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Person-Based Versus Generalized Impulsivity Disinhibition in Frontotemporal Dementia and Alzheimer Disease

Pongsatorn Paholpak, MD[1,2], Andrew R. Carr, PhD[1,3], Joseph P. Barsuglia, PhD[3], Robin J. Barrows, MD[1,3], Elvira Jimenez, MPH[1,3,4], Grace J. Lee, PhD[5], and Mario F. Mendez, MD, PhD[1,3,4]

Abstract

Background: While much disinhibition in dementia results from generalized impulsivity, in behavioral variant frontotemporal dementia (bvFTD) disinhibition may also result from impaired social cognition. **Objective:** To deconstruct disinhibition and its neural correlates in bvFTD vs. early-onset Alzheimer's disease (eAD). **Methods:** Caregivers of 16 bvFTD and 21 matched-eAD patients completed the Frontal Systems Behavior Scale disinhibition items. The disinhibition items were further categorized into (1) "person-based" subscale which predominantly associated with violating social propriety and personal boundary and (2) "generalized-impulsivity" subscale which included nonspecific impulsive acts. Subscale scores were correlated with grey matter volumes from tensor-based morphometry on magnetic resonance images. **Results:** In comparison to the eAD patients, the bvFTD patients developed greater person-based disinhibition ($P < 0.001$) but comparable generalized impulsivity. Severity of person-based disinhibition significantly correlated with the left anterior superior temporal sulcus (STS), and generalized-impulsivity correlated with the right orbitofrontal cortex (OFC) and the left anterior temporal lobe (aTL). **Conclusions:** Person-based disinhibition was predominant in bvFTD and correlated with the left STS. In both dementia, violations of social propriety and personal boundaries involved fronto-parieto-temporal network of Theory of Mind, whereas nonspecific disinhibition involved the OFC and aTL.

Keywords

disinhibition, frontotemporal dementia, Alzheimer disease, Frontal System Behavior Scale

Introduction

Disinhibition, or unrestrained behavior with disregard for rules or consequences, is one of the hallmark manifestations of behavioral variant of frontotemporal dementia (bvFTD) and an important diagnostic criterion for this disorder.[1] Behavioral variant of frontotemporal dementia, which after Alzheimer disease (AD), is the most common neurodegenerative dementia among those 65 years or younger,[2] specifically targets the areas of the brain involved in social behavior. Behavioral variant of frontotemporal dementia results in disinhibition involving interpersonal interactions and loss of empathy or sympathy and impairments in other aspects of social cognition.[3] Neuroimaging studies demonstrate the focus of pathology in the mesial frontal and anterior temporal lobes (aTLs),[4] and neuropathology reveals atrophy with intraneuronal inclusions, most commonly containing abnormal τ or transactive response DNA-binding 43 proteins.[5]

The behavioral construct of disinhibition includes both inappropriate social behaviors involving disturbed interpersonal interactions[6] and impulsive acts involving general rule violations. Some disinhibited behaviors in bvFTD are highly associated with violating social tact and personal boundaries, for example, patients with bvFTD may say inappropriate things to others or touch strangers.[7] In contrast, impulsive disinhibitions may manifest as opportunistically putting viewed food in their mouths or taking items of interest from stores without first paying for them.[8] Prior investigations have associated behavioral disinhibition in bvFTD with gray matter loss in different brain regions, including the right superior temporal sulcus

[1] Department of Neurology, David Geffen School of Medicine, University of California at Los Angeles, CA, USA
[2] Department of Psychiatry, Khon Kaen University, Khon Kaen, Thailand
[3] Greater Los Angeles VA Healthcare System, West Los Angeles, CA, USA
[4] Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, CA, USA
[5] Department of Psychology, School of Behavioral Health, Loma Linda University, Loma Linda, CA, USA

Corresponding Author:
Pongsatorn Paholpak, Neurobehavior Service (116AF), Greater Los Angeles VA Healthcare Center, 11301 Wilshire Blvd, Los Angeles, CA 90073, USA.
Email: ppaholpak@yahoo.com

Table 1. Person-Based and Generalized Impulsivity Disinhibition Subscale Items.

Person-Based Disinhibition	Generalized Impulsivity Disinhibition
9. Makes inappropriate sexual comments and advances, is too flirtatious	2. Is easily angered or irritated; has emotional outbursts without good reason
10. Does or says embarrassing things	4. Does things impulsively
18. Talk out of turn, interrupts others in conversations	6. Laugh and cries too easily
27. Gets in trouble with the law or authorities	12. Cannot sit still, is hyperactive
30. Is overly silly has childish sense of humor	28. Does risky things just for the heck of it
43. Is sensitive to the needs of other people[a]	31. Complains that food has no taste or smell
44. Gets along well with others[a]	32. Swears

[a]These items were rated in a reversed direction.

(STS),[9] right orbitofrontal cortex (OFC),[10] and bilateral OFC.[11] Nevertheless, different disinhibited acts may have fundamentally different mechanisms and neurological substrates in the brain. Disinhibited behaviors that violate others' boundaries may result from an impairment in social cognitive processes, such as theory of mind (ToM), or the ability to appreciate that others' have thoughts, feelings, and beliefs.[12,13] The ToM results from a network involving the medial prefrontal cortex (medial PFC), the temporoparietal junction (TPJ), the posterior STS, and the anterior temporal cortex.[14] In contrast, those disinhibited behaviors presenting with generalized impulsivity may be related to a basic loss of impulse control from orbitofrontal dysfunction. Overall, the subcategorization of disinhibited behaviors into "person-based" (inappropriate behavior specific to a social context) versus "generalized impulsivity" (opportunistic, general rule violations) subtypes may help clarify the underlying mechanisms and localization of these behaviors.

This study sought to classify and measure person-based and generalized impulsivity disinhibition in patients with bvFTD in comparison to those with AD and to define the neural correlates of these disinhibition subtypes using tensor-based morphometry (TBM) analysis of magnetic resonance imaging (MRI). We used Frontal System Behavioral Scale (FrSBe), rather than other instruments such as the Neuropsychiatric Inventory (NPI), because the FrSBe measures severity of each disinhibited behavior separately and permits subcategorizing the scale. Given the prominent disturbances of social behavior in bvFTD, these patients may have disinhibited behaviors that are more person based and linked to neuropathology in brain regions associated with social cognition rather than generalized impulsivity disinhibition due to a loss of impulse control. We further predicted that person-based disinhibition would correlate with disease in regions involved in the neuroanatomy of ToM, whereas generalized impulsivity disinhibition would correlate with disease in OFC.

Methods

Populations

A total of 37 patients, 16 with bvFTD and 21 with early-onset AD (eAD), were recruited from an outpatient behavioral neurology clinic in an academic university medical center. All patients were seen and evaluated at the University of California, Los Angeles (UCLA) Neurological Clinics. All participants were examined by a neurologist and underwent neuropsychological testing by a neuropsychologist. Patients with bvFTD were diagnosed with clinically "probable bvFTD" per International Consensus Diagnostic Criteria.[1] Participants with eAD were diagnosed with clinically "probable AD" using National Institute of Aging-Alzheimer's Association criteria.[15] The patients with eAD were selected to match with the patients with bvFTD in terms of age, age of onset, duration of the illness, years of education, ethnicity, sex, and cognitive performance on the Mini–Mental State Examination (MMSE; see Table 1). Most eAD is sporadic, and none of the patients with eAD had a family history consistent with an autosomal-dominant eAD nor evidence of neurological manifestations suggestive of familial AD.[16]

The institutional review board (IRB) of UCLA reviewed and approved the study, and participants were enrolled according to the IRB guidelines. Information from caregivers was ascertained when the patients were not simultaneously present. Most caregivers were the participant's spouse (82.1%), and the others were participants' child, parent, sibling, or partner.

Measurement of Behavioral Disinhibition

The FrSBe,[17] caregiver version, is a behavioral scale that has been used to quantify frontal behaviors, including disinhibition, apathy, and executive dysfunction. The FrSBe is composed of 46 Likert-type scale questions for problematic behaviors, which contained 15 questions measuring disinhibited behaviors. The severity of each problematic behavior was rated as: (1) almost never, (2) seldom, (3) sometimes, (4) frequently, and (5) almost always; each positive behavior was rated in a reverse direction (5 to 1) in order to maintain the same direction of less desirable scores. The caregivers rated severity of each behavior at 2 different time points: at the baseline before an onset of symptoms (BEFORE score) and at the current time point after the onset of symptoms (AFTER score). A degree of change in each behavior (CHANGE score) was calculated as the difference between the BEFORE score and the AFTER

score. The CHANGE score better represents the extent of change in behavioral disinhibition due to disease progression[17] and was used as the main outcome variable to correlate with the neuropsychological and neuroimaging variables in this study. Prior work has shown associations of the FrSBe subscales with frontal–subcortical circuits,[17] and the FrSBe has been previously validated as a standardized measurement to detect behavioral changes in traumatic brain injury, AD, and bvFTD with good validity and reliability.[18]

Disinhibition items were further categorized into 2 subscales (Table 1): (1) a person-based subscale and (2) a generalized impulsivity subscale. Three investigators (neuropsychologist, psychiatrist, and neurologist) reached consensus on the categorization of items as having a significant person-based component based on the necessity for interaction with others, such as violations of social propriety or interpersonal boundaries, for example, "makes inappropriate sexual comments and advances, is too flirtatious," and "is sensitive to the needs of other people." Some items required operationalization of concepts, for example, the consensus group concluded that displaying a sense of humor (item 30) meant ease of making others laugh, whereas ease to laughter (item 6) did not require others. In other words, items that did not clearly have a person-based component were included in the generalized impulsivity group. For validation, we used the NPI, the most commonly used scale for disinhibition in dementia,[19] and the comparable person-based disinhibition item from the Scale of Emotional Blunting (SEB),[20] previously used in bvFTD and eAD,[8] which ascertains information from caregivers about inappropriate social behavior associated with violation of personal spaces.

Table 2. Demographic Data of the Participants.

	bvFTD (n = 15)		eAD (n = 21)	
	n	Mean (SD)	n	Mean (SD)
Patients				
Sex (female)	7 (46%)		11 (52%)	
Right handedness	14 (93%)		19 (91%)	
Ethnic (white)	15 (100%)		19 (91%)	
Age		61.2 (11.5)		59.1 (5.2)
Duration of illness		3.9 (3.3)		3.9 (2.2)
Years of education		15.5 (2.4)		16.1 (2.0)
MMSE score		24.5 (4.4)		23.5 (4.7)
CDR (sum of boxes)		6.8[a] (1.9)		4.2[a] (1.6)
Caregivers				
Sex (female)	8 (53%)		10 (48%)	
Ethnic (white)	14 (93%)		15 (71%)	
Relationship (spouse)	14 (93%)		20 (95%)	
Years of marriage		32.5 (15.2)		29.8 (12.0)
Age		59.2 (11.8)		61.5 (12.3)
Years of education		15.8 (2.3)		15.8 (1.7)

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; CDR, Clinical Dementia Rating Scale; eAD, early-onset AD; MMSE, Mini–Mental State Examination; SD, standard deviation.
[a]$P < .05$ using t test compared between groups.

Measurements of Cognitive Function and Functional Impairment

Selected standardized neuropsychological tests previously associated with frontal, temporal, and parietal lobe were administered to the patients as follows: Consortium to Establish a Registry for Alzheimer Disease (CERAD) word list delayed recall,[21] Stroop C test,[22] Trail Making Test, part B,[23] Verbal Fluency (Animals and "F, A, S" Words),[24] and Delis-Kaplan Executive Function System (D-KEFS) Design Fluency test.[25] Caregivers also completed both global Clinical Dementia Rating Scale (CDR)[26] and Frontotemporal Lobar Degeneration (FTLD) CDR[27] to ascertain patterns of functional impairment.

Neuroimaging Data Acquisition, TBM Analysis, and Statistical Analysis

The participants underwent MRI using a standardized protocol on the same 1.5 T Siemens Avanto MRI scanner. High-resolution T1-weighted 3D MRI scans were acquired in the coronal plane using a magnetization prepared rapid gradient echo sequence with the following acquisition parameters: repetition time (TR) = 2000 milliseconds, echo time (TE) = 2.49 milliseconds, inversion time (TI) = 900 milliseconds, flip angle = 8°, slice thickness = 1 mm, 25.6-cm field of view, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3. To adjust for global differences in brain positioning and scale across individuals, all scans were linearly registered to the stereotaxic space defined by the International Consortium for Brain Mapping[28] with a 9-parameter transformation. Globally aligned images were resampled in an isotropic space of 230 voxels for each axis (x, y, and z), with a final voxel size of 1 mm^3.

To quantify 3D patterns of volumetric brain differences for each patient, an individual change map, or Jacobian map, was computed by nonlinearly registering each individual scan to a template using a nonlinear inverse-consistent elastic intensity-based registration algorithm, with a built-in smoothing kernel, driven by a mutual information-based cost function (3DMI), which has been described previously.[29] For each patient, a map of the Jacobian determinants was computed from the gradient of the deformation field to illustrate the voxel-wise expansion or contraction factors of relative volume differences between each patient's regions of interest and of the templates.

Removal of the skull and other nonbrain tissue (ie, scalp, dura, meninges) was achieved with an automated brain surface algorithm and manual editing using BrainSuite software (version 2).[30] All algorithms used in creating TBM Jacobian maps, including linear registration, nonlinear registration, and linear regression algorithms, developed at the Laboratory of NeuroImaging (LONI), were successfully used in previous studies measuring brain volumetric changes in neurodegenerative disorders[31] and were implemented using the LONI pipeline.[32]

Table 3. FrSBe Disinhibition Scores.

	bvFTD (n = 15)		eAD (n = 21)	
FrSBe Disinhibition Scores	Median	IQR	Median	IQR
BEFORE scores				
Total	22	10	19	10
Person-based	12	8	9	5
Generalized impulsivity	12	4	10	6
AFTER scores				
Total[a]	39	22	22	10
Person-based[a]	23	15	11	8
Generalized impulsivity	15	7	11	7
CHANGE scores				
Total[a]	11	23	2	4
Person-based[a]	10	12	1	3
Generalized impulsivity	4	10	1	2

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; eAD, early-onset AD; FrSBe, Frontal System Behavioral Scale; IQR, interquartile range.
[a]$P < .05$ using Mann-Whitney *U* test compared between groups.

Statistical Analyses

Data from a total of 37 participants (bvFTD = 16, eAD = 21), who had both FrSBe scores and TBM analyses, were analyzed with SPSS version 22. We excluded 1 participant in the bvFTD group because of unexpectedly extreme value from TBM analyses. Remaining data from 36 participants (bvFTD = 15, eAD = 21) were analyzed in the final analyses. Testing for normality of data used the Shapiro-Wilk test. Analyses for significant difference between means from 2 groups used *t* test and Mann-Whitney *U* test. Whole-brain TBM regression analyses controlling for age and diagnosis were performed to estimate the correlations between FrSBe scores and brain regions. The statistical threshold was set at $P < .05$ corrected for multiple comparisons at the voxel level.

Results

Clinical Characteristic of the Patients and the Caregivers

There were no statistically significant differences between the bvFTD and eAD groups in age, estimated age of onset, duration of the illness, years of education, MMSE score, caregivers' years of education, and years of marriage (Table 2). Despite similar severity of cognitive impairment, patients with bvFTD were significant higher in CDR sum of boxes scores ($df = 33$, $P = .001$, 95% confidence interval [CI] = 1.39-3.8), indicating different patterns of functional impairment. Patients with bvFTD had greater impairment in the following CDR domains: judgment and problem-solving ($z = -3.92$, $P < .001$), community affairs ($z = -3.23$, $P = .001$), home and hobbies domains ($z = -2.23$, $P = .026$), and personal care ($z = -3.19$, $P = .001$), whereas patients with eAD demonstrated a strong trend of having greater memory impairment ($z = -1.862$, $P = .063$). When calculating a standard CDR global score, there were no differences in functional impairment across the groups ($z = -1.05$, $P = .24$). The bvFTD group scored significantly higher on a behavior/comportment/personality domain ($z = -4.9$, $P < .001$) but not on a language domain ($z = -0.736$, $P = .46$) from the FTLD-CDR score. On the NPI, the patients with bvFTD had significantly higher total disinhibition scores compared to the patients with eAD ($\bar{x}_{bvFTD} = 6.5 \pm 4.6$, $\bar{x}_{eAD} = 0.3 \pm 0.7$, $P < .001$). On the NPI, bvFTD compared to AD also had higher agitation, elation, apathy, aberrant motor behaviors, and total scores ($P < .05$).

The FrSBe disinhibition scores. On both disinhibition subscales, the component items achieved very good internal consistencies; the person-based subscale had Cronbach α at a level of .89, and the generalized impulsivity disinhibition subscale had an α at a level of .76 (Table 3).

The FrSBe BEFORE and AFTER scores. On the BEFORE scores, there were no significant group differences in total disinhibition score ($z = -0.95$, $P = .343$), person-based ($z = -1.05$, $P = .29$), or generalized impulsivity ($z = -0.89$, $P = .38$) subscale scores. On the AFTER scores, patients with bvFTD showed higher scores in total disinhibition ($z = -3.12$, $P = .002$) and in person-based subscales ($z = -3.95$, $P < .001$) but not in the generalized impulsivity subscales ($z = -1.68$, $P = .09$).

The FrSBe CHANGE scores. From CHANGE scores, similar to AFTER scores, the patients with bvFTD had higher total disinhibition scores ($z = -3.794$, $P < .001$) and higher person-based disinhibition subscale scores ($z = -3.95$, $P < .001$). The difference did not reach a level of statistical significance in the generalized impulsivity disinhibition subscale scores ($z = -1.62$, $P = .11$). There were no significant correlations on bivariate correlation analyses between total disinhibition CHANGE scores and clinical characteristics, including duration after the onset of illness and years of education.

Across all the groups, the NPI disinhibition score significantly correlated with both person-based ($r = .635$, $P < .001$) and generalized impulsivity ($r = .823$, $P < .001$) subscale CHANGE scores. The person-based disinhibition subscale CHANGE score was significantly correlated with the SEB person-based disinhibition item ($r = .497$, $P = .004$) but not the generalized impulsivity disinhibition subscale CHANGE score ($r = .029$, $P = .875$).

Neuropsychological tests. In our sample, there were no significant correlations of age and years of education with performance on any neuropsychological test. The patients with eAD performed worse on the CERAD delayed free recall ($df = 30$, $z = -2.27$, $P = .023$). On the other hand, the bvFTD group performed worse in executive function on the Delis-Kaplan Executive Functioning System (D-KEFS) proverbs test ($df = 28$, $z = -2.240$, $P = .025$) and the FAS verbal fluency test ($df = 21$, $z = -2.34$, $P = .019$). There was no significant difference between groups in total D-KEFS design fluency total score

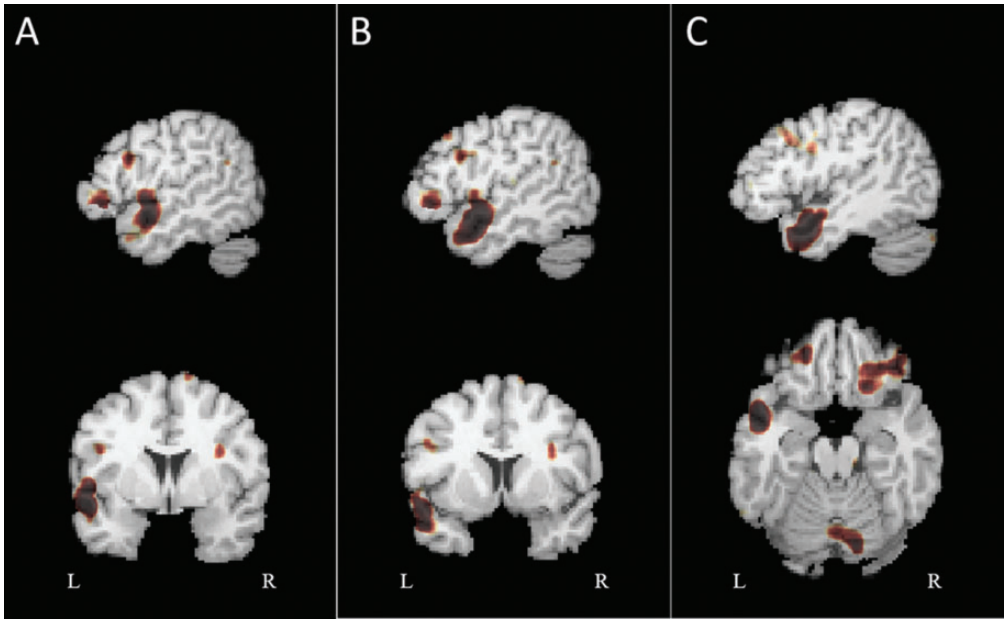

Figure 1. A, Person-based disinhibition subscale score significantly correlated with the left anterior superior temporal sulcus. B, Total disinhibition score significantly correlated with the left anterior superior temporal sulcus and the anterior temporal lobe. C, Generalized impulsivity subscale score significantly correlated with the left anterior temporal lobe and the right orbitofrontal cortex.

($df = 26$, $z = -0.34$, $P = -.736$). However, during the testing, the patients with bvFTD demonstrated more repeats ($df = 26$, $z = -3.65$, $P < .001$), whereas the patients with eAD violated rules more often ($df = 27$, $z = -2.11$, $P = .035$). There were no differences between groups in performances on number of errors made during testing with Stroop C test ($df = 16$, $z = -0.46$, $P = .65$) and Trail Making B test ($df = 22$, $z = -1.856$, $P = .067$).

TBM Analyses

General findings. Duration after the onset of illness, years of education, and CDR sum of boxes score did not show any significant correlation with any specific brain regions. The bvFTD group had significantly smaller volume from TBM analyses than the eAD group in the following brain regions: left dorsolateral prefrontal cortex (DLPFC; $z = -2.26$, $P = .038$), right DLPFC ($z = -2.07$, $P = .007$), and left OFC ($z = -2.68$, $P = .007$). On the other hand, the eAD group had significantly smaller volume than the bvFTD group in left temporal lobe ($z = -2.78$, $P = .006$), right temporal lobe ($z = -2.68$, $P = .007$) and hippocampus ($z = -2.134$, $P = .033$). The analyses also showed a trend that the eAD having smaller volume in the left parietal lobe, but the difference did not reach statistical significance ($z = -0.1845$, $P = .065$).

Correlations Analyses Between Both Groups

Whole-brain regression analyses controlling for age and diagnosis demonstrated a significant relationship between the person-based disinhibition subscale score with the left STS, especially in an anterior region and the right OFC. When using more stringent cutoff (voxels with $P < .01$), correlations with the left STS remained robust but correlations with the right OFC were not statistically significant. The generalized disinhibition subscale score is significantly correlated with the right OFC and the left aTL. The total disinhibition score is significantly correlated with both the left STS and the left aTL (Figure 1).

Table 4. Pearson Correlation Coefficients (*r*) Between FrSBe Disinhibition Scores and Performance on Neuropsychological Testing.

	Disinhibition Scores			
Neuropsychological Tests	Total	Person-Based	Generalized Impulsivity	*df*
CERAD delayed recall	.252	.182	.292	30
Stroop test				
Stroop C errors	−.099	−.072	−.126	13
Trail Making B test				
Trail errors	.348	.144	.573[a]	16
Verbal fluency				
FAS words	.232	.129	.344	18
D-KEFS				
Proverb	.030	.035	.017	26
Design fluency				
Total repeats	−.036	−.066	.002	23
Total rule violations	−.068	−.133	−.018	23

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer Disease; D-KEFS, Delis-Kaplan Executive Functioning System; FrSBe, Frontal System Behavioral Scale.
[a]$P < .05$.

To explore possible different neuroanatomical correlations between NPI disinhibition and FrSBe disinhibition in our sample, we also performed correlation analyses using NPI disinhibition score with TBM analyses. The NPI disinhibition score is significantly correlated only with the left OFC but also had trends of correlation ($P < .1$) with the right OFC, right parietal lobe, and left parietal lobe.

Correlations Between FrSBe Disinhibition CHANGE Scores and Performances on Neuropsychological Tests

Results from correlation analyses between performances on neuropsychological tests and FrSBe disinhibition CHANGE subscale scores are detailed in Table 4. The only significant result found was that frequent errors made on Trail Making B test were correlated with higher score in generalized impulsivity disinhibition subscale score ($P = .01$).

Discussion

This study found differences in subtypes of disinhibition, with differences in neurological localization and implications for differences in pathophysiology, in the 2 dementia groups, bvFTD and eAD. These patients had comparable disturbances in generalized-impulsivity disinhibition, but the bvFTD had greater person-based disinhibition involving social propriety and interpersonal behavior. As expected, generalized impulsivity disinhibition corresponded to orbitofrontal disease, particularly on the right, whereas person-based disinhibition correlated with the left anterior STS. The former implies impairment in the well-known circuits for impulse control, whereas the latter may suggest impairment in the frontoparietotemporal circuitry involved in ToM.

Early behavioral disinhibition is a common manifestation of bvFTD,[1,33] whereas disinhibitions and aberrant motor behaviors usually occur in later stages of eAD.[34] In fact, the International Consensus Criteria for the diagnosis of bvFTD[1] relies on both person-based disinhibition items (A1: a socially inappropriate behavior, A2: a loss of social decorum, C1: diminished response to other people's needs and feelings) and generalized impulsivity disinhibition items (A3, impulsivity, rash, and careless action). Although the commonly used NPI documents the presence of disinhibition in general, it does not distinguish person-based from generalized impulsivity disinhibition in bvFTD. In comparison, the FrSBe disinhibition scale used in this study measures the severity of each disinhibited behavior separately and permits reclassification of the items into those that are person-based versus generalized impulsivity. Using the FrSBe, the patients with bvFTD showed much greater severity of person-based disinhibition than patients with eAD, while both dementia syndromes showed comparable severity in generalized impulsivity disinhibition.

Our finding that generalized impulsivity disinhibition correlated with OFC atrophy fits well with the literature localizing frontal–subcortical connection as an inhibitory circuit. In healthy controls, serotonin and dopamine in OFC function as a negative feedback in learning, delayed gratification, and impulsivity,[35] and OFC damage has produced opportunistic aggression, disinhibition, and impulsivity in many lesion studies.[36] The MRI studies in bvFTD have consistently demonstrated an association between OFC atrophy and higher NPI disinhibition scores compared to healthy controls,[37] patients with mixed dementia,[10] and patients with AD.[11] Functional imaging studies with FDG-PET in bvFTD have also demonstrated an association of disinhibition with hypometabolism in bilateral OFC[38] and left medial frontal structures including anterior medial frontal cortex, gyrus rectus, and the subcallosal area.[39] It is possible that much of the OFC associated with disinhibition in the NPI studies was driven by the item measuring impulsive behavior. On neuropsychological testing, the finding that generalized impulsivity disinhibition was highly correlated with errors made in the Trail Making B test further suggests that generalized impulsivity disinhibition is associated with impaired ability in set shifting and maintaining rule-based behavior from frontal dysfunction.

A finding of correlation between the left aTL and generalized impulsivity disinhibition is also noteworthy. Lesions involving the aTLs may impair an ability to recognize the meaning of stimuli and lead to generalized indiscriminate responses, as well as impulsive acts, for example, hyperorality in Klüver-Bucy syndrome. Lobectomy of either left or right aTL can cause rapid mood swing and severe irritability within few weeks after surgical removal.[40] In addition, another study using FDG-PET in patients with early-onset dementia, mainly AD and FTD, found consistent results showing correlations between disinhibition score from NPI and hypometabolism in bilateral aTLs and orbital gyri.[41] Taken altogether, our finding suggests that generalized disinhibition in both bvFTD and eAD manifested as impulsivity, irritability, and emotional outbursts is highly correlated with dysfunction of OFC and aTL.

Our results of correlations between total disinhibition and person-based disinhibition with the left anterior STS may indicate disruption of the circuitry for ToM, especially in bvFTD. Previous studies have reported impaired ToM in patients with bvFTD associated with the involvement of the left posterior STS,[42] as well as the OFC, [43] aTL, [44] and bilateral insular cortex.[42,45] The STS, the TPJ, the aTL, and the ventromedial PFC form part of the circuitry for ToM,[46] and each region serves different, although overlapped, functions. These interconnected brain regions may be affected as a network in disease and impair the ability to understand that others have agency, thoughts, feelings, and beliefs.[47] A recent study and a meta-analysis demonstrated that different dimensions of social cognition and ToM recruited different subregions of STS: an anterior portion for both language processing and affective ToM[48] and a posterior portion for detecting biological motion and both cognitive and affective ToM.[49,50] There is substantial evidence for impaired ToM ability in bvFTD, including worse performances in both cognitive ToM, for example, faux pas and false beliefs, and affective ToM, for example, reading the minds in eyes test[51] and recognition of basic emotion from pictures of others person.[3] These findings along with our findings suggest that dysfunction or disruption within the neural

circuitries of ToM in bvFTD may facilitate person-based disinhibition from an impaired understanding of personal boundaries, appropriate social manners, and emotion. In sum, the results suggest that person-based disinhibition in bvFTD may involve frontoparietotemporal circuit of ToM and that need not be the result of generalized OFC-mediated impulsivity.

This was one of the few studies to explore clinical and neuroanatomical differences in disinhibited behavior in bvFTD; however, this study has potential limitations. First, it did not rely on standardized disinhibition scales such as the one present in the NPI. Nevertheless, there are no existing scales that different disinhibition based person-based versus generalized impulsivity mechanisms; hence, we had to choose a less commonly used instrument, the FrSBe, which permitted the derivation of these subscales. Second, this study categorizes the FrSBe disinhibition scale into further subscales based on themes of ''social appropriate'' and generalized impulsivity and then explores their neural correlates. Future validation needs to compare these subscales with additional measures reflecting the person-based versus generalized impulsivity distinction. Third, although this study had small sample sizes, the group differences were quite significant. In addition, although the groups were matched for demographic variables and general cognition and global CDR scores, the bvFTD group scored worse on 4 frontal behavior domains in CDR sum of boxes and another behavior domain in FTLD-CDR. This suggests that greater functional impairments in patients with bvFTD may result from predominant frontal behaviors measured in CDR sum of boxes. Finally, this study did not include a direct measurement of ToM. However, the literature strongly substantiates the prominent impairment in ToM, a singular measures of social cognition, in bvFTD compared to other dementias.

In conclusion, this study suggests that disinhibited behaviors in bvFTD and eAD result from at least 2 mechanisms, some based on disturbance in social and interpersonal cognition and others more associated with generalized impulsivity. Our results further suggest an alternative neural correlate in disinhibition that person-based disinhibition may result from dysfunction of frontoparietotemporal networks at the anterior STS subserving ToM rather than from OFC and aTL dysfunction. This supports the view that complex behavioral disturbances in dementia may not result from a single mechanism and can be dissected and analyzed regarding underlying pathophysiology. Much more work can be done to explore other components of disinhibition and of other behavioral changes among patients with dementias and other neurological disorders.

Authors' Note

This work was performed at the Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, and at Greater Los Angeles VA Healthcare System, West Los Angeles.

Declaration of Conflicting Interests

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