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# Diminished baseline autonomic outflow in semantic dementia relates to left-lateralized insula atrophy

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ABSTRACT

In semantic dementia (SD), asymmetric degeneration of the anterior temporal lobes is associated with loss of semantic knowledge and alterations in socioemotional behavior. There are two clinical variants of SD: semantic variant primary progressive aphasia (svPPA), which is characterized by predominant atrophy in the anterior temporal lobe and insula in the left hemisphere, and semantic behavioral variant frontotemporal dementia (sbvFTD), which is characterized by predominant atrophy in those structures in the right hemisphere. Previous studies of behavioral variant frontotemporal dementia, an associated clinical syndrome that targets the frontal lobes and anterior insula, have found impairments in baseline autonomic nervous system activity that correlate with left-lateralized frontotemporal atrophy patterns and disruptions in socioemotional functioning. Here, we evaluated whether there are similar impairments in resting autonomic nervous system activity in SD that also reflect left-lateralized atrophy and relate to diminished affiliative behavior. A total of 82 participants including 33 people with SD (20 svPPA and 13 sbvFTD) and 49 healthy older controls completed a laboratory-based assessment of respiratory sinus arrhythmia (RSA; a parasympathetic measure) and skin conductance level (SCL; a sympathetic measure) during a two-minute resting baseline period. Participants also underwent structural magnetic resonance imaging, and informants rated their current affiliative behavior on the Interpersonal Adjective Scale. Results indicated that baseline RSA and SCL were lower in SD than in healthy controls, with significant impairments present in both svPPA and sbvFTD. Voxel-based morphometry analyses revealed left-greater-than-right atrophy related to diminished parasympathetic and sympathetic outflow in SD. While left-lateralized atrophy in the mid-to-posterior insula correlated with lower RSA, left-lateralized atrophy in the ventral anterior insula correlated with lower SCL. In SD, lower baseline RSA, but not lower SCL, was associated with lower gregariousness/extraversion. Neither autonomic measure related to warmth/agreeableness, however. Through the assessment of baseline autonomic nervous system physiology, the present study contributes to expanding conceptualizations of the biological basis of socioemotional alterations in svPPA and sbvFTD.

## 1. Introduction

Semantic dementia (SD) is a clinical subtype of frontotemporal dementia (FTD) that results from predominant neurodegeneration of the anterior temporal lobes (Hodges et al., 1992; Neary et al., 1998; Snowden et al., 2001). In SD, early atrophy is often asymmetric and causes loss of semantic knowledge. People with left-lateralized (i.e., left-greater-than-right) anterior temporal atrophy typically lose verbal and object-related semantic knowledge, a syndrome known as "semantic variant primary progressive aphasia" (svPPA; Gorno-Tempini et al., 2011). Those with right-lateralized (i.e., right-greater-than-left) anterior temporal atrophy, in contrast, often exhibit loss of socioemotional

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semantic knowledge and empathy as well as gains in compulsions or rigidity, a syndrome we recently named, "semantic behavioral variant FTD" (sbvFTD; Younes et al., 2022). In svPPA and sbvFTD, neurodegeneration has a focal onset but progresses from one anterior temporal lobe to the other before spreading onward to the insula and orbitofrontal cortex, among other regions (Guo et al., 2013; Kumfor et al., 2016; Seeley et al., 2005). SD, therefore, reflects a spectrum of semantic knowledge impairment, and the eventual anatomical overlap between svPPA and sbvFTD gives rise to shared language and behavioral features despite early syndromic differences (Brambati et al., 2009; Chan et al., 2009; Ding et al., 2020; Gainotti, 2017; Seeley et al., 2005; Snowden et al., 2018; Ulugut Erkoyun et al., 2020). As both svPPA and sbvFTD are often associated with the same molecular class, frontotemporal lobar degeneration with TDP-43 Type C, they are thought to reflect opposite ends of a single neuropathological continuum (Borghesani et al., 2020).

The impairments in semantic knowledge that characterize SD are well understood (Battistella et al., 2020; Battistella et al., 2019; Binney et al., 2010; Borghesani et al., 2021; Borghesani et al., 2019a; Borghesani et al., 2019b; Gorno-Tempini & Price, 2001; Ralph et al., 2017), but less is known about the changes in behavior and emotion that also arise (Kumfor & Piguet, 2012; Rosen et al., 2006). Studies of SD have found poor emotion recognition (Brown et al., 2020; Fittipaldi et al., 2019; Kumfor et al., 2018; Rosen et al., 2002), atypical eye contact (Sturm et al., 2011), diminished sadness reactivity (Hua et al., 2019), and dysregulated positive emotional responding (Chen et al., 2021; Kumfor et al., 2019; Shdo et al., 2022; Sturm et al., 2015). On measures of personality, people with SD have notable reductions in gregariousness/extraversion and, to a lesser extent, warmth/agreeableness (Sollberger et al., 2011). Right anterior temporal lobe degeneration in SD, in particular, has been associated with reduced interpersonal warmth (Rankin et al., 2006; Sollberger et al., 2009). Socioemotional impairments in sbvFTD are often more pronounced than in svPPA (Landin-Romero et al., 2016), including lower facial expressivity (Edwards-Lee et al., 1997), lower empathic concern (Irish et al., 2013), and poorer emotion recognition (Marshall et al., 2018).

Socioemotional alterations in FTD are associated with dysfunction in the autonomic nervous system. Studies of behavioral variant FTD (bvFTD), an FTD syndrome characterized by disruptions in empathy and social behavior (Multani et al., 2017; Rankin et al., 2005; Seeley, 2019), have found diminished autonomic nervous system reactivity (i.e., phasic autonomic changes that capture physiological differences between a resting baseline and a task) in response to stimuli that typically elicit disgust, sadness, and embarrassment (Eckart et al., 2012; Hua et al., 2019; Sturm et al., 2006; Sturm et al., 2013). Laboratory-based studies in SD are limited but suggest lower parasympathetic reactivity (i.e., attenuated cardiac deceleration during emotion identification task; Marshall et al., 2019) and lower sympathetic reactivity (i.e., limited change in skin conductance in response to positive and negative emotional videos; Kumfor et al., 2019) to a variety of affective cues. The autonomic nervous system not only activates during emotions but also maintains basal physiological levels at rest (Berntson, Cacioppo, Quigley, & Fabro, 1994; Levenson, 2003). In bvFTD, baseline measures of tonic parasympathetic and sympathetic activity are impaired compared to healthy older controls (Guo et al., 2016; Joshi et al., 2014; Sturm et al., 2018a; Sturm et al., 2018b) and related to disruptions in socioemotional behavior. While lower baseline parasympathetic activity is associated with lower agreeableness (Guo et al., 2016) and diminished prosocial helping behavior (Sturm et al., 2018b), lower baseline sympathetic activity is related to greater examiner-rated emotional blunting (Joshi et al., 2014). Whether reduced baseline autonomic activity also underlies the behavioral changes that characterize the SD spectrum is unknown.

In bvFTD, diminished baseline autonomic activity relates to atrophy and dysfunction in left-lateralized systems anchored by the insula. In our previous studies of bvFTD, we found lower baseline parasympathetic activity was associated with atrophy in the left ventral anterior insula and left inferior temporal gyrus, among other areas (Guo et al., 2016; Sturm et al., 2018a). On measures of task-free functional connectivity, left-hemisphere structures also played critical roles in regulating baseline autonomic outflow. Weaker functional connectivity between the left ventral anterior insula and bilateral pregenual anterior cingulate cortex related to attenuated parasympathetic activity (Guo et al., 2016; Sturm et al., 2018a). Lower baseline sympathetic activity in bvFTD also related to atrophy in numerous left hemisphere regions including the left mid-insula, anterior temporal lobe, inferior temporal gyrus, parahippocampal gyrus, and orbitofrontal cortex as well as some right hemisphere regions including the middle frontal gyrus, frontal pole, orbitofrontal cortex, and fusiform gyrus (Sturm et al., 2018a). Functional connectivity analyses revealed that lower baseline sympathetic activity in bvFTD was associated with lower functional connectivity between the left anterior cingulate cortex and right hypothalamus (Sturm et al., 2018a). Taken together, these findings suggest that whereas the right hemisphere plays a central role in the generation of phasic emotional reactions, the left hemisphere is essential for maintaining tonic physiological levels within ranges that are critical for homeostasis.

In the present study, we investigated whether baseline autonomic activity was impaired in SD. Building on our prior research in bvFTD, we hypothesized that lower baseline autonomic activity would relate to left-lateralized atrophy in the insula, a structure that plays a central role in maintaining basal autonomic outflow (Seeley et al., 2007) and a site of prominent atrophy in SD as well as bvFTD (Brambati et al., 2009; Mummery et al., 2000; Seeley, 2010; Seeley et al., 2005). Unlike the sympathetic nervous system, which promotes self-focused attention and a narrow attentional focus (Critchley, 2002), the parasympathetic nervous system promotes other-oriented attention and interpersonal engagement by slowing cardiac and respiration rates and creating variability in their patterned outflow at rest (Critchley, 2009; Kogan et al., 2014; Oveis et al., 2009; Porges, 2001; Stellar, Cohen, Oveis, & Keltner, 2015). Thus, we also expected that lower baseline parasympathetic activity, but not sympathetic activity, would relate to diminished affiliative behavior in SD.

## 2. Materials and methods

### 2.1. Participants

Eighty-two participants including 33 people with SD—20 svPPA, 13 sbvFTD—and 49 healthy controls, were included in the study. Participants with SD met criteria for either svPPA or sbvFTD (Gorno-Tempini et al., 2011; Younes et al., 2022). Healthy controls were recruited from advertisements and underwent an identical neurological, cognitive, and imaging work-up as those with svPPA and sbvFTD and were free of current or previous neurological or psychiatric disorders. Although data were available for five additional healthy controls, we removed these participants from the sample to ensure that the healthy control and SD groups were matched on age, gender, and education. The study was approved by the Committee on Human Research at the University of California, San Francisco. All participants, or their surrogates, gave their informed consent before completing the study.

Participants underwent a multidisciplinary team evaluation at the University of California, San Francisco (UCSF) Memory and Aging Center that included a clinical interview, neurological exam, functional assessment, and neuropsychological testing within 90 days of the laboratory assessment (see next section for details). Participants provided information about their age, gender, race/ethnicity, handedness, and education. The Clinical Dementia Rating Scale (CDR), an informant-based measure of dementia severity, was used to assess daily functioning (Morris, 1993). The CDR Total (scores range from 0 to 3) and Sum of the Boxes (CDR-Box) scores (scores range from 0 to 18) were computed for each participant, with higher scores on both measures

indicating greater functional impairment. The Mini-Mental State Examination (MMSE) was used to assess global cognition; scores range from 0 to 30, with higher scores indicating better cognitive functioning (Folstein et al., 1975). All healthy controls had a CDR Total score of 0 and a MMSE score of 27 or higher (i.e., indicating no functional impairment and cognitive abilities within normal limits).

### 2.2. Neuropsychological assessment

All participants completed a neuropsychological battery that included tests of verbal and visual episodic memory (e.g., word list and figure recall), executive functioning (e.g., set-shifting, working memory, and verbal and nonverbal fluency), language (e.g., confrontational naming, repetition, and syntax comprehension), and visuospatial processing (figure copy; Kramer et al., 2003).

Thirty-one participants with SD (18 svPPA and 13 sbvFTD) also underwent additional testing to assess their semantic knowledge. These participants completed a modified version of the Peabody Picture Vocabulary Test, a 16-item test of verbal semantic knowledge in which they matched a verbalized word to a picture that represented a verb, adjective, animate object, or inanimate object from four picture choices (Dunn & Dunn, 1981; Kramer et al., 2003). Scores range from 0 to 16, with lower scores indicating greater verbal semantic knowledge impairment. Twenty participants (9 svPPA and 11 sbvFTD) completed the recognition subtest of the UCSF Famous Faces battery (Borghesani et al., 2019a). In the recognition subtest, a 20-item test that measures nonverbal semantic knowledge, participants identified which one of four faces was famous, which did not require retrieval of proper names or person-specific details (Gorno-Tempini & Price, 2001). Scores range from 0 to 20, with lower scores indicating greater nonverbal semantic knowledge impairment.

### 2.3. Informant-rated socioemotional behavior

Close informants of 27 participants with SD (16 svPPA and 11 sbvFTD) completed the Interpersonal Adjective Scale within two weeks of the autonomic assessment. Twenty-five of the close informants were participants' spouses or significant others (e.g., long-term partners), and the remaining two were adult children. Because self-awareness and insight can decline in the context of neurodegenerative disease (Rankin et al., 2003), informant-based measures are a valid and reliable approach for assessing changes in behavior and personality in people with dementia (Smith-Gamble et al., 2002; Sutin et al., 2019).

The Interpersonal Adjective Scale is a well-validated questionnaire that measures individual differences in interpersonal traits (Sollberger et al., 2011; Wiggins, 1995; Wiggins et al., 1988). Based on a circumplex model of personality, the Interpersonal Adjective Scale evaluates functioning along two main axes of power and affiliation. We focused on the Gregariousness/Extraversion and Warmth/Agreeableness subscales, which assess personality traits known to decline in SD (Sollberger et al., 2011). Using an eight-point scale that ranged from "extremely inaccurate" to "extremely accurate," informants rated the extent to which 64 interpersonal adjectives (e.g., cheerful, friendly, sympathetic, and kind) characterized participants' current behavior. Scores for each subscale were summed and converted to *T*-scores based on four normative samples (Wiggins, 1995) that included over 4000 healthy participants, aged 16–89 years old (approximately 45% men and 55% women). The majority of these participants were White/European American and college educated, a demographic profile that is comparable to the sample in the present study (see below).

### 2.4. Laboratory assessment

#### 2.4.1. Procedure

Participants completed a laboratory assessment of autonomic nervous system physiology at the UCSF Center for Psychophysiology and Behavior. After being seated in a comfortable chair in a well-lit experiment room, sensors were applied to participants to obtain continuous measures of physiological activity. We recorded participants' prescribed medications, caffeine consumption that day, and the time of day that they completed the laboratory assessment. The room temperature in the laboratory at the time of testing was also noted. Throughout the session, participants were recorded with a remotely controlled video camera; they were notified that they were being filmed during the informed consent process at the beginning of the testing session.

To assess baseline physiology, participants were asked to clear their minds and to watch a black "X" on a white background for two minutes.

#### 2.4.2. Physiological recordings

Continuous recordings of autonomic nervous system activity were obtained using Biopac MP150 bioamplifiers and a computer equipped with data acquisition software. Measures included (1) *inter-beat interval (IBI):* electrodes were placed in a bipolar configuration on opposite sides of the participant's chest; inter-beat interval was calculated as time interval in milliseconds between R waves from the electrocardiogram, (2) *inter-cycle interval (ICI):* a pneumatic bellows or respiration transducer was stretched around the thoracic region, and the inter-cycle interval was measured as the time interval in milliseconds between inspirations, (3) *respiratory sinus arrhythmia (RSA):* RSA was calculated as the difference in milliseconds between the shortest IBI during inspiration and the longest IBI during expiration, which follows the peak-valley approach to RSA measurement (Grossman et al., 1990), and (4) *skin conductance level (SCL)*: a constant-voltage device was used to pass a small voltage between Ag/AgCl Silver 8 mm electrodes (using an electrolyte of sodium chloride) attached to the palmar surface of the middle phalanges of the ring and index fingers of the non-dominant hand. We used RSA as a measure of vagally-mediated parasympathetic activity (Berntson et al., 1993) and SCL as a measure of sympathetic activity (Critchley, 2002). Ambient room temperature was also continuously recorded during the testing session with a thermistor positioned near the participant.

Physiological data were processed using a custom pipeline scripted in AcqKnowledge software (v4.4, www.biopac.com), as reported in our previous work (Pasquini et al., 2023; Sturm et al., 2018b). We optimized standard Biopac scripts to calculate IBI, ICI, RSA, and SCL. For the electrocardiogram channel, we used a band pass filter with a Blackman window AC (Blackman61, 1.0, 35.0, 4000) to improve accuracy when marking QRS peaks. For the respiration channel, we used a band pass filter to eliminate frequencies outside of 0.05–1.00 Hz to increase detection of inhalation and exhalation points. For the skin conductance level channel, we performed a smoothing function, which reduces abrupt changes or noise in the data by computing the moving average of a series of five data points and replacing each value with the mean value of the moving average "window."

The scripts identified and marked the signature components of each waveform, and these marks were then visually inspected for errors and noise. Outliers in the raw data for each participant were considered +/- 3 standard deviations from the mean level during the baseline period; these periods were interpolated if their duration was three seconds or less and deleted if their duration was greater than three seconds. Second-by-second averages were exported for each physiological channel. To ensure only complete waveforms for cyclic measures (i.e., IBI and ICI) were included in our analyses of RSA, we removed the first and last five seconds of the baseline period. Next, we computed average levels of IBI, ICI, SCL, and RSA during the remaining 110-second baseline period. In the averaged data, outliers $\pm 3$ standard deviations from the mean of each diagnostic group were identified. We reviewed these outliers (IBI for one healthy control, ICI for one healthy control, and SCL for one person with svPPA), but, as their values were within biologically plausible ranges, and results for group differences did not change with or without them, they were retained. SCL data were not available for two people with svPPA, one person with sbvFTD, and one healthy control

due to technical difficulties. The natural log of RSA was used in all analyses to improve proximity to a normal distribution.

### 2.5. Structural neuroimaging acquisition and preprocessing

#### 2.5.1. MRI acquisition

Participants underwent research-quality structural magnetic resonance imaging (MRI) at the UCSF Neuroscience Imaging Center. Images were acquired on either a 3.0 Tesla Siemens TIM Trio (Siemens, Iselin, NJ) or 3.0 Tesla Siemens PRISMA (Siemens, Iselin, NJ) scanner, both equipped with a 12-channel head coil. For the TIM Trio scanner, whole brain images were acquired using volumetric MPRAGE (160 sagittal slices; slice thickness = 1.0 mm; matrix = 256 × 230; in-plane resolution = 1.0 × 1.0 mm; repetition time = 2300 ms; echo time = 2.98 ms; medium inversion time = 900 ms; flip angle = 9°). For the PRISMA scanner, whole brain images were acquired using volumetric MPRAGE (160 sagittal slices; slice thickness = 1.0 mm; matrix = 256 × 230; in-plane resolution = 1.0 × 1.0 mm; repetition time = 2300 ms; echo time = 2.9 ms; medium inversion time = 900 ms; flip angle = 9°).

#### 2.5.2. MRI preprocessing

Consistent with previous studies from our center, MRIs were visually inspected by trained research staff and flagged for excessive motion if it was difficult to distinguish between white matter and gray. White matter disease burden was rated on a 0–3 scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), similar to guidelines outlined by prior work (Fazekas et al., 1987). Scans rated as moderate or severe were excluded. After visual inspection, the structural T1-weighted images were corrected for bias field and segmented into gray matter, white matter, and cerebrospinal fluid. Consistent with recent neuroimaging studies of similar clinical samples (Brown et al., 2019; Dial et al., 2023; Montembeault et al., 2023; Pasquini et al., 2020; Roy et al., 2023; Shdo et al., 2022), the images were spatially warped and normalized to Montreal Neurological Institute (MNI) space using Statistical Parametric Mapping 12 (SPM12; Friston, 2004). Although syndrome-specific templates are an area of ongoing development (Dadar et al., 2021; Ridwan et al., 2021; Van Hecke et al., 2011), the heterogeneity of atrophy patterns within a sample may limit how well that template performs in other samples, and there is no current consensus that a syndrome-specific template is the preferred approach. In all preprocessing steps, default SPM12 parameters were utilized except that we used the light clean-up procedure in the morphological filtering step. Default tissue probability priors (voxel size: $2.0 \times 2.0 \times 2.0\ mm^3$) of the International Consortium for Brain Mapping were used. Segmented images were visually inspected for adequate gray-white segmentation. To reduce interindividual variability in anatomy while maintaining the ability to distinguish between regional differences in tissue content (Ashburner & Friston, 2000; Whitwell, 2009), we smoothed the gray matter maps with an 8 mm full-width at half-maximum Gaussian kernel, in line with previous studies (Perry et al., 2017; Roy et al., 2023; Sturm et al., 2018a).

#### 2.5.3. MRI at time of diagnosis

Given that atrophy becomes more bilateral with disease progression in SD (Seeley et al., 2005), we used each participant's first research MRI scan to confirm the expected lateralized atrophy pattern at the time of diagnosis. Thirty-two participants with SD (20 svPPA and 12 sbvFTD) underwent structural MRI at their first UCSF research visit (one person with sbvFTD did not have an available scan, but their clinical evaluation offered strong support for suspected anterior temporal lobe atrophy). Following visual inspection, the scan of one person with sbvFTD had excessive motion and was excluded. In total, 31 participants with SD had useable MRI data at the time of their diagnosis (20 svPPA and 11 sbvFTD). Of these, 19 scans (13 svPPA and 6 sbvFTD) were acquired on the TIM Trio scanner, and 12 scans (7 svPPA and 5 sbvFTD) were acquired on the PRISMA scanner.

#### 2.5.4. MRI at time of laboratory assessment

As the laboratory assessment of autonomic activity occurred at a later research visit for 19 (58%) participants with SD (mean interval = 1.25 years after their first research MRI), we used a subsequent research MRI scan in these cases to: (1) characterize atrophy patterns at the time of the physiological assessment, and (2) correlate lateralized atrophy patterns with autonomic activity. In total, 31 participants with SD (19 svPPA and 12 sbvFTD) had an MRI scan acquired within one month of the laboratory assessment (mean interval = 3.5 days). Forty-two healthy controls had an MRI scan acquired within 13 months of the laboratory assessment (mean interval = 165 days). Following visual inspection, 8 participants (4 svPPA, 3 sbvFTD, and 1 healthy control) were excluded for significant motion and only one participant was excluded (1 svPPA) for excessive white matter disease. Thus, 64 participants (14 svPPA, 9 sbvFTD, and 41 healthy controls) had useable MRI data. Of these, 29 scans were acquired on the TIM Trio scanner (9 svPPA, 3 sbvFTD, and 17 healthy controls) and 35 scans (5 svPPA, 6 sbvFTD, and 24 healthy controls) were acquired on the PRISMA scanner.

### 2.6. Statistical analyses

#### 2.6.1. Anterior temporal lobe asymmetry at time of diagnosis

Using each participant's first research MRI scan, we first confirmed that the svPPA and sbvFTD groups had the expected pattern of lateralized anterior temporal lobe atrophy at the time of diagnosis. We calculated an anterior temporal lobe laterality index using previously described methods (Borghesani et al., 2020). In brief, we extracted the mean gray matter volume from the left and right anterior temporal lobe regions of interest using the combined anterior temporal lobe subregions derived from inferior-medial, superior-medial, inferior-lateral, and superior-lateral regions (Papinutto et al., 2016). Gray matter volumes from these regions were then rescaled to the minimum and maximum total gray matter volume in the whole sample and then divided by the average total gray matter volume of the healthy controls in our sample to account for the distance from the expected values. Asymmetry scores for the left and right anterior temporal lobes were computed by inputting these scaled and normalized values into the following formula: (left – right) / (left + right). Negative values reflected greater left-lateralized (i.e., left-greater-than-right) anterior temporal lobe atrophy, and positive values reflected right-lateralized (i.e., right-greater-than-left) anterior temporal lobe atrophy.

#### 2.6.2. Demographic and clinical status at time of laboratory assessment

To characterize the groups, we ran *t*-tests to compare the SD and healthy control groups and *t*-tests with Bonferroni correction to compare all three groups (svPPA, sbvFTD, and healthy controls) on demographic measures, clinical data, and room temperature at the time of the laboratory assessment. Chi-square and Fischer's exact tests, as needed, were used to test for group differences in gender, handedness, race/ethnicity, flagged medications, caffeine consumption on the day of laboratory assessment (yes/no), and time of day of physiology acquisition (morning vs. afternoon).

#### 2.6.3. Baseline autonomic activity

Analyses of covariance (ANCOVAs) were used to compare baseline RSA, SCL, IBI, and ICI in the SD and healthy control groups. In all analyses, we controlled for age and gender, variables that can influence physiology (Eisdorfer et al., 1980; Geovanini et al., 2020; Koenig & Thayer, 2016; Zhang, 2007). Given that RSA can be influenced by IBI and ICI, we ran a follow-up analysis that included those variables as additional covariates. Finally, we compared all three groups (svPPA, sbvFTD, and healthy controls) on the autonomic measures in exploratory analyses and used Bonferroni-corrected *t*-tests to adjust for multiple comparisons.

We ran additional analyses of baseline autonomic activity to ensure that several potential confounding variables did not account for our

results. In each follow-up analysis, we included one of the following variables as an additional covariate (with age and gender). (1) Medications. We flagged participants who were prescribed acetylcholinesterase inhibitors, beta-blockers, or acetylcholinesterase inhibitors as these may alter heart rate variability and heart rate (Kontopoulos et al., 1997; Kotecha et al., 2017) and created a medication variable (0 = no flagged medications, 1 = yes flagged medications). (2) Caffeine consumption. To ensure that caffeine did not influence our results (Corti et al., 2002; Grant et al., 2023), we also coded participants' caffeine consumption on the day of testing (0 = no caffeine consumption that day, 1 = yes caffeine consumption that day). (3) Physiology testing time. To ensure that the time of day of the physiology data acquisition did not influence our results (Chellappa et al., 2017; Morris et al., 2012; Venables & Mitchell, 1996), we coded whether participants completed the laboratory assessment in the morning or afternoon (0 = morning, 1 = afternoon). (4) Room temperature. We accounted for whether room temperature at the time of the laboratory assessment influenced our results. See Table 1 for more details.

#### 2.6.4. Behavioral correlates of diminished baseline autonomic activity

We ran linear regressions, controlling for age and gender (Wiggins et al., 1988), to examine whether lower baseline RSA, but not lower baseline SCL, was associated with lower affiliative behaviors (as measured by the Interpersonal Adjective Scale) in SD. As control analyses, we also examined whether lower baseline RSA or SCL in SD related to impairments in verbal (Peabody Picture Vocabulary Test) or nonverbal (UCSF Famous Faces) semantic knowledge.

#### 2.6.5. Analyses of MRIs acquired at the time of laboratory assessment

Using the MRI scans that were acquired in close temporal proximity to the laboratory assessment of physiological activity, we first conducted whole-brain voxel-based morphometry analyses using SPM12 to compare the SD combined group, svPPA group, and sbvFTD group to the healthy controls. Age, gender (0 = men, 1 = women), scanner type (0 = Trio, 1 = PRISMA), and total intracranial volume (TIV; which accounts for individual differences in head size) were included as covariates.

Next, we computed voxelwise asymmetry scores given bilateral and asymmetric atrophy in svPPA and sbvFTD. Scores were calculated by subtracting the gray matter volume in each voxel in the right hemisphere from its gray matter volume in the left, divided by the sum of the gray matter volume in both voxels (i.e., [left – right] / [left + right]), as described above. The voxelwise asymmetry scores provided an index of relative atrophy in every voxel in one hemisphere while accounting for its atrophy in the opposite hemisphere. To identify voxels in which lateralized atrophy related to lower baseline autonomic activity, we used vlsm2 (Bates et al., 2003) to correlate the voxelwise asymmetry maps with the baseline autonomic measures, an approach we have used in prior studies (Guo et al., 2016; Sturm et al., 2018b). We next derived a study-specific error distribution by conducting 5,000 permutation analyses to calculate the one-tailed *T*-threshold ($p_{FWE} < .05$) using vlsm2, a voxel-based-lesion-symptom mapping method used to study the relationship between tissue damage and behavior on a voxel-by-voxel basis (Bates et al., 2003). This permutation analysis used a resampling approach for determining significance whereby a test statistic was compared with the null distribution calculated from the present dataset and, thus, provided an accurate representation of Type 1 error at $p < .05$ across the entire brain. We focused these analyses on the autonomic measures that were diminished in SD (given no differences in these autonomic measures between svPPA and sbvFTD; see below) and masked our analyses to the bilateral insula (from the Brainnetome Atlas; https://atlas.brainnetome.org/bnatlas.html) in our primary analyses. We next removed the insula mask to determine whether there were other neural correlates of baseline autonomic activity. Age, gender, disease severity (CDR-Box), scanner type (0 = Trio, 1 = PRISMA), and TIV were included as covariates in these analyses. The *a priori* significance level was set to $p_{FWE} < .05$ when masked to the bilateral insula and

**Table 1**
Demographic, cognitive, and clinical information by diagnostic group. Means and standard deviations, unless otherwise noted. Significant differences are noted.

| | Healthy Controls | Semantic Dementia | svPPA | sbvFTD | Significant Differences |
|---|---|---|---|---|---|
| *n* | 49 | 33 | 20 | 13 | |
| Age | 68.45 (6.14) | 66.44 (7.00) | 65.34 (6.94) | 68.12 (7.03) | |
| Gender (Men: Women) | 18:31 | 16:17 | 11:9 | 5:8 | |
| Handedness (Right: Left) | 46:3 | 33:0 | 20:0 | 13:0 | |
| Race/Ethnicity (*n* = ) | | | | | |
| Asian/Pacific Islander/ Asian American | 5 | 3 | 2 | 1 | |
| Black/African American | 1 | 0 | 0 | 0 | |
| Latine/ Chicane/ Hispanic American | 1 | 1 | 0 | 1 | |
| White/ European American | 42 | 29 | 18 | 11 | |
| Education (years) | 17.41 (1.71) | 17.30 (2.88) | 17.20 (2.75) | 17.46 (3.18) | |
| Flagged medications (*n* = ) | 3 | 9 | 4 | 5 | SD vs. HC sbvFTD vs. HC |
| Caffeine consumption (% Yes) | 74.5 | 69.7 | 70.0 | 69.2 | |
| Physiology Testing Time (morning: afternoon) | | | | | SD vs. HC svPPA vs. HC |
| Room Temperature (Fahrenheit) | 77.82 (5.69) | 78.37 (6.14) | 77.64 (5.03) | 79.74 (8.00) | |
| Clinical Dementia Rating, Total Score | 0.00 (0.00) | 1.00 (0.52) | 0.90 (0.50) | 1.17 (0.54) | SD > HC; svPPA > HC; sbvFTD > HC |
| Clinical Dementia Rating, Sum of Boxes Score | 0.00 (0.00) | 5.53 (2.49) | 4.75 (2.23) | 6.83 (2.45) | SD > HC; svPPA > HC; sbvFTD > HC; sbvFTD > svPPA |
| Mini Mental Status Exam (/30) | 29.54 (0.73) | 20.96 (5.88) | 21.21 (4.66) | 20.67 (7.27) | SD < HC; svPPA < HC; sbvFTD < HC |
| California Verbal Learning Test short form 10-min recall (/9) | 8.40 (0.55) | 1.04 (1.80) | 0.73 (1.16) | 1.45 (2.42) | SD < HC; svPPA < HC; sbvFTD < HC |
| Benson figure copy 10-min recall (/17) | 11.89 (2.04) | 3.92 (4.59) | 4.93 (5.34) | 2.75 (3.36) | SD < HC; svPPA < HC; sbvFTD < HC |
| Modified trails (correct lines per minute) | 42.38 (12.37) | 20.86 (11.87) | 20.38 (13.66) | 21.71 (8.65) | SD < HC; svPPA < HC; sbvFTD < HC |
| Phonemic fluency (# correct in 60 s) | 17.15 (3.74) | 7.28 (5.25) | 6.14 (4.54) | 8.73 (5.93) | SD < HC; svPPA < HC; sbvFTD < HC |
| Semantic fluency (# | 23.08 (5.19) | 8.04 (6.48) | 7.23 (5.21) | 9.00 (7.87) | SD < HC; svPPA < HC; |

(*continued on next page*)

**Table 1** (*continued*)

| | Healthy Controls | Semantic Dementia | svPPA | sbvFTD | Significant Differences |
|---|---|---|---|---|---|
| correct in 60 s) | | | | | sbvFTD < HC |
| Design fluency (# correct in 60 s) | 12.19 (3.67) | 7.17 (3.77) | 7.29 (3.69) | 7.00 (4.08) | SD < HC; svPPA < HC; sbvFTD < HC |
| Digits backward | 5.78 (1.36) | 4.33 (1.75) | 4.13 (1.25) | 4.58 (2.27) | SD < HC; svPPA < HC; sbvFTD < HC |
| Benson figure copy (/17) | 15.62 (0.73) | 14.81 (2.33) | 15.57 (0.76) | 13.92 (3.18) | sbvFTD < HC |
| Boston Naming Test spontaneous correct (/15) | 14.68 (0.65) | 4.58 (3.67) | 3.73 (3.33) | 5.73 (3.95) | SD < HC; svPPA < HC; sbvFTD < HC |
| Peabody Picture Vocabulary Test modified (/16) | 15.89 (0.33) | 7.94 (4.46) | 6.72 (4.28) | 9.62 (4.31) | SD < HC; svPPA < HC; sbvFTD < HC |
| Famous Faces Recognition (/20) | – | 12.75 (5.68) | 16.00 (2.45) | 10.09 (6.27) | svPPA > sbvFTD |
| Interpersonal Adjective Scale, Gregarious-Extraverted subscale (*T*-score) | – | 42.59 (15.96) | 45.13 (14.56) | 38.91 (17.87) | |
| Interpersonal Adjective Scale, Warm-Agreeable subscale (*T*-score) | – | 35.56 (18.84) | 34.94 (17.89) | 36.45 (20.99) | |

to $p < .005$, uncorrected, for the whole-brain analyses.

## 3. Results

### 3.1. Demographic and clinical variables

The healthy controls (HC) were 18 men and 31 women, on average 68.45 years of age, mostly White American (85.71%), mostly right-handed (93.88%), and had on average 17.41 years of education. Participants with SD were on average 66.44 years of age, 16 men and 17 women, mostly White American (87.87%), all right-handed, and had on average 17.30 years of education. The participants with SD did not differ from the healthy controls in age (HC vs. svPPA $p = .07$, HC vs. sbvFTD $p = .87$), gender (HC vs. svPPA $p = .26$, HC vs. sbvFTD $p = .99$) education (HC vs. svPPA $p = .70$, HC vs. sbvFTD $p = .93$), handedness (HC vs. svPPA $p = .55$, HC vs. sbvFTD $p = .27$), race/ethnicity (HC vs. svPPA $p = .99$, HC vs. sbvFTD $p = .67$), caffeine consumption (HC vs. svPPA $p = .94$, HC vs. sbvFTD $p = .98$), or room temperature at time of testing (HC vs. svPPA $p = .91$, HC vs. sbvFTD $p = .39$). A greater proportion of the participants with SD completed the physiology testing during the afternoon than the healthy controls (HC vs. svPPA $p = .04$, HC vs. sbvFTD $p = .053$), and a greater proportion of the participants with sbvFTD had flagged medications than the healthy controls (HC vs. svPPA $p = .20$, HC vs. sbvFTD $p < .01$).

Participants with SD had CDR Total Scores ranging from 0 to 2, CDR-Box scores ranging from 0 to 11, and MMSE scores ranging from 4 to 29. As expected, the SD groups had higher disease severity (CDR-Box: HC vs. svPPA, $p < .001$; HC vs. sbvFTD, $p < .001$) and lower scores than the healthy controls on global cognitive screening (MMSE: HC vs. svPPA, $p < .001$; HC vs. sbvFTD, $p < .001$), verbal episodic memory (California Verbal Learning Test 10-min recall, HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), visual episodic memory (Benson figure copy 10-min recall, HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), set-shifting (Modified Trails, HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), phonemic fluency (D words: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), semantic fluency (animal fluency: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), figural fluency (design fluency: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), digits backward (digits backward: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p = .04$), confrontation naming (Boston Naming Test total correct: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$), and semantic knowledge (Peabody Picture Vocabulary Test: HC vs. svPPA $p < .001$, HC vs. sbvFTD $p < .001$). Only the sbvFTD group had lower performance than the healthy controls on figure copy (Benson figure copy: HC vs. svPPA $p = .84$, HC vs. sbvFTD $p = .009$). See Table 1 for the demographic, cognitive, and functional data.

When compared directly, the svPPA and sbvFTD groups did not differ in their demographic profiles (age: $p = .27$, gender: $p = .57$, education: $p = .80$, handedness: $p = .33$, race/ethnicity $p = .73$) or variables related to the laboratory assessment (flagged medications $p = .45$, caffeine consumption: $p > .99$, physiology testing time: $p > .99$, room temperature: $p = .42$). A comparison of the svPPA and sbvFTD groups on clinical and cognitive measures revealed higher disease severity in sbvFTD than in svPPA (CDR-Box: $p = .02$). Although not significantly different, the svPPA group performance on confrontation naming and verbal semantic knowledge trended to be worse than the performance of the sbvFTD group (PPVT, $p = .07$), as expected. Nonverbal semantic knowledge as assessed with famous faces recognition was worse in participants with sbvFTD than in those with svPPA ($p = .014$).

Examination of the anterior temporal lobe asymmetry scores from participants' earliest MRIs confirmed that the svPPA group was characterized by left-lateralized anterior temporal lobe atrophy and that the sbvFTD group was characterized by right-lateralized anterior temporal lobe atrophy. See Fig. 1.

### 3.2. Diminished baseline autonomic physiology in SD

ANCOVAs (controlling for age and gender) revealed lower baseline RSA, $F(3,78) = 9.84$, $p < .01$; lower baseline SCL, $F(3,74) = 11.93$, $p < .001$; and shorter baseline ICI (i.e., faster respiration rates), $F(3,78) =$

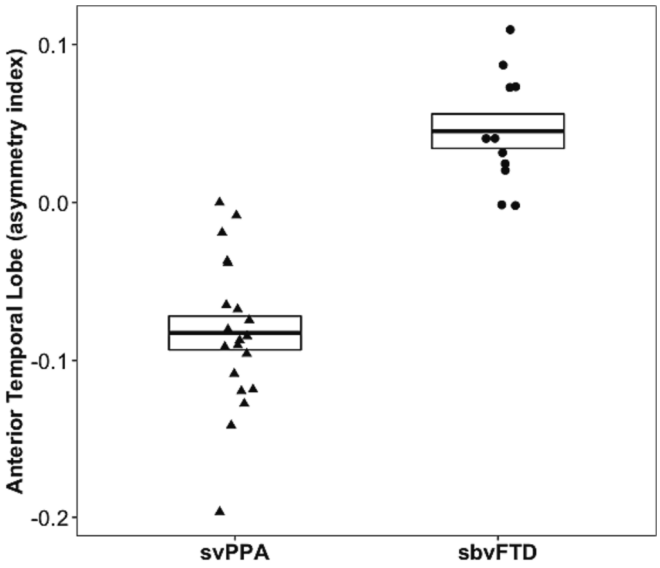


**Fig. 1.** The anterior temporal lobe asymmetry index confirmed the expected lateralization in svPPA and sbvFTD at the time of diagnosis. Negative values reflect greater left-lateralized (i.e., left-greater-than-right) atrophy, and positive values reflect greater right-lateralized (i.e., right-greater-than-left) atrophy.

5.56, $p < .05$, in SD than in healthy controls. The SD group did not differ from the healthy controls in baseline IBI, $F(3,78) = 0.22$, $p = .64$, however. When we also controlled for IBI and ICI to account for their contributions to baseline RSA (in addition to age and gender), baseline RSA in SD was still lower than in the healthy controls, $F(5,76) = 14.15$, $p < .001$.

In *post hoc* Bonferroni-adjusted comparisons, both the svPPA and sbvFTD groups had lower baseline RSA (svPPA vs. healthy controls: $p < .05$ and sbvFTD vs. healthy controls: $p < .01$) and baseline SCL (svPPA vs. healthy controls: $p < .05$ and sbvFTD vs. healthy controls: $p < .01$) than the healthy controls. Neither the svPPA group nor the sbvFTD group differed from the healthy controls on baseline IBI (svPPA vs. healthy controls: $p = .95$ and sbvFTD vs. healthy controls: $p = .48$) or baseline ICI (svPPA vs. healthy controls: $p = .11$, sbvFTD vs. healthy controls: $p = .073$), however. See Fig. 2.

We conducted several follow-up analyses to test the robustness of our results. In each analysis, we added an additional covariate (with age and gender) to confirm that other factors were not accounting for the group differences in autonomic activity that we detected. When we included medication use, our results for baseline RSA, $F(4,77) = 11.01$, $p < .01$; baseline SCL, $F(4,73) = 11.84$, $p < .001$; and baseline ICI, $F(4,77) = 5.52$, $p < .05$, were unchanged. When we included caffeine consumption, our results for baseline RSA, $F(4,75) = 9.93$, $p < .01$; baseline SCL, $F(4,71) = 12.81$, $p < .001$; and baseline ICI, $F(4,75) = 4.58$, $p < .05$, remained significant. In analyses that included the time of day for the physiology testing, our results for baseline RSA, $F(4,77) = 9.77$, $p < .01$; baseline SCL, $F(4,73) = 12.57$, $p < .001$; and baseline ICI, $F(4,77) = 5.52$, $p < .05$, also endured. Finally, when we included room temperature, our results for baseline RSA $F(4,68) = 9.62$, $p < .01$; baseline SCL, $F(4,64) = 7.16$, $p < .01$; and baseline ICI, $F(4,68) = 5.49$, $p < .05$, were the same. As none of these additional variables had a significant effect on our results, we did not include them as covariates in subsequent analyses.

### 3.3. Lower baseline RSA, but not SCL, related to lower gregariousness/extraversion in SD

On the Interpersonal Adjective Scale, people with SD had an average *T*-score of 42.59 for gregariousness-extraversion, which falls in the low-average range, and an average *T*-score of 35.56 for warmth-agreeableness, a score that is below average. In an exploratory *t*-test with Bonferroni correction, the svPPA and sbvFTD groups did not differ on gregariousness-extraversion or on warmth-agreeableness ($p = .84$). As these groups are small when considered separately, this result should be interpreted with caution, however. Linear regressions in SD found lower RSA was associated with lower gregariousness/extraversion, $t = 3.32$, $\beta = .33$, $p < .01$, but not lower warmth/agreeableness, $t = .46$, $\beta = .06$, $p = .65$. As expected, lower SCL was not associated with lower gregariousness/extraversion, $t = .79$, $\beta = .13$, $p = .44$, or lower warmth/agreeableness, $t = -.63$, $\beta = -.10$, $p = .54$, in SD. See Fig. 3.

### 3.4. Neither RSA nor SCL related to verbal or nonverbal semantic knowledge in SD

Linear regressions indicated that baseline RSA in SD was not associated with performance on either the Peabody Picture Vocabulary Test, $t = -.33$, $\beta = -.04$, $p = .74$, or the UCSF Famous Faces task, $t = 1.56$, $\beta = .31$, $p = .14$. Baseline SCL was also not associated with performance on the Peabody Picture Vocabulary Test, $t = .69$, $\beta = .09$, $p = .49$, or the UCSF Famous Faces task, $t = .85$, $\beta = .17$, $p = .41$, in SD.

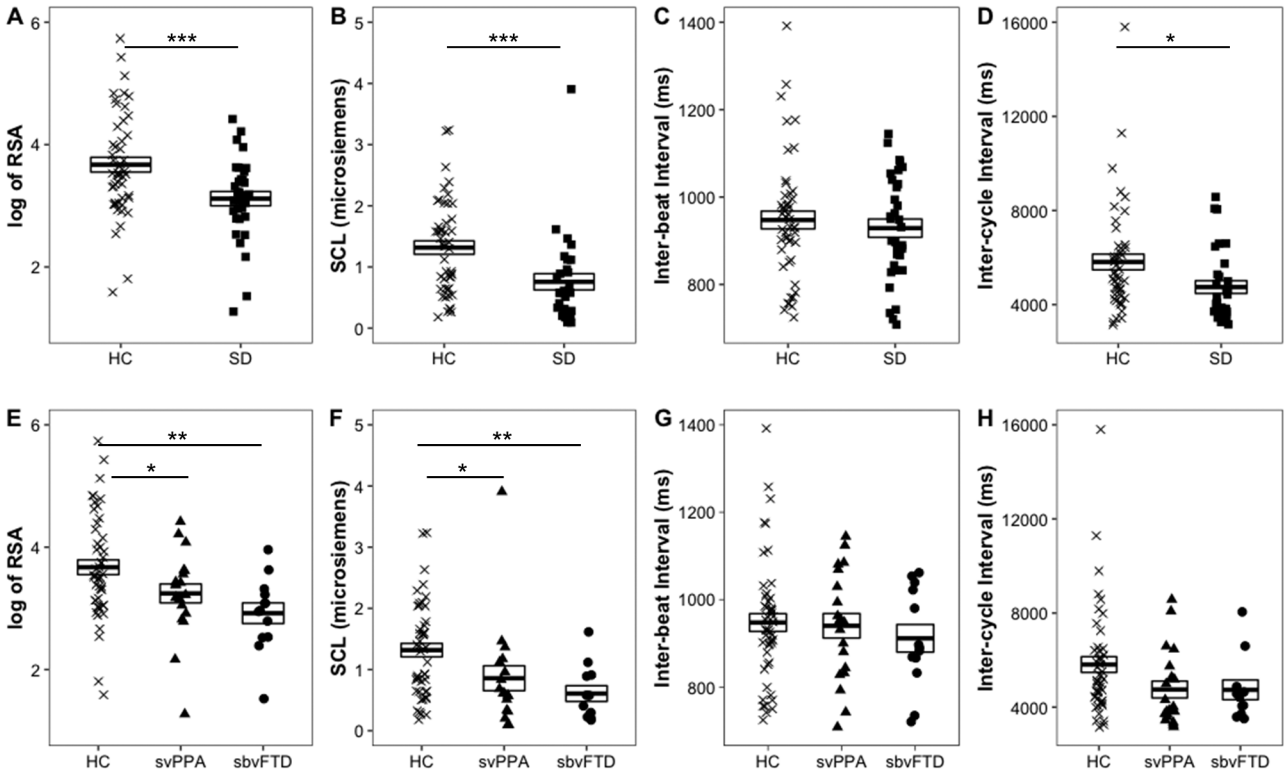


**Fig. 2.** Boxplots of baseline autonomic measures with means and standard errors. Panels A-D: Compared to healthy controls, participants with SD had lower baseline RSA, lower SCL, and shorter ICI. No difference was found between the two groups on IBI. Panels E-H: When comparing the svPPA, sbvFTD, and healthy control groups using Bonferroni-corrected *t*-tests, both the svPPA and the sbvFTD groups had lower baseline RSA and SCL than the healthy controls. No differences were found among the three groups for IBI or ICI. HC = healthy controls. IBI = inter-beat interval. ICI = inter-cycle interval. SCL = skin conductance level. RSA = respiratory sinus arrhythmia. *$p < .05$ **$p < .01$ ***$p < .001$.

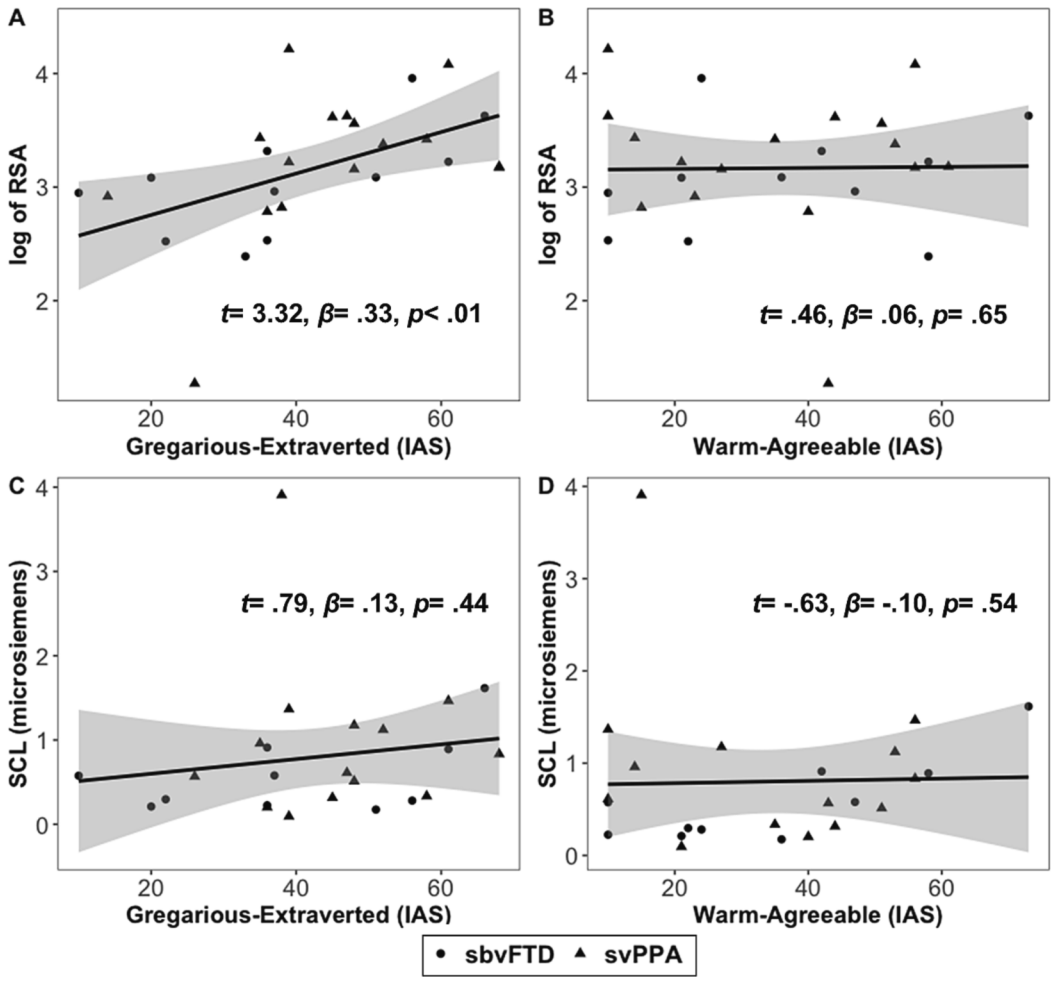


**Fig. 3.** Scatterplots illustrate associations that baseline RSA had with affiliative behavior, as measured by the IAS. Lower (log transformed) baseline RSA was associated with lower (A) gregariousness/extraversion but not (B) warmth/agreeableness. Lower baseline SCL, however, was not associated with either lower (C) gregariousness/extraversion or (D) warmth/agreeableness. IAS = Interpersonal Adjective Scale.

### *3.5. Diminished baseline autonomic activity in SD related to left-lateralized insula atrophy*

At the time of the laboratory assessment of autonomic activity, participants with SD had smaller gray matter volume in the temporal lobes, amygdala, insula, orbitofrontal cortex, anterior cingulate cortex, caudate, and putamen than the healthy controls ($p_{FWE}$< .05). While the svPPA group had smaller gray matter volume in bilateral, but predominantly left, anterior temporal, insular, and orbitofrontal regions ($p_{FWE}$< .05), in the sbvFTD group the atrophy pattern was less lateralized, with smaller gray matter volume in the bilateral anterior temporal lobes, insula, and orbitofrontal cortex than the healthy controls ($p_{FWE}$< .05). See Fig. 4.

Linear regression analyses correlating autonomic measures to voxelwise asymmetry maps revealed that lower baseline RSA in SD was associated with left-greater-than-right atrophy in the mid-to-posterior insula (MNI peak: −39, 0, −2; k= 210, maximum $T$= 3.84, $p_{FWE}$< .05), and lower baseline SCL was associated with left-greater-than-right atrophy in the ventral anterior insula (MNI peak: −36, 12, −12; k= 135, maximum $T$= 3.96, $p_{FWE}$< .05). When we included IBI and ICI as additional covariates in the RSA analysis, lower baseline RSA was still associated with left-greater-than-right atrophy in the mid-to-posterior insula (MNI peak: −42, −12, 6; k= 305, maximum $T$= 5.33, $p_{FWE}$< .05). Neither lower RSA nor lower SCL was associated with right-greater-than-left atrophy in any areas. To ensure that our results reflected linear associations between the autonomic measures and the gray matter asymmetry scores, we extracted the mean asymmetry scores from these clusters and plotted them against baseline RSA and SCL. These plots confirmed that our results held true across the sample and were not accounted for by group status. See Fig. 5.

After removing the insula mask, whole-brain analyses of the gray matter asymmetry maps uncovered no additional correlates of baseline RSA or SCL in SD at $p_{FWE}$< .05. At uncorrected thresholds, lower baseline RSA was associated with left-greater-than-right atrophy in the posterior insula, frontal regions (inferior, orbitofrontal, and superior medial), temporal regions (inferior, middle, and superior gyri), precentral gyrus, supramarginal gyrus, postcentral gyrus, and cerebellum ($p$< .005, uncorrected). At this threshold, lower baseline RSA was also associated with right-greater-than-left atrophy in the inferior parietal gyrus. At uncorrected thresholds, lower baseline SCL was associated with left-greater-than-right atrophy in the ventral anterior insula, middle frontal regions, supramarginal gyrus, middle and superior temporal regions with ($p$< .005, uncorrected). At this threshold, lower baseline SCL was also associated with right-greater-than-left atrophy in parietal and middle frontal gyri. See Supplemental Figure 1 and Supplemental Table 1.

## 4. Discussion

Our findings indicate that baseline autonomic functioning is diminished in SD. The participants with SD had lower resting RSA and SCL than the healthy controls, and these basal parasympathetic and

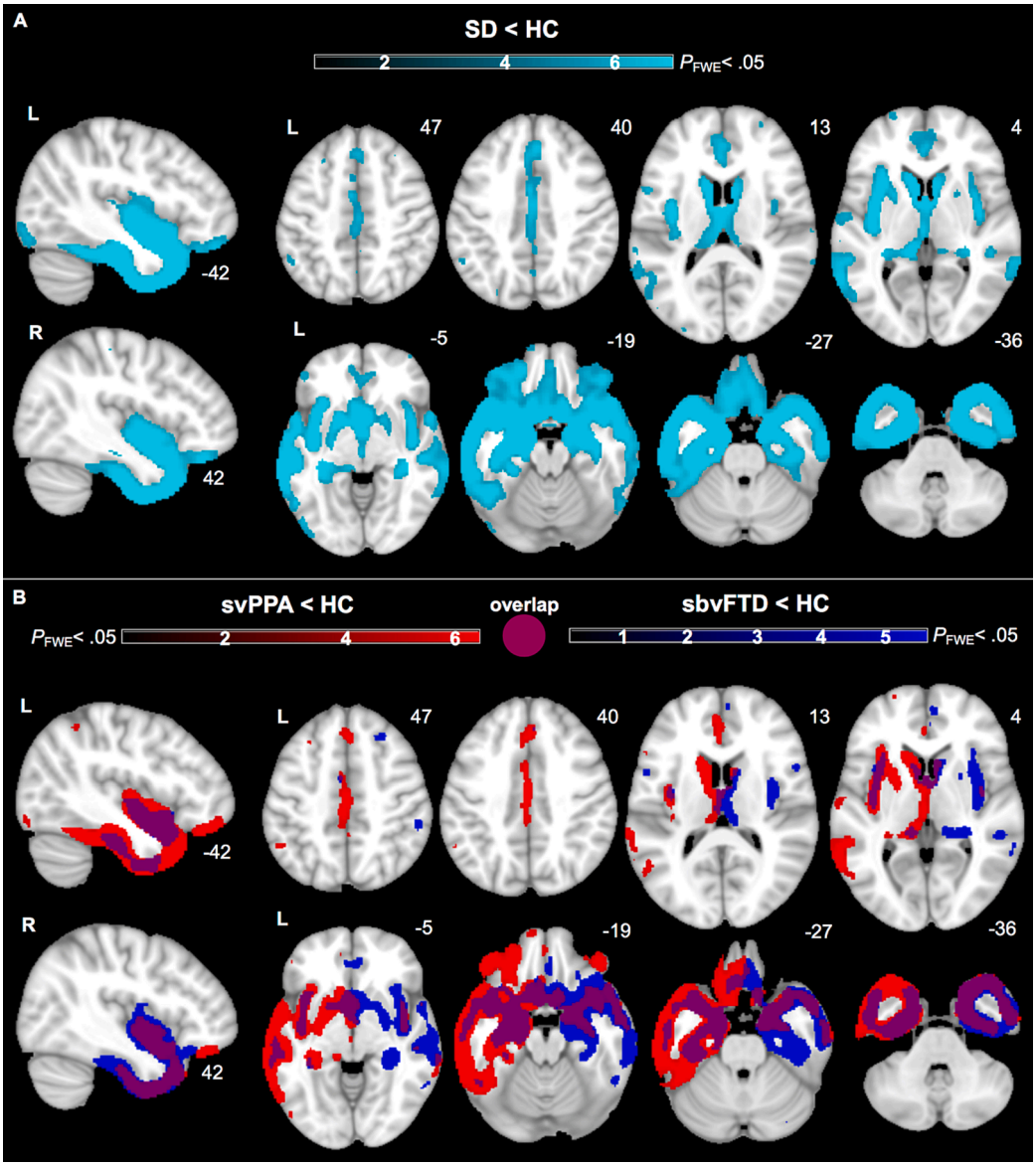


**Fig. 4.** Whole-brain atrophy maps using MRIs acquired at the time of physiology testing. Panel A: Brain regions where the SD group had smaller gray matter volume than the healthy controls (controlling for age, gender, scanner type, and TIV). Panel B: Regions in which gray matter volume was smaller in svPPA (shown in red) and sbvFTD (shown in blue) than healthy controls (controlling for age, gender, scanner type, and TIV). Areas where both the svPPA and sbvFTD groups had smaller gray matter volume than the healthy controls are also provided (shown in purple). Color bars refer to *T*-scores, and results are shown at $p_{FWE}$< .05. HC = healthy controls. TIV = total intracranial volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sympathetic impairments were also evident in each of the svPPA and the sbvFTD groups. Although respiration rate (as measured by ICI) was also faster in SD than in the healthy controls, this difference did not remain significant in the svPPA and sbvFTD groups when compared separately to the healthy controls. The structural neuroimaging analyses emphasized the importance of the insula in baseline autonomic physiology. In SD, left-greater-than-right atrophy in the mid to posterior insula was associated with lower baseline RSA, and left-greater-than-right atrophy in the ventral anterior insula was associated with lower baseline SCL. Lower baseline RSA, but not lower SCL, was associated with diminished extraversion/gregariousness in SD. Impaired semantic knowledge was related to neither baseline RSA nor to baseline SCL, however.

The present study builds on previous research by showing that tonic autonomic activity, in addition to phasic autonomic reactivity (Kumfor et al., 2019; Marshall et al., 2019), is impaired in SD. Baseline autonomic impairments were evident in SD and in follow-up analyses of svPPA and sbvFTD, although each of these groups was relatively small when considered on its own. On average, baseline RSA and SCL was lower in sbvFTD than in svPPA, but this difference was not significant. Whereas in bvFTD, people with lower baseline RSA also had faster heart and respiration rates (i.e., shorter IBI and ICI; Sturm et al., 2018b), in SD, people with lower baseline RSA had a faster respiration rate (i.e., shorter ICI) but a heart rate that did not differ from the healthy controls (i.e., typical IBI). Additional research is needed to replicate this result in SD and, if robust, to determine the physiological mechanisms underlying this autonomic pattern.

Consistent with our hypotheses, the structural neuroimaging analyses revealed that lower baseline autonomic outflow was associated with left-greater-than-right insula atrophy in SD. While left-lateralized atrophy in the mid to posterior insula was associated with lower RSA, left-lateralized atrophy in the ventral anterior insula was related to lower SCL. The whole-brain neuroimaging analyses offered additional support for a prominent role of the left hemisphere in parasympathetic functioning as left-lateralized atrophy in orbitofrontal and temporal

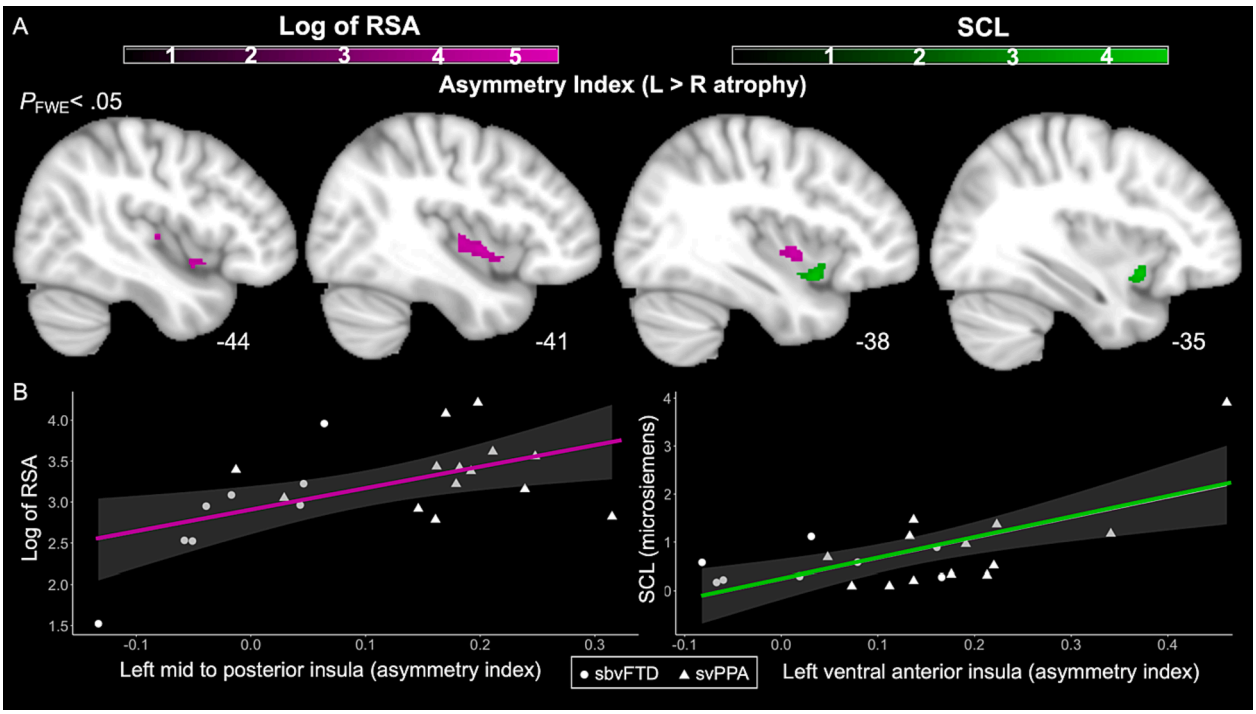


**Fig. 5.** Panel A: Voxelwise insula asymmetry map correlations with baseline RSA and SCL in SD. In SD, lower baseline RSA was associated with left -greater-than-right atrophy in the mid- to posterior insula ($p_{FWE}$< .05), and lower SCL was associated with left-greater-than-right atrophy in the ventral anterior insula ($p_{FWE}$< .05). Covariates in these analyses included age, gender, CDR-Box, scanner type, and total intracranial volume. Color bars refer to *T*-score. Panel B: Correlations between asymmetry scores from insula clusters and baseline RSA and SCL. Results reflected linear correlations and held true across the sample and were not accounted for by group status.

regions was also associated with lower baseline RSA. In the whole-brain analyses, lower baseline SCL was also associated with left-lateralized atrophy, though the pattern was less asymmetric, and atrophy also extended to some right hemisphere structures. Left-lateralized atrophy in the superior frontal, supramarginal, and temporal regions, in addition to the insula, as well as right-lateralized atrophy in superior parietal and middle frontal regions was associated with lower baseline SCL.

The left and right hemispheres both support autonomic outflow, but our results offer additional evidence that the left hemisphere is crucial for maintaining basal physiological levels. Prior studies of healthy and clinical populations (e.g., epilepsy, stroke, and bvFTD) have suggested that left hemisphere structures, and the insula in particular, play a central role in maintaining baseline parasympathetic functioning (Ghchime et al., 2016; Guo et al., 2016; Sturm et al., 2018a; Wittling et al., 1998). Although there is some evidence that the sympathetic nervous system depends more heavily on the right hemisphere than the left (Cereda et al., 2002; Colivicchi et al., 2005; Hilz et al., 2001), the asymmetric contributions of the right hemisphere to sympathetic outflow may be more apparent in the generation of phasic reactions than in the regulation of tonic basal levels, at least at the cortical level. Our prior work in bvFTD found lower baseline SCL was associated with predominant atrophy in left-sided inferior and anterior temporal regions as well as preserved functional connectivity between the anterior cingulate cortex and central pattern generators (i.e., central nucleus of the amygdala and hypothalamus) in the right hemisphere (Sturm et al., 2018a). As participants with SD in the present study had severe bilateral amygdala atrophy, it is likely that this impeded our ability to detect associations between lateralized amygdala atrophy and baseline physiological deficits. Given that more people in our sample had svPPA than sbvFTD, it is also possible that predominant left-lateralized atrophy across the group may have driven the left-sided associations we found with SCL. Empirical support for this alternative explanation was not evident in the scatterplots that showed linear associations between SCL and gray matter asymmetry scores, however, and this explanation would also not explain similar left-lateralized correlates of basal autonomic outflow in bvFTD, a syndrome that is often characterized by right-lateralized or bilateral atrophy patterns (Seeley, 2008). Future studies with larger svPPA and sbvFTD cohorts will be needed to resolve these issues.

Unlike our prior studies of bvFTD that found lower basal parasympathetic activity related to smaller gray matter volume in the left ventral anterior insula, here the posterior and mid-insula emerged as the regions in which left-greater-than-right atrophy was associated with lower RSA in SD. The insula is comprised of distinct subregions with different functional specializations (Jezzini et al., 2012). The posterior insula transmits primary interoceptive and sensorimotor (e.g., visceral and motor) and chemical sensory (e.g., olfactory and gustatory) information (Craig, 2002; Jezzini et al., 2012; Kurth et al., 2010; Uddin et al., 2017) to the mid-insula, which provides contextual refinement before passing these signals to the ventral anterior insula. The ventral anterior insula serves as the final waystation for afferent pathways and represents the internal changes that form the basis of subjective experience (Craig, 2002, 2009; Critchley, 2005; Critchley et al., 2004). Our findings suggest that in SD, baseline parasympathetic impairments may be due to disruption at earlier points in afferent pathways than in bvFTD, thereby impeding the transfer of bodily signals that inform homeostatic regulation and maintain autonomic setpoints at rest.

By fostering a quiet baseline milieu, the parasympathetic nervous system fosters social attunement and empathy (Critchley, 2009; Kogan et al., 2014; Oveis et al., 2009; Sturm et al., 2018b). At rest, the vagus nerve inhibits the heart, slowing its rate from that set by intrinsic pacemaker cells and creates beat-to-beat variability in the cardiac cycle that wax and wane across respiration (Allen et al., 2007; Berntson et al., 1994; Friedman & Thayer, 1998). In SD, decline in the parasympathetic nervous system may contribute to the reductions in interpersonal engagement and reduce gregariousness/extraversion, personality changes that are especially common in sbvFTD. Although the comparisons yielded no significant differences between the SD variants, baseline

RSA and SCL were lower in sbvFTD than in svPPA on average. We speculate that, like in bvFTD (Sturm et al., 2018a), bilateral atrophy and disrupted inter-hemispheric salience network connections in sbvFTD might cause more notable impairments in baseline autonomic functioning than in svPPA, a syndrome with predominant left-lateralized atrophy. As svPPA and sbvFTD are often considered to be syndromes that lie on opposite ends of a single clinicoanatomical spectrum (Borghesani et al., 2020; Ralph et al., 2017), our findings are consistent with a model in which these disorders have shared physiological impairments of varying severity that arise from a continuum of lateralized dysfunction in autonomic pathways.

In the early stages of disease, asymmetric brain atrophy in svPPA and sbvFTD produces distinct yet overlapping language and behavioral syndromes. In SD, the anterior temporal lobes degenerate and have reduced functional connectivity with both the dorsal posterior and ventral anterior insula (Guo et al., 2013), areas that we found were associated with lower baseline autonomic activity. Interoceptive, sensorimotor, and chemical sensory signals that are relayed from the body to the insula embed visceral, sensory, and motor changes in multimodal semantic networks and imbue verbal (language) and nonverbal (socioemotional) concepts with personal significance. Early and predominant atrophy and dysfunction in the anterior temporal lobes could disrupt interoceptive pathways and contribute to impairments in semantic knowledge and changes in behavior in SD. Decline in semantic knowledge may contribute to the alterations in social behavior that arise in people with svPPA and sbvFTD by making it difficult for them to recognize, approach, and connect with familiar people. We found no associations between impairments in baseline autonomic activity and semantic knowledge, however, as neither baseline parasympathetic nor sympathetic activity was associated with performance on tests of verbal (Peabody Picture Vocabulary Test) or nonverbal (UCSF Famous Faces recognition subtest) semantic knowledge. Although the autonomic and semantic systems likely interact, these null findings suggest they make distinct contributions to the symptoms that arise in the svPPA and sbvFTD syndromes. How autonomic impairments may contribute to impairments in socioemotional semantics, including higher-order social concepts (Pexman et al., 2022), will require further investigation.

The present study has several limitations to consider. First, the standard measures of verbal and nonverbal semantic knowledge that we used to examine associations between autonomic functioning and socioemotional semantic knowledge may not be ideal for this purpose. Although standard tests of emotion recognition find impairments in SD (Bertoux et al., 2020; Macoir et al., 2019), novel tools that measure multimodal socioemotional semantic knowledge and its association with objective measures of physiology and behavior will be an important topic for future studies. Second, we measured affiliative traits with informant reports of interpersonal behavior in those with SD. Informant-based measures have been immensely useful in characterizing socioemotional changes in neurodegenerative diseases (Clark et al., 2015; Eslinger et al., 2011; Rankin et al., 2005a,b; Rosen et al., 2006; Sollberger et al., 2011; Toller et al., 2019) but can be subject to observer and retrospective biases (Schulz et al., 2013). As questionnaire measures rely on language and verbal descriptions of social behavior, they may also overlook changes in emotion that are difficult for others to observe, such as subjective experience, which may also be altered in people with SD (Shdo et al., 2022). Studies that include objective measures of behavior and physiology will be important for elucidating how alterations in autonomic nervous system outflow relate to personality and interpersonal functioning in SD. Third, our ability to comment on the generalizability of our findings to other demographic groups is limited given the lack of race/ethnicity (i.e., mostly White) and socioeconomic (i.e., highly educated) diversity in our sample. It will be critical for additional studies to determine whether our results hold in studies that include research participants more representative of the population.

The autonomic nervous system is essential for regulating homeostasis and guiding socioemotional behavior (Critchley, 2005; Sturm et al., 2018b). Although research on behavior and emotion in SD is relatively limited, our study suggests baseline parasympathetic and sympathetic dysfunction, which has been found in bvFTD, also characterizes svPPA and sbvFTD and relates to lateralized atrophy in the insula. Diminished activity in the parasympathetic nervous system, a branch of the autonomic nervous system that promotes affiliative behaviors and is impaired in bvFTD (Sturm et al., 2018b), was associated with lower extraversion/gregariousness but not lower warmth/agreeableness or lower semantic knowledge in SD. Our findings contribute to emerging conceptualizations of the autonomic, neural, and socioemotional changes in svPPA and sbvFTD.

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## CRediT authorship contribution statement

**Alice Y. Hua:** Formal analysis, Software, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Ashlin R.K. Roy:** Writing – review & editing, Data curation, Investigation, Formal analysis. **Eena L. Kosik:** Writing – review & editing, Data curation, Investigation. **Nathaniel A. Morris:** Writing – review & editing, Data curation, Investigation. **Tiffany E. Chow:** Writing – review & editing. **Sladjana Lukic:** Methodology. **Maxime Montembeault:** Writing – review & editing. **Valentina Borghesani:** Methodology. **Kyan Younes:** Writing – review & editing. **Joel H. Kramer:** Funding acquisition, Resources. **William W. Seeley:** Resources. **David C. Perry:** Writing – review & editing. **Zachary A. Miller:** Resources. **Howard J. Rosen:** Funding acquisition, Resources. **Bruce L. Miller:** Funding acquisition, Resources. **Katherine P. Rankin:** Funding acquisition, Resources. **Maria Luisa Gorno-Tempini:** Funding acquisition, Resources. **Virginia E. Sturm:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition, Resources.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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