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IN THE FOG: NEURAL CORRELATES OF PSYCHIATRIC SYMPTOMS IN MIXED NEURODEGENERATIVE AND DEPRESSED POPULATIONS

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Abstract

IN THE FOG: NEURAL CORRELATES OF PSYCHIATRIC SYMPTOMS IN MIXED NEURODEGENERATIVE AND DEPRESSED POPULATIONS

Kelly A. Gola

This dissertation study examined the accuracy of early stage neurodegenerative disease patients' psychiatric self-reports; compared patient groups to clinically normal age-matched controls on specific psychiatric symptoms; and examined the neural substrates of psychiatric symptoms. To determine whether patients could accurately self-report psychiatric symptoms, 59 participants-informant dyads (11 with possible or probable typical or atypical Alzheimer's disease (AD), 13 behavioral variant frontotemporal dementia (bvFTD), 11 semantic variant primary progressive aphasia (svPPA), 13 late-life depressed patients (LLD), and 11 clinically normal controls (NC)) completed a comprehensive battery of psychiatric measures and participated in separate video-taped interviews about the participants' psychiatric history and experiences of loss. Video observers rated participant interviews for signs of psychiatric phenomena, and the psychometric qualities of participant self-reports were analyzed. Once validated, participant self-report data of 38 additional participants (14 AD, 14 bvFTD, 3 svPPA, 5 LLD, and 2 NCs) were added to group comparison and imaging analyses; symptoms were compared to structural and functional magnetic resonance imaging data. Results showed that early stage neurodegenerative patients did accurately self-report psychiatric symptoms. svPPA

and LLD patients rated themselves higher in depression than controls, and grief, negative affect, and mania were related to volumes of intrinsically connected networks observed in healthy adults. Implications for neurology and psychiatry research and clinical diagnoses and are discussed.

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In the Fog: Neural Correlates of Psychiatric Symptoms in Mixed Neurodegenerative and Depressed Populations

Neurodegeneration disease is a costly and growing public health crisis that requires early, accurate detection for effective clinical care. It is estimated that by mid-century a US adult will be diagnosed with neurodegenerative disease every 33 seconds and one in three Medicare dollars will be spent on neurodegenerative disease treatment and care (Alzheimer's Association, 2016), making the need for clear understanding of signs, symptoms, and neural mechanisms of neurodegenerative disease urgent. A common factor that has confounded early, accurate detection of neurodegenerative disease is psychiatric misdiagnosis. This is due to a number of considerations such as a) lack of research on psychopathology in neurodegenerative disease patients due to assumptions about the validity of patient self-reports in neurodegenerative patients, b) symptom overlap between neurological and psychiatric disorders, c) a lack of training by psychiatrists to detect neurodegeneration, and d) the lack of symptom specificity of the Diagnostic and Statistical Manual of Mental Disorders (DSM; Benjamin, Travis, Cooper, Dickey, & Reardon, 2014). In fact, by the time neurodegenerative patients have been referred to a neurologist, they often have been misdiagnosed with heterogeneous psychiatric diagnoses such as depression, bipolar affective disorder, and schizophrenia (Woolley, Khan, Murthy, Miller, & Rankin, 2011).

While neurodegeneration is often misdiagnosed by psychiatrists, neurodegeneration does not preclude the presence of comorbid psychiatric symptoms. News of a fatal diagnosis may catalyze extreme mood changes in patients. Also,

neurological symptoms, such as memory decay or loss of communication abilities, may contribute to feelings of isolation and despair. Further, changes in neural function may directly lead to psychopathological changes. In sum, the relationship between psychopathology and neurodegeneration is not clearly understood. Therefore, the goals of the present study are to determine whether psychopathology can be accurately assessed in neurodegenerative patient groups in the early stages of their diseases; to identify the prevalence of specific psychiatric symptoms in distinct neurodegenerative diagnostic groups; and to identify neural underpinnings of psychiatric symptoms.

Understanding psychopathology in the context of neurodegeneration

Neurodegeneration describes the progressive loss of structure and function of neurons. Neurodegenerative disease syndromes with socio-emotional and behavioral (e.g., versus motor) presentations are at a particular risk for psychiatric misdiagnosis. Both psychiatric syndromes and a class of neurodegenerative syndromes that affect the frontal and temporal lobes of the association cortex (known as frontotemporal lobar degeneration) are characterized by cognitive, socio-emotional, and motivational deficits, which are often confused for psychopathology (Woolley et al., 2011). While overlapping symptoms between neurodegenerative syndromes and psychiatric syndromes can result in diagnostic confusion for clinicians, psychopathology and neuropathology can also co-occur.

Psychopathology appears in up to 90% of patients with neurodegenerative disease diagnoses (Robert et al., 2005), with depressive phenomena accounting for half of

those symptoms (Margari et al., 2012; Prado-Jean et al., 2010). Neurodegeneration with comorbid depression is associated with higher rates of suicidal ideation (Koyama et al., 2015; Prado-Jean et al., 2010) and behavioral problems, such as irritability and aggression (Prado-Jean et al., 2010). It is also associated with increased cognitive deficits and may accelerate the disease process (Margari et al., 2012; Peters et al., 2013). Yet, relatively little is known about how neurodegenerative patients experience psychiatric symptoms because it is assumed that neurodegenerative patients cannot accurately self-report on historical changes in emotional responding and mood. In the following, I will outline prior research on the validity of psychiatric assessment in neurodegenerative disease groups, and discuss possible neurodegenerative disease group differences on specific psychiatric symptoms, as well as possible neural substrates of symptom specific psychopathology.

Accuracy of psychiatric assessment in neurodegenerative groups.

Assumptions about the response accuracy of neurodegenerative patients' self-reports have stalled needed research on the relationship between psychiatry and neurodegeneration. Neurodegenerative patients are commonly excluded from psychiatric studies on the basis of their diagnosis because it is assumed that symptoms associated with neurodegenerative disease undermine the validity of self-report data. For instance, a common feature of behavioral variant frontotemporal dementia (bvFTD) is loss of insight into one's own deficits/behavior, or 'anosognosia'. These patients are clinically characterized by deficits in social

judgment and disinhibition as well as changes in personality and behavior of which they are unaware (Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005; Rascovsky et al., 2011). Alternatively, anosognosia is not characteristic of Alzheimer's disease but episodic memory deficits may affect Alzheimer's patients' ability to accurately report their changes in mood over time. Finally, semantic language deficits seen in progressive aphasia syndromes, such as semantic variant primary progressive aphasia (svPPA) and some variants of Alzheimer's disease, may undermine data quality as these patients may not sufficiently comprehend questions on psychiatric assessment forms. While these disease symptoms are important considerations for researchers interested in investigating psychopathology in neurodegenerative disease, little work has been done to examine whether patients' loss of insight into their neurodegenerative symptoms or other deficits generalizes to deficits in the ability to self-report emotional suffering or depression, which is inherently an intrapsychic phenomenon that is often best subjectively understood.

To circumvent problems of response accuracy in psychiatric assessment of neurodegenerative disease patients, researchers have often relied on informant reports such as the Neuropsychiatric Inventory (NPI); which assesses observable behaviors like "seeming" as if one is in low spirits. However, the NPI does not adequately capture symptoms that predict the onset and duration of depression such as rumination and a persistent sense of worthlessness or hopelessness, which are often key to the differential diagnosis of DSM syndromes. Further, even within non-neurodegenerative psychiatric populations, there is low correspondence between self-

and informant- psychiatric reports (Kraemer et al., 2003; Zucker, Morris, Ingram, Morris, & Bakeman, 2002). Thus, using informant assessments to measure psychiatric phenomena in neurodegenerative disease patients may fall short of valid study, and methods of assessing psychopathology in these patients must be carefully considered.

While neurodegenerative patients do exhibit memory and socio-emotional deficits that can undermine the validity of psychiatric self-reports, the degree to which these deficits actually affect data validity may be determined by such factors as neurodegenerative diagnosis and disease severity. Snow et al. (2005) found that when self-reporting their level of depression, neurodegenerative patients were no less accurate than depression patients. Also, Robinson et al. (2011) found that patients indeed reported feelings of shame and loss of self upon receiving a neurodegenerative diagnosis, suggesting that many patients can and do report on aspects of psychological and emotional suffering; however, this may be mediated by disease severity and type. For instance, Ott and Fogel (1992) found that disease severity in AD mediated the ability to accurately self-report symptoms. Because it is unclear whether patients can adequately report on psychiatric status, the first aim of this paper is to assess the accuracy of psychiatric self-reports in early stage neurodegenerative disease syndromes by analyzing patient self-report psychometrics.

Possible neurodegenerative group differences in psychiatric symptoms.

Psychiatric syndromes classified by the DSM are characterized by heterogeneous symptom clusters plausibly mediated by distinct neurological

substrates. For instance, DSM criteria for depression involve symptoms of context-insensitive sadness/dysphoria (distinct from contextualized sadness in grieving populations), diminished interest in activities (or anhedonia), sleep disturbances, fatigue, psychomotor agitation, changes in appetite, feelings of guilt or worthlessness, difficulty concentrating, indecisiveness, and recurrent thoughts of suicide (American Psychiatric Association, 2013). These symptoms involve discrete aspects of cognitive, affective, and biological functioning that may differ across neurodegenerative disease groups due to neural dysfunction particular to the disease. For instance, apathy is a core features of bvFTD (Rascovsky et al., 2011), and is related to volumetric changes in the salience network (a constellation of distributed, but temporally coactivating neural regions; Yuen et al., 2014). bvFTD is also associated with appetite changes and deficits in executive functioning, which can be confused for depression symptoms. Alternatively, Alzheimer's disease (AD) is characterized by mnemonic cognitive deficits associated with default mode network atrophy and dysfunction, and is also commonly linked to sleep disturbances (Witting, Kwa, Eikelenboom, Mirmiran, & Swaab, 1990), which are also symptoms of depression.

Such symptom overlap between neurological and psychiatric syndromes can result in depression misdiagnoses for both AD and bvFTD. Further, psychiatric symptoms often overlap across DSM syndromes and can undermine accurate diagnoses within psychiatry itself. Apathy, for instance, is a symptom of schizophrenia, dysthymia, and cyclothymia in addition to depression, bvFTD and

other neurodegenerative syndromes. Thus, any assessment of psychopathology in neurodegenerative patients must be done with careful attention to symptoms that cut across both psychiatric and neurological disorders.

While symptoms overlap between psychiatry and neurology may lead to psychiatric misdiagnosis, neural atrophy patterns and neural network dysfunction may confer particular vulnerability to- or alternatively protection from- psychiatric symptoms. Focal neurodegenerative syndromes target intrinsically connected networks (ICNs; i.e., functionally connected, but spatially distributed cortical and subcortical regions that synchronically coactivate/deactivate during repeated activity and rest) that have been implicated in psychiatric syndromes in non-neurodegenerative populations. However, the relationship between ICN functioning and specific psychiatric symptoms has not been clearly established.

ICNs are defined by statistical patterns of brain activation measured *in vivo* according to fluctuations in cerebral blood flow. They develop over the course of learning and development to manage common human functions (e.g., cognition, vision, etc.), and are predicted by axonal connections between neurons (Damoiseaux, Prater, Miller, & Greicius, 2012; Honey et al., 2009). During development, axonal connections among proximal and anatomically similar cells form and reform to support complex human functions (Mechelli, Friston, Frackowiak, & Price, 2005). For example, identity development during adolescence corresponds with the segregation of an ICN that mediates self-reflection and another that mediates cognitive control (Sherman et al., 2014). In focal neurodegenerative diseases, ICN

degeneration is believed to occur through the spread of neurotoxins along axonal pathways (Raj, Kuceyeski, & Weiner, 2012; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012), and ICNs observed in healthy adults during tasks and rest begin to decay.

Resting state studies of psychiatric populations have found that the ICNs that are particularly vulnerable in focal neurodegenerative disease patient groups are commonly implicated in psychopathology, yet the exact contributions of these networks to psychopathology remain unclear. The networks of particular interest to this study are the default mode network (DMN) which is associated with memory deficits in Alzheimer's disease; the salience and cingulo-opercular networks (SN/CON) which are associated with socio-emotional deficits in behavioral variant frontotemporal dementia; and the semantic appraisal network (SAN) which may be associated with deficits in encoding and storage of valenced personalized beliefs in semantic variant primary progressive aphasia (svPPA; though less is known about this latter network due to imaging constraints of its constituent regions). Because these networks are selectively affected in focal neurodegenerative disease populations, neurodegenerative disease subgroups may differ according to network-driven psychiatric symptoms, and subsequently these patients provide a unique human lesion model for understanding the role these networks play in psychopathology.

AD and default mode network damage

Alzheimer's disease (AD) comprises a diverse cluster of clinical syndromes, each involving distinct atrophy patterns, but which are unified by the presence of amyloid deposits and neurofibrillary tangles (McKhann et al., 2011). Amnestic AD is the most common form of AD, however AD can also present with primary symptoms of focal language, visuospatial, or executive deficits. Most forms of AD target posterior regions (hippocampal and posterior cingulate cortex) and dysfunction of the default mode network (DMN) in the early stages (Greicius, Srivastava, Reiss, & Menon, 2004). AD is predominantly characterized by memory deficits; however behavioral changes such as apathy, anxiety, and irritability are also common (Gauthier et al., 2010). Depression is common in AD and appears to be both a risk factor (Butters et al., 2008; Steenland et al., 2012) and prodrome of AD (Bhalla et al., 2009; Teng, Lu, & Cummings, 2007) , and a number of studies have tried to identify specific depression symptoms that predict conversion to AD, though the findings are mixed (Zahodne, Ornstein, Cosentino, Devanand, & Stern, 2015), and even less is known about depression in AD after onset.

The DMN covers a substantial area of the association cortex and was the first ICN to be discovered. Early functional imaging findings showed that the medial frontal, medial temporal, and posterior cingulate regions synchronically deactivate during focused tasks, thus this network was initially labeled the default mode or task negative network (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). More recent imaging and task-based evidence suggests that this network also has a number of task positive functions, and can be fractionated into a minimum of two,

likely multiple, functionally distinct subsystems (J. R. Andrews-Hanna et al., 2010, 2014; Buckner, Andrews-Hanna, & Schacter, 2008; Robin et al., 2015) that appear to mediate related but separate memory processes. Specifically, the ventral subsystem of the DMN is comprised of the medial temporal lobe (MTL; the hippocampal formation and the parahippocampal cortex), the ventral posterior cingulate cortex (vPCC)/retrosplenial cortex (Rsp) and the posterior inferior parietal lobule (pIPL) and is attributed with memory encoding and the accessibility of concrete episodic memories (Andrews-Hanna et al., 2010, 2014; Robin et al., 2015; St Jacques, Kragel, & Rubin, 2011; Yeo et al., 2014). The medial and dorsal subsystems are comprised of the anterior-dorsal mPFC and the tempoparietal junction (TPJ), PCC, and precuneus (PCun), and appear to mediate top-down selection, indexing, and comparison of memories, i.e., memory control (Andrews-Hanna et al., 2010; St Jacques, Kragel, & Rubin, 2011; Yeo et al., 2014).

Since its discovery, the DMN has been linked to a variety of psychiatric syndromes including depression, schizophrenia, anxiety anorexia nervosa, and bipolar disorder (Cowdrey, Filippini, Park, Smith, & McCabe, 2014; Whitfield-Gabrieli & Ford, 2012) though its exact role in psychopathology remains unclear. DMN hyperconnectivity has been observed in individuals with high familial risk of depression (Posner et al., 2016) and yet DMN hypoactivity has been observed in depressed and schizophrenic populations (Schilbach et al., 2016). To better clarify the role of the DMN in psychopathology, clear delineation of the DMN subsystems with attention paid to specific psychiatric phenomena is critical. In fact, studies that have

begun to do this have found that anxiety and depression were specifically linked to hyperconnectivity of dorsal DMN (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015) and that, in these groups, the dorsal DMN is negatively correlated with the ventral DMN (Zbozinek et al., 2012). While the authors did not investigate the precise psychiatric phenomena linked to dorsal DMN hyperactivity in these populations, known functions of the dorsal DMN may point to pathological memory processes such as intrusive past and future memory simulations and counterfactual thinking (e.g., intrusive and chronic worry about the future in anxiety, regret, etc., in depression) as possible DMN-related psychopathological symptoms (Zbozinek et al., 2012).

bvFTD and the salience and cingulo-opercular networks

The bvFTD syndrome is characterized by progressive deterioration in personality and social comportment. Symptoms include behavioral disinhibition, loss of empathy, emotional blunting, apathy, compulsions, gluttonous overeating, and executive dysfunction (Rascovsky et al., 2011; Woolley et al., 2011). bvFTD causes alterations in the salience and cingulo-opercular networks (SN/CON) which mediate awareness of and attention to salient emotional stimuli, respectively. While over 50% of bvFTD patients receive a psychiatric diagnosis prior to the correct bvFTD diagnosis (Woolley et al., 2011), few studies have attempted to characterize psychiatric phenomena in properly diagnosed bvFTD patients; and, there is tremendous symptom heterogeneity across patients within bvFTD, including with respect to depressive phenomenology (Blass & Rabins, 2009; Chakrabarty, Sepehry, Jacova, & Hsiung,

2015). Psychiatric symptoms such as depression, psychosis, anxiety, and mental rigidity are frequently seen in these patients (Banks & Weintraub, 2008).

The salience network (Seeley et al., 2007) and the cingulo-opercular (or "task control") network (Dosenbach et al., 2007) are tightly coactivating, but distinct ICNs that are that are grounded by the dorsal anterior cingulate cortex (dACC) and anterior insula (AI; Allman et al., 2010; Morel, Gallay, Baechler, Wyss, & Gallay, 2013; Seeley et al., 2007).

The SN was first discovered in patients with bvFTD (Seeley, Crawford, Zhou, Miller, & Greicius, 2009), and since its discovery, this network has been implicated in a variety of psychiatric disorders such as anxiety disorder, Williams Syndrome, schizophrenia, and autism; the specific phenotypic expression of SN disorders depends on SN tuning. Specifically, SN hyperactivation is associated with anxiety disorders and Williams Syndrome (a disorder of abnormally high levels of social engagement), whereas hypoactivation of this network is associated with Schizophrenia and autism (for a review see Zhou & Seeley, 2014).

The cingulo-opercular network has also been linked to a variety of psychiatric disorders including depression, (Wu et al., 2016), autism (Di Martino et al., 2009) and ADHD (Plessen et al., 2015), which are disorders that each include abnormal attentional engagement. Given their known functions in clinically normal adults, and their contribution to psychiatric syndromes, these networks may be especially related to pathological cognitive functions and an inability to inhibit behaviors and thoughts in the context of provoking stimuli.

svPPA and the semantic appraisal networks

The svPPA syndrome is characterized by progressive semantic knowledge loss with preserved grammar and motor speech (Rascovsky et al., 2011). The svPPA syndrome is marked by prominent atrophy in the anterior temporal lobe (most commonly Left>Right) and dysfunction of the semantic appraisal network (SAN). In addition to semantic language deficits, socio-emotional and psychiatric symptoms are also observed in svPPA. Patients with concomitant right temporal atrophy often present with emotion processing deficits, perseverative self-focus, and mental rigidity (Irish, Hodges, & Piguet, 2014; Kamminga et al., 2015). Common early psychiatric symptoms reported in svPPA patients, compared to other types of aphasia, include depression, irritability, hostility, abnormal appetite and weight loss, emotional blunting, social withdrawal, insomnia, decreased sexual interest, and increased alcohol intake (Rohrer & Warren, 2010; Seeley et al., 2005). Additionally, a premorbid history of depression may increase svPPA patients' risk of suicide after onset (Hsiao, Kaiser, Fong, & Mendez, 2013; Sabodash, Mendez, Fong, & Hsiao, 2013), highlighting an urgent need for clear understanding of depression in svPPA.

The semantic appraisal network (SAN) is comprised of ventral medial prefrontal regions, the anterior temporal lobes (aTL), basolateral and central amygdalae and the ventral striatum (Guo et al., 2013; Seeley, Zhou, & Kim, 2011; Yeo et al., 2011). Relative to other ICNs, however, this network's behavioral functions are less well-characterized. This may be due to the fact that the behavioral/task-based fMRI studies that could be used to delineate the cognitive and

behavioral functions mediated by this ICN have been subject to a number of limitations, including the custom of defining networks by their cortical (v. subcortical) connections (Bressler & Menon, 2010), or the susceptibility of regions within this network to signal dropout (i.e., the inability to detect blood oxygen level dependent, i.e., BOLD, fMRI signals (Devlin et al., 2000; Weiskopf, Hutton, Josephs, & Deichmann, 2006)). However, emerging evidence suggests that this network combines limbic and cortical structures to facilitate valuation and contextual appraisal of socioemotional information (Seeley et al., 2011) and may be related to reward processing and the encoding and storage of valenced personalized beliefs (Amodio, 2014).

Functional imaging studies of diverse psychiatric and non-psychiatric populations have found that regions within the SAN are linked to mood abnormalities such as dysphoria, anhedonia (or loss of pleasure; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005), and euphoria (i.e., mania in the case of bipolar disorder; Carhart-Harris et al., 2015). The SAN is hypoactive during periods of dysphoric depression (Hamani et al., 2011; Sabatinelli et al., 2015) and depressed patients show more rapid deceleration of activity in these regions following the presentation of rewarding stimuli compared to clinically normal controls, suggesting that feelings of reward in these patients are short-lived (Epstein et al., 2006; Heller et al., 2009). Thus, in the context of depression this network may be particularly implicated in abnormal reward processing, loss of motivation, and distorted personalized beliefs

(Whitton, Treadway, & Pizzagalli, 2015), whereas the DMN and CON/SN may be more strongly related to dysfunctional cognitive styles in depression.

Disease context and predicted group differences

Clear understanding of the boundaries and functions of ICNs can provide researchers with a conceptual framework for understanding the neural contributions to psychopathology in both psychiatric and neurodegenerative patients. However, any understanding of psychopathology in neurodegenerative patients must be examined with the disease context in mind. While neurological changes may confer vulnerability to specific psychiatric symptoms, news of a fatal diagnosis can also place one at a higher risk for profound psychological changes. In non-neurodegenerative populations, news of a fatal diagnosis is almost always followed by preparatory grief (Block, 2000; Hotopf, Chidgey, Addington-Hall, & Ly, 2002; Kubler-Ross, 1997; Peryakoil & Hallenbeck, 2002), which is clinically distinct from depression. Whereas depression involves context-insensitive and persistent sadness, preparatory grief is characterized by feelings of extreme sorrow surrounding missed past (e.g., unreconciled relationships) and future (e.g., not seeing a grandson graduate college) opportunities in the face of imminent loss (Mystakidou et al., 2008; Peryakoil & Hallenbeck, 2002). Because neurodegenerative disease is often the basis of participant exclusion in grief and depression studies, very little is known about preparatory grief in neurodegenerative populations.

Because preparatory grief involves the ability to contextualize current mood states according to past and future losses, preservation of the DMN, and specifically

the dorsal DMN (involved in memory control processes), may predict the ability to experience preparatory grief. In fact, prior studies of recently bereaved mothers have linked viewing pictures of their children to activity in DMN regions such as the prefrontal and temporal cortexes (Najib, Lorberbaum, Kose, Bohning, & George, 2004), and in recently separated young couples, activity of dorsal DSM is heightened (O'Connor, Irwin, & Wellisch, 2009), suggesting that memory plays an important role in grief processing. The neural correlates of preparatory grief have not been investigated; however, because past and future self-projections feature prominently in preparatory grief, DMN regions may be particularly implicated.

Hypotheses:

Given the role of past and future self-projections in preparatory grief and the role of the DMN in processing past and future events, I predict that:

Hypothesis 1a: Early stage AD patients will be less likely to report grief/sense of loss than the other groups
Hypothesis 2a: The capacity to experience grief/sense of loss will be associated with preserved volume in- and hyperactivity of- the default mode network (DMN).

Whereas grief may involve cognitive abilities related to past and future simulations, overall mood states may be related to functioning of the SAN. Lesions in the SAN (the vmPFC, specifically) are linked to diminished depression symptoms overall (Koenigs & Grafman, 2009) and over activation of SAN regions is linked to viewing negatively valenced stimuli in depressed adults (Smith, Baxter, Thayer, & Lane, 2016). Further, SAN regions are also implicated in bipolar mania (Blumberg et

al., 1999; Blumberg et al., 2000, 2003). Past studies showing that the SAN correlates with both depression and mania suggests that this network may contribute to overall emotional valence effects in psychopathology. Therefore, I predict that:

Hypothesis 1b: Early stage svPPA patients will be more likely to report euphoria and dysphoria than any other group
Hypothesis 2b: Clinically significant levels of euphoria or dysphoria will be associated with volume loss in- and hypoactivity of- the semantic appraisal network (SAN).

Whereas the SAN and the DMN may be linked to emotional valence and preparatory grief respectively, the SN/CON may be linked to cognitive styles that confer risk for developing depression symptoms. Rumination is particularly relevant to depression. It is a dysfunctional style of thinking characterized by a negative and evaluative self-focused attention (Rude, Maestas & Neff, 2007), and has been shown to mediate the relationship between stressful life events and depression and anxiety symptoms (Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013), as well as the relationship between depression and deficits in inhibition and attentional control (Davis & Nolen-Hoeksema, 2000; De Lissnyder et al., 2010) – important risk factors for depression (Joorman & D'Avanzato, 2010). While rumination begins with a negative self-evaluation, its core engine involves cognitive impairments in inhibitory and attentional control, key functions of the SN/CON (Koster, De Lissnyder, Derakshan, & De Raedt, 2011). Given the relationship between the SN/CON and attention and cognition, I predict that:

Hypothesis 1c. Early stage bvFTD patients will be more likely to ruminate than any other group
Hypothesis 2c. Rumination will be associated with atrophy in- and hypoactivity of- the salience network (SN) and/or the cingulo-opercular network (CON).

Methods

Participants

A total of 97 participants (25 with possible or probable typical or atypical Alzheimer's disease (AD), 27 patients diagnosed with behavioral-variant frontotemporal dementia (bvFTD), 14 with semantic variant primary progressive aphasia (svPPA), 13 clinically normal older adults (NC), and 18 late-life depressed controls (LLD) participated in this study. Inclusion criteria for participants included a Mini-mental state exam score ≥ 15, thus all neurodegenerative participants were in the relatively early stages of their disease. A subset of 57 participants who participated in all aspects of this study was used (11 AD, 13 bvFTD, 11 svPPA, 13 LLD, and 11 NC) to assess the validity participant self-report measures. 40 participants who did not participate in all aspects of this study were added once the validation subset was analyzed, and the final set of 97 participants (including the validation subset) was considered in the final group and imaging analysis. bvFTD patients were diagnosed according to FTDC criteria (Rascovsky et al., 2011), svPPA patients met new International PPA criteria (Gorno-Tempini et al., 2011), and the AD patients met the National Institute on Ageing-Alzheimer's Association criteria (McKhann et al., 2011). Patients' diagnoses were determined by a team of

neurologists, neuropsychologists and nurses, following thorough neurological, neuropsychological and neuroimaging assessments. LLD diagnosis was determined by trained clinical interviewers using Structured Diagnostic Interview (SCID-I for DSM IV-TR; Ferentinos et al., 2011; First, Spitzer, Gibbon, & Williams, 2002), and the Hamilton Depression Rating Scale (Williams, 1988). Please see Table 1 for demographic characteristics of the sample.

Patients were recruited from a dementia specialty clinic and were excluded if they had a Clinical Dementia Rating (CDR) score greater than 2 (indicating neuropsychological impairment) or were not fluent in English. Normal controls (NCs) were recruited though newspaper advertisements and from a local senior community center. Inclusion criteria for normal controls included a normal neurological exam, CDR score = 0, Mini-mental state exam score ≥ 28/30, and delayed memory performance ≥ 25^{th} percentile in both verbal and visual-spatial domains. LLD controls were recruited from a pool of available participants enrolled in a larger depression and Alzheimer's study (ADNI-D) at UCSF's Langley Porter Psychiatric Institute. Inclusion criteria also included a normal neurological exam, CDR score = 0, Mini-mental state exam score ≥ 28/30.

All participants were required to have an informant who could answer questions on their behalf. Informants were typically a relative who lived with the participant, and were required to have known the participant for more than 5 years. All participants were expected to have received a resting-state and structural magnetic resonance imaging scan (rsMRI and MRI, respectively) within 3 months of their visit.

The participants and their informants signed an institutional review-board-approved research consent form to participate in the study. The research was approved by the University of California, San Francisco Committee for Human Resource Independent Review Board.

Procedures

During recruitment, participants were told that the purpose of the study was to understand how people experienced loss. After consenting to participate in the study, participants were asked to complete a series of psychiatric symptom questionnaires and to participate in a video-taped 20-30-minute semi-structured interview. Informants were also consented and asked to complete surveys on the participant's behalf and also to participate in a semi-structured interview. To control for the accuracy of self- and informant-measures, several confounds were considered (participants' level of state anxiety, participants' perceived authenticity, informant's perceived credibility, the degree of closeness between the participant and the informant, and the length of the relationship between the participant and informant; see below).

Semi-Structured Interviews. Semi-structured interviews were conducted at the Memory and Aging Center's (MAC) Neurosciences Clinical Research Unit by either the first author (conducted 59% of interviews) or a trained research coordinator (conducted 41% of interviews). Participants and participant informants were interviewed separately. Due to scheduling restrictions, the order of participant and participant informant interviews was not controlled, nor was the order of participant

interviews and participant survey responses. Neurodegenerative patients and late life depressed controls were asked to describe any noticeable changes in their self-esteem, thought patterns, mood and emotions since receiving their diagnosis. Informants were asked to report on any perceived changes in the participant's self-esteem, thought patterns, mood and emotions that may have coincided with the participant learning about his/her diagnosis. In the case of clinically normal control participants, controls and their informants were asked to report on such changes in the participant that may have coincided with a significant loss that incurred within the past five years (see Appendix A for semi-structured interview questions and protocol).

Interviews were conducted in English. Participants and participant informants were given the option of being audio recorded, video recorded or to decline participation in the study (n=4 interviewees declined). The interviewer sat across from the participants or the informants in a well-lit room with the video camera positioned next to the interviewer (diagonal to the interviewee), and the interviewer was occluded from view. If the participant declined to be video-recorded but agreed to audio recording (n=3 interviewees audio recorded), the lens cap was placed on the video recorder. Each interview lasted approximately 30 minutes (M =30 min, SD =3.44 min; Range=11-44mins).

Video coding. Reliability coders were two trained research volunteers who were blind to participants' diagnoses. Informant videos were rated for aspects of informants' credibility. Participant videos were rated for participants' authenticity, and participants' psychiatric symptoms using the coding rubric in Appendix B.

Additionally, coders documented time markers and explicit behaviors/statements that illustrated psychiatric symptoms of interest for later review.

Measures

Informant Credibility. Participants and informants were asked to rate the degree of closeness they felt towards their partner on a 10-point (1=not at all close/10=extremely close) scale both before and after the participant learned of their diagnosis (or experienced loss in the case of clinically normal controls). Informants also reported the length of their relationship to their partner in years and months.

Video observers also rated informants on aspects of observed informant credibility using a rating form designed for this study, the Informant Credibility Scale. This rating form measured aspects of credibility such as the degree to which informants' responses were consistent, their ability to provide anecdotal evidence of participants' emotional states and psychiatric symptoms, their perceived level of concern for the participant, perceived bias (overly attending to one's own emotions), their capacity to engage with emotional material, their ability to connect with the interviewer, the degree of (caregiver) distress, as well as an overall rating of informant credibility on a 1 (extremely credible) to 4 (extremely not credible) scale (see Appendix C). After removing the item measuring informants' distress, the internal consistency of this scale was good (ICC=0.84) and interrater reliability was moderate (K_w=0.56, p =0.115).

Participant Authenticity: Video observers also rated participants' overall emotional expressivity as proxy for the authenticity of participants' self-reports.

Emotional expressivity was measured according to the participant's ability to access, describe, and express emotions, as well as their ability to emotionally connect/respond to the interviewer. Video observers also provided an overall rating of the authenticity of the participant interview and the degree of perceived suffering. Each of these behaviors was rated on a 1 (e.g., totally expressive) to 5 (e.g., totally inexpressive) scale (see Appendix D). After removing the item measuring the participants' perceived suffering, the internal consistency of this scale was also good (ICC=0.89) and interrater reliability was good (K_w=0.64, p=0.045)

Dysphoria was assessed using the Center for Epidemiologic Studies Depression – Short Form (CES-D; (Irwin, Artin, & Oxman, 1999). The CES-D is a 10-item scale measuring the frequency of depressive symptoms (e.g., "I felt lonely") and is rated from 0 (rarely) to 3 (all of the time). Dysphoria was also be assessed using the 10-item negative affect subscale of the Positive and Negative Affect Schedule (PANAS-NA), in which participants rate the degree to which they have experienced negative emotions (e.g., "Upset") over the past week on a 1(not at all) to 5(extremely) scale (Watson, Clark, & Tellegen, 1988).

Video observers rated signs of dysphoria according to a modified version of the Calgary Depression Scale for Schizophrenics (CDSS; Addington, Addington, & Maticka-Tyndale, 1993). The CDSS controls for symptoms of apathy and blunted affect, which are common to depression, schizophrenia and neurodegenerative disease populations, thus it was an optimal, established measure to screen for signs of depression in our sample. The CDSS is an 8-item questionnaire measuring signs of

depressed mood, guilt, hopelessness, and self-deprecation. Items are rated on a 0 (not at all depressed) to 3 (extremely depressed) scale. For coder reliability purposes, we distinguished between verbal (e.g., monotonous voice, delayed responding) and behavioral symptoms (e.g., slow body movement, slouching, poor eye contact), thus adding an additional item to the original CDSS (scores range from 0-30) (see Appendix E). The internal consistency of the CDSS was excellent (ICC=0.90) and interrater reliability was very good (K_w=0.89, p =0.03).

Euphoria was measured using the 10-item positive affect (e.g., "Proud") subscale of the PANAS (PANAS-PA) and the Altman Mania Rating Scale (AMRS; Altman, Hedeker, Peterson, & Davis, 1997). The Altman's is a 5-item rating scale in which participants choose between statement options (e.g., "I often talk more than usual") on a 5-point (1 = not at all manic, 5 = extremely manic) scale. Observer-rated signs of mania were assessed using the Clinical-Administered Rating Scale for Mania (CARS-M), which is a 15-item rating scale that yields two subscales measuring manic and psychotic symptoms, respectively. Items are scored on a 0 (no mania) to 5 (high mania) scale (see Appendix F; Altman, Hedeker, Janicak, Peterson, & Davis, 1994). The internal consistency of the CARS-M was poor (ICC=0.45) and interrater reliability was poor (K_w=0.13, p=0.62)

Grief was measured using a 12-item subscale of the Inventory for Complicated Grief-Revised (ICG-R; Jacobsen, Zhang, Block, Maciejewski, & Prigerson, 2010; Prigerson et al., 1995) adapted for terminally ill cancer patients. Each item (e.g., "In the past month, to what extent have you felt bitter over your

illness?") is scored on a 5-point scale (1 = never, 5 = constantly). Video observers rated signs of participants' grief using a rating form designed for this study that measured signs of bitterness (e.g., "I was angry at how unfair it seemed"), contextualized sadness (e.g., "The diagnosis made me sad for me and my family"), and former-self statements (e.g, "I feel like I've lost myself"), on a 1 (low) – 4 (high) point scale (scores ranged from 3-12; see Appendix G). The internal consistency of observer ratings of grief was poor (ICC=0.49) and interrater reliability was poor (K_w=0.16, p=0.35).

Rumination was measured using the Rumination subscale of the 24-item Rumination-Reflection Questionnaire (RRQ; Trapnell & Campbell, 1999). The RRQ measures two types of self-focus: rumination motivated by perceived loss or injustice (e.g., "I often reflect on episodes in my life that I should no longer concern myself with") and reflection motivated by curiosity about the self, or reflection (e.g., "I love to meditate on the nature and meaning of things") and uses a 5-point item response scale (1 = strongly disagree, 5 = strongly agree). Only the rumination subscale was used to assess rumination. Observers also rated participants' reports of- and perceived-rumination on a 1 (low) – 4 (high) point scale (scores ranged from 2-8). For instance, a participant may have returned to an event or topic multiple times in the interview (perceived rumination) or may have reported difficulty taking their mind off current thoughts or circumstances (reported rumination; see Appendix H). The internal consistency of the observer ratings of rumination was excellent (ICC=0.90) and interrater reliability was good (K_w=0.65, p=0.05)

Additional measures. In order to assess the discriminant validity of each measure of interest, additional surveys were administered. These included the Buss Durkee Hostility Inventory-Irritability subscale (BDHI; Buss & Durkee, 1957), which measures agitation and irritability; the Generalized Anxiety Disorder-7 (GAD-7), which measures general and persistent state anxiety; Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), which assesses aspects of emotional dysregulation (e.g., non-acceptance, impulsiveness, awareness); Center for Neurological Diseases –Lability Scale (CNS; Moore, Gresham, Bromberg, Kasarkis, & Smith, 1997), which assess the perceived frequency of affective lability episodes due to pseudobulbar affect; the Yale-Brown Obsessive Compulsive Scale (YBOCS), which measures the severity and frequency of obsessions (Obs) and compulsions (Comp; Goodman, Price, & Rasmussen, 1989); and Adolescent Psychotic Symptoms questionnaire (Kelleher, Harley, Murtagh, & Cannon, 2011), which is a brief 7-item measure used to assess psychosis.

Finally, to control for the influence of participants' current emotional state on both interview and questionnaire responses, state anxiety was measured using the 20-item state subscale of the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Items on this scale (e.g., "I feel calm") are rated on a 5-point scale (1 = extremely anxious, 5 = extremely calm).

All participant self-report surveys were adapted to the informant respondent. For a summary of questionnaires and the constructs they measure, see Appendix I.

Neuroimaging procedures

MRI scanning and VBM preprocessing. All structural MRI studies were performed using a 3T Magnetom VISION system equipped with standard quadrature head coils. T1-weighted magnetization prepared either rapid gradient echo (MP-RAGE) images of the entire brain were obtained (15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 x 1.0 mm2 in-plane resolution and 1.5 mm slab thickness) or GRAPPA images. All imaging was done within three months of assessment (M_{days}= 10.7, *SD*=2.2).

The structural T1-weighted images were corrected for bias field, segmented into grey matter, white matter, and CSF, and initially normalized to Montreal Neurological Institute (MNI) space using the Unified Segmentation procedure (Ashburner & Friston, 2005) implemented in the SPM8 software package (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2014b (MathWorks, Natick, MA). More anatomically precise intersubject registration was then performed with the Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) toolbox (Armstrong & Munoz, 2003) by warping each subject's image to a template created from 300 normal control subjects (M_{age}=67, SD_{age}=7.24; 38% female). The grey and white matter smoothed images were then combined using the voxel lesion-symptom mapping (VLSM) toolbox running on MATLAB (http://neuroling.arzona.edu/resources.html; vlsm version 2.55). DARTEL has been reported to achieve optimal registration in neurodegenerative diseases (Costa-Pereira et al., 2002).

rsMRI and Preprocessing. Functional images were also acquired on a 3T Siemens MRI scanner at the Neuroscience Imaging Center, UCSF. Functional MRI scans were acquired using a T2*-weighted echo planar sequence and co-registered to a volumetric T1-weighted image. Functional images were realigned and warped, slice-time corrected, motion-corrected (motion parameters were regressed out), co-registered to the skull-stripped structural T1-weighted image, normalized, and smoothed with a 4mm full-width at half-maximum Gaussian kernel. The first 10 frames were discarded to allow for magnetic field stabilization, and the waveform of each brain voxel was filtered using a bandpass filter ($0.0083/s < f < 0.15/s$). A general linear model (GLM) was used to regress out the time series of 3 nuisance covariates (global, white matter, CSF), and 6 motion parameters. Finally, correlation matrices were derived on single subjects based on the preselected seeds below.

Seed regions of interest (ROIs) for each ICN were selected based on prior resting state fMRI studies. A complete list of ROIs, including MNI coordinates, for each ICN is listed in Appendix J. Default mode network ROIs were based Andrews-Hanna et al. (2010). Salience and cingulo-opercular ROIs were based on Seeley et al. (2007) and Dosenbach et al. (2007), however ROIs that overlapped with other networks (e.g., amygdala) were selected out. The semantic appraisal network ROIs were based on Yeo et al. (2011). Yeo's seeds did not include bilateral ROIs in all cases, therefore homologous ROIs that were missing were added.

Statistical Approach

I.) Confounds and Validation.

Statistical analyses of behavioral and imaging data were carried out in SAS (9.4) and R (3.1.3). In order to determine whether psychopathology could be reliably measured in neurodegenerative patients, we first calculated the internal consistencies of all self- and informant- report measures using Cronbach's alphas. Up to 20% of survey items that were not consistent with the dimension of interest were dropped. If internal consistency was still poor after dropping 20% of the items, the measure was considered unreliable and not considered for further analysis. To determine inter-rater reliability between video observers for each of the observer rating scale, Cohen's weighted kappas (*wK*) – an agreement index for use with ordinal data – were used.

Confounds. To determine whether informant survey reports were influenced by potential confounds (the degree of closeness, the relationship length, or observer ratings of informant credibility), confounds were first compared across diagnostic groups. In order to determine if informant reports were compromised by informant confounds, confounds were then compared to discrepancy scores between informant and self-reports for each measure using Pearson's product-moment correlations. Discrepancy scores were calculated as the difference between informant and self-report scores on the same measure. To determine whether confounds such as state anxiety and emotional expressiveness should be included as covariates in participants' self-report analyses, and due to violations of the normality assumption for a number of self-report variables (STAI, CES-D, ICG, Altman's, and NA), STAI and expressiveness were compared across groups, using GLM, and then Spearman's

Rank Order correlations were calculated to compare possible participant confounds to self-report measures.

Validation. In order to determine the validity of participant self-reports, video observer ratings, informant reports, and self-reports were compared to each other using partial correlations controlling for identified confounds (i.e., assessed the convergent validity). Because there is no gold standard against which to compare participants' measures to assess validity (e.g., Beck's Rumination Inventory for Dementia Patients), a multi-trait matrix was constructed to assess the convergent and divergent validity of participants' self-reports was approximated using partial correlations comparing among all self-report measures (measures of interest and theoretically similar measures), after controlling for identified confounds.

II.) Main analyses of interest.

Behavioral data. Psychiatric symptoms were compared across participant groups using general linear models (GLMs), with Dunnett-Hsu post hoc tests comparing each diagnostic group to the NC group controlling for confounds.

Neuroimaging data. Neural imaging analyses aimed to 1) identify selective network damage (atrophy) and dysfunction (reduced connectivity) for each diagnostic group as a preliminary step and to 2) identify any relationships between network damage / dysfunction and psychiatric symptoms.

Because the hypotheses partially relied upon assumptions of network integrity and functioning in focal neurodegenerative disease patients, we first aimed to establish the atrophy and connectivity patterns of each neurodegenerative patient

group. Statistical models were used to show voxel-wise gray matter volume in neurodegenerative diagnostic groups, derived in reference to the MRIs of a set of 36 clinically normal, age-matched NCs, controlling for identified covariates. Whole network volume scores were also derived using ROIs defined by Neuromorphometrics, Inc, brain atlas (http://www.neuromorphometrics.com), and which corresponded to original resting state seed ROIs identified in previous studies (see Appendix J). The volume estimate for each ROI within a network was computed as a fraction of the total intracranial volume (thus controlling for TIV), and ROI volume estimates were summed to derive a total network volume score.

Network connectivity scores were calculated as the average connectivity correlation coefficient among all network node-pairs, which were derived from single-subject correlation matrices (see above). Thus, each subject received a final connectivity average for each network. Group network atrophy and network connectivity scores were compared using general linear models (GLMs), controlling for identified confounds. Dunnett-Hsu post hoc tests were used to compare each diagnostic group to the NC group.

Finally, whole network volume scores and whole network connectivity scores were compared to psychiatric symptom scores, controlling for identified confounds, using partial correlations.

Results

Results are presented in four sections: I) diagnostic group comparisons across demographics and other possible confounds, as well as the relationship between

confounds and psychiatric measures, II) the results of all psychometric analyses of self-report data, including the internal consistencies and the convergent and discriminant validity of the self-report data compared to other data sources, III) diagnostic group comparisons of psychiatric symptoms according to the best information source, as well as case analyses of patient groups who were significantly difference from clinically normal controls on psychiatric symptoms and IV) comparisons of psychiatric symptoms to neural atrophy and network connectivity.

I.) Group demographics and confounds.

There were no demographic or disease severity differences between the validation sample (N=59) and the final sample which was used to analyze all behavioral and imaging analyses (N=97) [age $t(30)=0.15$, $p=0.87$), sex ($\chi^2=0.56$, $p<0.45$), MMSE (i.e., disease severity), $t(30)=-0.04$, $p=0.97$)]. Group demographics of the final sample are presented in Table 1. In the final sample, diagnostic groups differed significantly from clinically normal age-matched controls according to age, sex, and MMSE. AD (M =63.63, SD =8.58) and svPPA (M =67.72, SD =5.53) participants were significantly younger than controls (M =76.45, SD =8.01), $F(4,97)= 4.96$, $p<0.01$, $\eta^2=0.27$. LLD controls were disproportionately women, whereas bvFTD patients were disproportionately men ($\chi^2=18.77$, $p<0.0001$), and as a whole, neurodegenerative groups scored significantly lower on the MMSE [$F(4,54)= 10.93$, $p<0.0001$, $\eta^2=0.32$]; however, when comparing neurodegenerative disease groups to each other using Tukey's post-hoc comparisons, there were no significant differences on MMSE. Further, MMSE did not meaningfully contribute to the variance of our

overall statistical models, therefore to preserve statistical power, MMSE was not included as a standard confounding control variable in behavioral or imaging analyses, though age and sex were included as control variables.

Compared to clinically normal controls, there were no diagnostic group differences in the length of the participant-informant relationship, $F(4,39)=0.32$, $p=0.86$, $\eta^2=0.10$, informant rating of interpersonal closeness $F(4,39)=0.78$ $p=0.55$, $\eta^2=0.08$, or participant rating of interpersonal closeness $F(4,39)=0.42$, $p=0.83$, $\eta^2=0.06$. Video observer ratings of informant credibility did not differ according to patients' diagnostic group, $F(4,39)=0.79$, $p=0.35$, $\eta^2=0.09$ (for group comparisons on confounds, please see Table 2). Discrepancy scores between informant-participant surveys also did not differ by group on any measure [CES-D, $F(4,39)=0.84$, $p=0.51$, $\eta^2=0.06$; PANAS-NA, $F(4,39)=0.68$, $p=0.64$, $\eta^2=0.04$; ICG, $F(4,39)=1.96$, $p=0.11$, $\eta^2=0.09$; RRQ-Rum, $F(4,39)=0.54$, $p=0.75$, $\eta^2=0.05$; Altman's, $F(4,39)=0.40$, $p=0.84$, $\eta^2=0.06$; or PANAS-PA, $F(4,39)=0.98$, $p=0.44$, $\eta^2=0.03$].

Comparing relationship length to participant-informant discrepancy scores showed that longer relationship length was related to higher discrepancy scores for the PANAS-NA (negative affect), $r=0.38$, $p=0.02$, and PANAS-PA (positive affect), $r=0.42$, $p=0.01$, but not for any other measure. Across the entire sample, participants rated themselves lower on negative affect ($M=17.96$, $SD=7.72$) and higher on positive affect ($M=32.46$, $SD=7.86$) compared to informants ($M=19.44$, $SD=7.72$; $M=28.41$, $SD=7.80$, respectively). Video observer ratings of informant credibility, and informant and participant ratings of interpersonal closeness were not related to

participant-informant discrepancy scores. In sum, discrepancies between participant and informant psychiatry ratings were related to relationship length only in the context of affect ratings.

After controlling for age and sex, GLMs showed that video observers rated bvFTD participants significantly higher on emotional expressionlessness (i.e., inauthenticity) (M =11.06, SD =1.08) compared to controls (M =6.88, SD =1.18), $F(4,54)$= 3.00, p=0.03, η^2=0.21. However, this was not related to video observer ratings of depression or rumination, nor was it related to any psychiatric self-report measure of interest; thus it did not introduce a systematic bias and was not included as a confound in subsequent analyses.

II. Psychometric Results

Data Quality of Participant and Informant Reports. The internal consistencies of self-report scales ranged from acceptable to excellent: STAI (ICC=0.87), CES-D (ICC=0.86), PANAS-NA (ICC=0.90), ICG (ICC=0.89), RRQ-Rum (ICC=0.91), PANAS-PA (ICC=0.90), Altmans (ICC=0.77).

Convergent Validity. Controlling for age and sex, there were no significant correlations between self- and informant-reports on the same measure. Video observer ratings of rumination did significantly correlate with self-reports of rumination (r_s =0.46, p=0.02), and although video observer ratings of depression did not correlate with self-reports of depression or negative affect, they did significantly correlate with self-reports of grief (r_s =0.52, p=0.01; see Figure 1). In sum, video observer ratings more closely reflected participant self-report ratings of psychiatric

symptoms than did informant reports; however, because of the lack of internal consistency and interrater reliability of observer ratings of grief and euphoria/mania, convergent validity as assessed by comparing observer and self-reports, was incomplete.

GLMs showed that state anxiety (STAI) was significantly elevated in LLDs (M=39.49, SD=2.82) and svPPAs (M=38.58, SD=2.2) compared to controls (M=27.62, SD=3.33), $F(4,39)=3.40$, $p=0.03$, $\eta^2=0.21$. State anxiety also was significantly correlated with a number of the self-report measures of interest (CES $r_s=0.62$, p<0.0001; NA $r_s=0.69$, $p<0.0001$; RRQ-Rum $r_s=0.47$, p<0.001, ICG $r_s=0.46$, $p<0.001$; Altman's $r_s=-0.30$, $p<0.001$; PA $r_s=-0.36$, $p=0.01$); therefore state anxiety was included as a confounding covariate in subsequent analyses.

Discriminant Validity. To determine whether self-report psychiatric symptoms scores discriminated among similar theoretically similar measures a multitrait matrix was constructed. Partial correlations controlling for age, sex, and state anxiety showed that the CES-D (depression) was significantly correlated with grief (ICG: $r_s=0.43$, $p=0.02$), rumination (RRQ-Rum: $r_s=0.46$, $p=0.01$), obsession (YBOCS-Obs: $r_s=0.46$, $p=0.01$), emotional dysregulation (DERS: $r_s=0.36$, $p=0.03$), generalized anxiety (GAD: $r_s=0.42$, $p=0.02$), and irritability (BDHI: $r_s=0.40$, $p=0.02$). Grief (ICG) was negatively correlated with positive affect (PANAS-PA: $r_s=-0.38$, $p=0.03$). Rumination (RRQ-Rum) was positively correlated with obsessions (YBOCS-Obs: $r_s=0.45$, $p=0.00$), irritability (BDHI: $r_s=0.36$, $p=0.03$), emotional dysregulation (DERS: $r_s=0.35$, $p=0.03$), and self-reflection (RRQ-Ref: $r_s=0.47$, $p=0.00$). Finally,

mania (Altmans) was associated with known correlates psychosis (r_s=0.56, p=0.00), irritability (BDHI: r_s= 0.36, p=0.00), and affective lability (CNS-LS: r_s=0.43, p=0.00; see Figure 2).

In sum, participants answered consistently within measures and consistently with regard to other theoretically similar measures. Because participant and informant reports were not equally able to reflect patients' psychiatric status, self-report measures performed psychometrically well in our patient samples, and because psychiatric symptoms are intrapsychic in nature, only self-report measures of psychiatric symptoms were analyzed in subsequent analyses.

III. Behavioral Results.

Controlling for age, sex, and state anxiety, we found that svPPAs (M =13.01, SD =1.50) and LLD participants (M =17.23, SD =1.43) rated themselves as more depressed according to the CES-D than normal controls (M =7.61, SD =1.43), F=6.81 p<0.0001, η^2=23. LLDs also rated themselves higher in grief (M =26.71, SD =2.22), F=2.67, p=0.04, η^2=11, and lower in positive affect (M =24.16, SD =2.07) than controls (M =16.44, SD =2.57 and M =34.22, SD =2.39, respectively), F=4.22, p<0.001, η^2=16. svPPAs also rated themselves lower in positive affect, though this was a non-significant trend. Thus, the hypothesis that svPPA would report higher levels of dysphoria / euphoria was partially supported; svPPA patient were more depressed than controls, though they were not more euphoric. No other group differences were observed (see Table 3); that is, contrary to my hypotheses, ADs

were not more likely to report grief/sense of loss, and bvFTDs were not more likely to report rumination.

Case example of depression in svPPA (Mr. M.). svPPAs rated themselves more depressed compared to clinically normal controls, and to illustrate the look and feel of depression in svPPA, I will present a case analysis of an svPPA patient who scored 5 standard deviations above age-matched clinically normal controls on the CES-D and 2 standard deviations above clinically normal controls on video ratings of the CDSS. The patient, Mr. M, is a 63 year-old male with an svPPA presentation but Pick's disease pathology, thus this patient may not be representative of clinical svPPA patients. He presented to the Memory and Aging Center for his first visit in 2015 with a premorbid psychiatric history that appeared around the time that his semantic memory deficits first appeared; he has since deceased. Mr. M showed classic semantic appraisal network damage, with predominant atrophy in left anterior temporal lobe structures as well as the left putamen, caudate, and accumbens areas, though right anterior temporal regions were also damaged. He was an exceptional case of svPPA as his language abilities were relatively preserved; however, the preservation of semantic language abilities provides a unique window into the subjectivity of depression in svPPA. In the following, I present Mr. M's clinical case report as well as excerpts from the psychiatric interview conducted for this study.

Mr. M's neurological case report describes severe depression, suicidality, compulsivity, irritability, rigidity, lability, and anhedonia that appeared just prior to his semantic memory deficits and which persisted after his diagnosis.

Mr. M was a highly educated, well-read technical professional whose psychiatric and language symptoms onset occurred while pursuing a second career as a social worker for homeless youth in 2004. He was described by his wife as "warm, friendly, romantic and caring" prior to the onset of his symptoms. During graduate school, Mr. M became increasingly withdrawn, curt, and irritable. He became zealous in his beliefs about homeless youth rights, and was frequently forceful and hostile with family members when these topics were discussed, though he was never overtly violent. He displayed early symptoms of anhedonia in 2005-06, losing interest in holiday activities and sports. The latter may have been due to his noted loss of understanding of game strategies and loss of semantic knowledge about the players and teams, though Mr. M's language deficits were not obvious to the family until 2007.

Mr. M made his first suicide attempt in 2008 after starting Ritalin to help him concentrate on studying, which was becoming increasingly difficult for him. Mr. M had attempted to overdose on pain medication following a violent argument with his wife. He had three other suicide attempts that were precipitated by aggravated conflicts with his family.

During his interview, Mr. M. was articulate and composed and expressed relatively few explicit statements about his depression. However, he was rated high on depression by video observers for frequent and severe behavioral (e.g., slowed body movement, lack of eye contact, slouching) and verbal (e.g., monotone voice, delayed response time) signs. He acknowledged that his memory deficits began at the

end of 2005, though his first symptoms of depression were not apparent to him until 2008. According to Mr. M., his depression symptoms appeared as he was finishing graduate school and preparing to pass his qualification exam. He described feeling frustrated by his overall academic performance, and described his depression as "feeling sadder a lot more and more deeply sad about the things that were getting to [him]" and the feeling "seem[ed to have] intensified a little in the last 10 years".

When asked about how he felt upon hearing the news of his diagnosis, Mr. M responded:

> *Well…um…at first I was kind of flummoxed and felt a lil um…I'll say unhappy because I wasn't getting as good…ah what do you call it ahhh…grad school things on my exam as I used to get when I was in college before that.*
>
> *[…] in some ways, I felt almost happy to hear it. To find that there was something actually going on with me that could be diagnosed. You know…that kind of a thing. Um, nevertheless I can't say I was happy about the fact that I was suffering those kinds of things.*
>
> *[…] I first started getting um…the thought of a bit of depression and that sort of thing around 2008. And as I finished grad school and was getting ready to start the exams.*

When asked for a specific example of an event provoking his depression, Mr. M. responded:

> *Yeah well I would say that the first thing that hit me real hard was when I took the first exam. Um and I was trying to remember…I couldn't remember the actual case names or years…or the um…technical name of some kind of a thing. So a lot of the words...you know…you know I used to have what I call the eidetic memory…but I couldn't recall words that I once knew…you know and that's when I started…down that road that way.*
>
> *[…]*
>
> *I tried…you know I got myself one of those…ahh brain scans. And started dealing with a psychiatrist and started dealing with medications and it's not like they did*

anything to get me better…but that was my hope. I hoped that some of this would get better.

When asked about his current thoughts and feeling about himself, Mr. M responded:

You know what I feel about myself is that I'm no longer what I used to be…you know…that somehow some things in my neuroendocrine world has gone…strange or wrong or weird or something like that. And it's having an effect on me…you know…it's having a variety of effects. And sometimes I feel frustrated about that. Other times I feel sad that I'm not capable of what I used to be and those kinds of things."

[I feel bad about] well different kinds of forms of incompetence, you know. The whole mental incompetence about remembering things or um…I think it's a big variety of memories that I have issues about.

When asked how he felt about receiving a diagnosis, Mr. M expressed relief that his symptoms could be explained by a diagnosis. He also described feeling relief from his depression when spending time with his wife and taking walks in nature.

Mr. M is an interesting case example of depression in svPPA. svPPAs rated themselves more depressed than clinically normal controls, and while autopsy reports showed that Mr. M. had Pick's disease pathology rather than TDP-43 pathology (more common to svPPA), his unusual language preservation made him an ideal candidate for interview analyses. Video coders rated Mr. M. high on depression due to his behavioral symptoms (e.g., slow body movements, monotonous voice), he scored extremely high on his depression self-report survey, and in the interview Mr. M. described feeling deeply depressed, which had intensified over the course of his disease, due to his loss of cognitive abilities; however, he also described a sense of overall relief when he learned about his diagnosis.

IV. Neuroimaging Results

Group atrophy patterns. Atrophy patterns among the neurodegenerative groups in our sample using covariates-only (multiple regression design) were somewhat consistent with clinical diagnostic criteria (see Figures 3 and 4). When comparing Neuromorphometric atlas-derived neural networks, svPPAs and bvFTDs network atrophy patterns were consistent with clinical criteria, however ADs' atrophy pattern was not consistent with clinical criteria for amnestic AD (see Table 4).

AD. The AD group in our sample showed predominant atrophy in left posterior regions, including the supramarginal gyrus, angular gyrus, superior parietal lobule, and the occipital gyrus, as well as the left temporal lobe (inferior temporal gyrus, temporal pole). They also showed significant atrophy in left operculum, as well as left-sided subcortical regions (putamen, thalamus, and pallidum). Comparing whole network volumes, ADs did not differ from controls on any of the Neuromorphometric atlas-derived neural networks.

svPPA. The svPPA group showed predominant atrophy in the left>right temporal lobe, including the temporal pole, medial temporal lobe, and inferior temporal gyrus. The left>right insula and orbitofrontal cortex, putamen, subcallosal area, and basal forebrain were also significantly atrophied. The semantic appraisal network (M =1.38, SD =0.14) and ventral DMN (M =8.66, SD =0.38) were significantly atrophied in svPPA patients compared to controls (M =2.19, SD =0.14 and M =9.79,SD =0.38), F=8.21, p<0.0001, η^2=0.43 and F=5.69, p=0.0001, η^2=0.33, respectively.

bvFTD. bvFTDs showed predominant atrophy in the right>left orbitofrontal gyrus, anterior cingulate, and superior frontal gyrus, and the pre-and post-central gyri, as well as the left>right operculum and insula. They also showed significant atrophy in the cinguloopercular (M =6.82, SD =0.33) and semantic appraisal networks (M =1.75, SD =0.09) compared to controls (M =8.62, SD =0.49 and M =2.19, SD =0.14), F=4.30, p=0.001, η^2=0.25 and F=8.21, p<0.0001, η^2=0.43, respectively.

Controls. After family-wise error corrections, LLD patients and clinically normal controls (NCs) showed no significant regional or network volume loss. For patterns of atrophy across diagnostic groups, see Figures 3 and 4.

Group Connectivity Patterns. There were no diagnostic group differences on any network connectivity scores after controlling for age and sex (see Table 5).

Network Volumes and Psychiatric Measures. Comparing network atrophy scores, after controlling for age, sex and STAI, results showed that decreased volume in the DMN midline was associated with greater grief (ICG; r_s =-0.32, p =0.02) and negative affect (PANAS-NA; r_s =-0.31, p =0.02). Decreased volume in the semantic appraisal network was associated with higher levels of negative affect (PANAS-NA; r_s =-0.31, p =0.02). Finally, decreased volume in the SN/CON was associated with greater euphoria scores: atrophy in the SN/CON was associated with greater Altman's scores (r_s =-0.34, p =0.006 and r_s =-0.32, p =0.03) and atrophy in the SN only was associated with greater PANAS-PA scores (r_s =-0.31, p =0.01). Therefore, our network volume hypotheses were partially supported, grief was predicted by volumes in the DMN, and dysphoria was predicted by volumes in the SAN. Contrary to our

hypotheses, euphoria was predicted volume loss of the SN/CON rather than the SAN (see Figure 5).

Network Connectivity and Psychiatric Measures. There were no significant correlations between network connectivity scores and psychiatric symptoms, after controlling for age, sex and state anxiety.

Discussion

A major aim of this study was to determine whether psychiatric symptoms could be reliably measured in neurodegenerative patient groups in the early stages of their disease. I found that the psychometric properties of patient self-report data were good: patients answered consistently within self-report surveys, their responses were more closely related to video observer ratings of psychiatric symptoms than were informant reports (though participant self-reports and video observer scores were not correlated on all measures), and their responses were also associated with theoretically similar measures. Therefore, psychiatric self-report data in neurodegenerative disease patients were considered valid. Unexpectedly, patient self-reports of psychiatric symptoms were not, however, compatible with informant reports.

Behavioral Findings

When comparing self-report scores across diagnostic groups we found that LLD and svPPA patients rated themselves more depressed according to the CES-D than did clinically normal controls. LLDs and svPPAs also rated themselves lower on positive affect, though for svPPAs this was a non-significant trend. This pattern of

response in svPPA and LLD patients is consistent with recent studies that have shown that low positive affect is more predictive of depression and depression outcomes than high negative affect (Kovacs et al., 2015; Riskind, Kleiman, & Schafer, 2013). Thus, my behavioral hypothesis for the svPPA group was partially supported: these patients self-reported high levels of dysphoria compared to clinically normal controls, though they did not report higher levels of euphoria (i.e., mania).

In this sample, svPPA and bvFTD patient groups showed regional and network atrophy consistent with their diagnoses. svPPAs were atrophied in the semantic appraisal network, with predominant left temporal atrophy as well as L>R orbitofrontal/medial prefrontal atrophy and volume loss in the subcallosal area and putamen. These patients showed additional atrophy in ventral DMN areas, particularly in the medial temporal lobe. Overall svPPAs' atrophy pattern was characteristic of their disease group, and group differences on behavioral measures are considered meaningful.

To illustrate the texture of depression in svPPA, I presented the case of Mr. M, who was clinically diagnosed with svPPA and whose structural MRI showed classic semantic appraisal network (with predominant left sided) atrophy, though autopsy results showed Picks pathology. In this regard, Mr. M. is an unusual case of svPPA. Mr. M.'s relatively preserved language abilities, compared to classic svPPA, provided a unique window into the subjectivity of depression in an svPPA patient with semantic appraisal network damage.

Mr. M.'s overall description of his depression was rather unelaborate, which may be due to his semantic language deficits. He was rated highly depressed by video observers and described feeling a general loss of self, as well as "upset", "incompetent", and "depressed" over his loss of abilities. Such generalized negative self-evaluations may be particularly important for depression outcomes, and may also be predicted by semantic appraisal network atrophy. Regions within the semantic appraisal network are linked to reward processing, personalized semantic knowledge, and affective judgements, and damage to this network may result in negative personalized beliefs about the self as well as a failure to update self-concepts based on novel experiences, as reflected in Mr. M.'s critical self-judgements.

Consistent with my behavioral hypothesis for AD, these patients did not differ from controls on level of grief. However, the atrophy pattern of AD was inconsistent with clinical criteria for amnestic AD. AD is a clinically diverse set of syndromes with atrophy that often begins in the medial temporal lobe and spreads to temporoparietal regions that comprise the posterior default mode network (Ossenkoppele et al., 2015). Our AD sample did not show atrophy in overall DMN networks, but volume loss in the left posterior regions, including the supramarginal gyrus, angular gyrus, superior parietal lobule, and the left temporal lobe was observed. My behavioral hypotheses were partially guided by the premise that the DMN networks would be atrophied/disconnected in AD. While my hypothesis for AD patients was supported and grief was not significantly different from clinically

normal controls, in order for this finding to be meaningful, future research should examine a strictly amnestic AD sample with a cleaner pattern of DMN atrophy.

Interestingly, depressed controls reported significantly more grief than any other group. Grief symptoms were studied in order to distinguish contextualized dysphoria (i.e., preparatory grief due to fatal diagnosis) from decontextualized dysphoria (i.e., context-insensitive depression) in order to address possible psychiatric changes due to the news of a fatal diagnosis in neurodegenerative patients. While grief and depression are distinct psychiatric disorders, they often coincide. In depressed populations, acute sense of loss is reported in up to 96% of patients and complicated grief is observed in up to 22% (Kersting et al., 2009). This rate may be even higher in older adults with depression who are more likely to have experienced significant forms of recent loss (e.g., retirement, death of close others, etc). Strikingly, while preparatory grief is highly prevalent in terminally ill populations, and was slightly elevated in svPPAs and significantly higher in LLDs compared to clinically normal controls, bvFTD and ADs reported low levels of grief. This may be due to memory deficits in the AD sample and anosognisia or frontal anosodiaphoria in bvFTDs. Whereas anosognisia involves lack of awareness into one's deficits, anosodiaphoria involves the lack of concern over the implications of one's deficits and disease. This latter interpretation with regard to bvFTD is consistent with a recent study that showed that even when bvFTD patients are made aware of their disease, they show a significant lack of concern (Mendez & Shapira, 2011).

Contrary to the third hypothesis, bvFTD patients did not report more rumination than other groups. Neural atrophy patterns in bvFTD were consistent with clinical criteria. These patients showed atrophy in the cingulo-opercular network as well as the semantic appraisal network. Specifically, bvFTDs showed predominant atrophy in the right>left orbitofrontal gyrus, anterior cingulate, and superior frontal gyrus, and the pre-and post-central gyri, as well as the left>right operculum and insula. While dysfunction of the cingulo-opercular network has been shown to mediate attention deficits, these deficits may not generalize to perseverative self-focus (pathological attention towards the self) in the context of neurodegenerative disease. In fact, recent findings have shown that a repetitive self-focused style of thinking in mid-life may protect adults from developing neurodegenerative symptoms up to three decades later (Kersting et al., 2009), and in aging samples, rumination may be a sign of neuronal preservation.

Network Findings

Contrary to our network connectivity hypotheses, there were no significant findings with regard to network connectivity and psychiatric symptoms. Depressive disorders have been referred to as "system disorders" due to inconsistent network connectivity findings among studies and heterogeneous underlying biochemical signaling pathways (serotonin, glutamate, dopamine, etc) that originate in diverse subcortical nuclei (Alcaro, Panksepp, Witczak, Hayes, & Northoff, 2010). Recent theorists have posited that depression is the emergent property of subcortical hijacking of cortical structures (i.e., hyperactive subcortical connectivity and reduced

cortical activity; Hamilton et al., 2012). Thus, networks derived from imaging of clinically normal and neurodegenerative populations, and which often involve both cortical and subcortical structures (which was the case with the networks under investigation in this study), may show large variation of connectivity within network regions, such as hyperconnected subcortical regions and hypoconnection cortical regions. If this is the case, using mean scores of overall connectivity, as was the case for this study, may result in unremarkable results. Due to the significant role of subcortical nuclei in regulating the production of neurotransmitters associated with psychopathology, future studies should take special care to investigate connectivity within paired network regions, with special attention paid to subcortical structures.

While there were no significant relationships between network connectivity and psychiatric symptoms, there were several significant and interesting findings with regard to network volumes and psychiatric symptoms. Contrary to our first brain-behavior hypothesis, higher grief scores were related to decreased volume in the DMN midline areas, rather than preservation in these regions. Prior studies have shown that DMN midline structures predict grief: When showing pictures of deceased loved ones to recently bereaved widows, posterior cingulate regions became active (Gündel, O'Connor, Littrell, Fort, & Lane, 2003) and Najib et al. (2004) found that prefrontal DMN activation was linked to grief processing in recently separated women. These regions are associated with memory control processes such as counterfactual thinking and future simulations (St Jacques et al., 2011) and damage to

these structures may directly mediate "what-if" lamentations, or it may be related to ambiguous feelings of loss, instead.

Supporting my second brain-behavior hypothesis, negative affect was associated with decreased volume in the semantic appraisal network. Negative affect is a feature of both depression and anxiety (Riskind et al., 2013) and has been linked to regions in the semantic appraisal network regions such as the ventral medial prefrontal and the nucleus accumbens (Wacker, Dillon, & Pizzagalli, 2009). These structures are linked to reward identification and anticipation, generally (Pujara et al., 2016), and in the context of depression, have been linked to anhedonia and general distress (Young et al., 2016). Thus, this finding is consistent with prior studies showing that semantic appraisal network functioning predicts negative affect.

Negative affect was also related to DMN midline volume. This network was comprised of the bilateral precuneus and medial prefrontal cortex. Whereas the semantic appraisal network may be directly related to the experience of negative affect, DMN midline regions may be related to volitional suppression of negative affect. When evoking negative affect in clinically normal adults, Phan et al. (2005) found that cognitive reappraisal strategies aimed at reducing negative affect were linked to DMN midline structures (Phan et al., 2005). It may be the case that the DMN midline network coordinates with the semantic appraisal network to downregulate negative affect.

Contrary to my third hypothesis, euphoria, as indexed by Altman's Mania Rating Scale, was predicted by volume loss of the salience and cingulo-opercular

(SN/CON) networks rather than the semantic appraisal network. The SN/CON work in conjunction to bring awareness of and attention to salient socio-emotional stimuli. More specifically, the CON is linked to maintained focus and error detection during sustained task performance (Dosenbach et al., 2007; Neta, Schlaggar, & Petersen, 2014), and CON dysfunction is commonly observed in bipolar disorder (Mamah et al., 2013; Townsend et al., 2013). In addition to classic symptoms of euphoria/mania such as elevated mood, grandiosity, and decreased need for sleep, bipolar disorder is commonly associated with behavioral disinhibition and attentional deficits (Bora et al., 2009, 2011). It is possible that in psychiatric and neurodegenerative patients, the CON performs inhibitory functions that help to down-regulate episodes of mania. In fact, CON and SN volumes have been consistently linked to cognitive control impairments across diverse psychiatric groups, including bipolar disorder (McTeague, Goodkind, & Etkin, 2016).

The validation of neurodegenerative patients' psychiatric self-reports is a major contribution of this study. It generally has been assumed that such patients lack the ability to adequately self-report symptoms, though this may be specific to symptom domain (i.e., neurology v. psychiatry). Psychiatric symptoms in neurodegenerative patients are often assessed using informant reports. However, the data in this study show that informant reports did not concur with patient self-reports. While informant reports are critical to the diagnosis of neurodegenerative disease, psychiatric phenomena are often subjective, and caregivers may over- or under-estimate estimate psychiatric symptoms in these patients. In fact, caregivers

themselves are at a higher risk of clinical depression and anxiety compared to non-caregivers (Schulz, O'Brien, Bookwala, & Fleissner, 1995) due to feelings of social isolation and role captivity (Alspaugh, Stephens, Townsend, Zarit, & Greene, 1999), and it is possible that informant ratings of psychiatric symptoms are biased by caregivers own level of distress and depression. Further research on the concordance between informant- and self-reports in the context of depression and neurodegeneration is needed.

Network atrophy findings were also a major contribution of this work. The neural basis of psychopathology is poorly understood in psychiatry, and by using neurodegenerative patients with large variability in brain volumes, this study was able to identify structural networks that may be particularly important for psychiatry researchers to investigate. Studies of network connectivity in psychiatric populations often produce inconsistent results, and more careful analyses of the relationship between cortical volumes and specific symptoms may shed light on neural mechanisms of psychiatry in non-neurodegenerative populations.

This study was not without its limitations. For one, the connectivity analyses involved comparing overall mean network connectivity scores. In addition to considerations about possible network node asymmetries between cortical and subcortical regions within each network, volume loss in specific network regions may result in hypoactivation among network nodes affected by atrophy and hyperactivation among nodes that are not affected by atrophy within each network. More nuanced analyses of network node pairs, rather than overall network means,

may be more revealing of the relationship between network connectivity and specific psychiatric symptoms. Another limitation is that this study did not examine psychiatric symptoms across the neurodegenerative disease course. Self-report data were valid, though the findings are limited to early stage neurodegenerative disease patients. Future researchers should consider optimal ways to assess psychiatric symptoms across the disease course.

Conclusion

This study was an original study that investigated the neural substrates of specific psychiatry symptoms in neurodegenerative disease patient groups in the early stages of their disease. The findings of this study have important implications for broad audiences including neurologists, psychiatrists, patients, and caregivers. Understanding of the neural basis of psychiatric symptoms in general is unclear, and neurodegenerative patients provide an important model for investigating the neural basis of psychopathology. These findings also have important diagnostic implications for clinicians who may struggle to differentiate neurological from psychiatric syndromes. The finding that svPPA patients shared common symptoms with late-life depressed controls is important for clinicians to consider when diagnosing svPPA, or alternatively when patients present to psychiatric care with language deficits. Further, the finding that informant-report measures did not adequately capture what patients self-reported is important for researchers to consider when investigating neuropsychiatry in neurodegenerative disease.

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Table 1. *Group demographic least square means, standard deviations, and omnibus tests (N=97)*

	AD (n=11)	**bvFTD (n=13)**	**svPPA (n=11)**	**LLD (n=13)**	**NC (n=11)**	***F***	***p***	η^2
Age	**63.63(8.6)*** **	69(5.9)	**67.72(5.5)***	71.31(7.0)	76.45(8.0)	4.96	0.002	0.27
Sex (M/F)	9/16	**20/7***	7/7	**2/16***	7/6	χ^2=18.77	<0.001	0.45
Edu	16.42(0.57)	17.04(0.53)	18.01(0.17)	16.73(2.47)	17.69(0.69)	0.99	0.42	0.06
MMSE	**22.92(1.30)***	**25.47(1.21)***	**22.36(4.5)*** **	28.68(0.5)	29.09(1.5)	10.93	<0.0001	0.32
CDR Total	0.5 (0.14)	**0.95 (0.13)*** **	**0.70 (0.14)** **		0.0 (0.16)	7.56	0.0005	0.38
Box Score	2.8 (0.83)	**6.25 (0.75)*** **	**3.7 (0.82)***		0.06 (0.92)	9.33	0.0001	0.44

*p<0.05, **p<0.01, ***p<0.001 compared to healthy controls

AD=Alzheimer's Disease, bvFTD=behavioral variant frontotemporal dementia, svPPA=semantic variant primary progressive aphasia, LLD=late life depressed controls, NC=healthy controls; MMSE=Mini Mental State. CDR box scores measure cognitive and functional abilities in neurodegenerative disease populations and was not collected for the LLD population.

Table 2. *Group differences on self- and informant report confounds in method validation sample (N=39 Informants and N= 57 Participants)*

	AD (n=11)	**bvFTD (n=13)**	**svPPA (n=11)**	**LLD (n=13)**	**NC (n=11)**	***F***	***p***	η^2
Inf. Closeness	9.33(0.74)	7.6(0.71)	8.2(0.71)	8.8(1.0)	8.33(0.91)	0.78	0.55	0.08
Part. Closeness	9.73(0.53)	8.7(0.56)	9.57(0.66)	7.75(0.51)	8.3(0.53)	0.42	0.83	0.06
Relationship length	33.59(6.5)	39.26(6.0)	40.60(5.7)	34.06(8.7)	41.84(8.2)	0.32	0.86	0.10
Informant Credibility	9.41(2.3)	13.51(4.3)	10.8 (2.6)	13.98(8.4)	12.98(2.2)	0.79	0.35	0.09
Participant inauthenticity	8.13(1.17)	**11.06(1.08)***	10.59(1.09)	6.69(1.82)	6.88 (1.18)	3.00	0.03	0.21
STAI (controlling for age,sex)	31.76(2.4)	34.97(2.2)	**38.58(2.2)***	**39.49 (2.8)***	27.62(3.2)	3.40	0.03	0.13

*p<0.05, **p<0.01, ***p<0.001 compared to healthy controls

AD=Alzheimer's Disease, bvFTD=behavioral variant frontotemporal dementia, svPPA=semantic variant primary progressive aphasia, LLD=late life depressed controls, NC=healthy controls; Inf.=Informant; Part.=Particpant; STAI=State Anxiety Inventory

Table 3. *Least square means, standard deviations, and omnibus tests of self-report psychiatric measures controlling for age, sex, and state anxiety across whole sample (N=97)*

	AD (n=25)	**bvFTD (n=27)**	**svPPA (n=14)**	**LLD (n=18)**	**NC (n=13)**	***F***	***p***	η^2
CES-D	10.01(1.18)	11.21(1.13)	**13.01(1.50)***	**17.23 (1.43)*****	7.61(1.67)	6.81	<0.0001	0.23
PANAS-NA	16.43(1.60)	18.17(1.53)	20.69(2.03)	20.62(1.93)	13.58(2.23)	2.31	0.06	0.09
ICG	20.01(1.84)	20.43(1.76)	23.14(2.23)	**26.7(2.22)****	16.44(2.57)	2.67	0.04	0.11
RRQ-Rum	32.51(1.57)	33.84(1.48)	37.74(1.97)	42.12(1.88)	36.51(2.17)	4.41	0.003	0.20
Altman's	5.74 (0.76)	6.43(0.73)	5.15(1.09)	3.71(0.92)	4.48 (1.06)	1.41	0.24	0.03
PANAS-PA	34.35(1.72)	33.09(1.63)	27.54(2.16)	**24.16(2.07)****	34.22(2.39)	4.22	<0.001	0.16

*p<0.05, **p<0.01, ***p<0.001 compared to healthy controls

AD=Alzheimer's Disease, bvFTD=behavioral variant frontotemporal dementia, svPPA=semantic variant primary progressive aphasia, LLD=late life depressed controls, NC=healthy controls; CES-D=Center for Epidemiological Studies-Depression; PANAS-NA=Positive Affect Negative Affect Schedule-Negative Affect Subscale; ICG=Inventory for Complicated Grief; PANAS-NA=Positive Affect Negative Affect Schedule-Positive Affect Subscale; RRQ-Rum=Rumination-Reflection Questionnaire-Rumination Subscale

Table 4. *Diagnostic group differences of network volumes (N=97)*

	AD (n=25)	bvFTD (n=27)	svPPA (n=14)	LLD (n=18)	NC (n=13)	F	p	η2
DMN Dorsal	6.81 (0.33)	6.75 (0.25)	6.49 (0.39)	7.93(0.37)	7.61 (0.39)	5.81	<0..0001	0.27
DMN Midline	5.79 (0.21)	5.66 (0.17)	6.07 (0.25)	6.55(0.24)	6.14(0.25)	5.69	<0..0001	0.28
DMN Ventral	9.55 (0.31)	9.39 (0.23)	**8.66 (0.38)***	10.55 (0.35)	9.97 (0.38)	5.69	0.0001	0.33
SAN	2.08 (0.11)	**1.75 (0.09)***	**1.38 (0.14)*****	2.22 (0.13)	2.19 (0.14)	8.21	<0.0001	0.43
CON	7.38 (0.43)	**6.82 (0.33)**	7.62(0.52)	8.62 (0.49)	8.62 (0.49)	4.30	0.001	0.25
SN	4.43 (0.11)	4.00 (0.22)	4.12 (0.34)	4.96 (0.32)	4.81(0.34)	3.65	0.004	0.20

AD=Alzheimer's Disease, bvFTD=behavioral variant frontotemporal dementia, svPPA=semantic variant primary progressive aphasia, LLD=late life depressed controls, NC=healthy controls; DMN=Default Mode Network; SAN=Semantic Appraisal Network; CON=Cingulo-opercular Network; SN=Salience Network

Table 5. *Diagnostic group differences of network connectivity averages (N=97)*

	AD (n=25)	**bvFTD (n=27)**	svPPA (n=14)	LLD (n=18)	**NC (n=13)**	***F***	***p***	η^2
DMN Dorsal	0.28 (0.05)	0.27 (0.05)	0.33 (0.05)	0.31(0.04)	0.30 (0.05)	0.98	0.45	0.04
DMN Midline	0.47 (0.05)	0.51 (0.04)	0.51 (0.06)	0.53(0.05)	0.51(0.05	1.11	0.37	0.04
DMN Ventral	0.33 (0.04)	0.32 (0.04)	0.34 (0.04)	0.29 (0.03)	0.32 (0.04)	0.34	0.98	0.01
SAN	0.23 (0.04)	0.23 (0.03)	0.23 (0.04)	0.20 (0.03)	0.27 (0.04)	0.61	0.72	0.09
CON	0.35 (0.04)	0.30 (0.04)	0.34 (0.04)	0.35 (0.04)	0.38 (0.05)	1.55	0.19	0.12
SN	0.23 (0.03)	0.21 (0.03)	0.27 (0.03)	0.25 (0.03)	0.27 (0.03)	0.75	0.62	0.05

AD=Alzheimer's Disease, bvFTD=behavioral variant frontotemporal dementia, svPPA=semantic variant primary progressive aphasia, LLD=late life depressed controls, NC=healthy controls; DMN=Default Mode Network; SAN=Semantic Appraisal Network; CON=Cingulo-opercular Network; SN=Salience Network

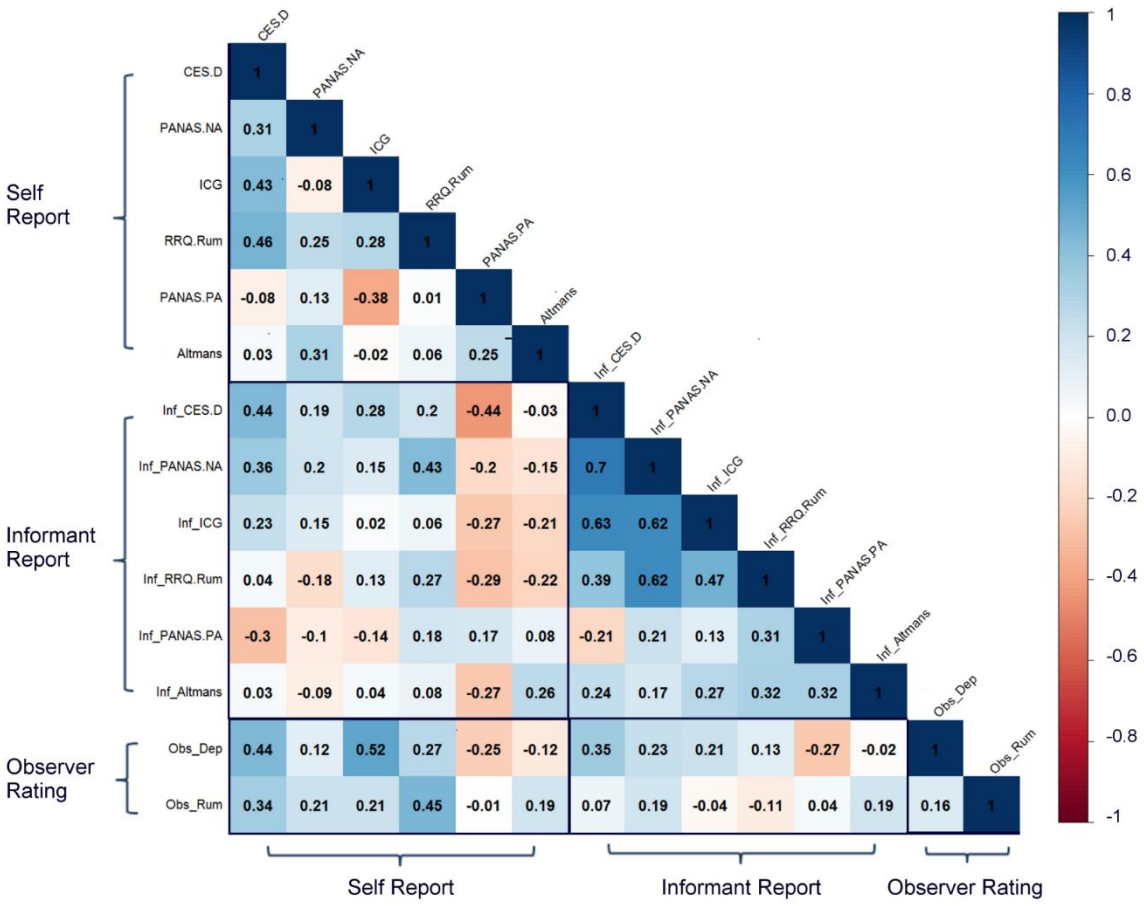

Figure 1. Partial correlation matrix comparing the reporting source for measures of interest (controlling for age and sex)

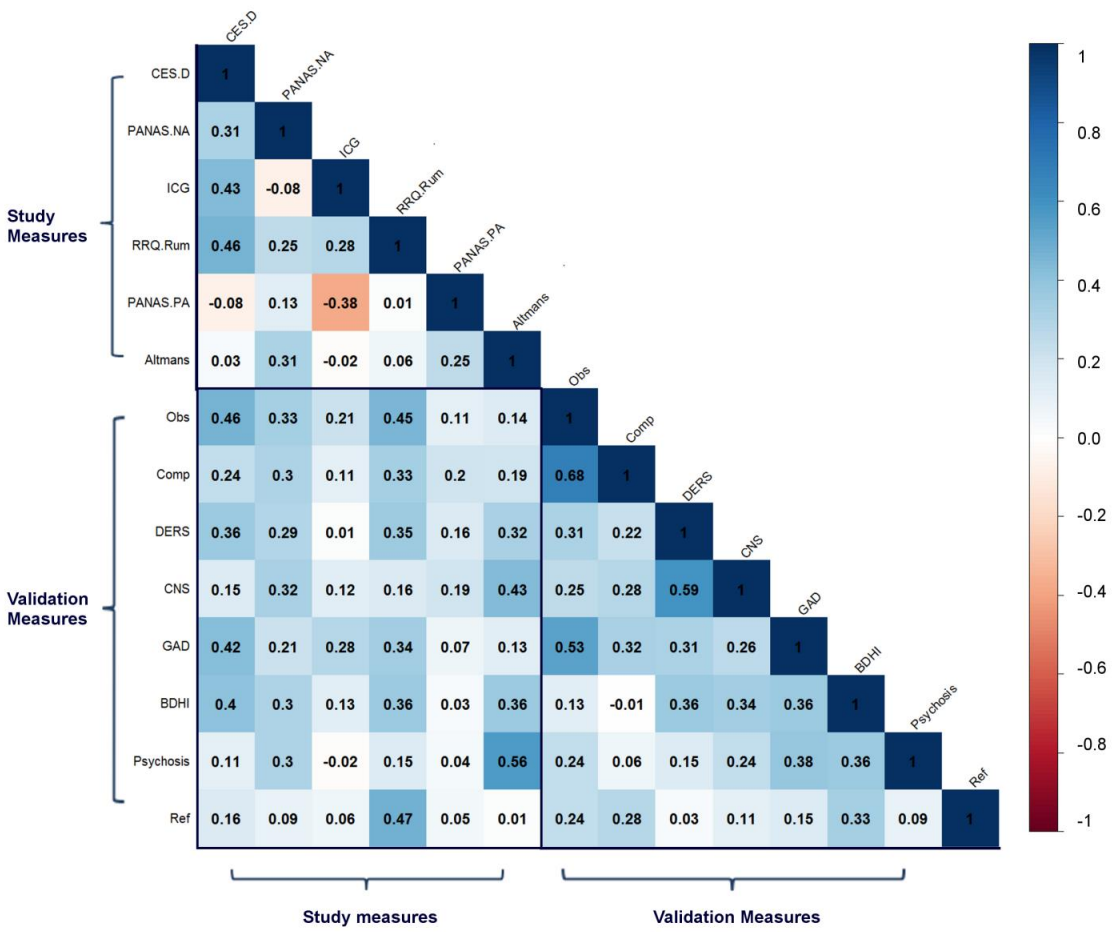

Figure 2. Partial correlation matrix comparing measures of interest to related psychiatric measures (controlling for age, sex, and state anxiety (STAI))

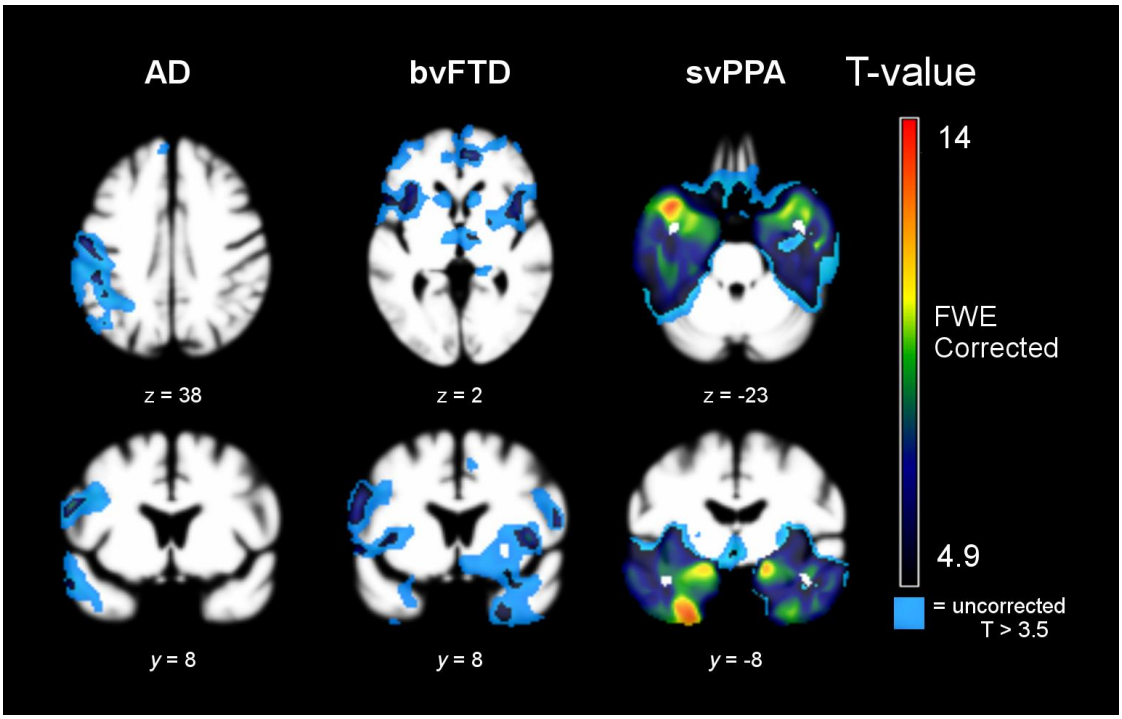

Figure 3. T-score atrophy maps of neurodegenerative diagnostic groups (controlling for age, sex, and TIV (P_{FWE}<0.05; light blue=uncorrected)).

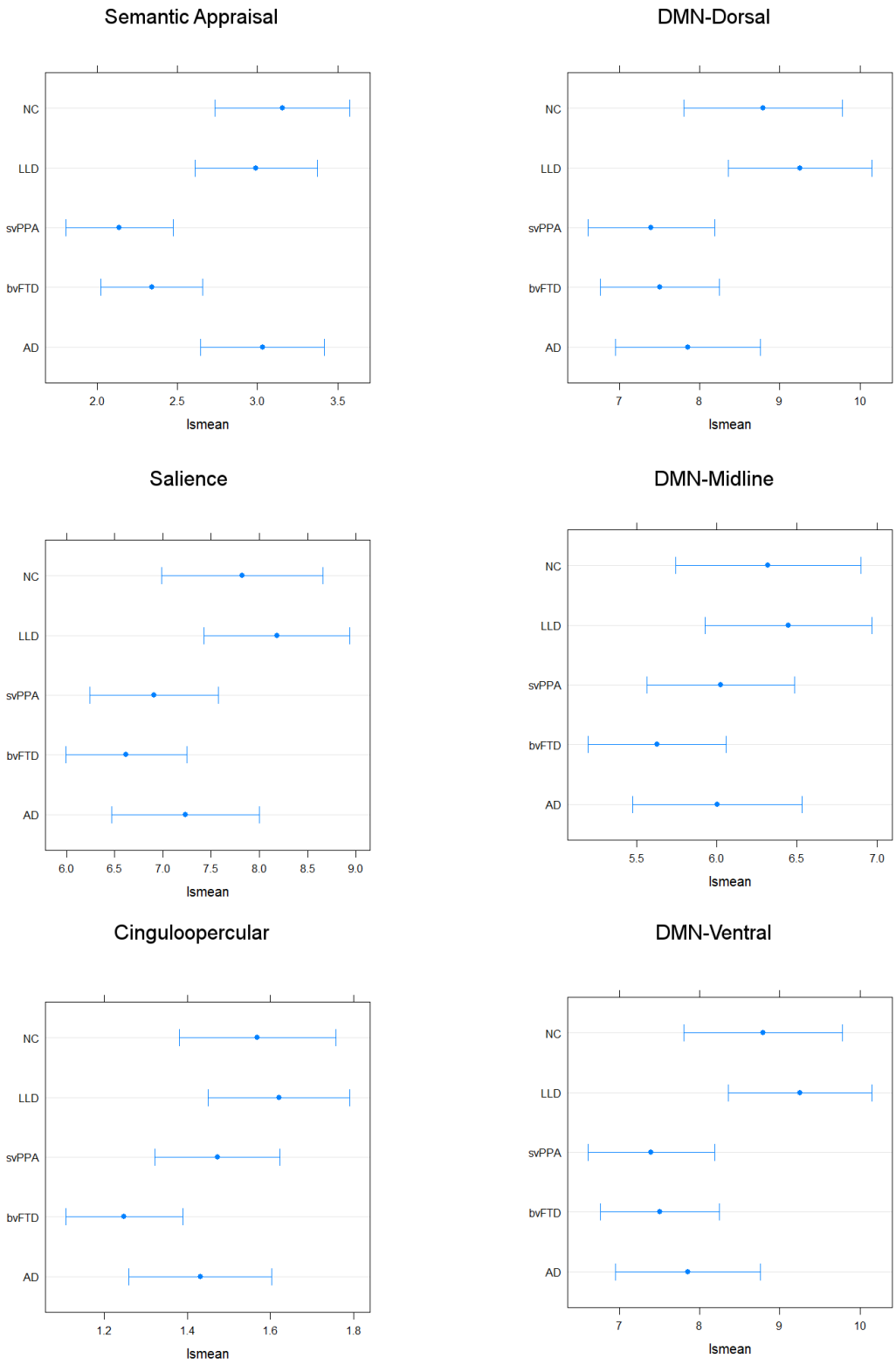

Figure 4. Diagnostic group comparison of least square means and confidence intervals for network atrophy (controlling for age, sex, and total intracranial volume)

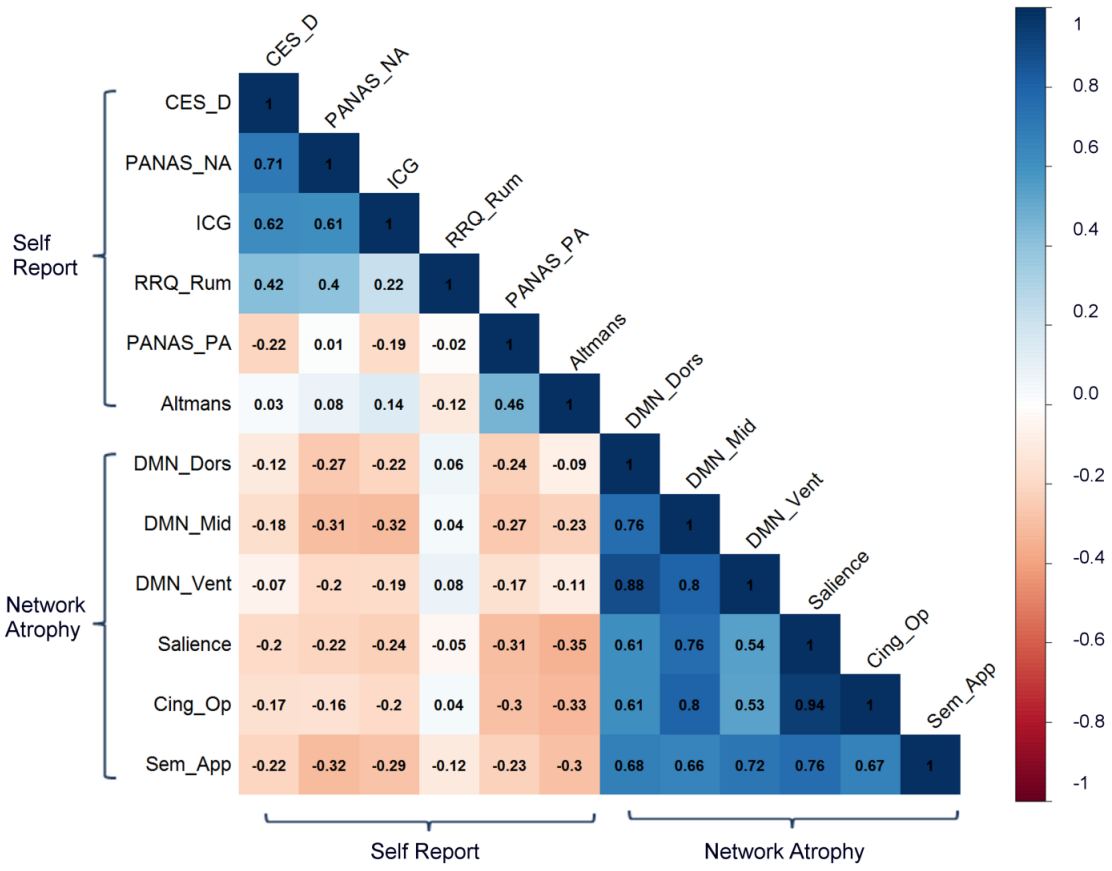

Figure 5. Partial correlation matrix comparing measures of interest to network volumes (controlling for age, sex, state anxiety (STAI), and total intracranial volume).

APPENDIX A

Semi-Structured Interview Questions: Patients

The kinds of questions I am going to ask will be a little different from the ones you've already been asked here at our center. Specifically, I am going to ask you about how you feel about your diagnosis and any changes you may have noticed in your feelings / mood both after you were given your diagnosis as well as before.

- When were you initially diagnosed?

- I'd like you to tell me about how you initially reacted to the news of your diagnosis. What kinds of feelings came up? How long did those feelings last?
    - What does [emotion] look like for you?
    - Can you give me an example of that?
    - Can you tell me about a memorable time you experienced this emotion?
    - Have you ever reacted this way to anything before being diagnosed? If so, can you tell me about that? Around when did5 this occur? Were there any circumstances that contributed to that reaction?

- Can you tell me about a time when you felt the most [name the emotion they referenced (e.g., sad, relieved)]?

- Did you do anything to make yourself feel different?

- Now, I'd like you to tell me about any significant changes you've noticed since you were diagnosed in the way you feel [or the way you've felt around others]. Could you give me an example of a time you've felt this way?
    - Have these kinds of feelings happened to you before your diagnosis?
    - If so, can you tell me about that? Around when did this occur? Were there any circumstances that contributed to it?

- Now I'd like you to tell me how you feel about yourself now.
    - Why do you think you feel that way?
    - What makes you feel good about yourself?
    - What makes you feel bad about yourself?

- Now I'd like you to tell me what you think will happen going forward. What do you think your life will look like in 2 years? 5 years?
    - How often do you think about these things?

    - Would you say you wished you thought about these things less often, about the same, or more often?

- Now I'd like you to tell me about <u>what you'd like to see</u> happen going forward [to you / people around you / generally].
    - How often do you think about these things?
    - Would you say you wished you thought about these things less often, about the same, or more often?

- Do you feel like you've been missing something meaningful since being diagnosed? If so, what?
    - It sounds like you think about these things often. Do you wish you could think about them less often, the same amount, or more often?
    - Do you sometimes feel like you want to stop thinking about them, but you can't?

- Do you feel like you've gained anything important since being diagnosed? If so, what?

- Can you describe a time when you felt really happy since being diagnosed?

- Is there anything I did not ask today that you think is important for researchers to know about [your emotions / how you feel about yourself / living with a neurodegenerative disease]?

How was it for you to be talking to me in this way? Do you have any questions for me?

ALWAYS ASK THEM TO DESCRIBE WHAT THEIR EMOTIONS LOOK LIKE (e.g., specific behaviors).
ALWAYS ASK THEM TO DESCRIBE EVENTS IN WHICH THEY REMEMBER EXPERIENCING THE EMOTIONS THEY DESCRIBE

APPENDIX B

Narrative Examples for Establishing Coder Reliability for Psychiatric Constructs

Construct	**Narrative Examples**
Grief	It's unfair. I'm just angry at how unfair it is (**Bitterness**).
	We had ideas on how to spend our lives together. This wasn't supposed to happen. (**Contextualized sadness**)
	I used to be someone who could handle anything. I can't handle anything anymore. (**Former self statement**)
Depression	I'm sad most of the time (**Depressed mood**)
	I was a horrible mother. I feel like it was all my fault (**Guilt**)
	It will never get better (**Hopelessness**)
	I feel so stupid (**Self-deprecation**)
Mania	I'll probably get drafted once I'm finished my law degree. I'm an extraordinary baseball player (**Grandiosity**)
	I have so many projects at home. I have no time for sleep. (**Sleep**)
Rumination	I think about what is going to happen to me all day (**Verbal**)
	1) Everything would be fine if they didn't take my license away 2) I really hate not having my license 3) I don't know what the doctors will say, but I'm hoping they can do something about my license. (**Behavioral**)

APPENDIX C

UCSF Memory and Aging Center

Informant Credibility Scale (ICS)

In the box next to each answer option, please write the score that best describes how reliable this informant was.

1=Not at all	2=Mild	3 = Moderate	4 = Moderately severe

1. CONSISTENT: Informant contradicted him/herself throughout the interview	
	1. Not at all conflicting. Provided consistent responses about patient's (subject's) mood and psychiatric symptoms. Did not waver. 2. Slightly wavered. Told conflicting stories when reporting on one symptom during the interview. 3. Wavered. Told conflicting stories when reporting on 2-3 symptoms during the interview. 4. Wavered multiple times on multiple symptoms. Reports of events and emotions of participants were considerably inconsistent.
2. EVIDENCE: Unable to provide any anecdotal evidence about patient's emotions or psychiatric symptoms.	
	1. Informant was readily able to provide clear examples of times when the patient demonstrated emotions / psychiatric symptoms. 2. Mostly able to provide examples of times when the patient demonstrated symptoms or emotions. Hedged / needed probing 1-2x's 3. Unable to provide clear examples of times when the patient demonstrated psychiatric symptoms or emotions without repeated probing. 4. Even with probing, the informant was unable to describe patient's psychiatric symptoms or emotions with any clarity.
3. CONCERN: Informant seemed generally unconcerned about the patient's inner experiences or psychiatric symptoms since the diagnosis. Not due to disease severity (e.g., patient's primary symptom is extreme apathy) NOR inability to engage with emotional material (see below).	
	1. Informant was very concerned about the patient's feelings and perspective. 2. Informant expressed concern about the patient's feelings during most of the interview. Expressed that they never thought about how the patient may have felt 1-2 times. 3. The informant expressed that they never thought about how the patient felt, but would do so in the future. 4. The informant was not concerned about the patient's feelings, and did not express interest in paying attention to them in the future.

4. SELF-BIAS: Informant seemed considerably biased when reporting on patient's psychiatric symptoms or patient's inner experiences (e.g., towards own emotions).	
	1. Entirely objective. Did not refer to own emotions. 2. Mostly focused on the patient's inner experiences. Deferred to own emotions 1-2 times when describing patient's inner experiences. 3. Noticeably focused on own inner experiences rather than the patient's. Was able to report on the patient's experiences when probed. 4. Unable to provide objective answers. Even when redirected, provided answers that referenced own inner experiences.
5. Capacity to engage with emotional material.	
	1. Completely comfortable speaking about emotional material. 2. Mostly comfortable speaking about emotional material. Had difficulty discussing certain emotional material, but otherwise able to reflect on emotions. 3. Had considerable difficulty discussing emotional material. Generally uncomfortable discussing emotions, though certain material was OK. 4. Very uncomfortable discussing emotional material. Seemed generally unable to engage when discussing emotional topics and events.

_____ PERSONAL CONNECTION: Please rate the ease of connection you felt with the informant during the interview (1=fluid, easy connection, 4=severely disconnected (noticeable wall between you and informant)).

_____ INFORMANT DISTRESS: Please rate the degree of distress the informant presented during the interview (1=not at all distressed, 4=severely distressed).

_____ OVERALL INTERVIEW RATING: Please rate the overall quality of this interview (e.g., was this a good description of what the patient may be experiencing (1= **GREAT INTERVIEW**: informant did their best to describe the patient's emotions; 4 = poor measure of patient's symptoms).

	Total Score

APPENDIX D

UCSF Memory and Aging Center

Emotional Expressivity Rating Scale (EERS)/Participant Inauthenticity

In the box next to each answer option, please write the score that best describes the interviewee's emotional expressiveness and reactivity during the interview.

1=Not at all	2=Mild	3 = Moderate	4 = Moderately severe	5 = Extremely severe

6. BLUNTED AFFECT: Restricted range of emotions of face, gesture, and voice. Marked indifference or flatness when discussing distressing events.	
	5. Not at all impaired, expressive during the interview 6. Emotional range is slightly subdued or reserved but displays appropriate facial expressions and tone of voice that are within normal limits 7. Emotional range overall is diminished, subdued or reserved, without many spontaneous and appropriate emotional responses. Voice tone is slightly monotonous. 8. Emotional range very diminished, individual doesn't show emotion, smile, or react to distressing topics except minimally, few gestures, facial expression does not change very often. Voice tone is monotonous much of the time
	9. Virtually no emotional range or expressiveness, stiff movements. Mechanical in speech and gestures. Voice tone is monotonous all of the time.
7. INABILITY TO CONNECT: Unable to relate emotionally during the interview. Invisible barrier between you and the interviewee	
	5. Not at all impaired. Was able to connect emotionally. Interview followed a natural flow. 6. Lack of emotional involvement shown by noticeable failure to reciprocate emotions, gestures, and social behaviors, or lacking in warmth, but responds to interviewer when approached. 7. Emotional contact not present for much of the interview because participant fails to make eye contact, doesn't seem to care if interviewer is listening. 8. Actively avoids emotional participation. Frequently unresponsive or responds with yes/no answers. Responds with only minimal affect.
	9. Consistently avoids emotional participation. Unresponsive or responds with yes/no answers. May leave during interview or just not respond at all.
8. INABILITY TO ACCESS EMOTIONS: Unable to access/spontaneously describe emotions. Had to repeatedly orient interviewee to emotions.	
	1. Readily and flexibly describes emotions throughout the interview. No probing required. 2. Mostly offered feelings and emotions spontaneously throughout the interview. Occasionally (1-2 times) needed reorientation to the emotional nature of the questions.

	3. Noticeable failure to offer emotions spontaneously, interviewer had to redirect to feelings and mood 3 or more times during the interview. 4. Unable to access emotions or feelings whatsoever throughout the interview without cueing or redirection.
	5. Entirely unable to access emotion or memory of emotions during the interview even with redirection and probing.
9. IMPOVERISHED EMOTIONAL DESCRIPTION: Unable to describe emotions with richness or detail (e.g., episodic scenes).	
	5. Emotions were richly described. Participant referenced complex emotions (e.g., bittersweet) and readily described affective behaviors (e.g., hitting, crying) / emotional episodes throughout the interview. 6. Mild difficulty in describing emotions with detail. Interviewee occasionally (1-2 times) needed probing in order to describe emotional behavior or scenes with detail. 7. Repeated probing (3 or more) required in order for patients to describe thoughts, feelings and events surrounding emotional reactions during the interview. Had to repeatedly ask interviewee to describe behaviors or scenes. 8. Totally unable to provide detail or describe any events that could help interviewer understand emotions, without probing.
	9. Even with probing, patient could not produce details or describe events that would help researchers understand their emotions.
	Total Score

_____ AUTHENTICITY: Please rate the degree to which you believe the participants account of emotional experiences, i.e., did their expressive behavior contradict how they described their emotions (1=totally authentic, 5 =totally inauthentic)

_____ SUFFERING: Please rate the degree you believe the patient is emotionally suffering generally, on a 1-5 scale (1=not at all suffering, 5=severely suffering).

APPENDIX E

Calgary Depression Scale for Schizophrenia (CDSS)

4pt measure

Addington, D., Addington, J., & Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophrenia research*, *3*(4), 247-251.

1. **Depressed Mood**

Subjective report of sadness, misery, low spirits. Its severity, variability and duration

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

2. **Delusions of Guilt**

A fixed false belief that the subject has committed a crime sinned greatly or is deserving of punishment.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

3. **Hopelessness**

The subjects view of the world is bleak and without comfort.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

4. **Self-deprecation**

The subject feels inferior to others to the point of worthlessness in extreme case..

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

5. **Guilty ideas of reference**

The subject feels he is blamed for some action or attribute.

Rarely	**Sometimes**	**Usually**	**Always**

1	2	3	4
☐	☐	☐	☐

6. **Pathological guilt**

The subject blames himself for some peccadillo which most people would not take seriously.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

7. **Suicide**

Scoring ranges from feeling that life is not worth living to serious suicide attempts.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

8a. **Behavioral signs**

Slow body movement, poor eye contact, slow eye blinking rate, slouching, staring at the ground, sighing, anger or irritability.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

8b. **Verbal signs**

Speaking slowly in monotonous voice, delayed response time, voice trails off.

Rarely 1	**Sometimes** 2	**Usually** 3	**Always** 4
☐	☐	☐	☐

APPENDIX F

Clinician-Administered Rating Scale for Mania (CARS-M)

PATIENT ID _____
DATE_____
RATER(S)_____
SUBSCALE 1 SCORE (ITEMS 1-10):_____
SUBSCALE 2 SCORE (ITEMS 11-15):_____
TOTAL SCORE:_____

Note: In completing this scale, information may be obtained according to what the participant explicitly states or how they behave during the interview. Please refer to bottom bullet points before rating each question.

1. Elevated/Euphoric Mood (Inappropriate optimism about the present or future which was out of proportion to the circumstances.)

0	Absent
1	Slight, e.g., good spirits, more cheerful than others, of questionable clinical significance.
2	Mild, but definitely elevated or expansive mood, overly optimistic and somewhat out of proportion to one's circumstances.
3	Moderate, mood and outlook clearly out of proportion to circumstances.
4	Severe, clear quality of euphoric mood.
5	Extreme, clearly exhausted, extreme feelings of well being, inappropriate laughter and/or singing.

- Did they mention recent periods of recent and prolonged cheerful or happiness?
- Some patients are at peace with their disease and mortality. This can present as calm acceptance. This would not be considered euphoric. Euphoria is exaggerated and extreme positivity.

2. Irritability/Aggressiveness: (Demonstrates or claims to have recently experienced overt expression of anger, irritability, or annoyance. Do not include mere subjective feelings of anger/ annoyance, unless expressed overtly.)

0	Absent
1	Slight, occasional annoyance, questionable clinical significance.
2	Mild somewhat argumentative, quick to express annoyance with patients, staff or interviewer, occasionally irritable during interview.
3	Moderate, often swears, loses temper, threatening, excessive irritation around certain topics, room seclusion may be required, frequently irritable during interview.
4	Severe, occasionally assaultive, may throw objects, damage property, limit setting necessary, excessive and inappropriate irritation, restraints may be required, interview had to be stopped due to excessive irritability.
5	Extreme, episodes of violence against persons or objects, physical restraint required.

- Did they say they have not been getting along with people in general?
- Did they say they had been angry?

- Did they mention recent yelling or violence?

3. Hypermotor Activity (Demonstrates generalized motor hyperactivity. Do not include mere subjective of feelings restlessness - not medication related.)

0	Absent
1	Slight increase, of doubtful clinical significance.
2	Mild, occasional pacing, unable to sit quietly in chair
3	Moderate, frequent pacing on unit, unable to remain seated.
4	Marked, almost constant moving or pacing about.
5	Extreme, continuous signs of hyperactivity such that the patient must be restrained to avoid exhaustion.

- Did they have trouble sitting still?

4. Pressured Speech (Accelerated, pressured, or increased amount and rate of speech, inside or outside of the interview.)

0	Absent
1	Slight increase, of doubtful clinical significance.
2	Mild, noticeably more verbose than normal, but conversation is not strained.
3	Moderate, so verbose that conversation is strained; some difficulty interrupting patient's speech.
4	Marked, patient's conversation is so rapid that conversation is difficult to maintain, markedly difficult to interrupt speech.
5	Extreme, speech is so rapid or continuous that patient cannot be interrupted.

5. Flight of Ideas/Racing Thoughts (Accelerated speech with abrupt changes from topic to topic usually based on understandable associations, distracting stimuli, or play on words. When severe, the associations may be so difficult to understand that looseness of association or incoherence may also be present. Racing thoughts refer to the patient's subjective report of having thoughts racing through his mind.) Scores in the 1-3 range may reflect tangential speech (many topic changes), high scores would reflect rapid speech.

0	Absent
1	Slight, occasional instances of doubtful clinical significance.
2	Mild, occasional instances of abrupt change in the topic with little impairment in understandable or patient reports occasional racing thoughts.
3	Moderate, frequent instances with some impairment in understandability or patient reports frequent racing thoughts which are disruptive or distressing to the patient.
4	Severe, very frequent instances with definite impairment.
5	Extreme, most of speech consists of rapid changes in topic which are difficult to follow.

- This is has to be evident in their behavior during the interview.

6. Distractibility (Attention is too easily drawn to unimportant or irrelevant external stimuli; i.e., noise in adjoining room, books on a shelf, interviewer's clothing, etc. Exclude distractibility due to intrusions of visual and/or auditory hallucinations or delusions. Rate on the basis of observation only.)

0	Absent
1	Slight, of doubtful clinical significance.
2	Mild, present but does not interfere with task or conversation.
3	Moderate, some interference with conversation or task.
4	Severe, frequent interference with conversation or task.
5	Extreme, unable to focus patient's attention on task or conversation.

7. Grandiosity (Increased self-esteem and unrealistic or inappropriate appraisal of one's worth, value, power, knowledge or abilities.)

0	Absent
1	Slightly increased self-esteem or confidence, but of questionable clinical significance.
2	Mild, definitely inflated self-esteem or exaggeration of abilities somewhat out of proportion to circumstances.
3	Moderate, inflated self-esteem clearly out of proportion to circumstances, borderline delusional intensity.
4	Severe, clear grandiose delusion(s).
5	Extreme, preoccupied with and/or acts on the basis of grandiose delusions.

- Did they claim to have a special skills in a boastful manner? (e.g., I was a master, expert, etc)
- Did they claim to have special powers, knowledge, or abilities that were out of the ordinary?
- Did they claim to have a special purpose in life?
- Did they claim to be "chosen" in some way?

8. Decreased Need For Sleep (Less need for sleep than usual to feel rested. Do not rate difficulty with initial, middle or late insomnia.)

0	Absent
1	Up to 1 hour less sleep than usual.
2	Up to 2 hours less sleep than usual.
3	Up to 3 hours less sleep than usual.
4	Up to 4 hours less sleep than usual
5	4 or more hours less sleep than usual.

- They need to have mentioned that they felt rested without sleep during the interview.

9. Excessive Energy (Unusually energetic or more active than usual without expected fatigue, lasting at least several days.)

0	Absent
1	Slightly more energy, of questionable significance.
2	Definite increase in activity level or less fatigued than usual, does not hinder functioning.
3	Clearly more active than usual with little or no fatigue, occasional interference with functioning.
4	Much more active than usual with little fatigue and clear interference with normal functioning.
5	Extreme, active all day long with little or no fatigue or need for sleep.

- Have you had more energy than usual to do things?
- Have you been more active than usual, or had the feeling that you could go all day without feeling tired?

10. Poor Judgment (Excessive involvement in activities without recognizing the high potential for painful consequences; intrusiveness, inappropriate calling of attention to oneself.)

0	Absent
1	Slight, but of questionable clinical significance (i.e., increased phone calling, occasional intrusiveness.)
2	Mild, but definite examples (i.e. somewhat intrusive, sexually provocative, inappropriate singing.)
3	Moderate, assumes tasks or responsibilities without proper training, financial indiscretions, buying sprees within financial limits, frequent intrusiveness.
4	Severe, sexual promiscuity, hypersexuality, extremely intrusive behavior, places self in significant economic difficulty.
5	Extreme, continuous intrusive behavior requiring limit setting, excessive phone calling at all hours, antisocial behavior, excessive involvement in activities without regard to consequences.

- This cannot be observed during the interview so they must have stated they were making poor decisions.

11. Disordered Thinking (Impaired understandability of patient's thoughts as manifested by his/her speech. This may be due to any one or a combination of the following: incoherence, looseness of association(s), illogical thinking. Do not rate simple flight of ideas unless severe.) Some patients have speech disorders and may have difficulty clearly expressing logical thoughts, though their thinking is coherent. It is important to ask whether their lack of clarity is due to language dysfunctions or incoherent though.

0	Absent
1	Occasional instances which are of doubtful clinical significance.
2	A few definite instances, but little or no impairment in understandability.
3	Frequent instances and may have some impairment in understandability.
4	Severe, very frequent instances with marked impairment in understandability.
5	Extreme, most or all of speech is distorted, making it impossible to understand what the patient is talking about.

12. Delusions (Fixed false beliefs, ranging from delusional ideas to full delusions - including grandiosity) Specify Type: Determine if mood-congruent or mood- incongruent .

0	Absent
1	Suspected or likely.
2	Definitely present but not fully convicted, including referential or persecutory ideas without full conviction.
3	Definitely present with full conviction but little if any influence on behavior.

4	Delusion has a significant effect upon patient's thoughts, feelings, or behavior (i.e., preoccupied with belief that others are trying to harm him/her.)
5	Actions based on delusion have major impact on patient or others (i.e., stops eating due to belief that food is poisoned, strikes others

- Did they mention experiences that may be impossible or unlikely for them (i.e., I was president of Tatarstan.)

13. Hallucinations (A sensory perception without external stimulation of the relevant sensory organ.) Specify type: Determine if mood-congruent or mood- incongruent .

0	Absent
1	Suspected or likely.
2	Present, but subject is generally aware that it may be his/her imagination and can ignore it.
3	Definitely present with full conviction, but with little if any influence on behavior.
4	Hallucinations have significant effect on patient's thoughts, feelings, or actions (e.g., locks doors to avoid imaginary pursuers.)
5	Actions based on hallucinations have major impact on patient or others (e.g., patient converses with voices so much that it interferes with normal functioning.)

- Have you heard sounds or voices of people talking when there was no one around? (Example.)
- Have you seen any visions or smelled odors that others don't seem to notice? (Example.)
- Have you had any (other) strange or unusual perceptions? (Example.)
- Have these experiences interfered with your functioning in any way?

14. Orientation (Impairment in recent or remote memory, or disorientation to person, place or time.)

0	Absent
1	Slight impairment but of doubtful clinical significance (i.e., misses date by one day.)
2	Mild, but definite impairment (i.e., unsure about orientation to place or time, or some impairment in a few aspects of recent or remote memory.)
3	Moderate (i.e., confused about where he is or cannot remember many important events in his Iife.)
4	Severe (disoriented or gross impairment in memory.)
5	Extreme (i.e., thoroughly disoriented to time, place, person and/or is unable to recall numerous important events in his/her life.)

- Did they mention memory problems?

0	Insight is present (i.e., patient admits illness, behavior change and need for treatment.)

1	Partial insight is present (i.e., patient feels he/she may possibly be ill or needs treatment, but is unsure.)
2	Patient admits behavior change, illness or need for treatment but attributes it to non delusional or plausible external factors (i.e., marital conflict, job difficulties, stress.)
3	Patient admits behavior change, illness or need for treatment but gives delusional explanations (i.e., being controlled by external forces, dying of cancer, etc.)
4	Complete lack of insight. Patient denies behavior change, illness or need for treatment.

APPENDIX G

Grief Observation Form

4pt measure

Total Score _____

8. **Bitterness**

Statements communicating anger, resentment, or frustration over deficits / diagnosis. (e.g., "I hate that he's not here anymore", "I hate not being able to drive")

Not at all	**Rarely / Mild**	**Sometimes / Moderate**	**Constantly / Severe**
1	2	3	4
☐	☐	☐	☐

9. **Statements about former self**

Subject references how they were before loss/diagnosis. (e.g., "I used to be so close to Jim", "I was someone who could handle anything")

Not at all	**Rarely / Mild**	**Sometimes / Moderate**	**Constantly / Severe**
1	2	3	4
☐	☐	☐	☐

10. **Contextualized Sadness**

Statements reflecting sadness or frustration related to deficits or loss (e.g., "My word-finding problems make me feel horrible", "I miss him everyday")

Not at all	**Rarely / Mild**	**Sometimes / Moderate**	**Constantly / Severe**
1	2	3	4
☐	☐	☐	☐

APPENDIX H

Rumination Rating

4pt measure

1. **Rumination report**

Subjective reports instances of rumination / inability to take their mind off of an event or idea (can be positively or negatively valenced)

Not at all	**Rarely (when something brings it to mind / once a month)**	**Sometimes (at least once a week)**	**All the time (many times a day)**
1	2	3	4
☐	☐	☐	☐

Please document what they said and time marker of interview:

Time marker:	**Quote:**

2. **Observed rumination**

Subject returns to the same event or idea multiple times throughout the interview.

Not at all	**Rarely (1-2xs)**	**Sometimes (2-3xs)**	**Usually (>3xs)**
1	2	3	4
☐	☐	☐	☐

Please document what they said and time marker of interview:

Time marker:	**Quote:**

APPENDIX I

List of Measures and Their Related Constructs

Construct	**Survey / Report Measures**	**Observer Measure**
Informant Credibility	Length/closeness of the Relationship	Informant Credibility Scale
Participant Authenticity		Emotional Expressivity Rating Scale
Grief	Inventory for Complicated Grief (**ICG**)	Grief Observer Form
Depression	Center for Epidemiologic Studies Depression Scale (**CES-D**)	Calgary Depression Scale for Schizophrenia (**CDSS**)
	Positive Affect Negative Affect Schedule – Negative Affect Subscale (**PANAS-NA**)	
Mania	Altman's Mania Rating Scale	Clinician Administered Rating Scale for Mania (**CARS-M**)
	Positive Affect Negative Affect Schedule – Positive Affect Subscale (**PANAS-PA**)	
Rumination	Reflection-Rumination Questionnaire – Rumination Subscale (**RRQ-Rum**)	Rumination Rating
ADDITIONAL MEASURES USED TO APPROXIMATE DISCRIMINANT VALIDITY		
Irritability	Buss Durkee Hostility Inventory-Irritability subscale (**BDHI**)	
Anxiety	Generalized Anxiety Disorder-7 (**GAD-7)**	
Emotional Instability/Lability	Difficulties in Emotion Regulation Scale (**DERS**) Center for Neurological Diseases –Lability Scale (**CNS**)	
Obsessions/ Compulsions	Yale-Brown Obsessive Compulsive Scale (**YBOCS**) – Obsessions (**Obs**) and Compulsions (**Comp**) subscales	
Psychosis	Adolescent Psychotic Symptoms Questionnaire (**Psychosis**)	

APPENDIX J

Seed regions of the intrinsically connected networks according to the Neuromorphometric atlas

Network		**Label**	**Hemi (L/R)**	**MNI**		
				x	***y***	***z***
Cingulopercular Nework		Middle frontal gyrus	R	27	50	23
		Middle frontal gyrus	L	-28	51	15
		Supplementary motor cortex	L	-1	10	46
		Anterior insula	R	36	16	4
		Anterior insula	L	-35	14	5
		Thalamus proper	R	10	-15	8
		Thalamus proper	L	-12	-15	7
DMN	*Dorsal*	Medial superior frontal	R	0	52	26
		Supramarginal gyrus	L	-54	-54	28
		Supramarginal gyrus	R	54	-54	28
		Middle temporal gyrus	L	-60	-24	-18
		Middle temporal gyrus	R	60	-24	-18
	Ventral	Middle occipital gyrus	L	-44	-74	32
		Middle occipital gyru	R	44	-74	32
		Precuneus	L	-14	-52	8
		Precuneus	R	14	-52	8
		Fusiform gyrus	L	-28	-40	-12
		FuG fusiform gyrus	R	28	-40	-12
		Parahippocampal gyrus	L	-22	-20	-26
		Parahippocampal gyrus	R	22	-20	-26
	Midline	Medial superior frontal	L	-6	52	-2
		Medial superior frontal	R	6	52	-2
		Precuneus	L	-8	-56	26
		Precuneus	R	8	-56	26
Salience		Anterior insula	R	36	16	4
		Anterior insula	L	-35	14	5
		Middle cingulate	R	8	18	34
		Anterior cingulate	L	0	26	20
		Supplementary motor cortex	L	-6	14	54
		Superior temporal gyrus	L	-52	-14	-8
		Lateral orbital gyrus	L	-36	46	-14
		Thalamus Proper	R	10	-16	6
		Thalamus Proper	L	-8	-12	8
		Thalamus Proper	R	6	-10	-2
		Entorhinal Area	R	26	4	-20
		Basal Forebrain	L	-28	4	-18

Semantic Appraisal Network	Temporal Pole	R	36	22	-34
	Temporal Pole	L	-36	22	-34
	Frontal Pole	L	-6	62	-18
	Anterior orbital gyrus	R	22	62	-15
	Anterior orbital gyrus	L	-20	59	-15
	Gyrus rectus	R	4	58	-20
	Gyrus rectus	L	-4	58	-20
	Subcallosal area	R	4	20	-15
	Subcallosal area	L	-3	16	-7