clinically significant. Thus, difference between each participant's premorbid and current warmth scores was divided by the NC group's standard error of the

Table 1
Demographic and clinical characteristics of study groups (n = 132).

Mean (SD)	NC (n = 33)	bvFTD (n = 21)	AD (n = 37)	svPPA (n = 19)	nfvPPA (n = 22)	Statistics	p-value	η^2
Age	68.5 (7.9)	58.9 (8.0)*	62.3 (8.1)*	63.0 (7.2)	67.4 (7.5)	F(df) = 6.5 (4)	< 0.0001	
Sex, M/F	9/24	13/8	16/21	10/9	6/16	χ^2(df) = 9.2 (4)	n.s.	
Education	17.6 (2.1)	16.2 (3.6)	16.5 (2.5)	17.8 (2.7)	16.4 (3.8)	F(df) = 1.6 (4)	n.s.	
MMSE (max = 30)[a]	29.7 (0.5)	24.1 (4.9)	19.4 (6.3)	24.6 (3.6)	25.5 (3.9)	F(df) = 9.1 (3)	< 0.0001	
CDR, total[a]	0	0.9 (0.2)	0.7 (0.3)	0.7 (0.3)	0.4 (0.3)	F(df) = 10.1 (3)	< 0.0001	
CDR, sum of boxes[a]	0	5.0 (1.7)	4.5 (2.1)	3.3 (1.7)	1.4 (1.5)	F(df) = 17.3 (3)	< 0.0001	
Disease duration[b]	–	4.6 (2.7)	4.9 (2.6)	5.4 (2.9)	4.9 (4.5)	F(df) = 17.3 (3)	n.s.	
Premorbid warmth	58.6 (2.4)	48.3 (2.5)	51.4 (2.2)	53.0 (2.5)	51.3 (2.5)	F(df) = 2.3 (4)	=0.06	0.11
Current warmth	56.8 (3.0)	31.3 (3.1)**	46.0 (2.6)	42.4 (3.1)**	47.6 (3.0)	F(df) = 8.7 (4)	< 0.0001	0.24
RCIwarmth	−0.3 (0.5)	−3.2 (0.5)**	−1.0 (0.4)	−2.0 (0.5)	−0.7 (0.5)	F(df) = 5.2 (4)	< 0.001	0.19
Translational motion (mRMS), mm	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	F(df) = 0.35 (4)	n.s.	
Rotational motion (mEuler), mm	0.6 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.5 (0.1)	F(df) = 1.57 (4)	n.s.	

General linear models (GLMs) were performed to investigate group differences in premorbid, current, and RCI (Reliable Change Index) warmth scores, and motion parameters, controlling for age, sex, and MMSE. Dunnett-Hsu post-hoc tests were used to compare mean least-square warmth scores between each patient group and the control group. Group differences in age, sex, MMSE, and CDR were analyzed using Tukey post hoc tests. NC = healthy older adults, bvFTD = behavioral variant frontotemporal dementia, AD = Alzheimer's disease, svPPA = semantic variant primary progressive aphasia, nfvPPA = nonfluent variant primary progressive aphasia, MMSE = Mini-Mental State Examination (max = 30 points), CDR = Clinical Dementia Rating (max 3 points).

[a] Pairwise statistical comparisons only across patient groups.

[b] Disease duration was estimated based on the informant's impression of the very earliest subjective sign of behavioral or cognitive change, thus represents prodromal and symptomatic phases; Group differs from NC at $p < .05$; ** Group differs from NC at $p < .01$.

difference (RCIwarmth) (Jacobson and Truax, 1991). Individual participants were classified into "Changer" and "Nonchanger" groups, depending on whether the absolute degree of change from premorbid to current warmth was greater than the typical amount of change seen in the neurologically healthy controls. There is some evidence suggesting that the clinical presentation, disease progression, and underlying neuronal substrates may sometimes differ between patients with bvFTD who have an autosomal dominant FTD mutation and non-carriers (Khan et al., 2012; Lee et al., 2014), as well as among patients with different FTD genes (Shinagawa et al., 2014; Snowden et al., 2012). Thus, we explored whether patients with a mutation in one of the three main FTD genes, microtubule-associated protein tau (MAPT) (Kantarci et al., 2010), progranulin (GRN) (Pickering-Brown et al., 2008), and chromosome 9 open reading frame 72 (C9) (DeJesus-Hernandez et al., 2011; Renton et al., 2011) showed specific patterns of change in interpersonal warmth.

We examined current warmth score to determine if it was predicted by current SN, SAN, or default-mode network (DMN) connectivity (including the DMN as a "control network" for which we hypothesized connectivity would not correspond significantly to warmth). *T*-transformed dominance and submissiveness subscale scores were used to create each participant's *current* ([IAS current dominance-50]-[IAS current submissiveness-50]/2 + 50) trait dominance composite score, which was included as a "control behavior" to test our hypothesis that individual differences in current warmth but not in current dominance would be more accurately reflected by SN than SAN functional connectivity.

2.3. Behavioral data analysis

Thorough regression diagnostics were performed on the warmth and dominance scores to check for outliers, leverage, influential data, heteroscedasticity, and multicollinearity of residuals, and confirmed that our data met the assumptions for linear regression analysis. Mixed effects general linear models (SAS Proc Mixed) were used to analyze group differences in change from premorbid to current warmth. The threshold for statistical significance was set at $p < .013$, Benjamini-Yekutieli (B-Y) corrected (Narum, 2006) for $n = 25$ multiple comparisons. General linear models (SAS Proc GLM) were performed to examine group differences in RCIwarmth score, and Dunnett-Hsu post-hoc tests were used to compare patient groups' least-square RCIwarmth score to the NC group.

2.4. Neuroimaging

2.4.1. Image acquisition and preprocessing

Functional and structural images were acquired on the same 3 T Siemens Magnetom scanner at the University of California, San Francisco, using a standard 12-channel head coil. A T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequence was used to obtain the structural images, with parameters as follows: 160 sagittal slices, 1-mm thick, skip = 0 mm; repetition time = 2300 ms; echo time = 2.98 ms; flip angle = 9°; field of view = 240 × 256 mm^2; voxel size = 1 mm^3; matrix size = 256 × 256. Two hundred and forty task-free functional MRI images were obtained over 8 min, during which subjects were instructed to relax with their eyes closed, using a T_2*-weighted gradient echo planar imaging sequence (repetition time = 2000 ms; echo time = 27 ms; flip angle = 80°; field of view = 230 × 230 mm^2; inplane voxel size = 2.5 mm^2; matrix size = 92 × 92). The sequence was acquired with an online gradient adjustment to compensate for head motion.

Functional imaging data were analyzed using Statistical Parametric Mapping (SPM)12 (https://www.fil.ion.ucl.ac.uk/spm/). After discarding the first 5 volumes to allow for magnetic field stabilization, functional images were spatially realigned, unwarped (reduction of artifacts due to movement-by-deformation interactions), co-registered to each subject's structural T1-weighted image, normalized to the Montreal Neurological Institute (MNI) T1 template, re-sampled at a voxel size of 2 mm^3, and smoothed with a 6 mm full-width at half-maximum Gaussian kernel. To reduce the effect of low frequency drift and high-frequency noise (Lowe et al., 1998), a low pass band filter ranging between 0.0083 and 0.15 was applied.

Structural T1-weigthed images were preprocessed using SPM12. The images were visually inspected for artifacts, and underwent bias-correction, segmentation into tissue compartments, and spatial normalization to MNI space using a single generative model with the standard SPM12 parameters. The default tissue probability maps for gray matter, white matter, cerebrospinal fluid, and all other voxels from SPM12 (TPM.nii) were used (Ashburner, 2007). To optimize inter-subject registration, each participant's image was warped to a template derived from 300 confirmed neurologically healthy older adults (ages 44–86, M ± SD: 67.2 ± 7.3; 114 males, 186 females) scanned with one of three magnet strengths (1.5 T, 3 T, 4 T), using affine and non-linear transformations with the help of the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) method, with standard implementation in SPM12 (Ashburner, 2007). In all

preprocessing steps, default parameters of the SPM12 toolbox were used. The spatially normalized, segmented, and modulated gray matter images were smoothed with an 8-mm FWHM isotropic Gaussian kernel for use in voxel-based morphometry (VBM) analysis.

2.4.2. Resting-state functional imaging

2.4.2.1. Head motion correction:. Because head motion can induce systematic but spurious correlations particularly in older and clinical populations (Power et al., 2012), only subjects who fulfilled all of the following criteria were included into the study: translational movement ≤3 mm, rotational movement ≤3°, maximum displacement ≤3 mm, and spikes (=max displacement > 1 mm) occurring in < 10% of the 235 volumes. 35 participants (17 bvFTD, 8 svPPA, 3 nfvPPA, 5 AD, and 2 NC) who were otherwise eligible and had complete data did not meet these criteria and were excluded from the initial sample (n = 165). Mean root-mean-square of volume-to-volume changes in translational (in mm) and rotational (mean Euler angle) movement was calculated because these metrics can be associated with ICN strength (Van Dijk et al., 2012). GLMs showed no statistical differences in translational and rotational movements between diagnostic groups (Table 1).

2.4.2.2. Region-of-interest-based ICN analysis:. Consistent with previous approaches applied at our center (Gardner et al., 2013; Lee et al., 2014; Seeley et al., 2009; Toller et al., 2018), region-of-interest (ROI)-based ICN analysis was applied to identify the SN, SAN, and DMN by selecting each ICNs hub region. MARSBAR toolbox (Brett et al., 2002) in SPM12 was used to create 4 mm radius spheres centered on the MNI coordinates that were chosen using a previously published 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 subjects in the right temporal pole (SAN) (Yeo et al., 2011) and posterior cingulate cortex (DMN) (Laird et al., 2009) (see supplementary material for details). MARSBAR toolbox 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 subject's SN, SAN, and DMN t-map. Independent component analysis (ICA) derived masks of CSF, white matter, and non-brain regions as well as each subject's 6 motion parameters and their time derivatives were included as covariates of no interest (36 in total) into the statistical model. Mean ICN connectivity was calculated separately for each participant's SN, SAN, and DMN t-map by computing the mean beta value across all voxels within an ICN specific mask that was height and extent thresholded at $p_{FWE} < .001$. Each ICN's specific mask was created from an independent sample of normal older subjects (n = 30; age [M ± SD]: 73.1 ± 7.6; sex [M/F]: 13/17; education [M ± SD]: 17.4 ± 2.9). 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.

2.4.2.3. ICN-behavior data analysis:. The relationship between current warmth and current ICN connectivity was examined both in the full sample (NC + patients) and within each diagnostic subgroup by entering mean ICN connectivity as a predictor of current warmth into a GLM, controlling for age, sex, and MMSE (=main effects analysis). In a second analysis, brain volume was added as a confounding covariate as described in the supplementary material (atrophy correction analysis). As an error check to confirm that diagnostic subgroup did not disproportionately impact the main effects 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 effects analysis (Rankin et al., 2009). The above series of three analyses were also performed to investigate the relationships between current warmth/current SAN, current warmth/current DMN, current dominance/current SN, current dominance/current SAN, and current dominance/current DMN. The statistical threshold for all behavior/ICN analyses was set at $p < .014$, Benjamini-Yekutieli (B-Y) corrected (Narum, 2006) for 20 multiple comparisons.

We then performed a secondary, exploratory analysis in which we mathematically estimated each participant's premorbid SN connectivity using the regression parameters (intercept and betas) of the NC group (current warmth = current SN connectivity + age + sex). These values were derived to approximate each patient's baseline functional connectivity (which is never available in clinical studies in which patients are identified and enrolled after symptom onset) in order to provide a preliminary investigation of how warmth change relates to change in SN connectivity in individual patients. Using the same approach as for the behavioral data analysis, we calculated the RCI SN connectivity (eRCIsn) score to examine change (decrease: eRCIsn < −2; increase: eRCIsn > 2) between estimated premorbid and current SN functional connectivity.

2.4.3. Voxel-based morphometry

2.4.3.1. Group differences in gray matter atrophy:. We took the previously-described classifications of participants into “Changer” and “Nonchanger” types based on the absolute degree of magnitude of change in warmth from premorbid to current, and used whole-brain and ROI-based VBM to investigate volumetric differences in gray matter between patient subgroups of particular interest (Changer vs. Nonchanger bvFTDs, and Changer vs. Nonchanger svPPAs). We had insufficient power for VBM comparisons between these pairs of patient subgroups (N's ranged from 6 to 16), so we instead performed two-sample t-tests to compare each patient subgroup's whole-brain gray matter map to the one of the NC group. Age, sex, and total intracranial volume (TIV) were entered as covariates of no interest into each design matrix. A study-specific familywise error corrected t-threshold at $p < .05$ was identified for each contrast using one thousand permutations. We used the Neuromorphometrics, Inc. brain atlas (http://www.neuromorphometrics.com/) to define 11 SN and SAN ROIs bilaterally (Supplementary Fig. 1). For each subgroup, we calculated the mean voxel intensity for each ROI as a proxy for gray matter volume, and performed GLMs to compare the ROI volumes among (1) Changer bvFTDs, Nonchanger bvFTDs, and NC, and (2) Changer svPPAs, Nonchanger svPPAs, and NC. A Benjamini-Yekutieli (B-Y) correction (Narum, 2006) for n = 22 multiple comparisons set the threshold for significance at $p < .014$.

3. Results

3.1. Demographic and clinical features

Average age in the bvFTD (M ± SD: 58.9 ± 8.0; $p < .05$) and AD (62.3 ± 8.1; $p < .05$) groups was significantly younger than in the NC group (68.5 ± 7.9), though no other age differences were found. No group differences were revealed in mean years of education or sex distribution. Average MMSE total and CDR scores were statistically different among patient groups ($p < .0001$); however, the range of CDR scores was very small and still within the very mild range (0.4–0.9), thus this is unlikely to reflect meaningful clinical differences in severity among patient groups. Viewed as a proxy for disease severity, these MMSE and CDR scores demonstrate that patients were in very early stage of these progressive degenerative diseases (i.e., presence of mild symptoms and mild functional impairment). In addition, to confirm that the average disease duration did not significantly differ between patient groups, years since symptom onset were calculated from the time the first behavioral or cognitive change was observed by the informant. This liberal interpretation of disease duration is likely an overestimate of the disease duration defined by other research centers (time from the first clear clinical symptom corroborated by a clinician)

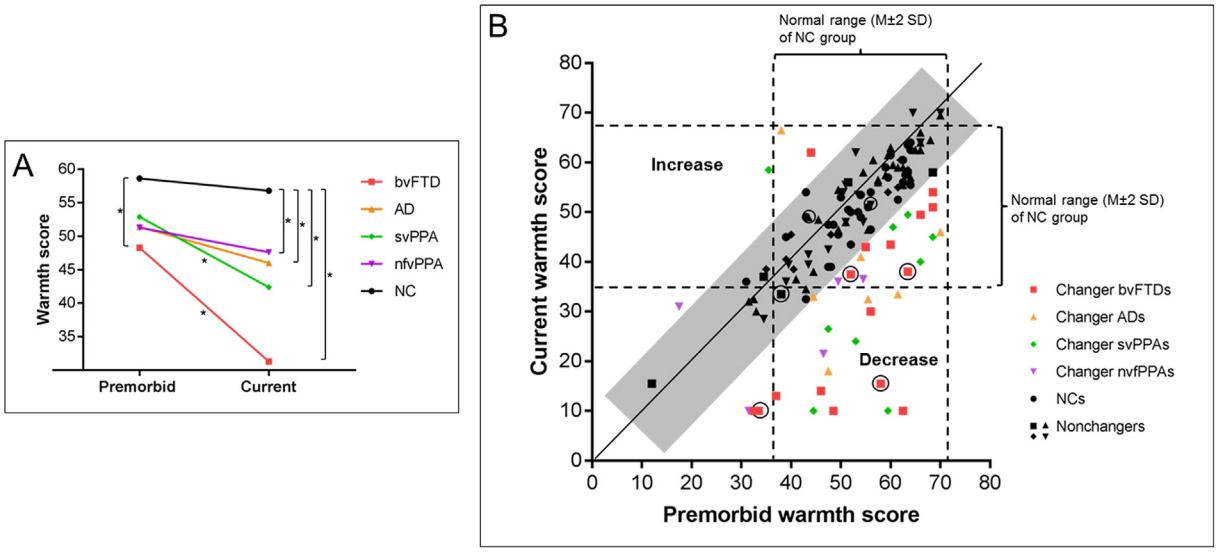

Fig. 1. Group analysis revealed that patients with bvFTD ($p < .013$) and svPPA ($p < .013$) showed a significant decline from premorbid to current warmth compared to the NC group. (A) All patient groups had significantly lower levels of current warmth than NC ($p < .013$). Though premorbid warmth was significantly reduced in patients with bvFTD ($p < .013$), their average score was well within the normal range of the NC group. (B) Calculation of individual patient's' Reliable Change Index (RCI) warmth scores revealed three different patterns of change in warmth that varied with regard to degree of change and current level of warmth: (1) Clinically significant drop in warmth to an abnormally low level, (2) clinically significant loss of warmth to a normal level, and (3) no change in warmth. The gray area shows the normal RCIwarmth range ($-2 < RCI < 2$) of the NC group. Circles refer to patients carrying an autosomal dominant FTD gene mutation (MAPT, GRN, C9). bvFTD = behavioral variant frontotemporal dementia, AD = Alzheimer's disease, svPPA = semantic variant primary progressive aphasia, nfvPPA = nonfluent variant primary progressive aphasia, NC = healthy older adults.

and includes a substantial minimally symptomatic prodromal phase that precedes clinical diagnosis. Age, sex, and MMSE total score were included as confounding covariates in subsequent analyses. Average disease duration (years since estimated symptom onset) was not significantly different among bvFTD (M ± SD; Cold Changer: 5.5 ± 2.1; Warm Changer: 3.5 ± 2.1; Nonchanger: 3.6 ± 1.5) and svPPA (Cold Changer: 4.5 ± 1.7; Warm Changer: 7.8 ± 4.0; Nonchanger: 4.5 ± 2.3) subgroups.

3.2. Between- and within-group differences in change in warmth

To investigate whether degree of loss of warmth differed between patient groups, we performed mixed effect model analysis. Group analysis demonstrated that all patient groups (*T*-score ± SD; bvFTD: 31.1 ± 2.7; AD: 46.7 ± 2.3; svPPA: 42.3 ± 2.8; nfvPPA: 47.7 ± 2.6) had significantly lower ($p < .013$) current warmth score than NC (56.3 ± 2.5). As expected, we found a significant interaction between diagnostic group and time (premorbid versus current warmth) ($p < .0001$) revealing that patients with bvFTD ($p < .013$) and svPPA ($p < .013$) showed significant declines from premorbid to current warmth compared to the NC group (Fig. 1A). Only patients with bvFTD (48.5 ± 2.5, $p < .013$) had statistically lower premorbid warmth score than NC (59.0 ± 2.4); however, bvFTD scores were average and well within the clinically normal range, and the statistical difference may be a reflection of this NC sample's very high warmth (+1 SD above average). As hypothesized, the bvFTD group (RCIwarmth score ± SD: −3.2 ± 0.5; $p < .001$) showed significantly greater change in RCI-warmth score (in the direction of loss of warmth) compared to NC (−0.3 ± 0.5) (Table 1).

After finding this significant decline from premorbid to current warmth in bvFTD and svPPA patients at the group level, we used individual patients' RCIwarmth scores to identify the subset of patients with clinically significant loss of warmth from premorbid level (set at RCIwarmth < −2, i.e., a drop 2 SD greater than the average amount of change), and examined patterns of change for individuals within and between syndromes. Individual patients exhibited one of three different patterns that varied on degree of change, and level of current warmth (Fig. 3B and D). One group (Cold Changers) showed a clinically significant drop in warmth to an abnormally low level (bvFTD: 38% [8 of 21]; svPPA: 21% [4 of 19]; nfvPPA: 5% [1 of 22]; AD: 11% [4 of 37]). The second group (Warm Changers) showed a significant drop in warmth from premorbid levels, but remained within the clinically normal range of warmth (M ± 2 SD, 51.2 ± 15.8; bvFTD: 33% [7 of 21]; svPPA: 21% [4 of 19]; nfvPPA: 9% [2 of 22]; AD: 5% [2 of 37]). The third group (Nonchangers) did not show clinically significant drop in warmth and were in the clinically normal range of warmth. Though at a group level bvFTD and svPPA patients showed a significant decrease from premorbid levels of warmth (Fig. 1A), examination of individual patients revealed that a large subset of patients in both of these groups were Nonchangers (bvFTD: 29% [6 of 21]; svPPA: 58% [11 of 19]) (Fig. 1B). Less surprisingly, the majority of individuals in the other diagnostic groups were Nonchangers (nfvPPA: 86% [19 of 22]; AD: 84% [31 of 37]). Four exceptional patients (one each bvFTD, svPPA, AD, nfvPPA) had a clinically significant increase in warmth (RCI-warmth > + 2) and were not included in any of the three groups for further analysis.

Additional clinical characterization of patients showed that having a mutation in one of the three main autosomal dominant FTD genes did not appear to predispose patients to membership in any of the three groups. The one patient with a MAPT mutation was a Nonchanger bvFTD; the three individuals with GRN mutation were a Warm Changer bvFTD, and Nonchanger nfvPPA and AD; the 3 patients with C9 mutations were Changer bvFTDs (1 Warm Changer, 2 Cold Changers) (Fig. 1B).

3.3. Relationship of warmth to functional network connectivity

3.3.1. Current data

To test our hypothesis that individual differences in current warmth would correspond primarily to current SN functional connectivity, we investigated whether current functional connectivity in the SN, SAN, or DMN predicted current warmth score across the entire sample (NC + patients). In initial main effects models examining each ICN separately, we found that higher connectivity in the SN ($p < .014$,

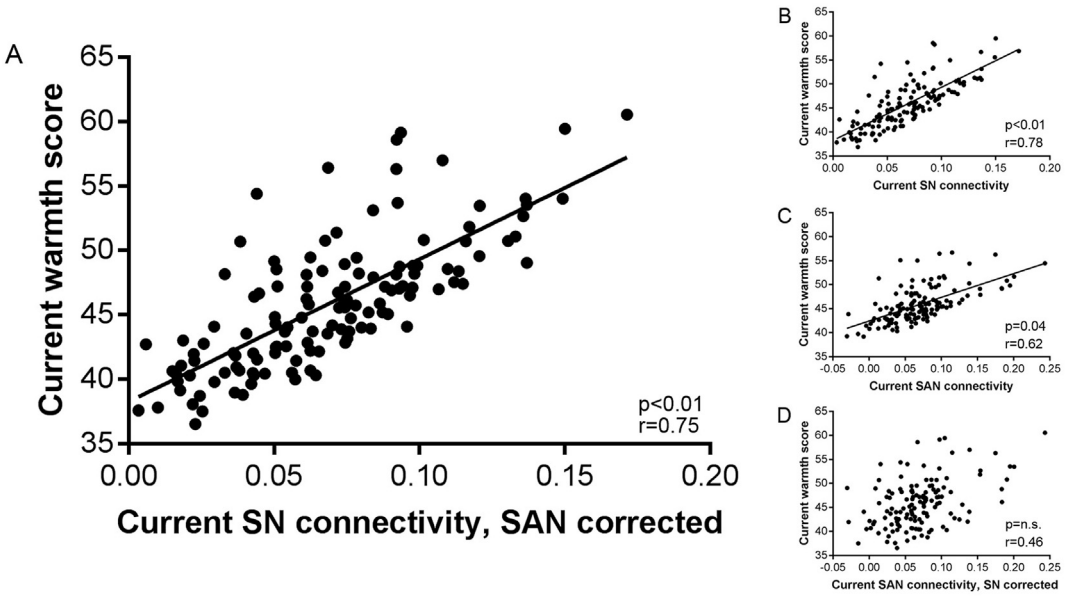

Fig. 2. Current SN connectivity significantly predicted current warmth score. (A) Higher current SN connectivity was significantly associated with higher current warmth score in the full sample (n = 132), in both the covariates (A; $p < .014$, $r = 0.75$, $\eta^2 = 0.11$) and main effects model (B; $p < .014$, $r = 0.78$, $\eta^2 = 0.10$). By contrast, higher current SAN connectivity significantly predicted higher current warmth score in the main effects at a nonsignificant trend (C; $p = .04$, $r = 0.62$, $\eta^2 = 0.06$) but not in the covariates model (D). Current warmth scores were adjusted for age, sex, and MMSE.

$r = 0.78$, $\eta^2 = 0.10$) (Fig. 2B) and at a nonsignificant trend also the SAN ($p = .04$, $r = 0.62$, $\eta^2 = 0.06$) (Fig. 2C) predicted higher current warmth score, but as predicted the DMN control network was not significant (Supplementary Fig. 2A). Current SN connectivity predicted current warmth after atrophy correction analysis ($p < .014$, $r = 0.77$, $\eta^2 = 0.11$) as well as in the diagnostic confounding analysis ($p < .014$, $r = 0.47$, $\eta^2 = 0.29$; diagnostic confounding model with atrophy correction: $p < .014$, $r = 0.46$, $\eta^2 = 0.30$). Current SAN connectivity lost significance in both the atrophy correction and diagnostic confounding analysis.

We then examined whether both of the two highly correlated ICNs (SN/SAN correlation: $r = 0.97$) independently predicted current warmth by (1) entering SN and SAN connectivity as covariates in the same model (covariates model), and (2) adding an interaction term to a model with both SN and SAN (interaction model). As hypothesized, only the SN retained statistical significance in the covariates model, with higher current SN connectivity significantly predicting higher current warmth score ($p < .014$, $r = 0.75$, $\eta^2 = 0.11$) (Fig. 2A; Fig. 2D). In the interaction model, the interaction between SN and SAN was not significant, but SN connectivity still predicted warmth at a nonsignificant trend in the presence of the interaction term ($p = .03$, $r = 0.74$, $\eta^2 = 0.11$). As expected, our control behavior analysis showed that individual differences in current SN connectivity did not significantly predict current dominance score, thus SN connectivity does not reflect a general social trait factor but is more specific to warmth (Supplementary Fig. 2B).

After identifying this significant relationship between current warmth and current SN functional connectivity in the full sample, we performed a secondary, exploratory analysis to investigate whether this relationship was detectable in any diagnostic group. The relationship did not retain statistical significance within any of the diagnostic groups, potentially due to high within-group variability in both current warmth score and current SN functional connectivity (Supplementary Fig. 3A) and small group sizes yielding insufficient power (subgroup N's ranged from 19 to 37 patients).

3.3.2. Change data (Retrospective estimates)

Estimated RCI scores were derived to explore change in SN functional connectivity (eRCIsn) in individual patients, based on the mathematically estimated premorbid SN functional connectivity scores. Results showed a relationship between the three different patterns of change in warmth and the degree of change in SN functional connectivity: (1) Overall, the majority of Cold Changers had a drastic estimated drop in SN connectivity (eRCIsn < -2) from normal premorbid to abnormally low current level (Fig. 3 B and D); (2) Warm Changers typically showed a modest drop from normal baseline SN functional connectivity (eRCIsn < -2) down to borderline or slightly below normal current SN connectivity; (3) The majority of Nonchanger patients had a nonsignificant estimated drop in SN connectivity (eRCIsn > -2). Group comparisons of the bvFTD and svPPA subgroups with NC showed that Cold (eRCIsn: -5.3 ± 0.5; $p < .0001$) and Warm (-0.8 ± 0.5; $p < .0001$) Changer bvFTDs, and Cold Changer svPPAs (-5.0 ± 0.6; $p < .0001$) showed significantly larger average estimated reduction in SN functional connectivity than NC (1.3 ± 0.3; $\eta^2 = 0.88$). Degree of estimated SN connectivity change observed in Warm Changer svPPAs, Nonchanger bvFTDs, and Nonchanger svPPAs did not significantly differ from the NC group. As a group, Nonchanger bvFTDs (M ± SD: 0.064 ± 0.01; $p < .0001$) showed significantly lower estimated baseline SN functional connectivity compared to NC (0.069 ± 0.01; $\eta^2 = 0.75$), though baseline estimated SN scores for all Nonchanger bvFTDs were in the clinically normal range. By contrast, no other patient subgroup's baseline SN level significantly differed from the NC group. Eleven participants had estimated SN baseline score below (1 Cold Changer bvFTD, 1 Warm Changer bvFTD, 2 Warm Changer svPPAs, 1 Nonchanger svPPA, 3 ADs, 1 nfvPPA) or above (1 NC, 1 nfvPPA) the normal range of the NC group.

3.4. Atrophy patterns of Changer and Nonchanger bvFTDs and svPPAs

To further investigate whether these subsets of patients showing clinically different patterns of change in warmth also differed from each other in gray matter volume of individual brain regions, we performed exploratory VBM analyses to compare the structural anatomy of (1) Changer and Nonchanger bvFTDs, and (2) Changer and Nonchanger svPPAs, with NC. When the Changer bvFTD group (n = 15) was compared to NC, whole-brain analysis revealed atrophy in bilateral, right greater than left, predominantly frontal and subcortical regions, including dorsolateral and dorsomedial prefrontal cortex, putamen,

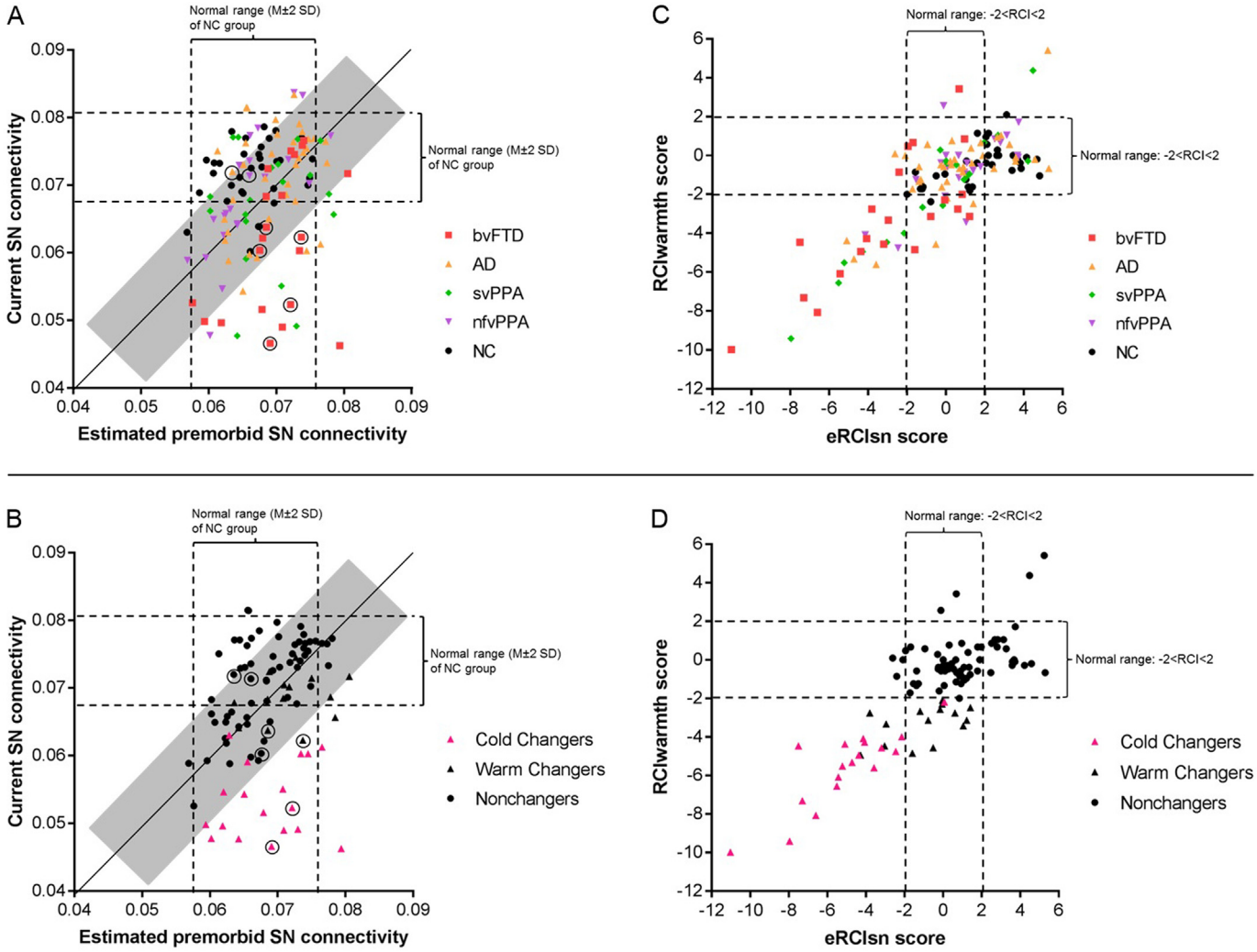

Fig. 3. The three different patterns of change in warmth were reflected in estimated change in SN functional connectivity. The majority of Cold Changers had clinically significant drop in SN connectivity to abnormally low current levels. A large subset of Warm Changers showed modest drop in SN functional connectivity and had borderline or abnormally low SN functional connectivity. The majority of Nonchangers showed no drop in warmth and SN functional connectivity. bvFTD = behavioral variant frontotemporal dementia, AD = Alzheimer's disease, svPPA = semantic variant primary progressive aphasia, nfvPPA = nonfluent variant primary progressive aphasia, NC = healthy older adults, RCI = Reliable Change Index.

thalamus, OFC, caudate, and insula (Fig. 4A and Supplementary Table 1). By contrast, in comparison to NC, Nonchanger bvFTDs ($n = 6$) showed a right temporal predominant atrophy pattern that included the temporal pole, amygdala, hippocampus, insula, and caudate. ROI analysis revealed that atrophy in the left AI, bilateral thalamus, left caudate, and left nucleus accumbens was unique to Changer bvFTDs (Supplementary Table 2). However, Changer and Nonchanger bvFTDs both showed gray matter loss in predominantly right SN and SAN ROIs, including right AI, right ACC, right amygdala, bilateral temporal pole, bilateral gyrus rectus, right posterior and medial orbital gyri, right caudate, and right nucleus accumbens.

Whole-brain VBM analysis of Changer ($n = 8$) and Nonchanger ($n = 11$) svPPAs revealed very similar patterns of bilateral, left greater than right, fronto-temporal and subcortical atrophy. Affected regions in both groups included the temporal pole, superior, middle, and inferior temporal gyri, fusiform gyrus, amygdala, hippocampus, insula, putamen, nucleus accumbens, caudate, and subcallosal area (all $p < .05$, FWE-corrected) (Fig. 4B and Supplementary Table 1). ROI analysis demonstrated that both Changer and Nonchanger svPPAs had significantly reduced gray matter volume compared to NC in both SAN- and SN-related regions, including bilateral temporal pole, nucleus accumbens, and amygdala (Supplementary Table 2). However, volume in the left subcallosal and left caudate ROIs was significantly reduced only in Changer svPPAs.

4. Discussion

This is the first study to directly examine the wide interindividual variability in degree of loss of interpersonal warmth in early bvFTD and svPPA, and to show that individual patients' observable interpersonal warmth corresponds to degree of functional connectivity in the intrinsically connected network mediating salience driven attention. Furthermore, rsfMRI and VBM analyses showed that these differences in change in warmth are more accurately reflected by trait level intrinsic functional connectivity in the SN, rather than by the SAN or by structural volume in either network. We replicated the well-documented group-level loss of warmth in patients with bvFTD and svPPA, but our patient-level quantitative approach revealed three distinct patterns of change in patients with bvFTD and svPPA syndromes that were not merely a reflection of disease severity, and were not seen in our neurodegenerative control patients with nfvPPA and AD syndromes: (1) One subset of patients showed clinically significant drop in warmth from normal to abnormally low levels (Cold Changers), corresponding to extreme drops in SN connectivity from premorbid estimates; (2) A

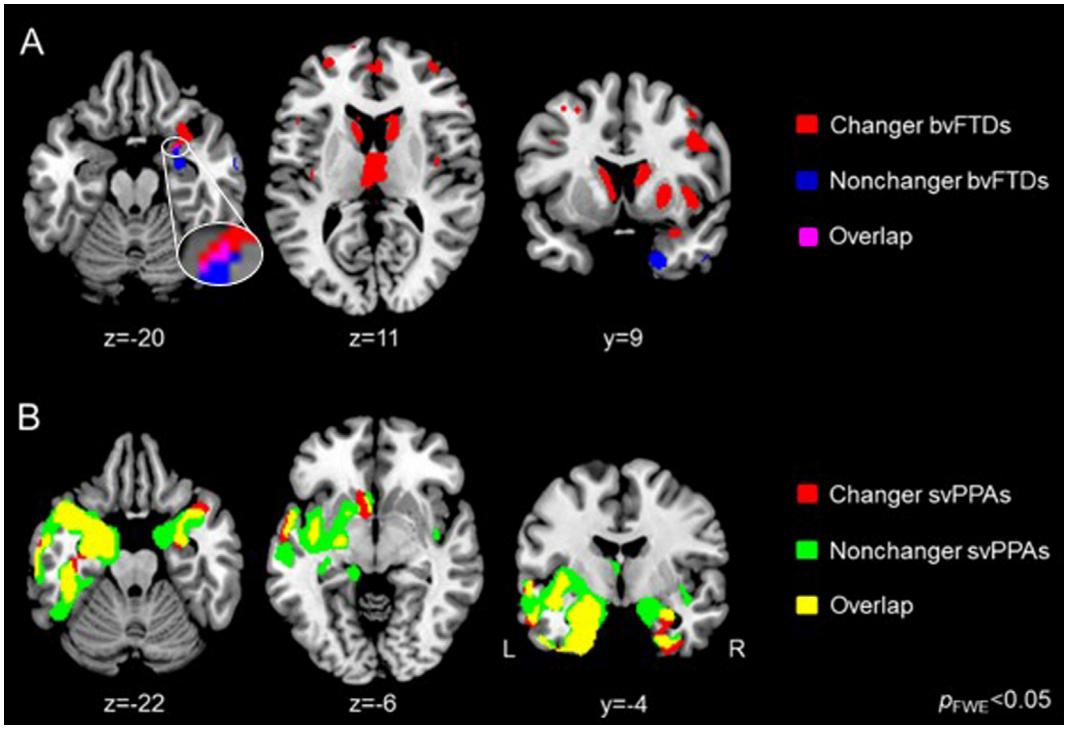

Fig. 4. FWE-corrected *t*-maps showing atrophy patterns of Changer and Nonchanger bvFTDs and svPPAs. (A) Changer bvFTDs (red) showed atrophy mainly in bilateral, right greater than left, frontal and subcortical regions, whereas Nonchanger bvFTDs (blue) demonstrated gray matter loss in the right temporal lobe. Overlapping atrophy between Changer and Nonchanger bvFTDs was found only in a small cluster in the right amygdala (pink). (B) Changer (red) and Nonchanger (green) svPPAs exhibited highly overlapping (yellow) atrophy in predominantly the bilateral, left greater than right, temporal lobe. Age, sex, TIV, and MMSE were included as covariates of no interest in the analysis. L = left, R = right.

second subset significantly dropped in warmth from their personal premorbid levels, but remained within the range of normal personality (Warm Changers), with smaller drops in SN connectivity from estimated premorbid levels; (3) A third subset of patients with bvFTD and svPPA did not drop in warmth, and their warmth and SN connectivity remained in the clinically normal range (Nonchangers). These findings suggest that one source of the individual variability of personality change seen among bvFTD and svPPA patients may be that some patients have greater neurologic resilience to loss of connectivity in the intrinsic network governing salience-driven attention. We did not find evidence in our data that this resilience resulted from greater "socioemotional reserve" (i.e., superior baseline social functioning, perhaps reflected in more sensitive, diverse, or adaptive socioemotional skills, which would presumably result from better functioning of the underlying neurologic circuits). These individuals did not have higher levels of estimated baseline warmth or SN connectivity than those with severe, extreme loss of SN connectivity and socioemotional warmth.

4.1. SN functional connectivity is a key neurologic mechanism underlying interpersonal warmth

We found that current SN functional connectivity predicted current warmth independent of the influence of SAN connectivity, despite high correlations between the two networks. Also, the relationship remained significant after including SN gray matter structure in the statistical model, which shows that individual differences in current warmth are predicted by functional connectivity regardless of volume in SN-related structures. This relationship remained significant after accounting for diagnostic group membership, suggesting that it generalizes across both healthy individuals and those with early neurodegeneration, and did not occur only in patients with SN damage. We did not find a significant relationship within any of the diagnostic subgroups, potentially due to small subgroup sample sizes (subgroup N's ranged from 19 to 37 patients) yielding insufficient power.

The SN integrates and interprets highly processed sensory stimuli with autonomic, emotional, and hedonic information, and adjusts arousal and attention on the basis of perceived relevance (Menon and Uddin, 2010; Seeley et al., 2007). Evidence from patient lesion models suggests that the network is crucial for healthy social function, and there is direct evidence that it mediates visceral socioemotional sensitivity and social alertness during face-to-face interactions (Toller et al., 2018). The SAN is involved in storage, retrieval, and evaluation of multimodal semantic concepts, and mediates personal evaluations of social-semantic entities including emotions, faces, and people (Kringelbach and Rolls, 2004; Olson et al., 2007; Patterson et al., 2007). Based on the functions of these networks, one could hypothesize that individuals with higher interpersonal warmth may engage with and attend closely to other people because social relationship is important for successful survival (SN), or because they evaluate social interactions as rewarding (SAN), or both. Consistent with our hypothesis, and extending our earlier findings showing that SN functional connectivity mediates complex social behaviors like socioemotional sensitivity (Toller et al., 2018), our results indicate that SN-mediated visceral socioemotional sensitivity and social alertness, but not SAN-mediated semantic appraisal of person-specific information, is a critical neurologic mechanism underlying interpersonal warmth. Furthermore, because our results link behavioral warmth with the SN, our findings suggest that patients with bvFTD and svPPA show loss of interpersonal warmth because they pay less attention and have reduced visceral-emotional responsiveness to social cues. They may fail to attend to personal and professional relationships that are necessary for social success. By contrast, we did not find direct evidence to suggest that altered personal evaluation of social relationships, which is often seen in patients with frontotemporal dementia (Binney et al., 2016; Shany-Ur et al., 2012), specifically predicts loss of interpersonal warmth in patients with bvFTD and svPPA. However, this does not preclude the

possibility that semantic evaluations could play an important role in warmth that our research design was unable to clearly reveal; the high within-individual correlations between SN and SAN connectivity suggests these networks may interact to support interpersonal warmth in a manner that requires further investigation.

4.2. Patients with bvFTD and svPPA show three differential patterns of change in warmth and SN functional connectivity

The finding of three different patterns of change in warmth in patients with bvFTD confirms the tremendous clinical and neuroanatomical heterogeneity seen in bvFTD syndrome, with recent evidence showing the existence of different subtypes with divergent patterns and severity of SN and SAN atrophy and corresponding differences in social behavior (Ranasinghe et al., 2016). Though progressive loss of interpersonal warmth is one of the core socioemotional symptoms for bvFTD diagnosis (Rascovsky et al., 2011), our results suggest that one group of bvFTD patients who had right temporal lobe predominant SAN atrophy showed no loss of warmth or SN functional connectivity. This confirms previous research showing that on average patients with the temporal-predominant SAN subtype of bvFTD show less reduction in interpersonal warmth than other bvFTD anatomic subtypes (Ranasinghe et al., 2016). Furthermore, we found that a subset of bvFTD patients (Warm Changers) showed drop in warmth but stayed within the clinically normal range, and had modest drop in SN functional connectivity from normal estimated baseline levels. This indicates (1) that this group of patients was resilient to drastic change in both warmth and underlying SN functional connectivity, and (2) that degree of SN functional connectivity reduction from normal initial levels varies across patients with bvFTD. It is very unlikely that the different degrees in drop of warmth and SN functional connectivity observed in Warm and Cold Changers is a result of bias coming from divergent disease stages because (1) the bvFTD subgroups did not significantly differ in mean years since estimated symptom onset, (2) we included only very early neurodegenerative disease patients, and (3) we controlled for disease severity in our analyses.

Though the SAN is selectively vulnerable in svPPA (Gorno-Tempini et al., 2004; Seeley et al., 2009), we found that a similar proportion of svPPA and bvFTD patients had clinically significant drop in warmth. Our data suggests that, like in bvFTD, early loss of warmth in patients with svPPA results from functional changes in the SN, which has not typically been considered to be a key selectively vulnerable network in early svPPA (Gorno-Tempini et al., 2004; Seeley et al., 2009). This sheds new light on the neurologic mechanisms of early socioemotional symptoms that have always been seen in a subset of patients with svPPA (Irish et al., 2014; Rankin et al., 2009; Rankin et al., 2006; Sollberger et al., 2011). Overall, our results derived from patients with very early neurodegenerative diseases suggest (1) that patients with bvFTD and svPPA are equally likely to show any of the three patterns of loss in warmth and SN functional connectivity, and that (2) drastic loss of interpersonal warmth to abnormally low levels is seen only in a subset of patients with either bvFTD and svPPA. These findings provide novel insights for early and accurate diagnosis of individual patients with bvFTD and svPPA syndromes that show heterogeneous behavioral symptom profiles. This in turn has important implications for phenotype-based enrollment into the clinical trials that are now proliferating for both tau- and TDP-43-related neurodegenerative disorders, and for assessment of symptom progression in such trials. Previous studies have shown that the IAS informant questionnaire is a valid measure for clinical use because it can differentiate patients with FTD from patients with AD at different disease stages (Sollberger et al., 2009; Sollberger et al., 2011). Our findings extend these earlier studies and suggest that the IAS warmth subscale may help clinicians and clinical researchers identify subsets of patients with bvFTD and svPPA who are more likely experiencing interpersonal disruption. However, one disadvantage of the IAS for clinical practice is that the questionnaire is relatively long (consists of 60 items). Thus, clinicians may also use other existing measures of interpersonal warmth that are shorter and easier to administer. Our study highlights the importance of using patient-level quantitative approaches to understand brain-behavior relationships and to go beyond means-based group approaches and identify the characteristic symptom profile of individual patients in neurodegenerative diseases whenever possible.

Several findings confirm our hypothesis that individual differences in loss of warmth in patients with bvFTD and svPPA were more accurately reflected in SN functional connectivity than in gray matter volume of individual SN regions. First, as mentioned earlier, SN functional connectivity predicted warmth independent of gray matter volume in SN-related regions. Second, significant volumetric differences between Changer and Nonchanger svPPAs were found only in SAN regions (left subcallosal area, left caudate), and the two svPPA groups had very similar patterns of bilateral, left greater than right, fronto-temporal (temporal pole, lateral temporal lobe, insula, subcallosal area) and subcortical (amygdala, hippocampus, putamen, caudate, nucleus accumbens) atrophy. Finally, ROI analysis revealed no region that was affected in both Changer bvFTDs (who showed predominantly fronto-subcortical SN atrophy, i.e., AI, thalamus, caudate, OFC, putamen) and Changer svPPAs (who showed mainly fronto-temporal and subcortical SAN atrophy). In contrast to the more uniform and linear brain-behavior relationship seen with SN functional connectivity, this high level of structural heterogeneity within and between the two Changer patient groups suggests no common gray matter structure is responsible for change in interpersonal warmth in patients with early bvFTD and svPPA. However, because of previous evidence showing that subcortical (bilateral thalamic) atrophy affects SN functional connectivity in gene-carriers (C9) for bvFTD (Lee et al., 2014), we cannot exclude that subcortical atrophy in Changer bvFTDs (thalamus) and in Changer svPPAs (caudate) may have altered SN functional connectivity, and thus indirectly affected interpersonal warmth. Also, because this study examined only patients in the earliest stages of the disease, future studies are warranted to disentangle whether this brain-behavior relationship is better reflected by structural than functional integrity in more advanced disease stages of the two syndromes.

The majority of patients with nfvPPA and AD did not show clinically significant change in interpersonal warmth and SN functional connectivity. This is consistent with previous research showing that patients with nfvPPA and AD typically show little socioemotional impairment (Rankin et al., 2009; Shany-Ur et al., 2012; Sollberger et al., 2009), and that the two syndromes target non-social networks early in the disease. Specifically, early nfvPPA affects the speech production network that consists of left fronto-insular and subcortical regions (Gorno-Tempini et al., 2004; Mandelli et al., 2014). This causes non-fluent and agrammatic speech which are the typical features of the disease (Gorno-Tempini et al., 2011). By contrast, early AD is characterized by changes in the DMN and is therefore frequently associated with memory and visuo-spatial impairment (Ossenkoppele et al., 2015; Ranasinghe et al., 2014; Zhou et al., 2010).

5. Limitations and conclusions

The sample sizes of our Changer and Nonchanger bvFTD and svPPA subgroups were small, thus our ability to detect statistically significant volumetric differences between Changer and Nonchanger bvFTD and svPPA patients was limited, particularly for smaller effect sizes. Also, because the overwhelming majority of patients with these syndromes have no brain imaging from before their illness, we had to mathematically estimate baseline SN functional connectivity using the regression parameters derived from the NC group. However, this data-driven approach to estimating premorbid neural connectivity may prove to be a useful way to circumvent this clinical obstacle in other studies of patients with neurodegenerative conditions. An alternate approach would be to utilize samples where prospective patient ascertainment is

possible (e.g., asymptomatic genetically-at-risk individuals), using longitudinal designs in both presymptomatic and symptomatic patients to assess interpersonal warmth and SN functional connectivity before and after neurodegenerative diagnosis.

Overall, we conclude that informant ratings on the IAS interpersonal warmth subscale directly correspond to SN functional connectivity. Groups of patients with early bvFTD and svPPA have similar proportions of individual patients who retain clinically normal levels of interpersonal warmth, or who show drastic loss of warmth, and in both clinical groups SN connectivity predicts those personality changes. Future studies are encouraged to use patient-level quantitative approaches to understand changing brain-behavior relationships and symptom profiles given the striking heterogeneity of symptom profiles within and between neurodegenerative disease syndromes.

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Appendix A. Supplementary data

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