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FRONTOTEMPORAL ASYMMETRY IN SOCIOEMOTIONAL BEHAVIOR: A PILOT STUDY IN FRONTOTEMPORAL DEMENTIA

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Abstract

Clinical studies report abnormal socioemotional behavior in patients with right frontotemporal disease, but neuroimaging studies of socioemotional behavior usually show bilateral activations in normal subjects. This discrepancy suggests that impaired interhemispheric collaboration for socioemotional functions results from asymmetric frontotemporal disease. Behavioral variant frontotemporal dementia (bvFTD) is a good model for evaluating the contribution of direction-independent frontotemporal asymmetry. In a two-part study, we evaluated patients who met Clinical Consensus Criteria for bvFTD using socioemotional scales and magnetic and resonance imaging measures. Part A compared 18 patients on scales of social dysfunction and emotional intelligence with degree of asymmetry in frontal lobe volumes and analyzed differences between lower and higher asymmetry groups. Part B compared 24 patients on scales of social observation and emotional blunting with degree of asymmetry in frontotemporal cortical thickness using multiple linear regression. Both results showed that left or right hemispheric-specific contributions did not account for all socioemotional differences and that frontal lobe and frontotemporal differences in atrophy between the hemispheres accounted for significant variance in abnormalities in social and emotional behavior. These preliminary results indicate that the degree of frontal lobe and frontotemporal asymmetric involvement, regardless of direction or laterality, significantly contribute to socioemotional dysfunction and support the hypothesis that interhemispheric collaboration is important for complex socioemotional behavior.

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Disclosure of Interest

The authors report no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author [MFM], upon reasonable request.

Keywords

behavioral variant frontotemporal dementia; socioemotional functioning; dementia; socioemotional agnosia; hemispheric asymmetry

INTRODUCTION

Laterality data has long suggested that the two hemispheres have different cognitive and behavioral abilities. There are cognitive differences, such as greater language representation in the left hemisphere and greater spatial attention in the right hemisphere; and scholars have suggested that the left brain is linear, rational, and analytic, and the right brain is intuitive, holistic, and creative. In addition, there is support for hemispheric differences in social and emotional behavior (For reviews see (Borod, Bloom, Brickman, Nakhutina, & Curko, 2002; G. A. Miller, Crocker, Spielberg, Infantolino, & Heller, 2013). Much of the literature on the laterality of social cognition and emotional processing has implicated the right frontotemporal region with right-hemisphere dominance for social behavior and emotional perception.

When carefully examined, this literature on the lateralization of socioemotional behavior has not been entirely consistent. Many, but not all reports involving lesions and brain disorders have shown that involvement of the right frontal or adjacent anterior temporal regions can result in impairments in the correct interpretation of social or socioemotional cues (Multani et al., 2017; Zahn et al., 2009), theory of mind and self-appraisal (Irish, Hodges, & Piguet, 2014; Rosen et al., 2010), the detection of sarcasm (Kipps, Nestor, Acosta-Cabrero, Arnold, & Hodges, 2009; Rankin et al., 2009), difficulty processing emotion from faces (Kumfor et al., 2016; Rosen et al., 2006), or recognizing empathy (Binney et al., 2016; Rankin et al., 2006). However, other studies in patient with bilateral or left predominant atrophy have also shown abnormal socioemotional behavior (Couto et al., 2013; Dermody et al., 2016). Furthermore, investigations in normal subjects using functional magnetic resonance imaging (fMRI) have found activation in both left and right frontotemporal areas (Castelli, Happe, Frith, & Frith, 2000; Frith & Frith, 2006; Gallagher et al., 2000; Samson, Apperly, Chiavarino, & Humphreys, 2004; Wager, Phan, Liberzon, & Taylor, 2003). Split-brain studies involving matching facial expressions to emotion words found poor performance with left, but not right, hemisphere presentations suggesting a left-hemisphere role in socioemotional functioning (Stone, Nisenson, Eliassen, & Gazzaniga, 1996), and amobarital injection (Wada Test) into the left internal carotid artery for epilepsy-surgery assessments found altered recall for the affective content of life events, also suggesting that complex social emotions require the left hemisphere (Ross, Homan, & Buck, 1994).

One explanation for the conflicting findings is that the two frontal or frontotemporal regions, as a whole, are an interacting, interdependent system required for complex socioemotional behavior such as social emotions. Although the right frontotemporal cortex may be necessary for socioemotional behavior, it is not sufficient, and complex socioemotional behavior requires simultaneous involvement and cooperation of both frontotemporal regions. When there is right frontotemporal disease, in addition to localized effects, there is

disruption of interhemispheric cooperation; this is not present in neuroimaging experiments in normal subjects. Research indicates that processing of social emotions is best when both hemispheres work together to decode social, and by definition complex, emotions (Tamietto, Adenzato, Geminiani, & de Gelder, 2007).

Investigators can explore the effect of interhemispheric cooperation on socioemotional behavior by assessing direction-independent, i.e. either left>right or right>left, asymmetry of the frontal or frontotemporal regions in patients with behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al., 2011). In early stages, bvFTD can affect one hemisphere more (Jeong et al., 2005). Reports show that right-sided predominant bvFTD results in impaired social conduct (Boccardi et al., 2005; Eslinger et al., 2007; B. L. Miller, Chang, Mena, Boone, & Lesser, 1993; Whitwell et al., 2013), greater difficulty resolving social dilemmas (Boccardi et al., 2005; Eslinger et al., 2007; B. L. Miller et al., 1993; Whitwell et al., 2013), atypical reward-seeking in socially relevant behaviors (Mendez & Lim, 2004; Perry et al., 2014), and errant use of social feedback in self-monitoring (Eslinger et al., 2007; B. L. Miller et al., 1993; Mychack, Kramer, Boone, & Miller, 2001; Rankin et al., 2006). In a neuropathological examination with an asymmetry index (i.e., left-right asymmetry independent of direction) of advanced bvFTD patients, there was significant asymmetric pathology in frontotemporal regions (Irwin et al., 2018). However, some studies in bvFTD have not found asymmetric degeneration (Whitwell et al., 2013), and others report socioemotional dysfunction with either bilateral or focal left-sided involvement (Dermody et al., 2016; Jeong et al., 2005; Kamminga et al., 2015; Salmon et al., 2006; Tosun, Rosen, Miller, Weiner, & Schuff, 2012). These discrepancies may be due to the degree of direction-independent interhemispheric asymmetry present in patients with early or mid-stage bvFTD.

We hypothesize that differences in interhemispheric atrophy and its impact on the relationship between frontotemporal regions plays a significant role in socioemotional dysfunction, as evidenced in bvFTD. This finding would support the necessity for interhemispheric cooperation for complex social and emotional behavior. This study assesses measures of socioemotional functions and correlates them with the degree of frontal and frontotemporal asymmetry on magnetic resonance imaging (MRI) in a two-part evaluation of patients with bvFTD. The two parts assess frontal or frontotemporal involvement with different socioemotional scales, MRI measures of asymmetry, and statistical analyses. Part A and Part B are different studies designed to assess direction-independent asymmetry with different measures and procedures as a means of self-validating of the effects of interhemispheric socioemotional collaboration.

METHOD

Part A. Frontal Lobe Asymmetry

Part A focused on direction-independent asymmetry of the frontal lobes only as the source of socioemotional differences. Given small sample sizes, the anterior temporal lobes were excluded in order to limit the variables of interest on the effects of the frontal lobes, which are most implicated in social behavior and have a role in emotional behavior (Harmon-Jones, Gable, & Peterson, 2010; G. A. Miller et al., 2013; Whitwell et al., 2013). Eighteen patients with bvFTD were evaluated for the effects of interhemispheric asymmetry of frontal lobe

volumes on scores on the Social Dysfunction Scale (SDS) for social behavior and the Emotional Intelligence (EQ) Scale for emotional appraisal (Barsuglia et al., 2014; Schutte et al., 1998).

Participants and Procedures

The patients were sequentially recruited from the Neurological Clinics of the University of California (UCLA) Medical Center. The patients with bvFTD were diagnosed according to International Consensus Criteria as Clinically Probable bvFTD (Rascovsky et al., 2011). Diagnostic criteria included: apathy, loss of empathy, disinhibition, compulsive-like behaviors, dietary changes, disproportionate executive functioning on neuropsychological testing, and neuroimaging corroboration of regional frontotemporal disease. Individuals with major medical conditions, with the exception of hypertension and diabetes, and those with non-dementia related psychiatric illnesses were excluded. The study was reviewed and approved by the UCLA Institutional Review Board (IRB).

The 18 participants completed an initial screening interview and standard neurological examination. The participants additionally completed the Montreal Cognitive Assessment (MoCA) and the caregiver-rated Functional Activity Questionnaire (FAQ (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). A neuropsychological battery included the following: Wechsler Test of Adult Reading (WTAR); Wechsler Adult Intelligence Scale – 3rd Ed. (Tulsky, Zhu, & Ledbetter, 1997); Trail Making (Tombaugh, 2004); Controlled Oral Word Associates Test (FAS, Animals, Vegetables) (Tombaugh, Kozak, & Rees, 1999); California Verbal Learning Test – 2nd Ed. (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000.). Finally, they underwent the caregiver-rated Neuropsychiatric Inventory (NPI) (Cummings et al., 1994).

Socioemotional Scales

1. The Socioemotional Dysfunction Scale (SDS) is a 40-item informant-based rating scale which has been used to characterize social behavioral disturbances in bvFTD (Barsuglia et al., 2014). The SDS is completed by a spouse, family member, caregiver, or other informant who knows the patient well. The scale originates from the Social Competency Questionnaire (SCQ), a measure of adaptive social behaviors, with modifications for use with patients with bvFTD. Written instructions are, “For each item, base ratings on a comparison with typical behavior before disease symptoms emerged.” Informants rate items regarding the participant’s social behavior on a 5-point Likert scale (1-to-5) as follows: 1 = Very Inaccurate; 2 = Somewhat Inaccurate; 3 = Neither Accurate, Nor Inaccurate; 4 = Somewhat Accurate; 5 = Very Accurate. For example, “Makes inappropriate comments to others.” The 40-items are summed, yielding a total raw score with higher scores suggestive of greater social dysfunction.
2. Emotional self-appraisal is assessed with the Emotional Intelligence (EQ) Scale, a 33-item self-rating questionnaire of emotional appraisal (Schutte et al., 1998). High emotional self-appraisal on the EQ in the presence of socioemotional dysfunction reflects impaired socioemotional insight and awareness of their behavior. The participant are asked to rate their perceived ability in various

behaviors (e.g., “I am aware of my emotions as I experience them”) on a 5-point scale where “1-Strongly Disagree” and “5-Strongly Agree.” The average or mean of all items is computed to provide an overall score, with adequate reliability in this sample ($\alpha = .81$). These items are further divided into subdomains (Saklofske, Austin, & Minski, 2003), and the ability to appraise emotion subscale is the focus of this study and shows strong internal consistency in this sample ($\alpha = .82$).

Neuroimaging

All participants underwent MRI with a 1.5-Tesla Siemens Avanto scanner, and standard anatomical T1-weighted sequences (256×256 matrix; voxel size=1×1×1 mm³; inversion time = 900 ms, repetition time = 2000 ms; echo time = 2.89 ms; flip angle=40°) were examined. The MRI scans were obtained within a week of the Socioemotional Scales. FreeSurfer 5.3 automatically extracted cortical labels according to the 40 frontotemporal (22 frontal; 18 temporal) areas of the Desikan et al. (2006) atlas for T1-weighted structural scans (Desikan et al., 2006). In Part A, we examined the frontal lobe areas (n=22; 11 per hemisphere) known to be involved in bvFTD: the superior frontal, rostral middle frontal, caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral orbitofrontal, medial orbitofrontal, precentral, paracentral, and frontal pole. In order to improve FreeSurfer segmentations, control points were manually added within the white matter and used when intensity normalization failed due to poor delineation between white and gray matter boundaries, which is more likely for bvFTD due to atrophy. When needed, investigators manually adjusted these controls points. For Part A, we created two composite scores of left frontal lobe and right frontal lobe volumes.

Part B. Frontotemporal Asymmetry

Part B, using different outcome variables and analysis, was subsequently performed as an expanded and alternate form of validation of Part A. Part B focused on analyzing the direction-independent frontotemporal asymmetry in an alternative fashion, with two alternate socioemotional scales and MRI measures of cortical thickness rather than volume. Given small sample sizes, the amygdalae were excluded in order to limit the variables of interest on the effects of the frontotemporal cortex rather than the potentially large socioemotional effects of the amygdalae, which are major subcortical structures involved in emotion. Twenty-four patients with bvFTD were evaluated for the effects of direction-independent asymmetry involving frontal and anterior temporal cortical thicknesses on scores of two other social and emotional scales shown to discriminate patients with bvFTD, the Social Observation Inventory (SOI) and the Scale for Emotional Blunting (Abrams & Taylor, 1978; Mendez et al., 2014). This part also assessed the additional role of temporal involvement in socioemotional behavior.

Participants and Procedures

An expanded cohort of 24 patients with bvFTD (6 additional patients were sequentially recruited to the original 18 from Part A) were included for further analysis; all met International Consensus Criteria as clinically probable bvFTD (Rascovsky et al., 2011). The inclusion and exclusion criteria were the same as for Part A, as was UCLA IRB approval. As

in Part A, each participant completed an initial screening interview and standard neurological examination. For Part B, the investigators administered the Mini-Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) along with the socioemotional scales.

Socioemotional Scales

1. Instead of the SDS used in Part A, Part B uses an alternative social evaluation scale, the Social Observation Inventory (SOI), which has been used successfully to evaluate patients with bvFTD (Mendez et al., 2014). This clinician-rated observation scale is useful for observing patients interacting in an ecologically valid social setting, such as during sharing a meal at home. Clinicians rate as abnormal or normal a range of verbal and nonverbal behaviors crucial to social interpersonal behavior from a one-hour video-recording of the patients' interactions.
2. Instead of the EQ used in Part A, caregivers complete the Scale of Emotional Blunting (SEB), an instrument used successfully to evaluate patients with bvFTD (Abrams & Taylor, 1978). This scale queries domains such as absence of pleasure-seeking behavior (Behavior), affective blunting (Affect), and cognitive blunting (Thought). Each behavioral symptom was rated by indicating "condition absent" (zero points), "slightly present or doubtful" (one point), and "clearly present" (two points). The behavior subscale items included symptoms akin to reclusivity or avoiding social contact. The affect domain involved behaviors such as lacking warmth or empathy. The thought subscale included items of lacking plans, ambition, desires, or drive. The reliability coefficient proved strong ($\alpha = .91$) in this sample.

Neuroimaging

In addition to the neuroimaging description and time course described in Part A, Part B focuses on a the broader frontotemporal region beyond just the original 22 frontal lobe areas, and included 18 (9 per hemisphere) temporal regions: the entorhinal cortex, parahippocampal gyrus, temporal pole, fusiform gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, transverse temporal cortex, and banks of the superior temporal sulcus. For the contribution of asymmetry, Part B evaluated composite scores for left and right frontotemporal cortical thickness and direction-independent cortical thickness asymmetry by taking the absolute value of the left vs right discrepancy score such that higher values indicated a greater magnitude of asymmetry than lower scores.

Statistical analyses

SPSS 23.0 software was used for parametric statistical analysis after determining sufficient normality. The analysis included demographic statistics (e.g., age, education, gender, estimate of years since onset). For Part A, these characteristics were compared between lower and higher asymmetry groups using Chi-square and *t*-test for categorical and continuous variables, respectively. Pearson correlations (*r*) were computed to examine the relations between the socioemotional and demographic variables to identify any covariants. Postulated group differences were tested by analysis of variance (ANOVA). Bonferroni

corrections were made for multiple comparisons. Finally, hypothesis testing further employed a series of multiple regressions.

RESULTS

Part A:

Because this study was focused on direction-independent differences between bvFTD patients and not directional laterality, the initial 18 participants were divided into two groups based upon the direction-independent asymmetric difference in total volumes between the two frontal lobes. The study compared the 9 with the lower asymmetry (LA) and the 9 with the higher asymmetry (HA) in frontal lobe volumes.

There were no significant differences on demographic variable between the HA and LA groups (See Table 1). The differences between the groups in overall left frontal lobe volumes did not reach statistical significance ($p = .12$); however, the LA participants had smaller right frontal volumes than the HA participants ($\eta^2 = .37$, $F(1,18) = 10.84$, $p = .008$).

On neuropsychological measures, there were few group differences except that the HA group had greater impairment in functional activities of daily living (FAQ – higher score is greater impairment; $\eta^2 = .30$, $F(1, 18) = 6.03$, $p = .023$) and poorer digit symbol coding ($\eta^2 = .31$, $F(1, 18) = 6.04$, $p = .028$) and initial encoding on a list learning task (CVLT Trial 1) ($\eta^2 = .37$, $F(1, 18) = 7.80$ ($p = .011$), compared to the LA group (See Table 2). On the NPI, the HA group also had more agitation (NPI; $\eta^2 = .37$, $F(1, 18) = 10.01$, $p = .007$) and irritability (NPI; $\eta^2 = .32$, $F(1, 18) = 6.03$, $p = .030$), compared to the LA group. However, after Bonferroni adjustment, none of these measures remained significantly different between groups.

There were significant HA vs LA group differences based on the two socioemotional variables (See Figure 1). Caregivers rated the HA group, compared to the LA group, as having more socioemotional dysfunction (SDS; $\eta^2 = .38$, $F(1, 18) = 10.84$, $p = .004$). In addition, the HA participants, compared to the LA participants, rated themselves higher in their EQ ability to appraise others' emotions despite their greater socioemotional dysfunction ($\eta^2 = .36$, $F(1, 18) = 10.01$, $p = .008$), indicating impaired socioemotional insight and awareness. After Bonferroni adjustment, both the SDS and EQ differences remained significant.

Examining across groups, the asymmetry scores (i.e. the difference between the left and right frontal lobe volume) were positively associated with both higher levels of SDS symptoms ($r(18) = -.78$, $p = .010$) and higher perceived ability to appraise emotions ($r(18) = -.71$, $p = .004$). Examining within groups, in the HA group, greater SDS symptoms correlated with both reduced right frontal lobe volume ($r(9) = -.078$, $p = .015$) and reduced left frontal lobe volume ($r(9) = -.82$, $p = .003$), whereas higher levels of perceived ability to appraise emotions only correlated with reduced right frontal lobe volume ($r(9) = .91$, $p = .001$). Within the LA group, the SDS scores did not correlate with frontal lobe volumes, but higher levels of perceived ability was correlated with both reduced right frontal lobe volume ($r(9) = -.89$, $p = .005$) and reduced left frontal lobe volume ($r(9) = -.86$, $p = .007$).

On logistic regression for LA vs. HA group membership (dependent variables age, sex, year of onset, SDS scores, EQ self-appraisal scores), neither age, sex, nor year of onset was significant; however, inclusion of the SDS was significant ($\chi^2 = 9.64$, $p = .003$), and, with this scale in the equation, it discriminated 90% of the LA versus HA frontal patients ($B = .059$, $SE = .026$, Wald = 5.4, OR = 1.06, $p = .024$). The inclusion of emotional appraisal was also significant ($\chi^2 = 8.14$, $p = .005$), and, with this in the equation, it discriminated 95.2% ($B = .048$, $SE = .036$, Wald = 4.6, OR = 1.01, $p = .042$).

Part B:

The characteristics of the 24 patients with bvFTD are listed in Table 3 (See Table 3). A multiple linear regression was calculated to predict overall clinician ratings of aberrant social behavior (SOI) by asymmetric frontotemporal cortical thickness controlling for age and individual hemispheric thickness (given the absent effects of sex and year of onset in Part A, these variables were not included). Specific dependent variables were age, SOI scores, and the cortical thickness values. Neither individual hemispheric thickness nor left vs right contribution was significantly related to the SOI, $ps = .094-.502$. A significant regression equation was found when examining the SOI alone ($F = 7.64$, $p = .017$, with an $R^2 = .39$, and aberrant social behaviors increased by a factor of 2.69 per each millimeter in asymmetric discrepancy between the two frontotemporal regions ($\beta = .62$, $p = .017$).

A second regression was performed with the same dependent variables except for the inclusion of SEB scores instead of SOI scores. The regression was employed to predict emotional blunting (SEB) based upon relative cortical thickness and as before, neither age, cortical thickness or left compared right asymmetry reached significance, $p = .398-.679$. A significant regression equation was found when examining the SEB alone ($F = 4.38$, $p = .035$ with an $R^2 = .32$, and SEB scores increased by a factor of 8.31 per each millimeter in asymmetric discrepancy between the two frontotemporal regions ($\beta = .57$, $p = .035$).

DISCUSSION

This study examined cortical asymmetric contributions to socioemotional behavior among patients with bvFTD. In Part A, we divided the bvFTD patients into lower (LA) and higher (HA) frontal lobe asymmetric volume groups and found that the HA group compared to the LA group had significantly more social dysfunction and a greater belief in their ability to appraise others' emotions despite their social dysfunction, a measure reflecting poor insight or awareness of their socioemotional behavior. Although the LA group had smaller right frontal volumes than the HA group, the HA group had worse neuropsychological and functional measures, again suggesting a greater role for cortical asymmetry. In Part B, the asymmetry in frontotemporal cortical thickness contributed to a higher level of social disturbance and emotional disengagement on two alternative socioemotional scales. Only the degree of direction-independent asymmetry predicted clinician and caregiver rated socioemotional behavioral disturbances. The findings of this study indicate that the interrelationship between frontotemporal regions in the two hemispheres is a significant factor in socioemotional dysfunction and supports interhemispheric theories of socioemotional functioning.

Research on brain asymmetries has suggested socioemotional differences between left and right hemispheres. Investigators have proposed hemispheric lateralizations such as social and emotional dominance in the right hemisphere, negative valence in the right and positive valence in the left hemispheres, and an avoidance motivational system in the right and approach in the left hemispheres (For reviews see (Fettermann, Ode, & Robinson, 2013; Gainotti, 2018a, 2018b; G. A. Miller et al., 2013). Prior studies indicate that hemispheric asymmetry affects social responsiveness and emotional recognition scores and the ability to process information about the social world, the self, and from emotional stimuli (Compton, Feigenson, & Widick, 2005; Evans et al., 2015; Heilman, Barrett, & Adair, 1998; E. Salmon et al., 2008; V. E. Sturm & R. W. Levenson, 2011; Tamietto et al., 2007). Deviations of normal cerebral symmetry patterns are also associated with socioemotional changes in developmental brain dysfunction and autism spectrum disorder (Evans et al., 2015), depression (Bruder et al., 2012), and schizophrenia (Evans et al., 2015), where the asymmetry may be associated with avolition, diminished anxiety, and negative symptoms (Crow, 1995; Nunez et al., 2017; Oertel-Knochel & Linden, 2011). In addition, unilateral lesions may disturb interhemispheric collaboration as they incorporate loss of function not only in diseased tissue, but also in the healthy hemisphere due to disrupted interhemispheric connections and pathological inhibition of competence of the non-lesioned hemisphere (Zaidel, 2001).

Few studies have considered the effects of interhemispheric collaboration. Although the two hemispheres process information relatively independently, integrated and complex behavior, such as creativity (Lindell, 2011), requires that they coordinate across interhemispheric connections, neural networks, and integrated systems. Indeed, abnormalities in socioemotional behavior may result from the direction-independent asymmetry between the two frontal or frontotemporal areas rather than from specific atrophy of one side (Lane, Nadel, Allen, & Kaszniak, 2000).

BvFTD is a good model for evaluating the role of direction-independent asymmetric frontotemporal atrophy on socioemotional dysfunction. In bvFTD, investigators report greater socioemotional dysfunction in patients with right than left frontal or temporal disease, resulting in difficulty with social dilemmas and loss of control of social conduct (Eslinger et al., 2007; B. L. Miller et al., 1993; Mychack et al., 2001), and in abnormal emotional contagion and affective perspective-taking (Hillis, 2014; Rascovsky et al., 2011). However, other investigators of bvFTD show a left-sided frontotemporal role in social concepts (Pobric, Lambon Ralph, & Zahn, 2016) and in empathic concern or emotional processing (Dermody et al., 2016; Kamminga et al., 2015; Sturm et al., 2015). The common bilateral asymmetry of the frontal and temporal atrophy in bvFTD (Jeong et al., 2005), and the findings of a direction-independent asymmetry effect in this study, can explain this discrepancy in the literature.

Our findings are consistent with an integrative or interactive theory of interhemispheric functions (Jung et al., 2006). In bvFTD, the right frontotemporal region is involved in much social and emotionally related perception and action (Mendez & Lim, 2004; Perry et al., 2014), and an integrative model might mean that the left frontotemporal region is needed for counterbalance, behavioral regulation, or even the normative rules of social behavior

(Panchal et al., 2016). An integrative view of frontal dysfunction may also be compatible with a motivational view of interhemispheric differences, best exemplified by the left-sided approach/right-sided avoidance dichotomy with both frontal lobes needed for the correct balance of socioemotional interaction (Harmon-Jones et al., 2010). Finally, given that the HA group, compared to the LA group, claimed a greater ability to appraise emotions despite greater social dysfunction, their ability to process information about the self was significantly impaired (Eric Salmon et al., 2008; Virginia E Sturm & Robert W Levenson, 2011). Hence, asymmetry may contribute to socioemotional agnosia with inability to monitor and evaluate their own socioemotional performance.

Several methodological issues limit this study. First, the sample sizes in this study were small, and, hence, the cohort in Part B, which was done to validate Part A, was not a completely independent cohort. Nevertheless, the number of participants in this pilot study were sufficient to yield significant differences associated with direction-independent interhemispheric asymmetries. Second, there are potential problems in the two-part design of this study using different scales, selected MRI measures, and alternate analyses. Because of the focus on frontal lobes (Part A) and frontotemporal cortex (Part B), this study could have underestimated the effects of temporal variants of bvFTD and temporal structures. Moreover, this study reported on aggregated regions of the frontal lobes and frontotemporal cortices without further neuroanatomical or neuropathological specificity. BvFTD is a very pathologically heterogeneous disease and the lack of autopsy findings may limit interpretation. This study's findings need further replication with a larger and more varied cohort using less selective MRI ROI. Third, because of power considerations and the focus on direction-independent asymmetry, this preliminary work did not evaluate directional data. Finally, problems exist with caregiver ratings, which depend on whether the patient mentions behavioral or cognitive problems (Evers, Kilander, & Lindau, 2007). Future studies should examine socioemotional behavior with objective measures in a larger population of patients with bvFTD.

In summary, this study examined social and emotional behavior and asymmetric frontal and frontotemporal atrophy in bvFTD patients. In Part A, greater frontal lobe volume asymmetry was associated with greater social dysfunction along with an unjustified tendency to rate themselves higher in their ability to appraise emotions. In Part B, asymmetry in frontotemporal cortical thickness played a role in decreased social performance and increased emotional blunting. These preliminary findings are pertinent for interhemispheric theories, such as social or emotional lateralization and approach-avoidance motivational differences. Further systematic research on these differences with diffusion tensor imaging with tractography and other measures can help clarify the interhemispheric frontotemporal collaboration and communication necessary for the maintenance of complex socioemotional behavior.

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Figure 1:

Part A. Socioemotional Scale Differences between Lower Asymmetry (LA) and Higher Asymmetry (HA) Groups of patients with Behavioral Variant Frontotemporal Dementia. Light bars indicate group with lower asymmetry (LA) in frontal lobe volumes. Dark bars indicate group with higher asymmetry (HA) in frontal lobe volumes. SDS=Social Dysfunction Scale; EQ=Emotional Intelligence Scale for emotional appraisal. Error Bars 95% confidence interval; ** $p < .01$.

Table 1.

Part A: Group differences among patients with Behavioral Variant Frontotemporal Dementia

	Lower Asymmetry (LA) (n=9)	Higher Asymmetry (HA) (n =9)
CHARACTERISTICS		
Age	61.56 (11.19)	60.21 (9.56)
Sex (%= female)	46%	50%
Education (years)	14.89 (1.54)	16.43 (2.77)
Years since onset	4.14 (4.18)	3.93 (2.32)
SOCIOEMOTIONAL SCALES		
Social Dysfunction Scale**	122.22 (31.97)	160.20 (16.79)
EQ Self-Appraisal of Emotions *	3.33 (0.31)	3.70 (0.29)
NEUROIMAGING		
Left Frontal Volume	35451.67 (9305.93)	38923.22 (7447.72)
Right Frontal Volume**	43506.44 (6660.37)	52762.89 (6289.65)
Left-Right Difference	-8054.78 (3999.33)	-13839.67 (3800.72)

Means and standard deviations except for sex (percentage);

EQ=Emotional Quotient; Left-Right Difference: Subtract right from left frontal lobe volume such that “-“ is larger right frontal lobe;

*
p <.05,

p < .01,

, p <.001

Table 2.

Part A. Group differences on Neuropsychological and Functional Measures among patients with Behavioral Variant Frontotemporal Dementia

	Lower Asymmetry (LA) (n=9)	Higher Asymmetry (HA) (n =9)
MoCA	17.17 (5.84)	17.44 (7.23)
FAQ *	15.38 (8.09)	21.92 (3.55)
WTAR	101.14 (13.42)	103.44 (15.41)
Digit Span	7.57 (1.81)	6.00 (2.16)
Coding *	7.86 (3.13)	4.67 (2.06)
Trail Making A	54.43"(56.34)	78.90"(43.37)
Trail Making B	205.57"(118.62)	240.50"(83.08)
FAS	20.86"(16.22)	10.70"(9.13)
CVLT Trial 1 *	6.93 (1.10)	2.56 (1.05)
CVLT Short Delay	4.57 (2.94)	2.93 (0.86)
CVLT Long Delay	3.43 (2.82)	2.29 (0.89)
NPI Agitation *	2.44 (3.40)	3.00 (2.76)
NPI Irritability *	1.33 (2.83)	2.91 (3.59)

MoCA=Montreal Cognitive Assessment; FAQ=Functional Activity Questionnaire (higher scores indicated worse function); WTAR=Wechsler Test of Adult Reading; Digit Span and Coding subtests from the Wechsler Adult Intelligence Scale; FAS= Controlled Oral Word Associates Test; CVLT= California Verbal Learning Test; NPI=Neuropsychiatric Inventory. All Scores represented are raw scores with the exception of the WTAR which was recorded as a Standardized Score.

*
 $p < .05$,

$p < .01$,

 $p < .001$.

Table 3.

Part B: Characteristics of 24 patients with Behavioral Variant Frontotemporal Dementia

	Mean	S.d.
CHARACTERISTICS		
Age (years)	61.25	10.10
Sex (% female)	59%	---
Handedness (% Left)	8%	---
Education (years)	15.92	2.43
Years since onset	3.92	3.37
SOCIOEMOTIONAL SCALES		
Social Observation Inventory	34.00	10.11
Emotional Blunting Scale	104.73	34.42
NEUROIMAGING		
Left Frontotemporal Cortical Thickness	68.24	5.46
Right Frontotemporal Cortical Thickness	68.26	5.29
Left vs. Right Asymmetry	-.02	3.82
Direction-Independent Asymmetry	2.94	2.34

Neuroimaging refers to frontotemporal cortical thickness;

Left vs. Right Difference: Subtract right from left frontotemporal cortical thickness such that “-” is larger right frontotemporal cortical thickness