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LOSS OF EMOTIONAL INSIGHT IN BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA OR “FRONTAL ANOSODIAPHORIA”

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Abstract

Loss of insight is a prominent clinical manifestation of behavioral variant frontotemporal dementia (bvFTD), but its characteristics are poorly understood. Twelve bvFTD patients were compared with 12 Alzheimer's disease (AD) patients on a structured insight interview of cognitive insight (awareness of having a disorder) and emotional insight (concern over having a disorder). Compared to the AD patients, the bvFTD patients were less aware and less concerned about their disorder, and they had less appreciation of its effects on themselves and on others. After corrective feedback (“updating”), the bvFTD patients were just as aware of their disorder as the AD patients but remained unconcerned and unappreciative of its effects. These findings suggest that lack of insight in bvFTD is not due to “anosognosia,” or impaired cognitive and executive awareness of disease, but to “frontal anosodiaphoria,” or lack of emotional concern over having bvFTD and its impact on themselves and others.

Keywords

Insight; anosognosia; anosodiaphoria; dementia; frontotemporal dementia; Alzheimer's disease

1. INTRODUCTION

Loss of insight is characteristic of behavioral variant frontotemporal dementia (bvFTD). Consensus criteria for FTD include loss of insight as a core diagnostic feature of this disorder (Neary et al., 1998). These criteria defined loss of insight as a lack of awareness of mental symptoms which could be evidenced by either frank denial or unconcern for their consequences. Despite evidence that patients with bvFTD display a greater loss of insight into illness early in the dementia as compared to patients with Alzheimer's disease (AD) (Gustafson, 1993; Mendez & Shapira, 2005), recent studies suggest that loss of insight lacks specificity in dementia and does not effectively discriminate patients with these two conditions (Piquet, Hornberger, Shelley, Kipps, & Hodges, 2009). Moreover, some bvFTD patients may never experience impaired insight (Evers, Kilander, & Lindau, 2007), and this criterion has even been eliminated from the new, proposed International Criteria for bvFTD

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(Rascovsky et al., in press). It is likely that bvFTD is associated with a specific type of loss of insight not detected in some studies.

Loss of insight is common in dementia, the model of which is AD (Ott et al., 1996a; Ott, Noto, & Fogel, 1996b). Loss of insight occurs in up to 60% of patients with AD and correlates with severity and duration of illness (Mendez & Shapira, 2005; Migliorelli, Teson, Sabe, & Petracca, 1995). Loss of insight in AD also correlates with frontal dysfunction as evident by apathy, disinhibition, impaired mental flexibility, and other “frontal behaviors” and neuropsychological measures (Ansell & Bucks, 2006; Dalla Barba, Parlato, Lavarone, & Boller, 1995; Gallo, Chen, Wiseman, Schacter, & Budson, 2007; Hanyu et al., 2008; Kashiwa et al., 2005; Migliorelli et al., 1995; Michon, Deweer, Pillon, & Agid, 1994; Ott et al., 1996b; Reed, Jagust, & Coulter, 1993; Starkstein, Jorge, Mizrahi, & Robinson, 2006; Vasterling, Seltzer, & Watrous, 1997; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). In addition, studies searching for the neural correlates of insight in AD have indicated an association of recognition of one's illness with dysfunction of the frontal lobes, especially on the right, and the adjacent structures (Hanyu et al., 2008; Harwood et al., 2005; Ott et al., 1996b; Reed et al., 1993; Salmon et al., 2006; Shibata, Narumoto, Kitabayashi, Ushijima, & Fukui, 2008; Starkstein et al., 1995; Vogel et al., 2005).

Since loss of insight in AD involves the frontal lobes, this suggests that frontally-predominant dementias such as bvFTD may be particularly prone to impair insight (Mendez & Shapira, 2005). In fact, studies show greater loss of insight, particularly for personality traits, among patients with bvFTD compared to those with AD (Mendez & Shapira, 2005; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005; Salmon et al., 2008; Williamson et al., 2010). As compared to AD, where loss of awareness of memory and other cognitive deficits may predominate (Feher, Mahurin, Inbody, & Crook, 1994; Howorth & Saper, 2003; Ott et al., 1996a; Reed et al., 1993), in bvFTD, social and behavioral changes and personality traits may be particularly vulnerable to loss of insight (Eslinger et al., 2005; Rankin et al., 2005; Salmon et al., 2008). Patients with bvFTD tend to minimize negative behavioral changes, such as emotional detachment, and tend to exaggerate positive aspects of their behavior (Eslinger et al., 2005; Rankin et al., 2005; Zamboni, Grafman, Krueger, Knutson, & Huey, 2010). It appears that bvFTD may be particularly associated with a loss of the emotional and interpersonal aspects of insight.

Insight is a heterogeneous concept, and there may be specific mechanisms involved in loss of insight in bvFTD. Clinicians most frequently use “loss of insight” synonymously with loss of the ability to know or recognize one's own illness, or “anosognosia” (Babinski, 1914; Mograbi, Brown, & Morris, 2009; Starkstein et al., 2006). This term, originally referring to reduced awareness of hemiplegia in stroke patients due to parietal deficit in updating sensory-body representations, now applies to reduced awareness of any symptoms (Heilman, Barrett, & Adair, 1998; Spinazzola et al., 2008). Anosognosia for a disorder could result from inability to update information about the self, or a “petrified self” frozen in a time as proposed for AD (Hehman, German, & Klein, 2005; Mograbi et al., 2009; Morris & Hannesdottir, 2007). Anosognosia for a disorder could also result from inability to update awareness of the current self from lateral-frontal executive disturbances.

Among patients with bvFTD, who have more medial than frontal lobe involvement, this study proposes a different mechanism for loss of insight than anosognosia. As defined in the Consensus Criteria, “lack of insight” could be manifest, not only by lack of awareness, but also by lack of concern or “anosodiaphoria” (Mendez & Shapira, 2005). This term reflects a lack of emotional insight or concern over having a disorder or its potential impact on themselves and others. Among the bvFTD patients, we hypothesize that “updating” or

corrective feedback can improve cognitive insight or awareness of disease, but updating does not improve emotional insight, or concern for their disorder.

This study uses a novel Structured Insight Interview to assess insight in patients with bvFTD. The limitations of patient questionnaires and of caregiver assessments pose problems for the assessment of insight (Clare, Marková, Verhey, & Kenny, 2005; Williams et al., 2010). Patients do not correctly see themselves or report their disorder or deficits, and caregivers are biased observers who indirectly report on the patients' insight. Accordingly, this study devised the Structured Insight Interview approach in order to directly measure cognitive and emotional insight, response to updating, and the perceived impact of their illness among patients with bvFTD, compared to those with AD.

2. METHODS

2.1. Subjects

Twelve patients met the International Criteria for bvFTD (Rascovsky et al, 2011). These patients were recruited from the UCLA FTD&Neurobehavior Clinic, agreed to participate in a larger project on FTD or the UCLA Alzheimer's Disease Research Center, and gave informed consent. The criteria for a clinical diagnosis of probable bvFTD included progressive deterioration of behavior and/or cognition with three of the following: early behavioral disinhibition; apathy or inertia; loss of sympathy or empathy; perseverative, stereotyped or compulsive/ritualistic behavior; hyperorality and dietary changes; and deficits in executive tasks with relative sparing of episodic memory and visuospatial skills. These criteria were then supported by predominant frontal or anterior temporal hypometabolism on positron emission tomography imaging.

As a comparison group, 12 AD patients, age-matched for earlier age of onset, were recruited from the same program as a comparison group. These patients met criteria for clinically probable AD after an extensive evaluation involving clinical, neuropsychological, and neuroimaging. The severity of disease, and comparability of bvFTD and AD patients, was assessed using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Clinical Dementia Rating Scale (Morris, 1993), augmented with two additional items, a Behavioral Compartment and Personality Domain and a Language Domain, for the assessment of bvFTD patients (Knopman, Weintraub, & Pantratz, 2011).

2.2. Procedures

The bvFTD and AD patients underwent a Structured Insight Interview that probed knowledge of their disorder and their degree of concern (See Table 1). The interview consisted of three parts assessing awareness of the presence of a disorder (Part I); perception of decreased function from the disorder, or how it personally affects them (Part II); and perception of how their disorder affects others, particularly family and friends (Part III). Each of the three parts began with a lead question asking whether they were aware of having a disorder, its impact on themselves, or its impact on others. Following their response, regardless of whether they answered yes or no, the interviewer "updated" them with corrective feedback. Following each update or feedback statement, there were 12 yes-no questions, six assessed the patient's knowledge, or cognitive updating, and characterized by verbs such "know," "understand," "accept," "think," "believe," or "agree," and six other questions assessed concern, or emotional updating, and characterized by adjectives such as "concerned," "worried," "upset," "disturbed," "bothered," or "anxious." All questions were counterbalanced, both in cognitive and emotional updating and in the valence direction (positive or negative). Using the Structured Insight Interview, two clinicians in our program have shown inter-rater reliability ($r=0.654$) for 4 bvFTD and 4 AD patients.

As part of their initial evaluation, the dementia groups underwent neuropsychological mental status tests based originally on the Consortium to Establish a Registry in AD (CERAD) and the Neurobehavioral Cognitive Status Examination (NCSE) (Kiernan, Mueller, Langston, & Van Dyke, 1987; Welsh et al., 1994). In addition to the MMSE, the assessment included digit span, verbal fluency for animals names, the 15-item mini-Boston Naming Test, an auditory comprehension score modified from the Western Aphasia Battery (Shewan & Kertesz, 1980), the Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000), a calculations test modified from the NCSE, and the CERAD verbal memory test rendering a savings score (Delayed Recall Learning/Learning Trial III) and a recognition score (accurate Yes answers on true-false recognition). Finally, the construction test evaluated copies of a circle, rhombus, overlapping rectangles, and a cube, for figure closure, 3-dimensionality, parallel opposite sides, correct internal lines, and frontal face orientation.

2.3. Data Analysis

Their responses were contrasted across groups on the Structured Insight Interview, including subscores for emotional and cognitive insight and for each of its three parts, and on the neuropsychological measures. The Structured Insight Interview results were further correlated with the variables from the neuropsychological items. The Structured Interview Questions yielded a Total Insight score with subscores for cognitive insight, emotional insight and the three parts and their components. The subscore results are embedded post hoc scores. The individual correlations, however, were Bonferroni corrected for multiple comparisons.

3.0. RESULTS

There were no significant differences on basic demographic characteristics or most dementia severity measures (MMSE and standard CDR scores) between the two groups (See Table 2); however, the bvFTD patients had more impaired scores on the augmented CDR that included the additional domains of Behavioral Compartment and Personality (Knopman et al., 2011). On the neuropsychological measures, there were no group differences on most measures except, as expected, the bvFTD patients performed significantly better than the AD patients on the CERAD memory items and on constructions (See Table 3).

On the Structured Insight Interview, the bvFTD patients had worse Total Insight scores and emotional and cognitive insight subscores than the AD patients (See Table 4). Most bvFTD patients denied having a disorder or one with effects on themselves or others. The bvFTD patients differed significantly from the AD patients on the lead questions for presence of a disorder and for its effect on others. On Part I, after updated, there were no differences on cognitive awareness for presence of a disorder as most bvFTD and AD patients endorsed having a disorder. However, the bvFTD patients continued to show a relative lack of concern for the presence of their disorder. On Parts II and III, the bvFTD patients continued to show a lack of either cognitive awareness or emotional concern for the effects of having a disorder either on their own function and abilities or on their family and friends (See Table 4).

After correction for multiple comparisons, there was only one significant correlations between the scores and subscores of the structured Insight Interview and the neuropsychological measures (See Table 5). Part I, dealing with knowledge and concern for the presence of a disorder, correlated with better FAB scores, a measure of frontal-executive functions.

Finally, examples of patient responses to the Lead Questions were recorded. On the first Lead Question about having a disorder, bvFTD patients responded that “I have a dementia in my head, but I am getting rid of it,” and “I might have Alzheimer's disease.” For Lead Question II about the effects of the disorder on themselves, bvFTD patients responded: “It makes me lazy; I delay in responses and can't focus on anything else besides one thing,” and “I cannot get a job.” For Lead Question III, bvFTD patients responded “Now I let my children mess with my life,” and “my wife is not happy because she is taking care of me.”

4.0. DISCUSSION

4.1. General discussion

Loss of insight among patients with bvFTD may be due to a lack of emotional insight. Compared to AD patients, those with bvFTD initially deny the presence of their disorder. After being informed that they do in fact have a disorder, bvFTD patients continue to experience decreased concern over their dementia despite similar awareness of their disease as the AD patients. Furthermore, the bvFTD patients do not appreciate the impact of their disorder on themselves or others as much as do the AD patients. These findings point to a loss of emotional insight from anosodiaphoria rather than from loss of cognitive awareness or anosognosia.

We do not have solid models for the mechanism of loss of insight in bvFTD. Insight among dementia patients does not correlate with cognitive impairments, such as in estimating personal attributes, e.g., their weight and eyesight, or in accurately characterizing others' behavior (Banks & Weintraub, 2008; Ruby et al., 2007). A more common view is that the mechanism for loss of insight is anosognosia or inability to recognize one's own illness or deficits. Originally introduced by Babinski (1914) to refer to hemiplegic patients who ignore their paralysis, the term anosognosia has come to refer to lack or recognition of disease, disorder, symptoms, or dysfunction (Babinski, 1914; Heilman et al., 1998). Anosognosia could result from an inability to “update” awareness of having a disorder due to a loss of autobiographical memory and being “frozen” in outdated memories (Gallo et al., 2007; Hehman et al., 2005; Mograbi et al., 2009). Areas of the prefrontal cortex involved in bvFTD, especially on the right, may be activated when retrieving autobiographical memory (Cabeza & St Jacques, 2007; Gilboa, 2004; Keenan, Wheeler, Gallup, & Pascual-Leone, 2003). Anosognosia could also result from an inability to “update” awareness of having a disorder due to frontal-executive disturbances. In this “executive anosognosia” there may be an abnormal comparator or discrepancy detector for monitoring mismatches between relatively spared older memories and current performance (Abu-Akel, 2003; Hannesdottir & Morris, 2007; Mograbi et al., 2009; O'Keeffe et al., 2007). Executive anosognosia, however, may correspond to traditional lateral-frontal executive functions and cognitive awareness, which may not be the main cause of loss of insight in bvFTD.

Alternatively, loss of insight in bvFTD may result, not from a form of anosognosia, but from a loss of emotional insight or anosodiaphoria (Banks & Weintraub, 2009; Mendez & Shapira, 2005). Compared to the AD patients, the bvFTD patients are able to update awareness of their disorder at least to the level of the AD patients, but they remain more concerned and unable to update recognition of the effects of their disorder on themselves or on others. “Frontal anosodiaphoria” may represent a lack of concern for proper self-appraisal (Schmitz & Johnson, 2007; Williamson et al., 2010), and there is evidence that the ventromedial prefrontal cortex (VMPFC), especially on the right, and its adjacent connections are involved in this process (Kennan et al., 2003; Nakamura et al., 2001; Northoff, Heinzel, Bempohl, Dobrowolny, & Panksepp, 2006; Stuss & Anderson, 2004; Van der Meer, Costafreda, Aleman, & David, 2010). The VMPFC and adjacent anterior cingulate and anterior insula, especially on the right, are the focus of disease in bvFTD

(Amanzio et al., 2011; Bechara, 2004; Craig, 2009; Evers et al., 2007; Howorth & Saper, 2003; Mendez & Shapira, 2005; Thompson et al., 2005). Furthermore, along with the anterior cingulate, the anterior insula participates in interoceptive and emotional awareness, sensations involved in self-appraisal and self-reflection (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Gilboa et al., 2006; Schnyer et al., 2004; Singer, Critchley, & Preuschoff, 2009; Turner & Coltheart, 2010).

There are several methodological limitations of this study. First, insight can be difficult to assess in dementia without a caregiver or informant (Williamson et al., 2010). There are significant problems with clinician ratings (Clare et al., 2005), and patient interviews depend on whether the patient mentions cognitive problems without being prompted (Evers et al., 2007). This study used a novel Structured Insight Interview to try to get around these methodological issues and directly access the patients' insight, as well as dissecting the different potential mechanisms involved. Second, despite the advantages of this instrument, it does not allow validity testing among normal subjects, since it depends on the presence of a disorder. On the other hand, the Yes-No questions have face validity for insight for disease, and the instrument has adequate inter-rater reliability. Third, there is the possibility that the cognitive or awareness questions were easier than the emotional or concern questions. This does not account, however, for an apparent differential benefit only for awareness of disorder and between the two groups. Finally, this preliminary study is suggestive but not conclusive of the underlying frontal mechanisms of anosodiaphoria in bvFTD. Nevertheless, it offers a clear direction for further exploration of insight in bvFTD and related disorders.

4.2. Conclusions

This study found that the loss of insight in FTD was more properly described as a "frontal anosodiaphoria" rather than as anosognosia (Mendez & Shapira, 2005). There is a lack of emotional updating or concern for having an illness; an absence of an emotional self-referent tagging of information on their disorder, possibly from disease in the VMPFC-anterior cingulate-anterior insula area, especially on the right. Investigators can build on this work and further clarify the underlying mechanisms responsible for loss of insight in brain disorders.

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The Highlights of the article entitled: “Loss of Emotional Insight in Behavioral Variant Frontotemporal Dementia or “Frontal Anosodiaphoria.”

1. Loss of insight results from bvFTD, a disorder affecting the medial frontal area.
2. These patients have anosodiaphoria, or indifference, rather than anosognosia.
3. This anosodiaphoria may result from a loss of emotional updating.
4. Loss of emotional updating particularly impacts on self-referential processes.
5. Frontal anosodiaphoria is a failure to emotionally tag self-referent information.

TABLE 1**EXAMPLE OF STRUCTURED INSIGHT INTERVIEW & QUESTIONNAIRE**

I am going to ask you a series of questions about your condition. The questions ask about your beliefs and feelings using different words. Please listen carefully to the words in the questions and what they ask you about your beliefs and feelings. (Includes examples of 12 questions/part assessing cognitive or emotional updating.)

PART I. PRESENCE OF DISORDER answer each YES NO

Lead Question: Do you have a disorder affecting your brain?

Updating: You have been told that you have a disorder affecting your brain.

Do you know that you have a disorder affecting your brain?

Are you worried that you have a disorder affecting your brain?

PART II. IMPACT OF DISORDER ON THEMSELVES answer each YES NO

Lead Question: Do you have problems or inability to do some things due to your disorder?

Updating: You have been told that your disorder is causing you problems and keeps you from doing some activities that you used to do before.

Do you believe that you have problems or inability to do some things due to your disorder?

Are you upset that you have problems or inability to do some things due to your disorder?

PART III. IMPACT OF DISORDER ON THEMSELVES answer each YES NO

Lead Question: Does your disorder affect your family, friends and others?

Updating: You have been told that your disorder affects your family, friends and others.

Do you accept that your disorder affects your family, friends and others?

Are you anxious that your disorder affects your family, friends and others?

TABLE 2

Frontotemporal Dementia (bvFTD) versus Alzheimer's Disease (AD) Patient Characteristics

	bvFTD	AD	significance
Numbers	12	12	n.s.
Sex (M/F)	6/6	6/6	n.s.
Age (years)	63.4 (4.4)	64.6 (4.8)	n.s.
Duration (years)	3.3 (2.1)	3.2 (2.6)	n.s.
Education (years)	14.5 (4.1)	14.2 (4.3)	n.s.
MMSE^a	24.3 (2.8)	22.6 (4.1)	n.s.
Standard CDR-SB^b	5.9 (1.7)	5.3 (1.5)	n.s.
Augmented CDR-SB^c	8.3 (2.0)	6.3 (1.8)	t=2.58, p<.05

^a MMSE=Mini-Mental State Examination scores^b Standard Clinical Dementia Rating Scale with 6 item Sum of Boxes Scores^c Augmented Clinical Dementia Rating Scale with 8 item Sum of Boxes scores = CDR-SB plus Behavioral Compartment and Personality Domain and Language Domain.

TABLE 3

Frontotemporal Dementia (bvFTD) versus Alzheimer's Disease (AD) Neuropsychological Characteristics

	bvFTD	AD	significance
Digit Span	6.0 (.95)	6.50 (1.68)	n.s.
Verbal Fluency	13.50 (3.83)	12.17 (3.83)	n.s.
Mini-BNT (15)	12.50 (1.88)	12.0 (1.81)	n.s.
Comprehension (30)	27.0 (1.85)	27.58 (2.07)	n.s.
FAB Score (18)	11.17 (4.26)	12.17 (2.55)	n.s.
Calculations (12)	7.75 (1.22)	7.67 (1.37)	n.s.
CERAD Savings	6.91 (1.51)	5.42 (1.39)	t=2.55, p<.05
CERAD Recognition	7.75 (1.54)	6.25 (1.29)	t=2.58, p<.05
Constructions (12)	9.50 (1.78)	7.42 (1.62)	t=2.99, p<.01

Mini-BNT=mini-Boston Naming Test

CERAD: Consortium to Establish a Registry in Alzheimer's Disease

Savings Score (Delayed Recall Learning/Learning Trial III as proportion of 10 words) and the accurate Yes answers on Recognition (Welsh et al, 1994).

TABLE 4

FRONTOTEMPORAL DEMENTIA (bvFTD) versus ALZHEIMER'S DISEASE (AD) Structured Insight Interview

	bvFTD	AD	significance
TOTAL INSIGHT SCORE (36)	22.00 (2.02)	32.08 (2.24)	t=11.58, p<.001
Cognitive Insight subscore (18)	13.34 (1.78)	16.83 (1.35)	t=5.41, p<.001
Emotional Insight subscore (18)	8.66 (1.45)	15.25 (1.45)	t=11.13, p<.001
Part I			
<i>Lead Question: presence of disorder</i>	Yes=4, No=8	Yes=10, No=4	X ² =4.29, p<.05
INSIGHT UPDATING ITEMS (12)	8.42 (1.45)	10.42 (1.37)	t=3.47, p<.01
Cognitive updating subscore (6)	4.92 (0.79)	5.50 (0.80)	n.s.
Emotional updating subscore (6)	3.50 (1.17)	4.92 (1.00)	t=3.20, p<.01
Part II			
<i>Lead Question: effects on self</i>	Yes=5, No=7	Yes=9, No=3	n.s.
INSIGHT UPDATING ITEMS (12)	8.00 (1.35)	10.33 (1.37)	t=4.20, p<.001
Cognitive updating subscore (6)	4.92 (1.00)	5.83 (0.39)	t=2.94, p<.01
Emotional updating subscore (6)	3.08 (1.31)	4.50 (1.17)	t=2.86, p<.01
Part III			
<i>Lead Question: effects on others</i>	Yes=3, No=9	Yes=9, No=3	X ² =4.17, p<.05
INSIGHT UPDATING ITEMS (12)	5.58 (1.19)	11.33 (1.07)	t=12.45, p<.001
Cognitive updating subscore (6)	3.50 (1.17)	5.50 (0.80)	t=4.89, p<.001
Emotional updating subscore (6)	2.08 (1.00)	5.83 (0.39)	t=12.10, p<.001

TABLE 5

CORRELATIONS BETWEEN INSIGHT INTERVIEW and NEUROPSYCHOLOGICAL MEASURES: Frontotemporal dementia and Alzheimer's disease patients

	Total Insight Score	Cognitive Insight Subscore	Emotional Insight Subscore	Part I Insight Updating	Part II Insight Updating	Part III Insight Updating
Digit Span	.129	.111	.211	.309	.192	.257
Verbal fluency	.003	.376	.068	-.121	.002	-.043
Mini-BNT	-.015	.386	.122	-.007	.100	.025
Comprehension	.053	.098	.166	.530	.231	.244
FAB	.118	.206	.000	.642*	.373	.313
Calculations	-.019	.021	-.366	-.231	.042	-.009
CERAD Savings	-.385	-.067	-.420	-.281	-.374	-.394
CERAD Recogn	-.363	-.246	-.549	-.201	-.201	-.420
Constructions	-.567	-.551		-.291	-.354	-.515

Mini-BNT=15-item Boston Naming Test; FAB=Frontal Assessment Battery; CERAD Savings=Consortium to Establish a Registry In Alzheimer's Disease 10-item verbal learning test Savings Score; CERAD Recogn=CERAD recognition score

* Correlation significant at 0.0009 level (1-tailed, Bonferroni corrected significance level).