RESEARCH PAPER

Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale

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ABSTRACT

Patients with frontotemporal dementia (FTD) often exhibit prominent, early and progressive impairments in social behaviour. We developed the Social Impairment Rating Scale (SIRS), rated by a clinician after a structured interview, which grades the types and severity of social behavioural symptoms in seven domains. In 20 FTD patients, we used the SIRS to study the anatomic basis of social impairments. In support of hypotheses generated from a prior study of healthy adults, we found that the relative magnitude of brain atrophy in three partially dissociable corticolimbic networks anchored in the amygdala predicted the severity of distinct social impairments measured using the SIRS. Patients with the greatest atrophy in a mesolimbic, reward-related (affiliation) network exhibited the most severe socioemotional detachment, whereas patients with the greatest atrophy in an interoceptive, pain-related (aversion) network exhibited the most severe lack of social apprehension. Patients with the greatest atrophy in a perceptual network exhibited the most severe lack of awareness or understanding of others' social and emotional behaviour. Our findings underscore observations that FTD is associated with heterogeneous social symptoms that can be understood in a refined manner by measuring impairments in component processes subserved by dissociable neural networks. Furthermore, these findings support the validity of the SIRS as an instrument to measure the social symptoms of patients with FTD. Ultimately, we hope it will be useful as a longitudinal outcome measure in natural history studies and in clinical trials of putative interventions to improve social functioning.

Changes in social and interpersonal behaviour are often the earliest symptom of frontotemporal dementia (FTD). Patients may lose interest in friends or family, not understand or sympathise with other people's distress, behave callously towards loved ones or approach strangers in an overly familiar way. Such symptoms have been highlighted for more than 20 years as core clinical features of FTD.[1–3] Yet social symptoms have received less investigation than language, executive and other cognitive domains, in part because the component processes and neural substrates of social behaviour are less well understood. In this study, we employed a neuroanatomical framework for social behaviour that we have previously tested in healthy adults[4] to investigate the neural bases of social impairments in FTD.

To date, studies of FTD have assessed social behavioural symptoms using retrospective medical record coding,[5 6] informant-based questionnaires[7 8] and behavioural testing.[9–11] In addition, structured clinical interviews and clinician-rated instruments have been used. The disinhibition domain of the Neuropsychiatric Inventory[12] and a newly developed domain for the Clinical Dementia Rating (CDR) scale—the Supplemental Behaviour, Comportment and Personality box[13]—enable clinicians to rate the severity of social impairment, but both summarise a broad range of symptoms under a single rating. One clinician-rated instrument for FTD subdivides social function into multiple domains,[14] but each domain is only scored as present or absent. Thus, our first goal in this study was to develop and test the reliability and validity of a new structured clinical interview and clinician-rated scale: the Social Impairment Rating Scale (SIRS).

After quantifying multiple types of social impairments using the SIRS (box 1) in FTD patients, our second goal in this study was to test specific predictions about how these impairments relate to atrophy in large-scale brain networks that subserve processes involved in social behaviour. We previously defined three intrinsic brain networks in healthy adults and demonstrated that their connectivity predicts variation in social network size and complexity.[4] Each intrinsic brain network is anchored in a subregion of the amygdala and includes other brain regions known from animal tract-tracing work to share anatomical connectivity and which are engaged in humans during fMRI tasks probing distinct aspects of social behaviour.

The perception network, anchored in the ventrolateral amygdala, includes sensory association areas of the temporal and orbitofrontal cortices which detect and decode social signals from others (figure 1, yellow). The affiliation network, anchored in the medial amygdala, includes mesolimbic structures important for motivating prosocial behaviours (figure 1, red). The aversion network, anchored in the dorsal amygdala, includes insular, cingulate and other regions often involved in pain processing, which motivate avoidant behaviours (figure 1, blue).

We made the following predictions: patients with the greatest atrophy in the perception network would show the most prominent lack of attention to social cues and person recognition difficulty, those with affiliation network atrophy would exhibit socioemotional detachment, while those

> **Box 1   Domains of the Social Impairment Rating Scale (SIRS)**
>
> Lack of attention/response to social cues
> Inappropriate trusting or approach behaviour
> Lack of adherence to social norms
> Person recognition difficulty
> Social withdrawal
> Socioemotional detachment

with aversion network atrophy would demonstrate inappropriate trusting or approach behaviour.

MATERIALS AND METHODS
Participants
Twenty participants (mean age=62.9, SD=7.3; 12 females) with a diagnosis of FTD were recruited from a longitudinal study at the Massachusetts General Hospital FTD Unit. Patients had been diagnosed by a behavioural neurologist (BCD) using a structured clinical evaluation, which included (1) a semi-structured interview with the patient regarding the history of illness, (2) office-based cognitive and psychiatric assessment, (3) neurologic examination and (4) history from a knowledgeable informant. The diagnosis of FTD was made, in a manner congruent with McKhann criteria,[15] if (1) a gradually progressive impairment in behaviour or language was the most salient symptom prompting the patient/family to seek clinical evaluation; (2) the presence of a behavioural or language impairment was documented by the evaluation which also demonstrated the absence of other salient deficits; (3) this behavioural or language impairment was the cause of loss of social or occupational

functioning and (4) imaging characteristics typical of FTD were present based on visual inspection of a brain MRI scan. The patients had been diagnosed prior to the publication of new diagnostic criteria, but each was retrospectively classified according to the clinical subtypes (behavioural variant Frontotemporal Dementia (bvFTD) or agrammatic or semantic primary progressive aphasia (PPA)) in the recent criteria.[16 17] As part of each evaluation, patients had been rated using the CDR and CDR Supplemental Language and Behaviour boxes.[13] In addition, for this study, we required the absence of a premorbid history of major psychiatric disorders, developmental or learning disability, or other neurologic disorder.

We also included scans from controls (n=33; mean age=72.5, SD=6.9; 18 females); these participants in the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort undergo a comprehensive annual evaluation by experienced clinicians and were selected based on a diagnosis of 'normal cognition' (CDR=0; Mini Mental State Examination (MMSE)≥28; no neurologic or psychiatric history).

All participants gave written informed consent in accordance with guidelines established by the Massachusetts General Hospital/Partners Human Research Committee.

SIRS structured clinical interview and scoring method
The SIRS was modelled after the Initial Subject Protocol of the CDR[18] and the Progressive Aphasia Severity Scale.[19] We delineated six domains of social function (box 1) based on social behavioural symptoms described in the bvFTD diagnostic criteria,[17] contemporary theoretical models of social behaviour[20 21] and clinical experience.

In the newest diagnostic criteria for bvFTD,[17] behavioural disinhibition (A) and loss of sympathy or empathy (C) pertain most specifically to social symptoms. Subcriteria contained in
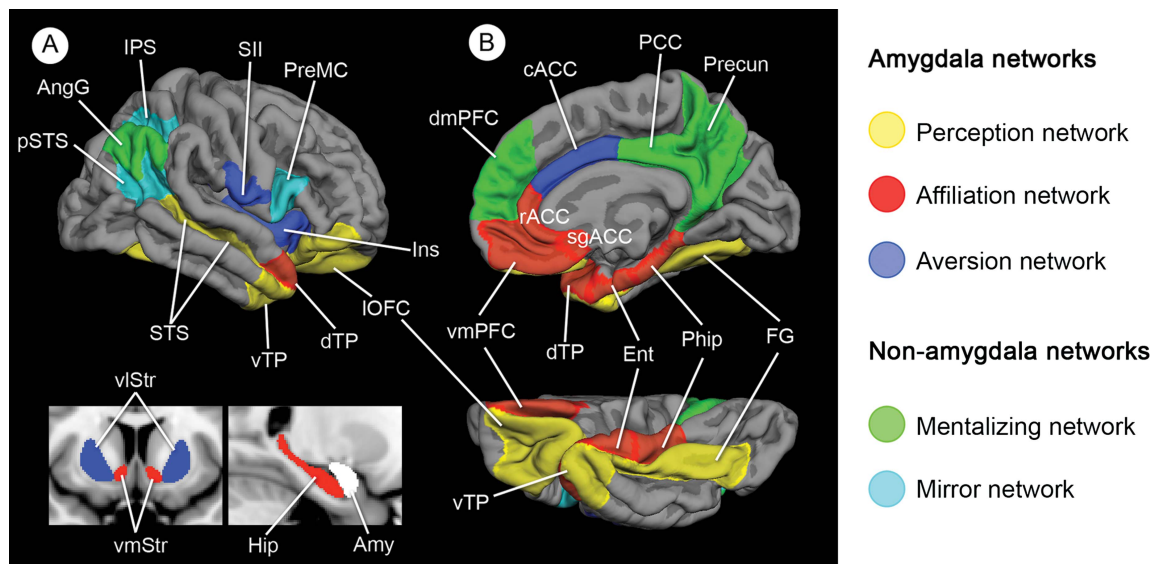
Figure 1   A schematic of five large-scale brain networks subserving processes important for social behaviour. Here, we show three networks that are anchored in the amygdala (amygdala-based networks) and two that are not (control networks). The amygdala is displayed in white indicating that it is the hub of the three amygdala-based networks. Perception network: lOFC, lateral orbitofrontal cortex; vTP, ventrolateral temporal pole; FG, fusiform gyrus; STS, superior temporal sulcus. Affiliation network: dTP, dorsomedial temporal pole; rACC, rostral anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; Ent, entorhinal cortex; PHip, parahippocampal cortex; vmSt, ventromedial striatum. Aversion network: cACC, caudal anterior cingulate cortex; Ins, insula; SII, somatosensory operculum; vlSt, ventrolateral striatum. Mentalising network: dmPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; Precun, precuneus; AngG, angular gyrus (temporoparietal junction). Mirror network: pSTS, posterior superior temporal sulcus; IPS, intraparietal sulcus; PreMC, premotor cortex.

item A appear to overlap with one another and lack specificity for our purposes. For example, *socially inappropriate behaviour* and *loss of manners* likely relate to a similar social dysfunction. Another symptom listed within item A, *lack of attention/response to social cues*, might reflect a distinct social deficit. To address this, we created two separate SIRS items: lack of adherence to social norms and lack of attention/response to social cues. Lack of adherence to social norms covers many of the symptoms listed as examples across the *socially inappropriate behaviour* and *loss of manners or decorum* subcriteria such as touching or kissing strangers or public urination, etc. Although *lack of attention/response to social cues* was listed as an example of the *loss of manners or decorum* subcriterion, we defined this as a separate SIRS domain, covering such symptoms as lack of eye contact or attention to other people's facial expressions. Although lack of attention/response to social cues captures some of the perceptual processes involved in social interactions, we also added a domain called person recognition difficulty to enable problems with this ability to be coded. We separated this domain in part because of the importance of face recognition and related higher-level perceptual abilities in social neuroscience and in part because of clinical observations indicating that some FTD patients exhibit progressive prosopagnosia as an early symptom which interferes with social function.

In addition, we believe there is another social deficit embedded in item A, which may or may not be present in all patients with this symptom and therefore deserves separate coding: *inappropriate trusting of other people*. In the *socially inappropriate behaviour* and *impulsive, rash or careless actions* subcriteria, the following two symptoms likely relate to a deficit in judging the trustworthiness of other people or using suitable caution when interacting with strangers: *inappropriately approaching strangers* and *giving out personal information inappropriately*. To address this, we created a SIRS domain, inappropriate trusting and approach behaviour.

Item C, *early loss of sympathy or empathy*, also contains subcriteria that may encompass separable social deficits. For example, *diminished social interest* or a *general decrease in social engagement* might not be specific to a loss of empathy per se. Thus, we separated lack of empathy/warmth from social withdrawal.

Finally, the new bvFTD diagnostic criteria, major social deficits, demonstrated in recent studies of FTD patients: loss of theory of mind. Thus, in the original development of the SIRS, we defined an additional social cognitive domain, lack of awareness of others' thoughts and intentions, to measure such symptoms as difficulty understanding others' perspectives or difficulty determining if someone is lying or being sarcastic. In the final version of the SIRS, we collapsed the domains lack of empathy/warmth and lack of awareness of others' thoughts/intentions into a single domain called socioemotional detachment (see Results).

The SIRS structured clinical interview, which takes an average of 1.5 h, emphasises change in social functioning from premorbid levels and requires the interviewer to probe for everyday examples from the informant. We initially interviewed patients and informants, but it became quickly clear that patients were generally not consistently capable of reporting on these symptoms. Therefore, we performed the interviews solely with informants. For each patient, an informant was selected on a case-by-case basis with consideration given to the informant's frequency of contact with the patient and their willingness to participate (80% spouses/partners and 20% children). The interviewer uses a scoring guide to rate the severity of impairment in each domain (table 1). The SIRS Sum-of-Boxes (SIRS-SB) summary score is calculated by adding the domain scores. The full material required to use the SIRS is available from BCD.

SIRS reliability and validity analysis

The primary interviewer (KCB) conducted and summarised all interviews and made initial ratings. Based on interview summaries, KCB re-rated 10 cases 5 months later after another researcher removed identifying information and randomised their order; a second trained rater (AN) also blindly rated them. To estimate the intrarater and inter-rater reliability, intraclass correlation coefficients were computed (two-way, random-effects single measures).

To assess convergent validity, we conducted Pearson correlation analyses between SIRS-SB scores and CDR Supplemental Behaviour box scores obtained by the behavioural neurologist prior to SIRS interviews.

Structural MRI data analysis

Quantitative morphometric analysis of T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) MRI data was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu; see online supplementary methods for details).[19] Based on study hypotheses, we examined three primary networks of interest derived from seed-based analyses of resting state functional MRI data in young healthy adults as we have previously described in detail.[4] In brief, these networks were defined by placing seed regions in specific subregions of the amygala (ventral, medial and dorsal) and generating whole-brain connectivity maps for each seed. Based on non-human primate tract-tracing literature and human functional neuroimaging literature, we interpreted these networks as subserving perceptual, affiliative and aversive behaviours important for social behaviour (see detailed rationale in our previous paper). These networks are convergent within the amygdala and would not be identified through independent component analysis, but are replicable in independent samples. The specific regions used in the present study included volumetric measures of amygdala, hippocampus, nucleus accumbens and putamen (each divided by total intracranial volume), and thickness measures within cortical areas of each network of interest as well as control networks which we predicted would not relate to SIRS measures, including a network encompassing brain regions important for thinking about others' thoughts or intentions (mentalising network: figure 1, green) and a network for simulating others' behaviours (mirror network: figure 1, cyan). We obtained cortical thickness measures for 19 regions of interest (ROIs) per hemisphere derived largely from previously developed parcellation schemes.

To quantify the magnitude of atrophy in each ROI, a z score was calculated: z=((individual ROI measure from patient–mean ROI measure from controls)/(SD of ROI measure from controls)). To facilitate interpretation, we multiplied all z scores by −1 so that greater atrophy is represented by a larger z score. Network atrophy scores were computed as the average of z scores for all ROIs within the network. For illustration in figures, per cent atrophy measures were used: % atrophy of ROI of individual=(1−(individual ROI measure from patient/mean ROI measure from controls)). In the figures, particularly for some subcortical structures, there are few patients with relatively large negative values for per cent atrophy. This simply indicates that the size of the structure is on the larger end of the spectrum suggesting that it is relatively spared by the disease and consistent with a size in the normal control distribution.

Table 1 Social Impairment Rating Scale (SIRS) scoring guide

	No impairment 0	Questionable or very mild impairment 0.5	Mild impairment 1	Moderate impairment 2	Severe impairment 3
Lack of attention/response to social cues					
	No change in attention/ response to social cues	Might pay slightly less attention to social cues or respond in a slightly unexpected way; still responds to subtle cues from family member like the raise of an eyebrow or smirk	Pays noticeably less attention to social cues, or sometimes responds awkwardly or unexpectedly to social cues (eg, might make less eye contact, stand closer than normal to others, respond less well to subtle gestures/expressions but understands basic hand pointing and head nods/shakes; might interrupt when another person is speaking).	Pays much less attention to social cues, or often responds awkwardly or unexpectedly to social cues (eg, makes less eye contact, stands closer than normal to others, much less responsive to gestures/expressions; interrupts without noticing expressions of the other person indicating for him/her to stop talking).	Pays almost no attention to social cues, or very often responds awkwardly or unexpectedly to social cues (eg, does not make eye contact, stands closer than normal to others, completely insensitive to conversational flow; hardly responds to overt hand gestures)
Inappropriate trusting or approach behaviour					
	No change in judgments of trustworthiness	May be somewhat more gullible or less cautious around others than before but no clear episodes have occurred	Has displayed a few clear but minor acts of poor judgment of other people (eg, may have purchased something from a salesman with less consideration than previously or given out personal information too easily).	Has displayed multiple minor acts or a few major acts of poor judgment of other people resulting in adverse consequences (eg, might have fallen for scams; given personal information away; interacted with strangers without exercising caution such as inviting them into the house).	Has displayed recurrent, in at least some cases severe, acts of poor judgment of other people resulting in adverse consequences (eg, may have spent a large amount of money on a scam; may have been taken advantage of financially or sexually).
Lack of adherence to social norms					
	No change in social behaviour	Might be slightly more socially inappropriate such as speaking more loudly than usual	Demonstrates mild but consistent socially inappropriate behaviour at least once per week (eg, mild loss in manners such as leaving the table before others have finished; may make rude or explicit remarks or jokes). Strangers may not perceive that something is 'wrong' with him/her or may question whether something is wrong. These behaviours are mostly observed in the home and around familiar people, whereas in public the patient appears relatively normal.	Demonstrates obvious socially inappropriate behaviour on a daily or near daily basis (eg, spitting, touching private parts or belching; moderate loss in manners such as he/she will eat with hands or 'wolf' down food while others are present; may make crude or sexually explicit remarks or offensive jokes about others; there may have been a minor instance of criminal behaviour such as shoplifting). Strangers perceive that something is 'wrong' with him/her. These behaviours occur in the home and also in public but can be curtailed by family members.	Demonstrates obvious socially inappropriate behaviour multiple times per day if the opportunity arises (eg, severe loss in manners such as passing gas at the table; may make crude or sexually explicit remarks or offensive jokes directed at others, loss of personal hygiene ie, obvious to others; there may have been an instance of serious criminal behaviour). Strangers perceive that something is 'wrong' with him/her without having to interact with him/her. These behaviours are not easily redirected by the caregiver and/or occur almost every time the patient is in public or around other people.
Person recognition difficulty					
	No difference in ability to recognise familiar people	Sometimes has trouble recognising acquaintances or distant coworkers	Often does not recognise acquaintances or distant relatives or friends; usually recognises close friends or family members; may have mistaken an unfamiliar person as familiar	Almost never recognises distant relatives or friends; sometimes does not recognise close friends or family members; or sometimes mistakes an unfamiliar person as familiar	Almost never recognises close family members, friends, etc; may have not recognised spouse; or often mistakes unfamiliar people as familiar
Social withdrawal					
	No change in interest in engaging in social activities	Might be slightly less social or initiate slightly less contact with friends or family, but still enjoys being around them and people in general.	Spends somewhat less time talking to and seeing friends and family; he/she may call or make plans with others less often; is less interested in meeting new people or going to social events. Even if he/she does not initiate plans, the patient will go along with plans and still appears to enjoy others' company.	Spends much less time talking to or seeing friends and family; he/she rarely if ever calls or makes plans with friends or family; much less interested in meeting new people or in interacting with close friends and family even when they visit him/her. The spouse/caregiver must convince him/her to go to family events or other social outings but he/she will eventually go along with at least some of these social events but shows diminished engagement.	Spends almost no time talking to or seeing friends and family; he/she almost never, if at all, calls or makes plans with others. Patient is almost completely indifferent or even resistant to caregiver's attempts at getting him/her to socialise. Shows almost no interest in other people.

Socioemotional detachment				
No change in empathy or warmth towards others, or awareness of others' thoughts or intentions	Might be slightly less warm towards others, or less aware of others' thoughts or intentions; at least one questionable instance of indifference to others has occurred that is a change from prior behaviour	Mildly but consistently less warm towards others, or less aware of others' thoughts or intentions; demonstrates clear instances of this on a daily or near daily basis; (eg, he/she rarely asks how others are feeling and shows no, or little, concern or sensitivity to friends' or family members' distress; rarely, if ever, acts happy or sad with others who are clearly happy or sad; may still take notice of spouse or loved one if in overt distress; and/or shows clear impairment in ability to recognise when someone is lying, being sarcastic, telling a joke).	Much less warm towards others, or less aware of others' thoughts and intentions; demonstrates instances of this on a daily or near daily basis; (eg, he/she rarely asks how others are feeling and shows no, or little, concern or sensitivity to friends' or family members' distress; rarely, if ever, acts happy or sad with others who are clearly happy or sad; may still take notice of spouse or loved one if in overt distress; and/or shows clear impairment in ability to recognise when someone is lying, being sarcastic, telling a joke).	Almost completely indifferent towards others, or shows essentially no awareness of others' thoughts or intentions; may demonstrates coldness or frank cruelty towards others (eg, he/she almost never asks how others are feeling and shows no noticeable concern to friends or family members in distress; and/or cannot recognise when others are lying, being sarcastic, or telling jokes).

Brain-behaviour analyses

To test hypotheses, we used each SIRS domain score as the dependent variable in separate hierarchical linear regression models. In the first block, we entered the atrophy z score for the a priori hypothesised network as the independent variable (only if it demonstrated a significant zero-order correlation with the SIRS domain). In the second block run as a stepwise analysis (criterion for variable entry, $p < 0.05$), we entered z scores for the amygdala and for the remaining networks that demonstrated zero-order correlations with the SIRS domain to assess whether they added to the model. We also examined these relationships after controlling for age, gender and global cognition (CDR Sum-of-Boxes (CDR-SB); MMSE) by adding these variables to the first block.

For networks in which atrophy predicted SIRS scores, we conducted regression analyses to explore which ROIs within the network explained the most SIRS variance. In the first block, we entered z scores for ROIs in the relevant network(s) as stepwise predictor variables; in a second stepwise block, we entered z scores for the ROIs in each other network with zero-order correlations with the SIRS score. We used this a priori hypothesis-driven approach because we previously published hypotheses about the behavioural roles of these partially independent brain networks.[4] In this study, we do not believe that a stepwise or other automated regression analysis is appropriate. Additional rationale for this choice is as follows. 'When an investigator has a large pool of potential independent variables (IVs) and very little theory to guide selection among them, stepwise regression is a sore temptation. If the software selects the variables, the investigator is relieved of the responsibility of making decisions about their logical or causal priority or relevance before the analysis. However, this atheoritical approach tends not to be viewed kindly. Most behavioural scientists believe that more orderly advances are made when researchers armed with theories provide a priori hierarchical ordering which reflects causal hypotheses rather than when computers order IVs post hoc and ad hoc for a given sample.'[22]

Analyses were conducted using PASW Statistics V.18 (SPSS, Inc., Chicago, Illinois; $\alpha = 0.05$, two-tailed).

RESULTS

Reliability and validity of the SIRS instrument

Demographic and clinical characteristics for each FTD patient, all of whom were very mildly or mildly impaired based on CDR, are summarised in online supplementary table S1. All but one of the SIRS domains showed high intrarater and inter-rater reliability (see online supplementary table S2). Supporting its convergent validity, the SIRS-SB score correlated with the CDR Supplemental Behaviour score ($r = 0.60$, $p < 0.005$). In contrast, we found no relationship between SIRS-SB and CDR rating, CDR-SB, or MMSE ($p > 0.12$), or between SIRS domain or summary scores and age, gender or education ($p > 0.3$). Taken together, these findings suggest that the SIRS is not an index of general cognitive impairment but rather that it provides a specific measure of social impairment.

SIRS domain scores were correlated with each other, but there was enough unique variance to consider all but two as distinct measures (see online supplementary tables S4 and S5). Two domains we originally attempted to separate, *lack of awareness of others' thoughts/intentions* and *lack of empathy/warmth*, were strongly correlated ($r = 0.78$, $p < 0.001$) so we averaged them, creating a *socioemotional detachment* domain. See online supplementary material for descriptions of specific symptoms in each domain.

Brain-behaviour relationships

Patients with more prominent atrophy across all three networks had greater social impairment (SIRS-SB, figure 2A; r=0.63, p<0.01), but not greater global cognitive impairment (CDR-SB, figure 2B; r=0.34, p=0.15). See online supplementary tables S6 and S7 for additional details regarding atrophy.

Consistent with our predictions, the degree of atrophy in each of the hypothesised networks of interest showed first-order correlations with the severity of impairment in their hypothesised SIRS domains (see table 2). Furthermore, although there were other unpredicted brain-behaviour relationships, the hierarchical regression analyses demonstrated that brain networks or regions with weaker first-order correlations with SIRS domains did not explain additional variance beyond that explained by the a priori hypothesised networks or regions. Nevertheless, we believe that these weaker relationships illustrate the complexity of social impairments in FTD and the need for additional methods to measure the behavioural processes underlying these symptoms.

Consistent with our predictions, patients with the greatest right perception network atrophy exhibited the most severe *lack of attention/response to social cues*, explaining 29% of the variance (figure 3A). These patients also exhibited the most severe *person recognition difficulty* (28% of variance; figure 3D). Patients with the greatest right affiliation network atrophy exhibited the most severe *socioemotional detachment* (52% of variance; figure 3B). Patients with the greatest left aversion network atrophy exhibited the most severe *inappropriate trusting/approach behaviour* (50% of variance; figure 3C); right amygdala atrophy explained an additional 14% of the variance (p=0.02). In all of these regression analyses, atrophy in other networks beyond the predicted ones did not explain additional variance. Patients with the greatest left affiliation network atrophy exhibited the most severe *lack of adherence to social norms* (27% of variance) (figure 3E). Atrophy in the control networks was not associated with SIRS domain impairments (table 2).

In addition to network-level results, amygdala atrophy predicted greater impairment within the three SIRS domains for which we were testing a priori hypotheses (table 2 and figure 4)

and showed a trend for *lack of adherence to social norms*. In hierarchical regression analyses, though, we found that regions other than the amygdala within each network carried most of the SIRS variance (see online supplementary table S8). Patients with more severe *lack of attention/response to social cues* exhibited greater atrophy in the right fusiform gyrus within the perception network (β=0.57, p<0.01, R^2=0.33; figure 5A). Patients with more severe *socioemotional detachment* exhibited greater atrophy in the right nucleus accumbens within the affiliation network (β=0.74, p<0.001, R^2=0.55; figure 5B). Patients with more severe *inappropriate trusting/approach behaviour* exhibited greater atrophy in the left ventral anterior insula within the aversion network (Step 1: β=0.61, p<0.01, R^2=0.37; figure 5C); right putamen atrophy explained additional variance (Step 2: right putamen, β=0.51, p<0.01, R^2=0.25; figure 5F). Patients with more severe *person recognition difficulty* exhibited greater atrophy in the right superior temporal sulcus of the perception network (β=0.61, p<0.01, R^2=0.37; figure 5D). Patients with more severe *lack of adherence to social norms* exhibited greater atrophy in the left ventromedial prefrontal cortex within the affiliation network (β=0.57, p<0.01, R^2=0.33; figure 5E). For all of these analyses, atrophy in other ROIs did not explain additional variance.

DISCUSSION

We created a reliable and valid instrument to enable clinicians to obtain structured information about the types and severity of symptoms in multiple domains of social behaviour in daily life. The SIRS is distinct from other informant-rated or interview-based instruments used in FTD clinical research (eg, the Cambridge Behavioural Inventory,[7] Frontal Systems Behavioural Inventory,[23] Frontal Behavioural Inventory[24]) in that (a) it is rated by a trained clinician rather than an informant (in the case of the former two) and (b) it focuses specifically on social function rather than including social function along with other behaviours (eg, eating behaviour, stereotyped movements, etc). Furthermore, we demonstrated a triple dissociation in the relationships between atrophy in distinct brain networks and impairment in specific SIRS domains they were predicted to subserve, providing further validation of the scale and support for
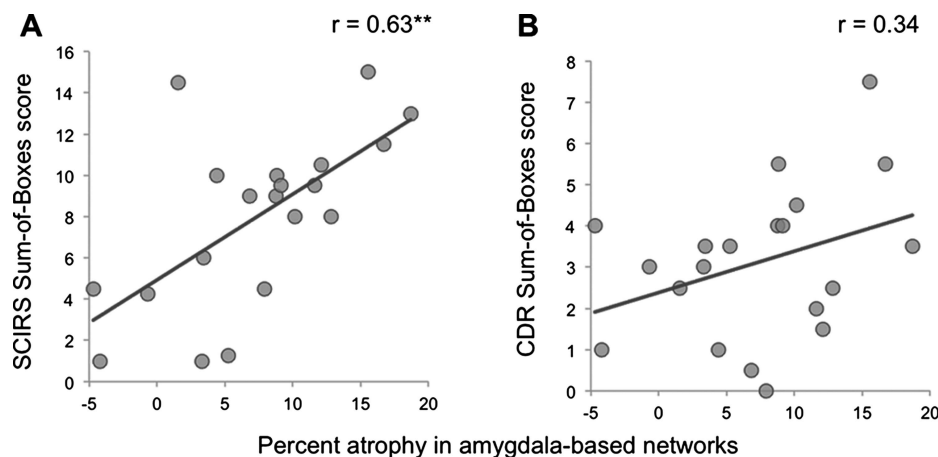

Figure 2 Atrophy in amygdala-based brain networks predicted more severe social impairment but not global cognitive impairment. In these scatter plots, the y-axis represents the sum of all domain box scores for the Social Impairment Rating Scale. (A) and the Clinical Dementia Rating (CDR) Sum-of-Boxes (B); the x-axis represents, for each frontotemporal dementia patient, the mean percentage of atrophy relative to healthy control participants for all regions in all three networks of interest averaged together (eg, 10% indicates 10% atrophy in the patient relative to controls). **p<0.01.

Table 2 Correlations between atrophy in brain networks and severity of social impairment in Social Impairment Rating Scale (SIRS) domains

SIRS domain scores	Lack of attention to social cues	Socioemotional detachment	Inappropriate trusting or approach behaviour	Lack of adherence to social norms	Person recognition difficulty	Social withdrawal	SIRS Sum-of-Boxes
Atrophy in amygdala-based networks							
Perception network							
Right	**0.53***	0.36	0.37	0.06	**0.53***	0.07	0.43***
Left	0.29	0.30	0.57**	0.20	0.30	−0.17	0.37
Affiliation network							
Right	0.52*	**0.72***	0.60**	0.47*	0.43	0.09	0.66**
Left	0.40***	**0.69***	0.67**	0.52*	0.29	−0.03	0.62**
Aversion network							
Right	0.37	0.54*	**0.66***	0.45*	0.37	0.01	0.57**
Left	0.02	0.37	**0.71***	0.41***	0.12	−0.20	0.38
Atrophy in the amygdala							
Amygdala							
Right	0.53*	0.58**	0.59**	0.43***	0.29	0.15	0.60**
Left	0.39***	0.43***	0.43***	0.34	0.00	0.06	0.40***
Atrophy in control networks							
Mentalising network							
Right	0.13	0.21	0.14	0.20	0.39***	−0.08	0.23
Left	0.00	0.10	0.15	0.20	0.24	−0.31	0.11
Mirror network							
Right	−0.03	0.12	0.32	0.26	0.11	−0.33	0.13
Left	−0.05	−0.11	0.21	0.14	0.16	−0.36	0.03

*p<0.05; **p<0.01; ***p<0.10.
Predicted correlations are displayed in bold font. ROIs included in each network: Perception network: lateral orbitofrontal cortex, fusiform gyrus, superior temporal sulcus and ventral temporal pole; Affiliation network: ventromedial prefrontal cortex, subgenual and rostral anterior cingulate cortices, dorsal temporal pole, entorhinal cortex, parahippocampus, hippocampus and nucleus accumbens; Aversion network: caudal anterior cingulate cortex, insula, somatosensory operculum and putamen; Mentalising network: dorsomedial prefrontal cortex, posterior cingulate cortex, precuneus and angular gyrus; Mirror network: premotor cortex, posterior superior temporal sulcus and intraparietal sulcus.
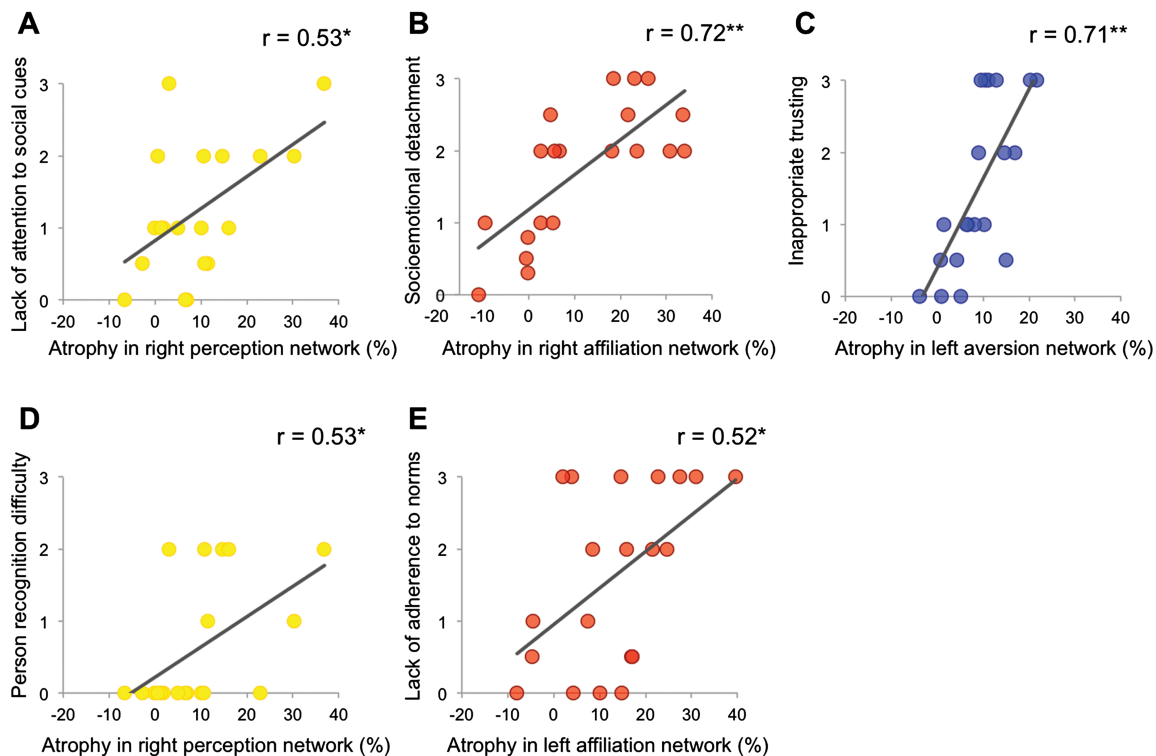
Figure 3 In frontotemporal dementia patients, atrophy in distinct brain networks predicted the severity of impairment in specific domains of social function measured by the Social Impairment Rating Scale (SIRS). Scatter plots (A–E) display the severity of social impairment in each SIRS domain (on the y-axis) and the percentage of brain network atrophy relative to healthy control participants (on the x-axis). Atrophy in each network shown here was the best predictor of the respective SIRS domain, and atrophy in the other networks did not explain additional variance in the domain. *p<0.05; **p<0.01.
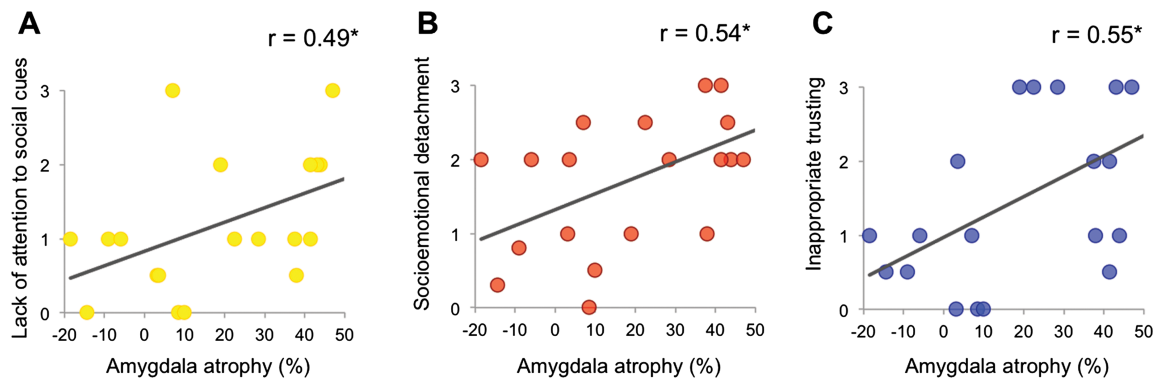
Figure 4 In frontotemporal dementia patients, atrophy in the amygdala predicted the severity of impairment in Social Impairment Rating Scale (SIRS) domains that reflect core deficits to social perception, affiliation and aversion. Scatter plots (A–C) display the severity of social impairment in each SIRS domain of interest (on the y-axis) and the percentage of atrophy relative to healthy control participants in the amygdala (on the x-axis). *p<0.05.

our neuroanatomical framework in which three amygdala-based networks play dissociable roles in perceptual, affiliative and avoidant aspects of social behaviour.

Neural substrates of impaired social perception in FTD
Patients with the greatest atrophy in the perception network exhibited the most severe *lack of attention/response to social cues*: they no longer made as frequent eye contact, had difficulty interpreting body language and gestures and were insensitive to others' facial expressions. Previous work employing cognitive/behavioural testing in FTD has revealed deficits in eye contact, interpreting others' facial expressions, vocal prosody and body

language, with two studies demonstrating relationships to atrophy in brain regions within the perception network including the amygdala, lateral orbitofrontal cortex and temporal pole,[25][26] although neither study measured the fusiform gyrus or superior temporal sulcus.

The ventral temporal cortex, superior temporal sulcus, amygdala and lateral orbitofrontal cortex have been implicated in social perception in a wealth of neuroimaging, electrophysiological and neuropsychological work. For example, electrophysiological work in monkeys[27] and functional neuroimaging work in humans[28] have demonstrated selective neural responses to featural and expressive aspects of bodies and faces in these
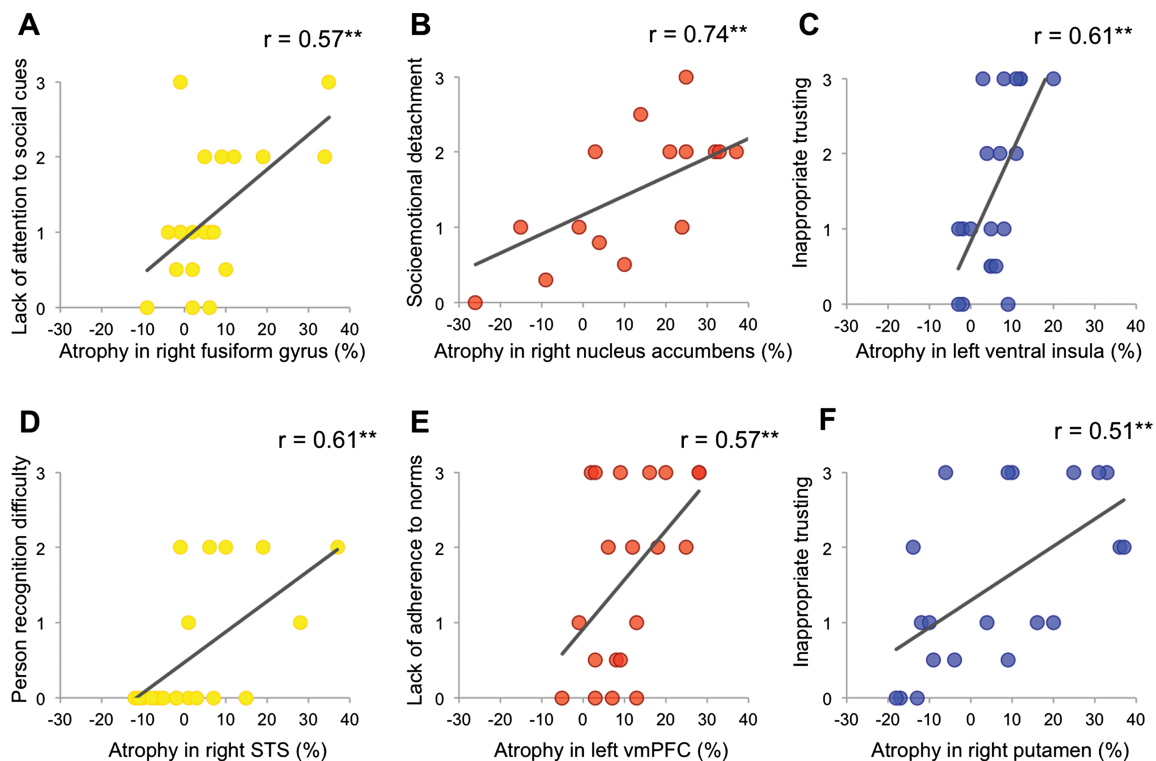
Figure 5 Atrophy in specific ROIs within each large-scale network were the best predictors of impairment in different domains of social function measured by the Social Impairment Rating Scale (SIRS). Scatter plots (A–F) display the severity of social impairment in each SIRS domain (on the y-axis) and the percentage of ROI atrophy relative to healthy control participants (on the x-axis). Atrophy in each ROI that is shown here was the best predictor of the respective SIRS domain, and atrophy in the other ROIs did not explain additional variance in the domain. vmPFC, ventromedial prefrontal cortex; STS, superior temporal sulcus. *p<0.05; **p<0.01.

regions—including the fusiform gyrus, the region we found to be most predictive of impairment in this domain.

Our findings are consistent with lesion neuropsychological results demonstrating difficulty directing attentional resources to relevant social stimuli, particularly the eye region of others' faces,[21] after damage to the amygdala, orbitofrontal cortex, superior temporal and fusiform cortex.

Neural substrates of impaired social affiliation in FTD

FTD patients with the greatest atrophy in the affiliation network exhibited the most severe *social and emotional detachment*. Indifferent to other people's feelings, these patients hardly comforted, helped or showed affection to their family, friends and loved ones. This has often been subsumed under the general description of personality change in prior literature, but we view it as a specific deficit in social affiliative behaviour. Consistent with our findings, three studies in FTD patients have mapped similar symptoms of socioemotional detachment onto brain regions within the affiliation network. Decreased right ventromedial prefrontal cortex volume correlated with diminished agreeableness,[29] while decreased grey matter in the right ventromedial prefrontal cortex, subgenual anterior cingulate cortex and the dorsomedial temporal pole correlated with reduced empathy[30] and interpersonal warmth.[8]

Previous focal lesion studies implicate mesolimbic and reward-related structures in sentiments and acts of social affiliation. For example, patients with ventromedial prefrontal cortex damage, including the subgenual and rostral anterior cingulate cortices, exhibit severely diminished empathy.[31]

Our region-level findings on the nucleus accumbens are consistent with functional neuroimaging studies of social affiliation. For example, the ventral striatum is activated when participants make a real charitable donation[32] or choose to trust or cooperate with another person.[33]

Two of the networks examined in this paper share substantial topography with the default mode network (DMN)—the affiliation and mentalising networks. Specifically, the affiliation network shares more substantial topography with the medial temporal lobe (MTL) subsystem of the DMN, whereas the mentalising network shares more substantial topography with the dorsomedial prefrontal (dmPFC) subsystem of the DMN.[34] These subsystems differ in the quantity of limbic tissue they contain and likely in the degree to which they contribute to affect components of social behaviours. In the present study, we show that patients with greater atrophy in the affiliation network, which strongly resembles the MTL subsystem of the DMN, have more severe losses in warmth and empathy, whereas patients with greater atrophy in the mentalising network, which strongly resembles the dmPFC subsystem of the DMN, do not show this pattern of social dysfunction. Our findings suggest that, in addition to memory, the MTL subsystem of the DMN may play a role in affective processes motivating prosocial behaviours such as warmth, concern and empathy.

Neural substrates of impaired social aversion in FTD

FTD patients who exhibited the greatest atrophy in the aversion network lost normal social avoidance behaviours, becoming less cautious around strangers and more willing to trust, approach and strike up conversations with them. They also tended to indiscriminately donate to charities and fall for scams. Thus, the aversion network plays a necessary role in appropriately judging others as untrustworthy, unfair or deceptive and in turn making decisions to avoid, punish or reject them. To our knowledge, no similar reports exist in the FTD literature.

Our region-level findings are consistent with neuropsychological work in amygdala-damaged patients who exhibit markedly diminished social apprehension.[21] Such patients tend to judge even the most seemingly untrustworthy people as trustworthy and approachable and cooperate with other people despite apparent violations in trust.[35]

Furthermore, that insula atrophy is the best predictor of impaired social aversion is consistent with functional neuroimaging studies of healthy adults. For example, participants recruit ventral insula when receiving an unfair offer from another person[36] or receiving feedback that a partner did not exhibit mutual trust.[37]

Our findings are also consistent with recent resting-state functional connectivity and neuroanatomical studies in FTD patients that have proposed the selective vulnerability of regions within the 'salience network' (which largely overlaps with our aversion network) in the pathology of FTD.[38] According to this work, the salience network is anchored by the frontoinsula and includes the adjacent anterior insula and caudal anterior cingulate/anterior mid-cingulate cortex as well as the amygdala, ventral striatum and brainstem autonomic nuclei. Outside the social realm, regions within this network have been implicated in evaluating and guiding behavioural and autonomic responses to physically aversive or threatening stimuli[39 40] and to the intensity of affective experience when viewing negative images.[41] Here we provide additional support for the hypothesis that regions within this network play a necessary role in evaluating and guiding responses to socially aversive stimuli as well and that damage to this network leads to impairment in normal avoidant responses (resulting in, eg, gullibility).

Further supporting the specificity of these brain-behaviour relationships, we found that impairments in SIRS domains could not be explained by atrophy in brain networks involved in thinking about or simulating others' behaviours to infer their thoughts, intentions and beliefs (the mentalising and mirror networks, respectively). Regions within these networks demonstrated atrophy, yet the degree of atrophy did not correlate with any SIRS score. We did not examine symptoms related to mentalising or mirroring in the present study because, in part, it is difficult to ask informants to infer how a patient was (or was not) thinking about or simulating another person's mind. These aspects of social behaviour might be best measured using psychometric theory-of-mind paradigms.[9]

Amygdala atrophy demonstrated moderate-sized correlations with impairment in multiple SIRS domains, supporting the hypothesis that the amygdala is a hub of networks responsible for effectively managing social interactions and maintaining social relationships.[21] The amygdala is a component of at least three distinct neuroanatomical circuits important for detecting and decoding social and emotional cues, as well as using these cues to guide affiliative and avoidant decisions in the service of adaptive social behaviour. These findings also help explain why amygdala volume and connectivity within three corticolimbic networks relate to individual differences in social connectedness in healthy adults.[4 42]

Although recent data emphasise the importance of the selective vulnerability of the salience network[38] (which bears strong resemblance to our aversion network)—particularly the frontoinsula and its von Economo neurons and fork cells—in FTD, we believe the present data also highlight the amygdala as a key brain region relevant to social impairments in FTD. The amygdala suffers substantial neuropathology early in the course of all pathologic subtypes of FTD.[43] Although it is a key component of the salience network, the amygdala is also part of at least two

other large-scale networks.[4] Our observation here that some patients exhibit relatively more prominent atrophy in one of these networks than the others, along with deficits referable to the function of the affected network, provides further support for the 'network degeneration hypothesis'[38] of bvFTD and extends it beyond the salience network.

The SIRS and the present study have limitations. Whereas structured clinical interviews provide valuable information for the characterisation and quantification of symptoms and are a mainstay in the field of psychiatry, they also suffer from patient or informant biases as well as clinician biases. We attempted to address some of these biases here by eliciting multiple concrete everyday examples of impaired or preserved function within each SIRS domain. In addition, the rating protocol requires that informants provide more than one clear example of a particular impairment for patients to receive a rating above 0.5 (which represents questionable or very mild impairment). Nevertheless, some might argue that psychometric tasks provide more objective data than structured interviews. Yet performance-based testing of social functions is particularly challenging because normal social behaviour is complex and depends heavily on interpersonal, situational and cultural contextual features that are difficult to study in the laboratory. We are currently working to investigate whether performance on tasks of social cognition correlate with SIRS measures; we believe that ultimately a combination of interview-derived information about real-world symptoms and psychometric data from social cognitive-affective tests will likely together provide the most comprehensive picture of the types and severity of impairment in FTD patients, as we have demonstrated for memory and executive deficits in AD.[44] In our assessment of SIRS reliability, we chose to re-rate the severity of impairments using interview summaries instead of repeating interviews. Future work to confirm the intrarater and inter-rater reliability of the SIRS should include a full-scale test–retest approach with repeated interviews.

As in previous brain-behaviour studies in FTD,[8 30 45–50] we chose here to study a mixed sample with patients who have variable clinical phenotypes within the FTD spectrum and variable degrees and distributions of social cognitive impairment and grey matter atrophy. This choice was made, as in the previous studies and also as in studies of patients with focal brain lesions such as stroke,[51] to increase the power of the planned regression analyses. Nevertheless, this also presents a potential weakness in that differences observed in the types and severity of social impairment and brain atrophy could be due to differences inherent to the diagnostic subgroups. We specifically examined whether diagnosis had an effect on our variables of interest and found that although the agrammatic PPA subgroup had lower severity scores in the *socioemotional detachment* domain than the other groups, they were not statistical outliers and controlling for diagnostic group did not change our main findings. Thus, in our study, diagnostic subgroup did not seem to play an appreciable role in our results. We further recognise, as another weakness, that a detailed neuropsychological assessment of the patients may have been helpful in reporting their clinical characteristics.

In the long run, we hope to use the SIRS to investigate impaired social behaviour in other neuropsychiatric disorders, including schizophrenia, autism, patients with focal brain lesions or other neurodegenerative disorders. It may also be of interest to apply the SIRS in longitudinal studies of healthy aging, even though we would not expect scores greater than 0.5 in people without neuropsychiatric illness. Ultimately, we hope that the SIRS will be useful for characterising the symptoms of FTD patients cross-sectionally and as a longitudinal outcome measure in clinical trials of putative interventions to improve social functioning, but its longitudinal properties have not yet been investigated.

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