VALIDATION OF THE DYNAMIC AFFECT RECOGNITION TEST: BEHAVIOR AND ANATOMY IN NEURODEGENERATIVE DISEASE

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by

Anneliese E. Radke

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VALIDATION OF THE DYNAMIC AFFECT RECOGNITION TEST: BEHAVIOR AND ANATOMY IN NEURODEGENERATIVE DISEASE

Anneliese E. Radke
The PGSP-Stanford Psy.D. Consortium, Palo Alto University, 2015

Tests allowing fast but valid evaluation of emotion reading deficits at the bedside via ecologically-realistic modalities are an essential component of a comprehensive neuropsychological evaluation of neurodegenerative disease. Frontotemporal dementia patients show disproportionately impaired emotion comprehension, yet traditional picture-based emotion test show deficits in patients without real-life impairment. This dissertation validated the Dynamic Affect Recognition Test (DART), a quick, novel video-based test, as an assessment of affect naming. One hundred and sixty-eight participants underwent a magnetic resonance imaging (MRI) scan and were administered a battery of assessment measures that included the DART, other commonly used measures of affect naming, and general measures of social functioning. Results demonstrated that the construct validity of the DART for measuring emotion identification deficits in cognitively impaired patients. Convergent validity was demonstrated by the divergent, clinically predictable patterns of performance across neurodegenerative patient groups, as well as the similar intrasubject performance on the DART as on already established tests of emotional functioning. The DART correlated with separate but related socioemotional measures score, demonstrating the tests' discriminant validity. The DART's concurrent validity was established by showing a correlation between DART test performance and focal atrophy in brain systems known to mediate emotion reading and naming. We found a cut score of 9/12 is useful in making differential diagnosis discriminations. The

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DART attempts to remedy some limitations of other dynamic tests with dementia populations by simplifying stimuli and shortening the test. Further, the DART essentially eliminates many costs in that it is open sourced and freely available.

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Validation of the Dynamic Affect Recognition Test: Behavior and Anatomy in Neurodegenerative Disease

This dissertation by Anneliese E. Radke, directed and approved by the candidate's committee, has been accepted and approved by the Faculty of The PGSP-Stanford Psy.D. Consortium, Palo Alto University in partial fulfillment of the requirements for the degree of

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DEDICATION

I dedicate my dissertation work to my mother, my hero.

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CHAPTER I

INTRODUCTION

Behavioral syndromes caused by underlying neurodegenerative disease processes are difficult to accurately diagnose. Distinguishing neurodegenerative diseases from each other is a specialized process, dependent on careful consideration of specific and nuanced symptoms. This study focused primarily on the behavioral syndromes of frontotemporal dementia (FTD): behavior variant frontotemporal dementia and semantic variant primary progressive aphasia, which has been increasingly recognized as having two distinct clinical phenotypes associated with the initial hemisphere impacted (Coon et al., 2012; Chan et al., 2009; Edwards-Lee et al., 1997; Gorno-Tempini et al., 2004b; Josephs, et al., 2009; Miller et al., 1993; Rankin et al., 2006; Rosen et al., 2002; Seeley et al., 2005; Snowden et al., 2001; Thompson, Patterson, & Hodges, 2003). As such, an FTD phenotype characterized by predominant right temporal atrophy is referred to here as right temporal FTD and was also a focus of this study. Other neurodegenerative diseases commonly considered as an FTD differential diagnosis were highlighted as well, including nonfluent variant primary progressive aphasia (also categorized as an FTD subtype), Alzheimer's disease, and progressive supranuclear palsy.

Disease Descriptions

Frontotemporal dementia is a progressive neurologic disease that has historically been known by several names (e.g., Pick's disease, frontotemporal lobar degeneration). FTD is the term most commonly used, and refers to a heterogeneous group of clinical syndromes. Frontotemporal lobar degeneration (FTLD) is a term that refers to the pathological diagnosis. In this paper, the term FTD will refer to the four clinical subtypes collectively and described more fully below. The various FTD clinical syndromes are caused by progressive and selective

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degeneration of the frontal lobes, temporal lobes, or both, with varying degree of right and left hemisphere involvement. The posterior cortical regions remain relatively preserved (Rosen et al., 2002). The subtypes of FTD are characterized by the distinct associated neuroanatomical changes, as well as the assorted degrees of behavior and language deficits (Gorno-Tempini et al., 2011; Rascovsky, et al., 2011).

Behavioral variant FTD is associated with predominant bilateral degeneration of the frontal lobe (Rascovsky, et al., 2011). Here, it is referred to as bvFTD, though it has also been referred to as the frontal variant (fvFTD) or simply, FTD in the literature. The hallmark symptoms of bvFTD are behavioral and personality changes. Specifically, disinhibition, apathy, and the early loss of social and emotional cognition (i.e., ability to empathize) are prominent symptoms of this disease (Lough et al., 2006; Passant et al., 2005; Rankin, Kramer, & Miller, 2005; Rankin et al., 2006, Rascovsky, et al., 2011). Closely related to the underlying loss of social and emotion functioning include a loss of self-conscious emotions (e.g., embarrassment) (Sturm et al., 2006), depletion of theory of mind capabilities (Eslinger at al., 2005; Evers, Kilander, & Lindau, 2006; Lough et al., 2001; 2006; Torralva et a., 2007; Adenzato, Cavallo, & Enrici, 2010), decline in higher-order reasoning, such as awareness of deficit/insight (anosognosia) (Mendez et al, 2005; Rankin et al., 2005; Lough et al, 2006; Rosen, 2011), reward processing (Perry et al., 2014), and moral sensibility (Chiong et al., 2013). Other behavioral and personality changes listed in the bvFTD diagnostic criteria include altered eating and perseverative or stereotypes behaviors (Rascovsky, et al., 2011). Executive dysfunction tends to be a later symptom of bvFTD, as degeneration of the dorsolateral prefrontal cortex tends to occur later in the disease process (Seeley et al., 2008). However, the behavioral and personality

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changes resulting from the loss of social emotional processing can lead to poor decision-making and impaired judgment, which is often interpreted as impaired frontal executive functions.

With respect to specific neuroanatomical changes, bvFTD is associated with early and progressive degeneration of the anterior brain areas, including the anterior cingulate cortex, rostromedial prefrontal cortex, lateral orbitofrontal cortex, anterior insula, and the amygdala and brainstem regions (Rosen et al., 2002; Varrone et al., 2002; Seeley, et al., 2007ab, 2008, 2009). These structures together comprise the salience network, an intrinsically connected network (ICN) that is impacted early in the disease process and is associated with attentional allocation underlying social functioning (Seeley et al., 2007ab, 2008, 2009). ICNs such as the salience network are comprised of neuroanatomical structures with individual components that, when in combination, serve a unique cognitive or behavioral characteristic/function (i.e., emergent property) (Buckner et al., 2009; Yeo et al., 2011). Seeley et al. (2009) first linked atrophy patterns in neurodegenerative disease with patterns of large scale brain networks (i.e., ICNs). The authors describe the degenerative process and its association with ICNs as having a pathologic epicenter that "incite[s] the neurodegenerative cascade throughout the network" (p. 163). Social cognition, including one's ability to empathize, is likely related to salience ICN functioning (i.e., one must have the ability to recognize and attend to salient, socially meaningful signals to successfully function in the social world) (Rankin, Kramer & Miller, 2005; Rankin et al., 2006; Sollberger et al., 2009).

While bvFTD has initial predominant frontal degeneration, the temporal lobes are initially affected in the semantic and the right temporal variants of FTD. Focal and asymmetrical hemispheric involvement is frequent in svPPA, with the initial disease symptom distinct to the hemisphere first impacted. Predominant left temporal degeneration, associated with language

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impairment, is significantly more common than predominant right hemisphere involvement, in which the initial symptoms tend to be socially undesirable behaviors (Chan et al., 2001a,b; Evans et al., 1995; Gainotti, Barbier, & Marra, 2003; Galton et al., 2001; Gorno-Tempini et al., 2004a,b; Joubert et al., 2006 Mummery et al., 2000; Rosen et al., 2002; Seeley et al., 2005; Thompson et al., 2003, 2004;). Comparing left to right-sided predominance, one study found a rate of 3 to 1, respectively (Seeley et al., 2005). Mychack et al. (2001) found that 11 of 12 right predominant patients exhibited social behavior change as the initial symptom, compared to just 2 of 9 left predominant patients. Despite the clear behavioral differences exhibited by left and right predominant individuals early in the disease process, the two syndromes merge as the degeneration spreads bilaterally, and symptoms of both variants are evident after approximately 3 years (Seeley et al., 2005). Thus, by the time patients are evaluated, it can be difficult to discern which variant they originally presented.

The semantic variant of FTD is categorized as both a frontotemporal dementia and a primary progressive aphasia (PPA). Here, it is referred to as svPPA, although it is also referred to as semantic dementia (SD) and temporal variant FTD (tvFTD) in the literature. The hallmark clinical syndrome associated with left-sided temporal atrophy is characterized by early progressive language impairment, specifically deficits in naming, single-word comprehension, semantic knowledge, and object recognition (Hodges et al., 1992; Neary et al., 1998; Thompson et al., 2003; Seeley et al., 2005; Gorno-Tempini et al., 2011). svPPA is associated with left anterior medial and lateral temporal lobe atrophy (Gorno-Tempini et al., 2011). More specifically, the left temporal pole begins to degenerate early in the disease process, followed by ventromedial prefrontal cortex, subgenual anterior cingulate cortex, and ventral striatum (Seeley et al., 2005; Brambati et al., 2009).

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The right temporal variant of FTD was first described by Miller et al. (1993). Here, it is referred to as rtFTD. The hallmark clinical features include early and isolated personality changes related to deficits in emotion processing and ability to empathize (e.g., lack of interpersonal engagement). These deficits likely underlie the behavior changes exhibited by patients, such as obsessions and compulsions (e.g., crossword puzzles, clock watching), rigidity (e.g., adhering to a strict schedule), restricted food preferences, and loss of insight (Chan et al., 2012; Coon et al., 2012; Edwards-lee et al., 1997; Gorno-Tempini et al., 2004b; Henry et al., 2014; Josephs et al., 2009; Miller et al., 1993; Mychack et al., 2001; Perry et al., 2001; Rankin et al., 2006; Rosen et al., 2002, 2006; Seeley et al., 2005; Snowden et al., 2001; Thompson et al., 2003). For example, the insula is linked to feelings of disgust, and degeneration of the insula results in the rigid food preferences observed in rtFTD patients (i.e., misprocessing of disgust inputs) (Wicker et al., 2003; Seeley et al., 2005).

rtFTD degeneration originates in the right anterior temporal lobe, an area associated with social emotional processing and theory of mind (Adolphs, 2003; Andenzato et al., 2010; Irish, Hodges, Piquet, 2013; Rankin et al., 2006). Individuals with damage to this region often exhibit emotional blunting and lack interpersonal warmth (Rankin et al., 2006; Zhan et al., 2009; Eslinger, Moore, Anderson, & Grossman, 2011). As the disease progresses forward to the ventromedial and orbital frontal cortices, disinhibition, mental rigidity, and obsessions and compulsions become more prominent (Cummings, 1995; Volle, et al., 2002; Seeley et al., 2005). Problems with face recognition (prosopagonsia) observed in rtFTD are associated with degeneration of the inferior temporal cortex and surrounding areas, specifically the fusiform gyrus (Gainotti, Barbier, & Marra , 2003; Joubert et al., 2003, 2006; Thompson, et al., 2003; Snowden, Thompson, & Neary, 2004; Chan et al., 2009; Josephs et al., 2009; Busigny et al.,

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2014). Also noteworthy is the observation that some rtFTD patients develop a fresh interest and increased productivity in the arts (verbally, visually, musically) as a result of the asymmetric neurodegeneration of the anterior temporal lobe (Wu at al., 2015; Chatterjee, 2004; Miller et al., 1998).

Many of the same brain regions impacted in bvFTD are impacted in rtFTD (i.e., the salience ICN), likely explaining the many similarities in symptom presentation (Liu et al., 2004). Patterns of atrophy observed in rtFTD patients appear to additionally target brain structures comprising the right side of the semantic appraisal network (also referred to as the limbic network ICN). This ICN underlies one's semantic knowledge and, ultimately, social functioning, via the application of semantically rich, personalized hedonic evaluations. While the salience network allows an individual to accurately discern and attend to important social information, and the semantic appraisal network allows the individual to estimate personal value to guide behavior. This network is critical to functioning within interpersonal exchanges, and injury to this network results in the failure to evaluate contextual valances that guide social behavior. The semantic appraisal ICN has a hub in the anterior temporal pole, and connections to the dorsal anterior cingulate cortex, medial orbitofrontal and opercular cortices, along with the head of the caudate. Semantic knowledge of emotions and social concepts relies on the temporal pole, while deciding the personal value of various behavioral options relies heavily on the prefrontal cortex (Guo et al., 2013; Simmons et al., 2010; Zhou et al., 2010).

The nonfluent variant of FTD is also characterized as a PPA, as well as an FTD subtype. Here, it is referred to as nfvPPA, though it is also referred to as PNFA in the literature. Patients with nfvPPA tend not to exhibit the striking behavioral features of other FTD subtypes until significantly later in the disease process (Le Rhun, Richard, & Pasquier, 2005). In contrast, these

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individuals are apt to have impairment exclusively within the language domain early in the illness, specifically difficulty with the motoric articulation of speech (Gorno-Tempini et al., 2004). Individuals with nfvPPA tend to maintain a sharp awareness of their language deficits for most of the disease (Rosen, 2011). Behavior and personality changes, including changes in social functioning, generally develop only later in the disease process as degeneration spreads more globally (Mesulam et al., 2003). Although most nvfPPA patients progress toward a behavioral presentation that resembles bvFTD eventually (Le Rhun et al., 2005), it is less common for caregivers to describe a decline in emotional functioning or loss of social decorum in these patients initially. Neuroanatomical degeneration begins in the dominant frontal operculum, supplementary motor area, and dorsal insula, resulting in dysfluent, effortful, and aggramatic speech (Seeley et al., 2005; Gorno-Tempini et al., 2004, 2011; Josephs et al., 2006a,b).

Progressive supranuclear palsy (PSP) is a neurodegenerative disease with early features of progressive balance and gait instability, as well as axial rigidity. These issues result in remarkable falls, often backward, a relatively distinct symptom of PSP. Other hallmark symptoms include problems with eye movements (i.e., difficulties with vertical gaze, and later with horizontal gaze) (Colosimo et al., 1995), difficulties with swallowing, and apathy (Litvan et al., 1996a). Cognitive deficits can occur early in the disease process, though rarely occur at the disease onset (Litvan et al., 1996b). These include executive dysfunction, cognitive slowing, apraxia of speech, nonfluent aphasia, and mental rigidity (Bak et al., 2005; Boxer et al., 2012; Dubois et al., 1988; Gerstenecker et al., 2013; Josephs et al., 2006; Litvan et al., 1996c; Pillon et al., 1995; Steele et al., 1964). As such, PSP is often mistaken for FTD. PSP is also often misdiagnosed as Parkinson's disease (PD) (Litvan, 2007) due to the motor difficulties, or as a psychiatric condition due to the prominent apathy and depression exhibited by these patients.

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Early degeneration targets subcortical and brainstem structures, with little cortical atrophy (Boxer et al., 2006; Josephs et al., 2008).

Alzheimer's disease (AD) is the most common neurodegenerative disease, comprising approximately 50-80% of all dementia cases (Alzheimer's Association, 2014). Rapid forgetfulness (i.e., problems with memory formation, especially for newly learned information) is the hallmark symptom of AD. Other common features include anomia, visuospatial difficulties, and some executive dysfunction, such as problems with planning and organizing. The diagnostic criteria for AD (McKhann et al., 2011) allows for predominant impairment not only in memory, but in executive functioning, visuospatial skills, language, and behavior domains as well, rendering it a disease that can mimic almost any of the other neurodegenerative syndromes thus far described, perhaps especially FTD (Hornberger et al., 2008; Perry & Hodges, 2000). Varma et al. (1999) and Galton et al. (2000) describe the spectrum of AD presentations beyond an amnestic syndrome. AD patients as a whole can present with a range of behavior and mood symptoms, including those typically seen in FTD (i.e., apathy, obsessive and compulsive behaviors, and socially unacceptable behaviors) (McKhann et al., 2011). The entorhinal cortex, followed by the hippocampus, tend to be the first areas impacted in typical AD (Braak & Braak, 1991), though the more frontal and more posterior brain regions can be predominantly impacted early in the illness in more atypical presentations (Galton et al., 2000).

Prevalence Rates and Societal Costs

Prevalence rates for many neurodegenerative diseases are not well understood. The spectrum of FTD diagnoses in particular has poor epidemiological data, partly due to clinical diagnostic difficulties, such as incorrect diagnoses (Small et al., 1997). The overall prevalence of FTD may range from 15-22/100,000 (Ratnavalli et al., 2002), though this figure is likely

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underestimated. FTD is the third most common neurodegenerative dementia in all age groups (Brunnstrom et al., 2009), and the second most common in patients under the age of 65 (Ratnavalli et al., 2002; Onyike & Diehl-Schmid, 2013). bvFTD and rtFTD appear to have earlier onsets than the other FTD subtypes, with estimated mean age of presentations of 58 years (Johnson et al., 2005; Rosso at al., 2003) and 54 years (Josephs et al., 2009), respectively. Roberson et al. (2005) found that FTD as a whole progressed faster than AD, with a median survival time from a retrospectively determined symptom onset of 8.7 years (+/- 1.2), and median survival from initial clinic presentation of 3.0 years (+/- .5).

There has yet to be a systematic epidemiological study of FTD's overall cost to society. However, it is useful to estimate the financial impact by comparing FTD to AD, the latter of which has been more thoroughly researched. The Alzheimer's Association (2015) indicates that the average lifetime cost of caring for an individual with AD is $174,000. In 2015, the U.S. is projected to collectively spend at least $214 billion on AD, with this figure expected to increase to $1.2 trillion in 2050. It is of note that unpaid care is often not accounted for, or is undervalued in cost-of-care estimates. 15.4 million caregivers provided approximately 17.5 billion hours of unpaid care in 2012, estimated at $216 billion. Unfortunately, no published data is available regarding the lifetime care or collective impact to the individual and society (e.g., loss of income potential, lost productivity) for younger persons with dementia. The cost of FTD to individuals, their families, and society as a whole is likely higher than that for individuals with neurodegenerative diseases that begin in the later years of life (e.g., AD). FTD tends to hit individuals at a younger age during a highly demanding phase of life during which they may still have caregiving and financial responsibilities to families (Mendez, 2006), that may include both dependent children and older adult parents ("sandwich generation") (Abaya, 2014).

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Diagnostic Challenges of FTD and their Consequences

Accurate diagnosis of behavioral neurologic disorders is difficult and misdiagnosis of FTD subtypes is particularly common. For example, Rosness, Haugen, Passant, and Engedal (2008) found 71% of their FTD sample initially received a non-dementia diagnosis, compared to 30% of AD patients. The authors found an average of 49-59 months from estimated disease onset to diagnosis of FTD, with an average 23-34 months from initial medical doctor visit to correct diagnosis. Josephs et al. (2009) also found a mean duration of 4.1 years at initial assessment in a cohort of rtFTD patients. This prolonged time period before an accurate diagnosis is made is extremely concerning. The constellation of behavioral symptoms in FTD tends to cause significant disruptions to the individual and family long before a patient is seen by a specialist and behavioral management strategies are established.

Although unique in some ways, the many overlapping cognitive, psychiatric, and neurologic symptoms and features of the FTD subtypes with other diseases and disorders makes FTD particularly difficult to diagnose. Like other neurodegenerative diseases, the FTDs have an insidious onset and progressive decline in functioning. However, FTDs lack overt neurological signs that could help differentiate the disease (Mendez, 2006). Physical examination may yield little findings specific for FTDs as a whole, especially early in the disease process (i.e., there are typically no appreciable motor or language symptoms). Cognitive testing may also look relatively normal early in the disease process, despite severe behavioral changes. This is because neuropsychological tests of executive functioning place heavy demand on the dorsolateral prefrontal cortex, a structure that is spared until relatively later in the FTD disease process (Wittenberg et al., 2008). Even when cognitive testing indicates executive dysfunction, deficits are not distinguishing of affected brain area or disease. Although the frontal lobes are deemed the

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primary neural substrate of executive functioning, brain regions involved are diverse (Stuss, 2011; Stuss & Knight, 2002), including the anterior temporal lobes (Hornberger et al., 2011; Robinson et al., 2014) and parietal lobe regions (Collette et al., 2005; Koenigs, Barbey, Postle, & Grafman, 2009). Thus, diseases with little initial frontal lobe damage can still produce a dysexecutive presentation. Moreover, the dorsolateral prefrontal cortex is impacted in both AD and bvFTD (Rabinovici et al., 2008), and thus does not help differentiate the two diseases.

The relatively younger age of onset often results in FTD being completely overlooked by non-specialist clinicians who may mistake patients' behavior as simply eccentric, problematic, or indicative of a "mid-life crisis," as opposed to reflective of a neurodegenerative disease (Small et al., 1997; Chan et al., 2009). Many individuals with FTD are initially misdiagnosed as having a non-progressive psychiatric illness with typical onset in young adulthood (e.g., depression, schizophrenia, bipolar disorder) (McKhann et al., 2001; Passant, Elfgren, Englund, & Gustafson, 2005; Mendez et al., 2007). Woolley et al. (2011) found that approximately 50% of patients in their FTD cohort were initially misdiagnosed with at least one psychiatric illness prior to their clinical diagnosis of FTD, while Passant et al. (2005) found that the majority of the FTD patients in their sample were admitted to the psychiatric ward prior to receiving an accurate diagnosis. The striking changes in personality and social behavior in rtFTD (Passant et al., 2005) and disinhibited behavior in bvFTD renders these patient groups particularly vulnerable to misdiagnosis. For example, ritualistic behaviors often seen in rtFTD can be misinterpreted as symptoms of obsessive-compulsive disorder (Huey et al., 2008), and apathy and disorganized thinking patterns seen in bvFTD may be misdiagnosed as depression and schizophrenia (Mendez, 2006).

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Misdiagnosis may also result from features of FTD that overlap with symptoms of early onset dementias due to non-neurodegenerative etiologies. Patients initially evaluated and without multiple evaluations that would demonstrate the progressive course may be particularly at risk. For example, difficulty shifting (i.e., mental rigidity), disinhibition, emotional blunting, and apathy may mimic a traumatic brain injury. Slowed processing speed may be misinterpreted as a sign of vascular dysfunction (Mendez, 2006). Symptoms including language problems and disinhibition may be mistakenly linked to substance or alcohol-related disorders, as the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5) (American Psychiatric Association, 2013) criteria for substance use disorders include impaired ability to control behavior. Further, there is an established link between increased disinhibition and impulsivity and substance abuse (e.g., Verdejo-Garcia, Lawrence, & Clark, 2008).

Even if the potential for a progressive neurodegenerative disease is considered, distinguishing the FTD subtypes from each other and from other neurodegenerative conditions early in the disease process is challenging. Many of the hallmark symptoms of FTD are not specific to the disease. For example, behavioral disinhibition is present in a variety of common neurodegenerative conditions, including vascular dementia, Dementia with Lewy Bodies (DLB), and Parkinson's disease dementia (PDD), and AD (Johnson, Watts, Chapin, Anderson, and Burns, 2011). Patients with bvFTD are especially vulnerable to being misdiagnosed as early-onset AD. Although AD tends to hit individuals at a relatively later age than FTD (95% of AD cases begin after age 65) (Alzheimer's Association, 2014), early onset AD cases (symptom onset prior to age 65) can be especially difficult to distinguish from FTD for a variety of reasons. Young-onset AD patients tend to present with more atypical features (e.g., predominant executive dysfunction and/or word finding difficulties with relatively spared episodic memory)

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(Koedam et al., 2010; Galton et al., 2000; Varma et al., 1999). Although a core feature of FTD, apathy manifests across neurodegenerative diseases presentations, including AD, with prevalence estimates of apathy in AD patients as high as 48-80% (Burns, Folstein, Brandt, & Folstein, 1990; Starkstein, Jorge, & Mizrahi, 2006; Levy et al., 1998). Apathy is also a common feature of vascular dementia, PDD, and DLB, and is not useful in distinguishing FTD (Johnson et al., 2011; Shea, Ha, & Chu, 2014). Several studies have found that episodic memory can be impaired even in the earlier stages of bvFTD, even though as a group, memory tends to be better than in patients with AD (e.g., Bertoux et al., 2013; Graham et al., 2005; Hodges et al., 2004; Hornberger & Piguet, 2012; Pennington, Hodges, & Hornberger, 2011). Alterations in eating behaviors, a prominent symptom of FTD, is also common in AD. Ikeda et al. (2002) found that bvFTD, svPPA, and AD patients all exhibited changes in eating behaviors even though as a whole, the bvFTDs and svPPAs exhibited a clearer developmental pattern and course (i.e., changes in food preferences followed by changes in appetite and habits) than the ADs.

Neuroimaging is a critical part of the diagnostic process. The 2011 FTD International Consensus Criteria (FTDC) criteria (Rascovsky, et al., 2011) require neuroimaging proof of selective atrophy on MRI or hypometabolism on positron emission tomography (PET) scan to elevate the diagnosis from “possible” to “probable” bvFTD diagnosis. Imaging diagnostic criteria for svPPA includes predominant anterior temporal lobe atrophy on MRI and/or predominant anterior temporal hypoperfusion on SPECT or PET. Imaging criteria for nfvPPA includes predominant left posterior fronto-insular atrophy on MRI and/or predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET (Gorno-Tempini et al., 2011).

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Imaging alone does not provide a complete diagnostic picture and has inherent problems. Imaging may appear normal early in the disease process, may not initially distinguish FTD from AD, or may not delineate which FTD subtype is present. Without a series of images taken at different time points, imaging provides a single snapshot of brain structure without characterization of disease progression or spread. It is unusual for patients to have had a series of images taken by the time of their initial evaluation, rendering it somewhat difficult to discern the neuroanatomical progression. Seeley et al. (2005) note that the delayed time period between initial symptom presentation and assessment by specialist significantly impacts the ability to properly diagnose. Caregivers often do not initiate an evaluation until behaviors have exceeded their ability to cope and manage. As such, the disease has often progressed, and atrophy patterns may mimic other diseases on imaging. The degeneration may have spread bilaterally or may appear more global the longer the lapse in time before initial evaluation. For example, in the period of time between initial onset and imaging, temporal atrophy in FTD can spread toward posterior regions, which can resemble a more progressed AD imaging profile.

Inaccurate diagnoses increases the likelihood that FTD patients receive inappropriate treatment, including unnecessary and potentially harmful medications (Mendez et al., 2007; Passant et al., 2005; Woolley et al., 2011). For example, acetylcholinesterase inhibitors are commonly used in the treatment of AD and Vascular Dementia, but this treatment can in fact exacerbate symptoms of FTD (Greicius, Geschwind, & Miller, 2002). Another potential harm that can result from misdiagnosis includes missed opportunities to enroll in clinical treatment trials before the disease progresses to a more globally (Woolley et al., 2011). The lapse in time prior to accurate diagnosis further keeps patients and families from appropriate treatment planning and preparation for the future, including end of life care.

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Alterations in personality and behavior have broad-reaching implications, with particularly devastating impact on familial relationships and functioning. The behaviors associated with FTD make these individuals and their families especially vulnerable to family discord and caregiver distress (Chow, Pio, & Rockwood, 2011; Kasier & Panegyres, 2007; Sollberger et al., 2009). Wong et al. (2012) found that on average, when compared to families of Alzheimer's disease patients, bvFTD caregivers experience greater strain and distress, more depressive symptoms, and have lower perceived control. Families of younger dementia patients as a whole are at particular risk for family discord (Green, 1996; Kaiser, 2007), perhaps because of the prolonged time period before an accurate diagnosis is made. The behavioral changes including physical outbursts, embarrassment in social situations, and interpersonal coldness can be especially devastating for families with dependent children (Passant et al 2005). Merrilees et al. (2013) highlight an increase in caregiver distress associated with apathy. Srikanth, Nagaraja, and Ratnavalli (2005) found that patients with FTD demonstrate earlier impairments in activities of daily living than patients with AD, thus requiring increased caregiver assistance earlier in the disease process.

Individuals with FTD are at particular risk for engaging in behaviors with catastrophic outcomes in the period of time between symptom onset and proper diagnosis and treatment planning. Errors in budgeting and declines in financial management skills are often an initial red-flag for caregivers, sometimes only recognized after a particularly disastrous outcome (e.g., emptied retirement savings). Impaired decision-making and judgment of risk/reward and punishment (Torralva et al., 2007; Perry et al., 2014; Perry & Kramer, 2014), as well as impaired ability to understand insincere communication (i.e., sarcasm and lies) (Rankin et al., 2009; Shany-Ur et al., 2012) renders individuals overly trusting and susceptible to financials scams

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(Rosen at al., 2005). For example, Passant et al. (2005) describe FTD patients giving away significant amounts of money to strangers and/or others engaging in pathological gambling. Given the lack of judgment and problems with impulse control, safety is a serious concern, particularly related to driving, cooking, and medication management. Early diagnosis is imperative to ensure that critical interventions occur, such as financial guidance and driving safety (Piget et al., 2011), physical security of the home, and early retirement if the patient is still working (Talerico & Evans, 2001).

Individuals with FTD tend to have poor self-awareness or insight as regards their condition (Rosen, 2011). As such, informant report (Mendez, Anderson, & Shapira, 2005) and behavioral observations are critically important to the diagnostic process. However, the reliability of information provided by caregivers can be of variable quality (Heun et al., 2000; Verweij, et al., 2011). Understanding the initial symptom is often the most helpful in the diagnostic process. However, as Seeley et al. (2005) note, informants may report the most striking symptom, as opposed to the earliest sign of illness. There are also times when an informant is not available or does not provide reliable information (e.g., has not known the patient prior to disease onset, may have personal biases or objectives, or may be an unreliable historian). Thus, more objective and standardized measures are an essential piece of the diagnostic process.

A striking and disproportionate decline in social emotion functioning is a distinct symptom of FTD. Not only is an alteration in emotional functioning a distinct symptom of FTD, it is often the very first symptom reported by families. For example, families often describe the affected individual as “not the same person anymore,” detailing changes in emotional functioning and a “cold” demeanor (Passant et al., 2005; Rankin et al., 2008). This emotionally

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distant presentation may be, at least in part, a reflection of changes in one's ability to recognize (and thus appropriately respond to) the emotional state of the other. Decety (2011) describes empathy as reflecting a critical aspect of human social exchange, comprising the capacity of sharing and comprehending the subjective experience of someone else. Rankin et al. (2005) found that when compared to healthy individuals and patients with AD, individuals with FTD show significantly diminished levels of real-life empathy, as measured by a questionnaire completed by caregivers. Further, the authors found that AD patients' empathy remains intact and the same as healthy controls. Thus, measuring a patient's social and emotional functioning through identifying their ability to be empathic is critical to differentiating FTD from other diseases processes, such as AD.

Empathy is a complicated construct, typically conceptualized as having both cognitive and emotional components (Cliffordson, 2002; Davis, 1983; Eslinger, 1998). The cognitive elements of empathy include identifying another's emotional state, such as possible factors that contribute to that person's affective experience (i.e., why they feel the way they do). Further, cognitive empathy demands attention and working memory, abstract reasoning, theory of mind and perspective taking, and mental flexibility. The affective elements of empathy include a level of emotional joining or sharing with the other person. There is a demand for recognition of others' emotions, emotional responsiveness, correctly identifying one's own emotional state, and offering of emotional expression (Rankin et al., 2005, 2008; Sollberger et al., 2010). In short, empathic capacity includes the ability to take another's perspective and have enough empathic concern to "share" the experience without "catching" their emotional state, ultimately facilitating a prosocial response/action. Changes in an individual's capacity to feel and express empathy tend to be some of the most distressing to families (Massimo et al., 2009; Massimo, Evans, & Benner,

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2013), likely because of the significance of empathic expression in interpersonal interactions. Rankin et al. (2005) describe the importance of empathy:

> The capacity to have an empathic response to another person is one of the most important elements of higher social functioning… empathy is self-reinforcing for both the responder and the recipient and allows social relationships to be experienced as inherently enjoyable and meaningful, even beyond any material benefits such relationships provide. (p. 28)

Sollberger et al. (2010) also highlight the importance of accurate perception of social signals in navigating the social world, noting that accurate evaluation of these cues first involves the recognition of the salience of environmental inputs, and then recognition of the other's affect and subjective experience of emotion. Thus, affect recognition, a core component of social functioning (specifically empathy), is one way to measure this fundamental component of social cognition. With improved diagnostic measures of this construct, catastrophic outcomes can possibly be averted via early diagnosis that is more accurate, with associated improved quality of care and treatment.

Current Measures of Affect Naming

Current diagnostic assessments of the ability to name emotion have proven to poorly differentiate disease processes. Traditional measures involve subjects viewing single static photographs of a person's face, and being asked to choose the label of the affect displayed from an array of choices, as in Ekman and colleague's *Pictures of Facial Affect series* (Ekman and Friesen, 1976) and the *Social Cognition and Emotional Assessment* (SEA, Funkiewiez et al., 2012). However, these tests of emotion reading may not distinguish disease processes well. In fact, individuals with FTD show disproportionately impaired emotion comprehension in their

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daily lives, but traditional emotion tests do not capture this difference in real-life impairment. AD patients seem to have preserved social affect naming abilities relative to their general cognitive ability (Bucks & Radford, 2004) and may even have heightened emotion sensitivity in the real world (Sturm et al., 2013). However, standardized testing does not always demonstrate this important difference in social emotion cognition. Bediou et al. (2009), for example, found that mildly demented AD individuals, as well as patients with FTD, were impaired in facial expression detection on a measure using static images.

The use of static facial expressions as a measure of emotion recognition has been called into question as an ecologically-valid task (Henry et al., 2008; Roark, Barrett, Spence, Abdi, & O'Toole, 2003). For example, using both static and voice prosody measures, Cadieux and Greve (1997) found preserved emotional processing functioning in ADs using the prosody task, but impaired affect processing using the static facial image task. The authors noted that static photographs may not be "as emotionally rich" (p. 418) as the other measures they used in their study, and question whether the difference in results is related to the use of a more ecologically-valid instrument (prosody) versus the static picture. Likewise, Hargrave, Maddock, and Stone (2002), who used static images in their study of emotion processing in ADs, also make note of the possibility that "facial photographs lack important dynamic information the AD patient needs to more accurately interpret facial expressions" (p. 70). The authors further note that future studies using videotaped emotion expression could address the issue. Baez, Manes, and colleagues' (2014) found that tasks depicting real-life scenarios had greater sensitivity with bvFTD patients than other commonly-used measures, such as self-report questionnaires. The authors highlight the importance of incorporating more ecologically-valid measures of empathy into clinical practice. Bucks and Radford (2004) also call for more investigation into ecologically

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valid emotion stimuli following their study of emotion processing in AD using both static and voice prosody tasks.

Social perception is a critical component of social competence. Thus, there is a need for assessment tools that are simultaneously sensitive to deficits of social perception, as well as predictive of real-world impairment (McDonald, 2004). A dynamic measure of social emotional cognition may better detect deficits early in the disease process than traditional static assessments. *The Awareness of Social Inference Test* (TASIT-2) (McDonald et al., 2002, 2003) is one such dynamic assessment of individuals' social perception (i.e., ability to understand and interpret social information). It is divided into three subtests (emotional evaluation test, test of social inference-minimal, and test of social inference-enriched). The emotional evaluation subtest (EET) evaluates emotion recognition using video-based examples of two people interacting. This assessment has been used extensively as a measure social functioning in neurodegenerative disease (e.g., Baez et al., 2014; Goodkind et al., 2012; Henry et al., 2008; Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009; Kumfor et al., 2011, 2014; Rankin et al., 2009; Shany-Ur et al., 2012) and TBI populations (McDonald et al., 2003). Although the dynamic nature of the assessment may improve diagnostic accuracy as compared a static modality, there are some limitations of the measure (e.g., length of test, characteristics of actors).

Goal of Study

The goal of this study was to demonstrate the construct validity of the DART for measuring emotion identification deficits in cognitively impaired patients. We hypothesized that DART performance would show divergent, clinically predictable patterns across neurodegenerative patient groups, which would support its convergent validity. We also

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hypothesized that subjects will perform similarly on the DART as on already established tests of emotional functioning, which would further support the convergent validity of the DART.

We hypothesized that the DART's discriminant validity would be demonstrated by a moderate correlation to separate but related socioemotional measures such as behavioral empathy, neuropsychiatric symptoms, and depression. Measures that are very similar to emotion reading were expected to have a higher magnitude of correlation with the DART total score, while more general measures of social functioning or behavior were expected to have smaller magnitude correlations.

The concurrent validity of DART performance would be demonstrated by showing a correlation between DART test performance and focal atrophy in brain systems known to mediate emotion reading and naming. We hypothesized that these brain regions would include language and emotion reading areas, which would suggest that the DART is, in fact, measuring emotion naming.

Finally, a further goal of the study was to provide more information about the effectiveness of the DART in making differential diagnosis discriminations, specifically by examining cut scores.

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CHAPTER II

METHOD

Participant Inclusion and Exclusion Criteria

To be included in this study, individuals must have met diagnostic research criteria for 1 of 6 diagnoses: 1 of 4 frontotemporal dementias (bvFTD, svPPA, nfvPPA, or rtFTD) (meeting the FTDC research criteria (Rascovsky et al., 2011)), Alzheimer's disease (meeting National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NIA-AA) research criteria (McKhann et al., 2011)), and progressive supranuclear palsy (meeting Litvan3 research criteria (Litvan et al., 1996a; Boxer et al., 2006)). Diagnoses were derived by a multidisciplinary team comprised of neurologists, neuropsychologists, psychiatrists, and nurses. Participants who were clinically diagnosed with svPPA who had a primary behavioral syndrome were classified as rtFTD in this study. Participants who were clinically diagnosed with bvFTD were then run through a subgroup classifier based on the work by Ranasinghe, Rankin, and colleagues (*under review*). If there was significant temporal damage (frontotemporal), these patients were classified as rtFTD in this study. If there was predominant frontal damage, they were classified as bvFTD in this study. To be included in the voxel-based morphometry (VBM) analysis, patients must have had a 3T MRI scan within 3 months of the DART administration and must have had a Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score of 7 or above. Finally, participants must have had an informant available with who they are in close contact and who has known the individual for at least five years to answer questions to corroborate the clinical history.

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Subjects were excluded from this study if they did not meet the above inclusion criteria. Other subjects who were administered the DART but were not included in this study included those with a diagnosis with mixed or unclear clinical presentation (i.e., mild cognitive impairment, non-amnestic type (MCI)). Likewise, subjects were excluded if their diagnosis was one that did not fit with a VBM analysis (i.e., Dementia with Lewy bodies (DLB), Amyotrophic lateral sclerosis (ALS), and MCI), or if the number of participants within that diagnostic group was too small (i.e., Corticobasal Syndrome (CBS) and ALS). A participant was excluded if he/she was initially screened into the study with one of the six diagnoses of interest, but the diagnosis later changed after evaluation by the multidisciplinary clinical team and they no longer met research criteria.

Normal control subjects were included only if they passed a phone screen ruling out current or historical physical and psychiatric health problems and substance abuse. Participants must have had proficient English language fluency to be accepted and must also have had an informant available with whom they are in close contact and have known for at least 5 years. Normal control subjects must have had a Clinical Dementia Rating Scale (CDR, Morris, 1993) score of 0, MMSE score equal to or greater than 28/30, and delayed memory performance equal to or greater than the 25th percentile in both verbal and visuospatial domains. Normal control patients were included in the VBM analysis only if they had had a 3T MRI image within 1.5 years of DART administration.

Participant Demographics

All subjects with neurodegenerative disease were recruited and tested over approximately 2-years out of a larger center-wide recruitment pool of patients enrolled in observational research studies at the University of California San Francisco Memory and Aging Center. One-hundred

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and sixty-eight subjects (83 male, 85 female) were included in this study. 153 subjects underwent 1-1.5 hours of neuropsychological testing and had a 3T MRI scan within the allowed time period. Two subjects' MRI scans were excluded from the VBM analysis due to issues with the preprocessing of scans and 15 subjects were either not administered an MRI due to medical (pacemaker) or administrative reasons, or their scan date was outside the allowed time period for this study. 22 bvFTD, 12 svPPA, 13 nfvPPA, 12 rtFTD, 39 AD, and 11 PSP patients are included in the study, with an average of 5.7 days (standard deviation of 13.8) between DART administration and MRI scan.

59 normal control (NC) subjects were recruited from the San Francisco Bay Area through advertisements in local newspapers and recruitment talks at local senior community centers. Interested individuals underwent a phone screen for history of physical and psychiatric health problems and substance abuse, medical status, and level of English fluency. Individuals who passed the phone screen were then administered a 1 hour neuropsychological evaluation, routine labs, and brain MRI, all of which were reviewed by a multidisciplinary team (neurologist, neuropsychologist, nurse) to verify the individual met criteria to be a healthy control. The average amount of time between DART administration and MRI scan was 288.8 days (standard deviation of 254.9). A larger interval between testing and MRI scan (i.e., within one year) was permitted for normal controls because by definition they are not undergoing rapid changes in brain or behavior, ensuring reasonable correlations for VBM. Older normal control subjects are followed by the larger center-wide study and re-evaluated yearly to confirm they continue to qualify as a healthy control. A normal controls subject whose status as a healthy control changed for whatever reason (e.g., received an updated diagnosis of MCI or neurodegenerative disease) is identified in the research database (and by default excluded from this study).

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Participants included in this study range in age from 41 to 90 years with a mean of 67.0 (SD=8.8). The majority of the participants are white (89.3%), followed by Asian (5.4%), Latino/Hispanic (3.0%), mixed/other (1.2%), and unknown (1.2%). The mean level of education is 17.1 years (SD=3.0). MMSE scores across participant groups range from 7 to 30, with an average of 25.3 (SD=5.3). The average CDR total score is 0.64 (SD=0.64), while the CDR box score ranges from 0 to 14, with a mean score of 3.4 (SD=3.4). Geriatric Depression Scale (GDS) scores range from 0 to 26, with a mean score of 6.0 (SD=5.8). This research was subject to approval by the University of California, San Francisco Committee for Human Resources Independent Review Board. In all cases, informed consent was gained from the patient or the primary caregiver. Table 1 summarizes group demographics comparisons.

Table 1

Participant Demographics: Means

	Normal controls	Alzheimer's disease	Behavioral-variant FTD	Right-temporal FTD	Semantic variant PPA	Nonfluent variant PPA	Progressive supranuclear palsy
N	59	39	22	12	12	13	11
Age	71.4(7.0)	65.5(9.7)*	59.7(7.9)*	63.3(6.4)*	63.2(6.5)*	70.2(9.1)	68.5(6.3)
Gender (% female)	50.8	43.6	50	58.3	58.3	46.2	63.6
Education	17.7(2.3)	16.0(2.8)*	18.1(4.1)	16.5(3.0)	16.8(6.3)	17.8(4.1)	16.0(2.3)
MMSE	29.4(0.9)	20.9(4.8)*	23.3(4.8)*	26.3(2.7)	22.2(8.1)*	24.5(5.1)*	26.5(3.8)
CDR Total	0(0)	0.9(0.6)*	1.3(0.7)*	1.0(0.5)*	0.7(0.5)*	0.5(0.3)*	0.8(0.5)*
CDR Box	0(0)	5.0(2.7)*	7.3(3.1)*	5.4(3.1)*	3.5(2.5)*	2.0(1.6)*	4.4(2.6)*
GDS	2.5(3.3)	7.6(5.6)*	9.4(7.3)*	6.6(7.8)	7.8(4.2)*	5.9(3.7)	11.0(5.9)*

* Differed from controls at $p<0.05$
Means(Standard Deviation)

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Measures

Social cognition tasks. The Dynamic Affect Recognition Test (DART): The DART is a video-based measure comprised of 12 20-second vignettes of an actor expressing one of the six basic emotions (happy, surprised, sad, angry, fearful, disgusted) (Ekman, 1984, 1992a,b, 1993) via ecologically realistic and congruent facial, vocal, and postural cues, and with semantically neutral scripts. Each vignette involves one actor. For this study, videos were presented on a computer, with subjects watching instructions on the screen first. Subjects watch the vignette video and are asked to identify the emotion being portrayed from a randomized visual array. The person can answer by either pointing/touching their response on the screen on verbally stating their answer to the examiner, who then records their response. Videos comprising the DART were coded via the Facial Action Coding System (FACS) (Ekman & Friesen, 1978) to ensure valid and reliable emotional expression. The FACS is a standardized system to classify the physical appearance of emotions.

The Emotion Evaluation Test (EET), a subtest of the Awareness of Social Inference Test (TASIT) (McDonald et al., 2003): The TASIT EET is video-based measure comprised of 28 vignettes of actors depicting 1 of 7 emotions. There are sometimes two actors involved in the scene. In this study, we used an abbreviated 14-item version of the test. Subjects are asked to choose the emotion displayed by the actor (happiness, surprise, anger, sadness, fear, disgust or neutral) via a pencil and paper multiple-choice response sheet.

Modified Comprehensive Affect Testing System Affect Matching Test (CATS) (Froming et al., 2006): The affect matching subtest of the CATS is a computerized test of unimodal emotion naming comprised of visual stimuli (a subset of black and white static facial images from the Pictures of Facial Affect series (Ekman and Friesen, 1976)). The subject views one

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image at a time and is required to choose one of seven characters that match a target character based on emotional expression (happy, sad, angry, surprised, disgusted, frightened, neutral). In this study, we used a modified, shortened 16-item version of the CATS, on which the stimuli were presented in paper format, as opposed to computer-based. In this study, the subject viewed a paper copy of the stimuli and the examiner recorded the subject's answer via pencil and paper.

Neuropsychological tests. A neuropsychological battery comprised of screening measures assessing various aspects of cognition, including general mental status, memory, language, visuospatial, and executive functioning abilities was administered to all subjects as part of their participation in the larger center-wide study. Tests included in this study from the larger test battery were the MMSE (a gauge for global cognitive functioning), the Geriatric Depression Scale (GDS) (a depression screen), and the Boston Naming Test (BNT) (a naming task of non-emotion stimuli) (Kaplan, Goodglass, & Weintraub, 1983).

Questionnaires completed by participants' informants. Interpersonal Reactivity Index (IRI) (Davis, 1980): The IRI is a 28-item questionnaire completed by an informant that includes four 7-item subscales measuring various characteristics of empathy. The subscales include perspective taking (PT), empathic concern (EC), personal distress (PD), and fantasy (FS). Informants rate how well each of 28 statements reflects the subject's current behavior on a scale of 1 (does not describe at all) to 5 (describes very well). The total score can range from 7 to 35. In this study, the PT and EC subscales were analyzed, which are most associated with real-life social functioning (Davis, 1983; Rankin et al., 2005). The PT scale assesses ability to consider or imagine the perspective of others. The EC scale assesses the propensity of the individual to be emotionally affected and/or concerned about others in distress or suffering.

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Neuropsychiatric Inventory (NPI) (Cummings et al., 1994): The NPI measures the existence and severity of ten behavioral disturbances that commonly occur in individuals with dementia. In this study, we analyzed the presence and severity of scales that are relevant or reflect real-life behaviors that might be related to emotion reading (disinhibition, euphoria, apathy, agitation, depression, anxiety, irritability, and eating changes). A behavior that is not present is scored as 0, while items that are rated as present are given a score that ranges from 1 (least severe) to 3 (most severe).

The Clinical Dementia Rating Scale (CDR) (Morris, 1993): The CDR is a rating scale comprised of scores derived from a semi-structured interview with a caregiver. The scale assesses a patient's cognitive functioning in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. A total box score (i.e., sum of box scores) is derived from the sum of ratings of each individual domain, while a global score is computed via the measure's scoring rules and can range from 0 (no dementia) to 3 (severe dementia).

Magnetic resonance imaging (MRI). MRI scans were obtained on a 3-T Magnetom VISION system (Siemens, Iselin, NJ) equipped with a standard quadrature head coil. A volumetric magnetization prepared rapid gradient echo MRI (MPRAGE, TR/TE/TI = 10/4/300 ms) was used to obtain T1-weighted images of the entire brain, 15_ flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 ·1.0 mm2 in-plane resolution and 1.5 mm slab thickness.

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Data Analysis

We took a number of approaches to demonstrate the construct validity of the DART, i.e., the ability of the DART to produce an observable measure of emotion reading capacity in patients and controls.

For our hypothesis testing, an analysis of group differences on potential confounds (age, sex, education, MMSE score) was conducted to identify covariates that were then included in later analyses. Also, the DART total score and other salient variables underwent regression diagnostics to identify inappropriately influential data points, as well as to examine the normality, heteroscedasticity, and multicollinearity of residuals. This analysis also allowed us to show the convergent validity of the DART by determining if it produces results consistent with known patterns of emotion recognition symptoms in patients. Diagnostic group differences on DART performance (total score) was evaluated using a general linear model (SAS PROC GLM), adjusting for confounds, with Dunnett-Hsu post-hoc tests comparing each diagnostic group to the NC group.

Convergent validity of the DART was further evaluated by measuring the degree to which DART total score performance in the same group of subjects correlates with other measures of emotion recognition (TASIT-EET and CATS), using partial correlations (adjusting for confounds).

Discriminant validity was evaluated by looking at the correlation between more general social and neuropsychiatric symptoms (IRI, NPI, and GDS) and the DART total score performance.

We examined concurrent validity of DART performance by identifying the brain-behavior relationships underlying DART test performance. We performed a whole brain analysis

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of atrophy patterns corresponding to individual differences in DART performance. To do this, we performed a voxel-based morphometry (VBM) analysis of gray matter maps derived from 3-Tesla structural MR scans of subjects who were administered the DART. First, MR images were preprocessed (inspected for movement artifact, corrected for bias field, and segmented into gray matter, white matter, and cerebrospinal fluid) using the default parameters of the Statistical Parametric Mappings (SPM8) software package (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm), running on Matlab R2014a (MathWorks, Natick, MA), for spatial normalization, segmentation, modulation and smoothing. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox was used to warp each participant's image to a custom healthy-aging template to optimize inter-subject registration. Then, DARTEL-processed gray matter images were smoothed with an 8 mm full-width at half-maximum kernel prior to analyses. All images were processed in a single batch and were manually curated for accurate segmentation. VBM analysis was performed using a covariates-only design matrix with DART score as the primary correlation, with the following covariates: age, sex, MMSE score (to account for individual variability in disease severity), and total intracranial volume (TIV) as nuisance covariates [1 0 0 0 . . .]. The threshold for family-wise error correction ($pFWE<0.05$) was determined from the study-specific error distribution of T-values derived from 1000 Monte-Carlo permutations of the analysis. For a secondary analysis to evaluate the DART's ability to predict brain volume independent of non-emotional naming ability, DART score was evaluated against gray matter volume controlling for total score on the Boston Naming test, with the same nuisance covariates.

To provide more information about the effectiveness of the DART in making differential diagnostic discriminations, as well as to determine appropriate score cutoffs to be used in those

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discriminations, receiver-operating characteristic (ROC) analyses were performed. Area under the curve (AUC) derived from to test the accuracy of the DART in dementia groups versus healthy controls. Sensitivity and specificity thresholds for patient classification were derived from these ROC plots and 2x2 contingency table analyses in order to determine appropriate cutoff scores for these pairwise discriminations. In this study, sensitivity (also called true positive rate) refers to the chance that a DART score of 9 will accurately identify the patients within an identified group (e.g., a score of 9 will accurately discriminate dementia versus healthy controls). Specificity (also called true negative rate) refers to the chance patient that do not fit within an identified group are accurately identified as such (e.g., a healthy control will not be identified as a dementia patient). See Figure 1 for example 2x2 sensitivity, specificity, accuracy table.

	Dementia Diagnosis	Healthy Control	
Score of 9 or less	a	b	a + b
Score above 9	c	d	c + d
	Sensitivity= a + c	Specificity= b + d	Total (t)
	Accuracy = (a+d)/t		

Figure 1. Example 2x2 sensitivity, specificity, accuracy table.

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CHAPTER III

RESULTS

Analysis of Subject Characteristics

The seven diagnostic groups (normal controls (NC), behavioral variant FTD (bvFTD), right temporal FTD (rtFTD), semantic variant PPA (svPPA), nonfluent variant PPA (nfvPPA), progressive supranuclear palsy (PSP) and Alzheimer's disease (AD)) were compared across demographic and clinical characteristics. Table 1 summarizes these group comparisons. The proportion of males and females was not statistically different across the seven diagnostic groups (X^2 =2.2, p>0.9). There was no statistically significant different in years of formal education (F=2.2, p>0.043), with the exception of ADs (16.0 ± 2.8 [(M ± SD)]), who had an average of approximately 2 years less education than NCs. The groups differed in age (F=7.1, p<0.001). The NC and the nfvPPA were the oldest groups, aged 71 and 70 on the average (NC: 71.4 ± 7.0; nfvPPA: 70.2 ± 9.1), and the bvFTDs was the youngest group, aged 60 on average (59.7 ± 7.9). Four groups differed in age significantly from NCs: bvFTDs, svPPAs (63.2 ± 6.5), rtFTDs (63.3 ± 6.4), and ADs (65.5 ± 9.7). As expected, patient groups had significantly lower MMSE scores than controls (F=20.2, p<0.001). NCs had an average score of 29 (29.4 ± 0.9) while 4 patient groups were significantly lower [nfvPPAs (24.7 ± 5.1), bvFTDs (23.3 ± 4.8), svPPAs (22.2 ± 8.1), and ADs (20.9 ± 4.8)]. Also, all patient groups had significantly higher CDR total scores (F=27.3, p<0.001) and CDR box scores (F=36.1, p<0.001) than controls. Per inclusion criterion, all NCs had a CDR total score and CDR box score of 0. bvFTDs showed the most impairment in both CDR total score (1.3 ± 0.7) and CDR box score (7.3 ± 3.1). Patient groups also had significantly higher GDS scores compared to NCs [(2.5 ± 3.3); PSPs (11.0 ± 5.9), bvFTDs (9.4 ± 7.3), svPPAs (7.8 ± 4.2), and ADs (7.6 ± 5.6)].

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Diagnostic Group Differences in Emotion Naming Test Performance

An omnibus analysis of variance using a general linear model, adjusting for sex, age, and MMSE, showed statistically significant diagnostic group differences in subjects' average scores on the DART total ($F=18.4$, $p<0.001$), with large effect size ($\eta_p^2=0.43$). See Table 2 and Figure 2 for summary of the least square means (LSM) DART performance having adjusted age, gender, MMSE and Table 3 and Figure 3 for summary of disease group performance comparisons across affect naming tests (percent correct). Pairwise comparisons indicated mean group differences in affect naming abilities, as measured by the DART. All groups performed significantly worse than NCs (9.4 ± 0.3) on the DART ($p<0.05$) based on a post-hoc Dunnett-Hsu test [rtFTDs (6.1 ± 0.5, $p<0.001$), bvFTDs (6.7 ± 0.4, $p<0.001$), svPPAs (6.7 ± 0.5, $p<0.002$), PSPs (7.5 ± 0.5, $p<0.012$), and nfvPPAs (7.7 ± 0.5, $p<0.016$)] with the exception of ADs (8.7 ± 0.3, $p<0.6$).

An omnibus analysis of variance using a general linear model, adjusting for sex, age, and MMSE, showed statistically significant diagnostic group differences in subjects' average scores on the TASIT-EET ($F=23.48$, $p>0.001$) with large effect size ($\eta_p^2=0.49$). Pairwise comparisons indicated mean group differences in affect naming abilities, as measured by the TASIT. Groups that performed significantly worse than NCs (10.6 ± 0.3) on the TASIT-EET ($p<0.05$) included rtFTDs (6.2 ± 0.7, $p<0.001$), bvFTDs (7.6 ± 0.5, $p<0.001$), and svPPAs (7.9 ± 0.7, $p<0.002$). PSPs (9.8±0.6, $p<0.780$), nfvPPAs (9.7± 0.6, $p<0.722$), and ADs (9.2±0.4, $p<0.087$) did not perform significantly different from NCs on the TASIT-EET.

An omnibus analysis of variance using a general linear model, adjusting for sex, age, and MMSE, showed statistically significant diagnostic group differences in subjects' average scores on the CATS ($F=6.58$, $p>0.001$), with medium effect size, ($\eta_p^2=0.24$). The bvFTDs (9.9 ±0.7, $p<0.028$) was the only group that performed significantly different from the NCs (12.4 ± 0.5).

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Notably, the ADs performed the same as the NCs (12.4±0.5, p<1.0), and the nfvPPAs (11.4±0.8, p<0.844), PSPs (10.9±0.8, p<0.480), rtFTDs (10.8 ±0.8, p<0.373), and svPPAs (12.8 ± 0.8, p<.997) performances were also not statistically different from NCs.

Table 2

Mean DART Performance

	DART Total Score	TASIT-EET	CATS
Normal controls	9.4(0.3)	10.6(0.3)	12.4(0.5)
Alzheimer's disease	8.7(0.3)	9.2(0.4)	12.4(0.5)
Behavioral-variant FTD	6.7(0.4)*	7.6(0.5)*	9.9(0.7)*
Right-temporal FTD	6.1(0.5)*	6.2(0.7)*	10.8(0.8)
Semantic variant PPA	6.7(0.5)*	7.9(0.6)*	12.8(0.8)
Nonfluent variant PPA	7.7(0.5)*	9.8(0.6)	11.4(0.8)
Progressive supranuclear palsy	7.5(0.5)*	9.7(0.6)	10.9(0.8)

Least Square Mean(SE)
* Differed from controls at p<0.05
**Adjusted sex, age, MMSE

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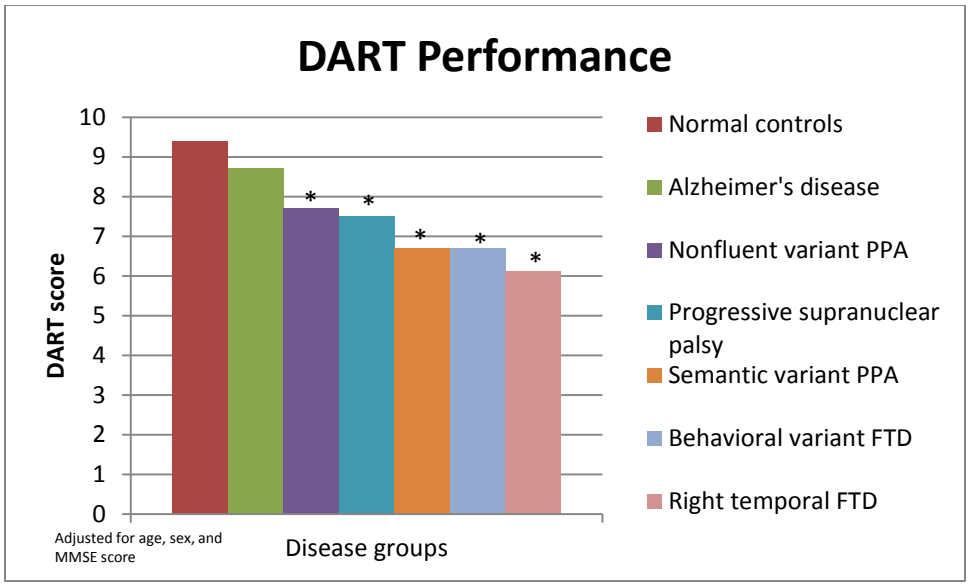

Figure 2. Mean DART performance.

Table 3

Affect Naming Test Performance: Percent Correct

	DART Total Score (max score = 12)	TASIT-EET (max score = 14)	CATS (max score = 16)
Normal controls	78.3(2.5)	75.7(2.1)	77.5(3.1)
Alzheimer's disease	72.5(2.5)	65.7(3.6)	77.5(4.4)
Behavioral-variant FTD	55.8(3.3)	54.3(3.6)	61.9(4.4)
Right-temporal FTD	50.8(4.2)	44.3(5)	67.5(5)
Semantic variant PPA	55.8(4.2)	56.4(4.3)	80.0(5)
Nonfluent variant PPA	64.2(4.2)	70.0(4.3)	71.3(5)
Progressive supranuclear palsy	62.5(4.2)	69.3(4.3)	68.1(5)

Percent Correct(Standard Error)

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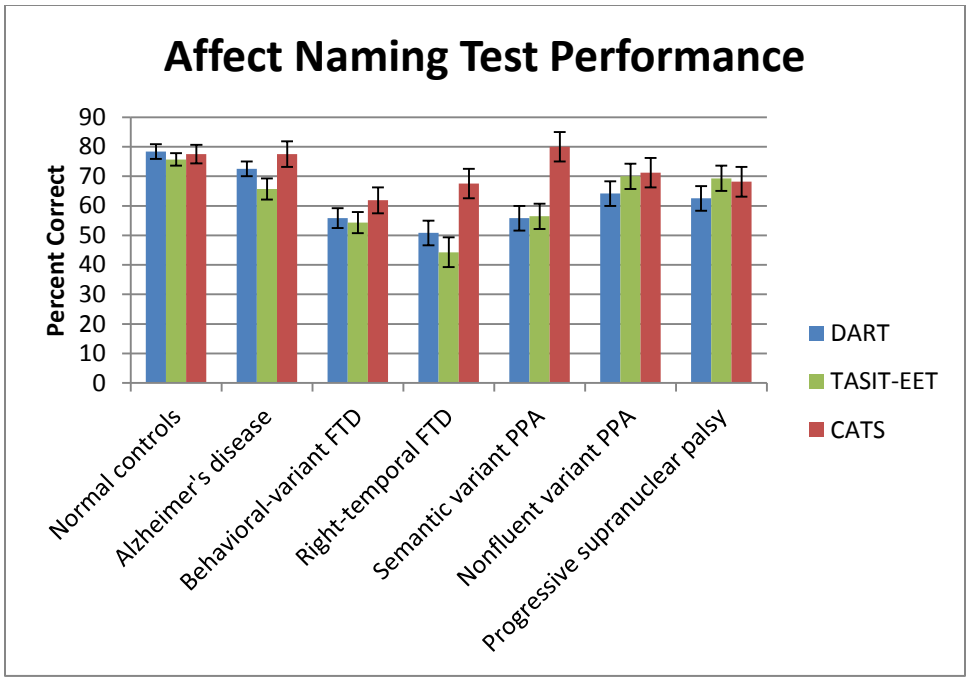

Figure 3. Affect naming test performance: percent correct.

DART Correlations with Tests of Emotion Naming and Measures of General Social and Neuropsychiatric Symptoms

The DART was strongly positively correlated with the TASIT-EET (r=0.6, p>0.001), with a large effect size (η_p^2=0.57). The DART was moderately positively correlated with the CATS (r=0.3, p>0.002), with a large effect size (η_p^2=0.28).

Partial correlations (adjusting for age, sex, and MMSE score) showed variable results for the relationship between the IRI and the DART total score. As expected, there was a modest positive correlation between the DART and the IRI-EC r=0.3, p>0.001) and the IRI-PT (r=0.3. p>0.001). The correlation between the DART and the IRI-FS and IRI-PD were not statistically significant (IRIFS: r=0.2, p>0.055; IRIPD: r=-0.02, p>0.064). The correlation between the DART and the GDS was not statistically significant (r=-0.1, p>0.123). The only statistically

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significant correlation between the DART and the NPI was the NPI-Eating scale (r=0.3, p>0.012). The NPI disinhibition (r=0.1, p>0.162), euphoria (r=0.1, p>0.266), apathy (r=0.2, p>0.052), agitation (r=0.1, p>0.615), depression (r=-0.2, p>0.057), anxiety (r=-0.1, p>0.619), and irritability (r=-0.2, p>0.074) scales were not statistically significant. Table 4 summarizes statistically significant DART test performance correlations with other measures of social functioning.

Table 4

DART Correlations with Other Measures

	DART (r)
TASIT-EET	0.6*
CATS	0.3*
IRIEC	0.3*
IRIPT	0.3*
NPI Eating	0.3*

* Differed from controls at p<0.05
**Adjusted sex, age, MMSE

Brain-Behavior Relationship Underlying DART Performance (Voxel-Based Morphometry)

As predicted, Dartel-based (SPM8) VBM of 3T MRI performed in a covariates-only analysis of DART showed poorer DART performance correlated with focal volume loss only in emotion-related areas. Specifically, the VBM demonstrated a correlation between the DART and focal atrophy in the left superior medial temporal pole, left medial temporal pole, left inferior temporal pole, left hippocampus, left caudate head nucleus accumbens, right caudate head / nucleus accumbens, right dorsal anterior insula, and the right anterior inferior temporal gyrus (pFWE<0.05). Notably, although the amygdala did not emerge on either hemisphere at the FEW

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corrected threshold of 4.5, the left amygdala began to appear at an uncorrected threshold of T=3.75. The analysis of DART controlling for BNT showed primarily right-sided structures, retaining insula and caudate/accumbens regions, while correlations with ventrolateral temporal regions did not appear. Table 5 and Figures 4 and 5 summarize VBM findings.

Table 5

Voxel-Based Morphometry of DART Performance

	x	y	z	t
left dorsal anterior insula	-35	11	-2	4.83
left orbital gyrus	-23	8	-15	4.68
left superior medial temporal pole	-30	8	-21	4.65
left medial temporal pole	-21	8	-35	4.73
left inferior temporal pole	-30	8	-41	4.74
left hippocampus	-36	-26	-9	4.61
left caudate head / nucleus accumbens	-11	12	-11	4.65
right caudate head / nucleus accumbens	15	12	-12	4.54
right dorsal anterior insula	38	11	-2	4.61
right anterior inferior temporal gyrus	50	3	-38	5.14

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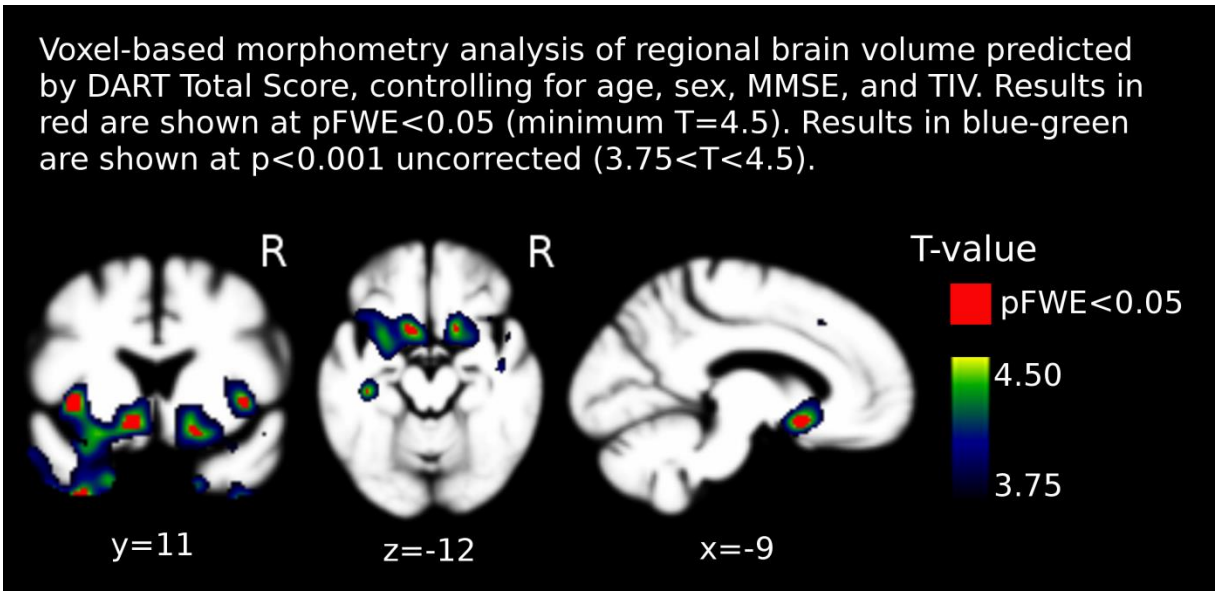

Figure 4. Voxel-based morphometry analysis of DART performance.

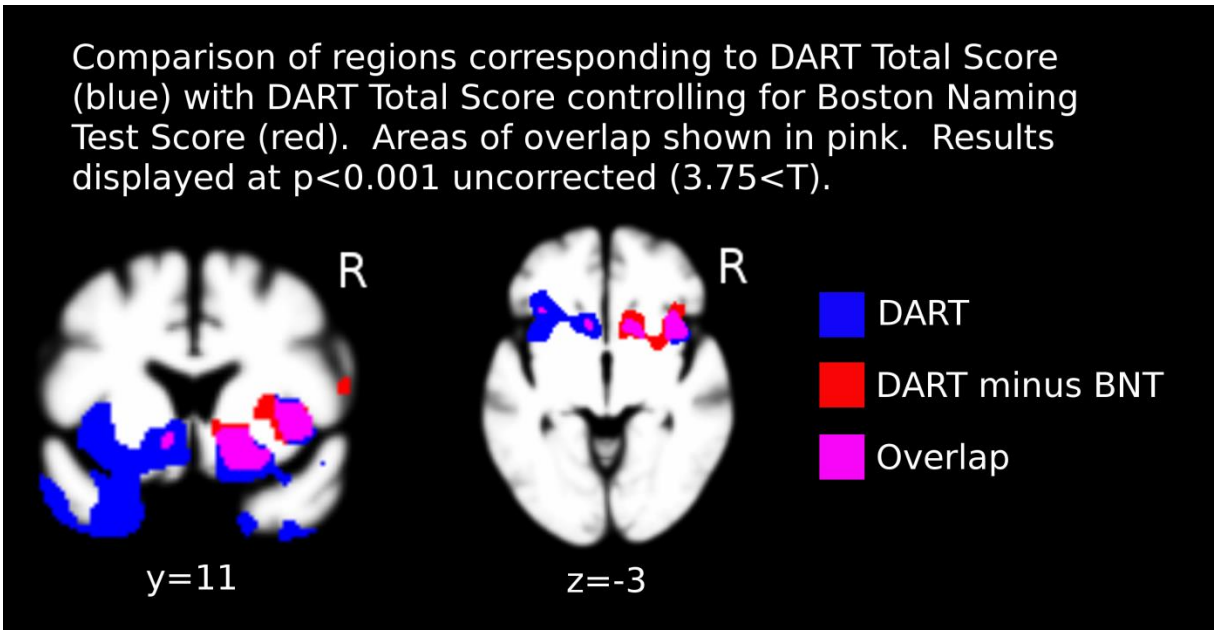

Figure 5. Voxel-based morphometry analysis of DART performance controlling for BNT performance.

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Effectiveness of the DART in Making Differential Diagnostic Discriminations and Determination of Score Cutoffs

Area under the curve (AUC) derived from the receiver-operating characteristic (ROC) analysis was used to test the classification accuracy of the DART in dementia groups versus healthy controls. Overall, the DART performed similarly to the TASIT-EET and somewhat better than the CATS across group comparisons. See Table 6 for summary of ROC analysis and Figures 6-13 for the ROC graph displaying the test comparison and 2x2 sensitivity, specificity, and accuracy tables for group comparisons.

A 9/12 cut score had a 71% sensitivity, 73% specificity, and accuracy score of 72 for discriminating bvFTD versus healthy controls (AUC: DART=0.93; TASIT-EET=0.91; CATS=0.85), while a cut score of 8/12 yielded a 77% sensitivity, a specificity of 95%, and accuracy score of 90.

In discriminating rtFTD from healthy controls, a DART cut score of 9/12 has a sensitivity of 83%, specificity of 73%, and accuracy score of 75 (AUC: DART= 0.97; TASIT-EET=0.92; CATS=0.71), while a score of 8/12 yielded a sensitivity of 75%, specificity of 95%, and accuracy score of 92.

In discriminating rtFTD and bvFTD grouped together (as they often are clinically) from healthy controls, a cut score of 9/12 had a sensitivity of 88%, specificity of 74%, and accuracy score of 76 (AUC: DART= 0.94; TASIT-EET=0.91; CATS=0.81), and a score of 8/12 had a 77% sensitivity, a specificity of 95%, and accuracy score of 88.

A 9/12 cut score had a 74% sensitivity, 73% specificity, and accuracy score of 82 for discriminating AD versus healthy controls (AUC: DART=0.76; TASIT-EET=0.85;

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CATS=0.76), while a cut score of 8/12 yielded a 62% sensitivity, a specificity of 95%, and accuracy score of 79.

Finally, in discriminating any dementia and healthy controls, a DART 9/12 cut score yielded a 80% sensitivity, a specificity of 73%, and accuracy score of 77 (AUC: DART= 0.84; TASIT-EET=0.83; CATS=0.76), while an 8/12 cut score had a 70% sensitivity, a specificity of 95%, and accuracy score of 79.

Table 6

ROC Analysis

	DART	TASIT-EET	CATS
bvFTD vs. NC	0.93	0.91	0.85
rtFTD vs. NC	0.97	0.92	0.71
rtFTD/bvFTD vs. NC	0.94	0.91	0.81
AD vs. NC	0.76	0.85	0.76
Any Dementia vs. NC	0.84	0.83	0.76

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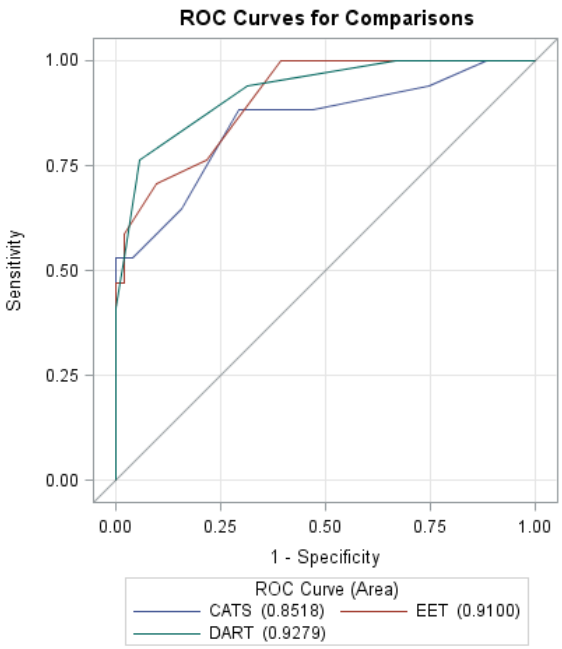

Figure 6. ROC: bvFTD versus NC.

	bvFTD n=22	NC n=59
Score of 9 or less	10	16
Score above 9	2	43
	Sensitivity= 71	Specificity= 73
	Accuracy= 72	
Score of 8 or less	7	1
Score above 8	5	58
	Sensitivity= 77	Specificity= 95
	Accuracy= 90	

Figure 7: bvFTD versus NC 2x2 sensitivity, specificity, accuracy table

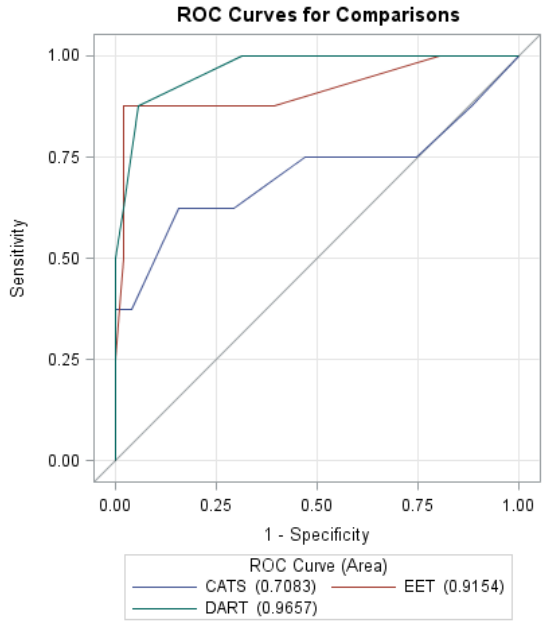

Figure 8. ROC: rtFTD versus NC.

	rtFTD n=12	NC n=59
Score of 9 or less	10	16
Score above 9	2	43
	Sensitivity = 83	Specificity= 73
	Accuracy= 75	
Score of 8 or less	7	1
Score above 8	5	58
	Sensitivity = 75	Specificity= 95
	Accuracy= 92	

Figure 9: rtFTD versus NC 2x2 sensitivity, specificity, accuracy table

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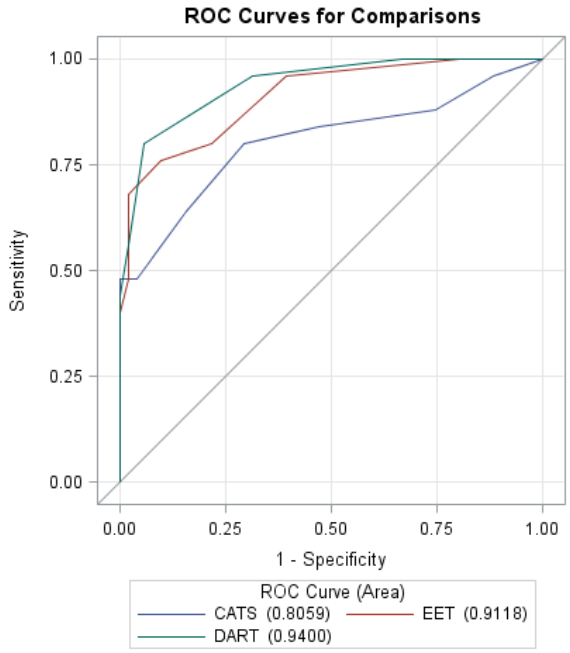

Figure 10. ROC: rtFTD/bvFTD versus NC.

	rtFTD/ bvFTD n=34	NC n=59
Score of 9 or less	10	16
Score above 9	2	43
	Sensitivity = 88	Specificity= 73
	Accuracy= 76	
Score of 8 or less	26	3
Score above 8	8	56
	Sensitivity = 77	Specificity= 95
	Accuracy= 88	

Figure 11: rtFTD/bvFTD versus NC 2x2 sensitivity, specificity, accuracy table

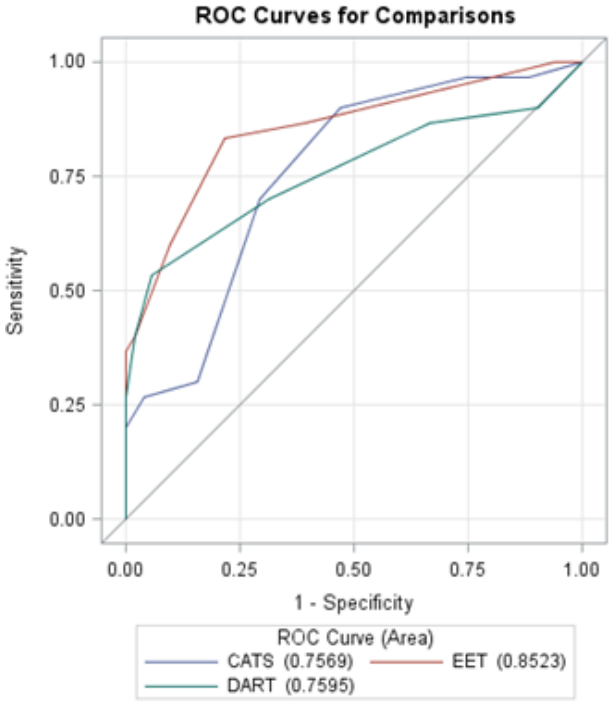

Figure 12. ROC: AD versus NC.

	AD n=39	NC n=59
Score of 9 or less	29	16
Score above 9	10	43
	Sensitivity = 74	Specificity= 73
	Accuracy= 74	
Score of 8 or less	24	3
Score above 8	15	56
	Sensitivity = 62	Specificity= 95
	Accuracy= 82	

Figure 13: AD versus NC 2x2 sensitivity, specificity, accuracy table

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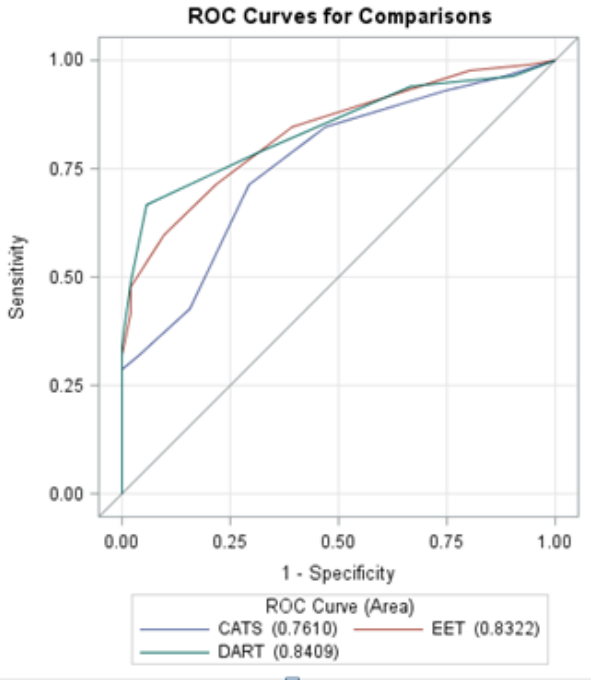

Figure 14. ROC: Any Dementia versus NC.

	AD n=109	NC n=59
Score of 9 or less	87	16
Score above 9	22	43
	Sensitivity = 80	Specificity= 73
	Accuracy= 77	
Score of 8 or less	76	3
Score above 8	33	56
	Sensitivity = 70	Specificity= 95
	Accuracy= 79	

Figure 15: Any dementia versus NC 2x2 sensitivity, specificity, accuracy table

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CHAPTER IV

DISCUSSION

In this study, we found significant group differences in average total scores on a novel measure of affect naming (the DART). All neurodegenerative disease groups performed significantly worse than healthy controls, except for Alzheimer's disease patients, who performed the same as healthy controls. We found similar findings, including the preservation of affect naming in the AD group, on an already-established dynamic measure of emotion reading (TASIT-EET), suggesting that the DART is an equivalent a measure of affect naming. The DART correlated with different but related measures of real-life empathy (IRI). A voxel-based morphometry analysis showed that total DART test performance was correlated with atrophy in brain areas necessary for emotion processing. The dynamic nature of the DART is likely an important feature of this test, given that disease groups with real-life affect naming impairments did not perform significantly worse than healthy controls on a measure of affect naming using static facial images (CATS).

Dynamic versus Static Tests of Affect Naming

Our findings support previous research that questions the ecological validity of static images in measuring emotion naming (Bucks & Radford, 2004; Cadieux & Greve, 1997; Roark et al., 2003). Adolphs (2003) writes, "Most studies on social cognition have used visual stimuli, but it is clear that real-life social interactions draw on additional modalities" (p. 168). Ranasinghe et al.'s (*under review*) work highlights the importance of ecologically-valid measures: while the authors found no performance difference among the frontal-predominant and frontotemporal subgroups on static affect naming tasks, there was a significant difference in performance when stimuli were presented in a dynamic modality. More specifically, rtFTD

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patients had greater difficulty with emotion recognition using a dynamic measure than bvFTDs, which would be expected given the importance of the temporal lobe structures in emotion functioning. Likewise, Henry et al. (2008) found that ADs did worse on a measure of affect naming using static images than they did on a dynamic measure (TASIT). Although the authors also discuss other distinguishing features of the tests (i.e., difference in number of stimuli, speed, number of response choices), they question the ecological-validity of the static facial images as a measure of emotion reading. They write, "…it is possible that deficits on more traditional measures of affect recognition over-estimate the degree of affect recognition impairment individuals with AD actually experience in day-to-day life" (p. 1368). Thus, it may be that the ability of AD patients to decode emotions improves when they receive affective input from multiple modalities (e.g. visual and auditory) in conjunction with the environmental context.

Photographs fail to capture the complex interactive social contexts in which real world emotion is generally rooted (Scherer, Matsumoto, Wallbott, & Kudoh, 1988). Interpretations of social signals and emotional information involve integrating multiple modes of sensory inputs, including visual (e.g., facial expressions, direction of gaze, posture, gestures) and auditory (e.g., prosody and volume of speech) information (Adolphs, 2003). However, traditional assessment measures utilizing photographs provide only one-dimensional (i.e., static) visual information (usually faces), and fail to capture the entire emotional experience. Fiorentini and Viviani (2011) describe how real-world facial expressions are dynamic and provide a richer representation of emotion than a static image can convey. Sato and Yoshikawa (2008) found that the interpretation of affective states in interpersonal relationships depends on an ongoing, instantaneous alertness to the nuances and changes in facial expressions. Thus, tests using dynamic facial expressions

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are more reflective of real-life emotion processing and are therefore more ecologically valid tools (Ambadar et al., 2005).

Our VBM findings showing DART correlations with brain areas important for emotion reading further support the validity of dynamic measures as ecologically-valid tests of emotion functioning. The literature suggests that dynamic and static measures demand different neural underpinnings. Adolphs, Tranel, and Damasio (2003) found dissociable neural systems for recognizing dynamic versus static facial expressions. Specifically, the authors describe the involvement of the occipitoparietal and dorsal frontal cortices in processing information about actions, and the bilateral and anterior temporal lobes for linking perception of static stimuli to affect recognition. Trautmann et al. (2009) found that dynamic stimuli elicited greater generalized brain activation, and Arsalidou et al. (2011) found that dynamic stimuli tended to yield greater activity than static images in the middle temporal gyri and superior temporal sulci, as well as the amygdala, brain areas related to the interpretation of social signals and emotion processing. Recio, Sommer, and Schacht (2011) found that dynamic measures generated more rapid responses in visual areas than did static stimuli.

DART Correlation with Brain Areas Important for Emotion Reading

DART scores correspond to brain regions associated with emotion naming, including the medial temporal, anterior insula, and caudate head and nucleus accumbens. The findings support the work of Seeley et al. (2007ab, 2008, 2009) on the connection between social functioning and the salience network, an intrinsically connected network (ICN) associated with detection and attentional allocation towards personally important or salient information. The ability to detect relevant affective stimuli, with associated generation of emotion, is thought to be essential for survival (Seeley et al., 2007b). The salience network has hubs in the pregenual anterior cingulate

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cortex and frontoinsula, as well as connections to the amygdala, hypothalamus, and brainstem, areas important for affect generation (Saper, 2002). Deficits in emotion reading are related to damage to the anterior cingulate cortex and orbital frontoinsula (Rosen et al., 2002; Schroeter et al., 2006; Sturm et al., 2012), as these regions are critical to having the awareness of and "feeling" of the emotion (anterior insular cortex), as well as the motivation initiation of appropriate behavior relevant to the emotion (orbital frontoinsular cortex) (Craig, 2009). Pathology studies show that atrophy in bvFTD begins in the medial frontal and orbital frontoinsular regions (Broe et al., 2003; Kril & Halliday, 2004; Kril et al., 2005) and is consistent with the changes in social behaviors demonstrated by these patients. Rankin et al. (2006) found an association between poor performance on a measure of real-life empathy and the right anterior temporal and medial frontal regions, areas critical for emotion reading. bvFTD patients in the early stages of the disease show anterior cingulate cortex and orbital frontoinsula atrophy, as well as focal damage to the frontal pole, rostromedial and dorsolateral prefrontal, striatal, and thalamic structures (Seeley et al., 2008). These neuroanatomical regions that are affected early seem to comprise an anterior social emotional functioning system (Boccardi et al., 2005), thus resulting in emotion dysfunction among this patient group.

The lack of empathy and interpersonal warmth observed in rtFTD patients makes sense given the importance of the right anterior temporal lobes in emotion reading. Our VBM findings further support previous work highlighting the importance of the anterior temporal pole. This hub is a critical region for connecting multimodal representations about semantic concepts (i.e., integrating multiple information inputs to construct the meaning given a given context) (Patterson, Nestor, & Rogers, 2007). Guo et al. (2013) highlight the possibility that the right and left anterior temporal pole may "receive and process related but distinct incoming sensory inputs

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that shape the concepts represented by each [anterior temporal lobe]" (p. 2989). The authors note that the right anterior temporal pole appears to mediate knowledge of high-level social concepts and may receive disproportionate inputs from right hemisphere structures critical to emotion processing structures. In contrast, the left anterior temporal lobe, critical to language functioning, may receive disproportionate inputs from left hemisphere word processing regions. Our VBM analysis results controlling for frank language impairment/non-emotion labeling deficits (as measured by the BNT) show correlation between DART performance and primarily right-sided brain structures. These findings further support the literature highlighting the importance of the right hemisphere in emotion labeling independent of non-emotional naming ability.

Neurodegenerative Disease Group Performance on Measures of Social Emotion Functioning

As expected, the rtFTD and bvFTD groups all performed significantly worse than both healthy controls and ADs on emotion naming when the stimuli were presented in a dynamic, video-based format, as measured by the DART and the TASIT-EET. bvFTDs performed significantly worse than both healthy controls and ADs on the paper version of a static affect naming test (CATS), but rtFTDs and svPPAs were not statistically different from normal controls or ADs. As expected, the DART is moderately correlated with a questionnaire measure of real-life empathy completed by caregivers (IRI). We expected a moderate correlation, as empathy is a related, but different, construct from emotion reading. These findings support the well-established previous literature demonstrating that patients with frontotemporal dementia show deficits in socioemotional functioning compared to healthy controls (e.g., Eslinger et al., 2011; Lough et al., 2006; Passant et al., 2005; Rankin et al., 2006; Torravala et al., 2009), specifically in affect naming (e.g., Baez et al., 2014; Diehl-Schmid et al., 2007; Keane et al.,

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2002; Kumfor et al., 2011, 2014; Lough et al., 2006; Rosen et al., 2004). Our finding that rtFTD and bvFTD patients perform significantly worse than ADs on the DART and TASIT-EET is consistent with research demonstrating that FTD patients show disproportionate socioemotional dysfunction compared to patients with Alzheimer's disease early in the disease process (Rankin et al., 2005; Sturm et al., 2015), especially in facial recognition or affect naming (Lavenu et al., 1999; Miller et al., 2012).

Few studies have directly compared AD and FTD patient samples on socioemotional test performance (Eslinger et al., 2005; Funkiewiez et al., 2011; Miller et al., 2012; Rankin et al., 2005, 2009; Shany-Ur et al., 2012). Literature examining these disease groups separately has mixed findings related to social emotion functioning in ADs, while deficits in FTD groups is well documented. Decreased affect recognition capabilities among patients with AD has been reported (e.g., Bediou et al., 2009; Hargrave et al., 2002; Kohler et al., 2005; Phillips et al., 2010). However, all of these studies utilized measures comprised of static facial images to test emotion recognition, which may be a flawed approach. Further, in some studies, patients' level of overall cognitive impairment was not controlled for (Bediou et al., 2009; Hargrave et al., 2002), or the patients' level of executive functioning, verbal memory, or visuoperceptual skills were correlated with emotion recognition test performance (Burnham & Hogervorst, 2004; Phillips et al., 2010; Spoletini et al., 2008; Teng, Lu, & Cummings, 2007). A 2012 meta-analyses (Klein-Koerkamp, Beaudoin, Baciu, & Hot) found significant deficits in emotion naming abilities in AD patients that could not be fully explained by cognitive deficits or type of test stimuli (i.e., static versus dynamic). However, with respect to comparing dynamic and static stimuli, the authors were limited by the lack of statistical power to detect an effect. Miller et al. (2012) also found a deficit in ADs' affect naming abilities using static stimuli even after

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accounting for cognitive functioning. However, the authors also found that despite their low scores, the ADs showed fewer changes in real-life emotional sensitivity compared to the bvFTD and svPPA groups, as measured by the IRI empathy questionnaire. They posited that ADs may use other emotional cues (e.g., prosody, gestures, posture) in addition to facial expression as guides in social interaction. This does not seem to be the case with the FTD group, given their striking behavior changes in the real-world and low scores on empathy questionnaires.

Our finding that ADs had intact affect naming abilities is consistent with Bucks and Radford's (2004) finding that ADs had preserved abilities to identify emotional facial expression and prosody relative to global cognitive functioning. Our findings further support the work of Sturm et al. (2013) on emotion contagion. The authors found that ADs have increased emotional sensitivity as measured by the personal distress subscale of the IRI empathy questionnaire. They hypothesized this heightened emotion sensitivity to be a result of increased salience network activity corresponding to the deterioration of the default mode network integrity observed in ADs (Greicius, Srivastava, Reiss, & Menon; 2004; Zhou et al., 2010). Rankin et al. (2005) found that FTDs have lower scores on measures of real-life empathy than ADs and healthy controls, indicating that caregivers do not report the same striking social and emotional changes in AD individuals in the real-world. In our study, the AD patients were at a mild level of clinical severity, which might explain why they performed similarly to NCs even on the purportedly more demanding static emotion naming test, where other studies have found that more executively impaired or severely affected AD patients can fail those tests.

Our finding that svPPAs performed significantly worse than healthy controls and ADs was expected and consistent with previous research showing deficits in emotion cognition in svPPAs (e.g., Eslinger et al., 2011; Rankin et al., 2006). However, our finding that svPPAs

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performed as poorly as the bvFTDs was unexpected. Previous research comparing bvFTDs and svPPAs has shown that bvFTDs have significantly worse social and emotion functioning (Eslinger et al., 2011). Further, while diagnostic criteria for bvFTD (Rascovsky et al., 2011) include impairment in social and emotional functioning, svPPA diagnostic criteria focus exclusively on language impairment (Gorno-Tempini et al., 2011).

Our results suggest that deficits in emotion labeling can occur in patients with relatively intact right temporal lobes, as patients classified as svPPA have predominant left temporal degeneration. Given the demands on both emotion and language systems of the DART and other tests of emotion functioning, it is difficult to discern if poor performance is reflective of a true affect naming impairment. It is quite possible that poor DART performance is a result of difficulty accessing the label for the emotion itself. It is also possible that the svPPA patients in our sample may have degeneration that has progressed into the right hemisphere, as left-predominant atrophy observed in svPPAs begins to spread to the right hemisphere within approximately three years of disease onset (Seeley at al., 2005). However, it is beyond the scope of this project to investigate these possible explanations.

Our findings regarding nfvPPA and PSP group performances on the DART were somewhat unexpected given that both groups were not statistically different from healthy controls on other measures of affect naming. Further, the current diagnostic criteria for both diseases do not include mention of impaired social and emotional functioning. With respect to nfvPPA, the diagnostic criteria describe motoric language deficits in the form of agrammatisms and apraxia of speech (Gorno-Tempini et al., 2011). It is expected that social and emotional functioning remains intact given the focal left frontal perisylvian atrophy with relatively spared right medial and orbital frontal and temporal regions (Gorno-Tempini et al., 2004; Rosen et al.,

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2006). The literature related to emotion and nfvPPA is limited and studies tend to have small sample sizes. Most reports describe relatively preserved non-verbal cognitive functioning, without specific attention to alterations in emotion processing (Eslinger et al., 2011; Karbe, Kertesz & Polk, 1993; Mesulam et al., 2008; Rankin et al., 2006; Weintraub, Rubin & Mesulam, 1990). Piguet et al. (2015) found that nfvPPAs had emotion processing disturbances in comparison to healthy individuals and patients with logopenic-variant PPA. A review by Kumfor and Piguet (2012) on emotion processing and FTD noted that any deficits observed in nfvPPA were mild in comparison to bvFTD and svPPA.

Our findings contribute to the growing literature exploring emotion reading capacity in nfvPPA, although few conclusions can be drawn from our results. It is possible that, as with the svPPA subject group, that the nfvPPAs' performance is reflective of impairments in emotion *labeling* (i.e., the language demands of the task), as opposed to deficits in emotion recognition. Potentially there is a breakdown in the language system that would cause them to mislabel these emotions, even though subjects can point, as opposed to verbalize, the response. Further, it is particularly difficult to characterize an nfvPPA patient's level of global impairment, given that the typical proxy, the MMSE, relies heavily on expressive language. It is possible that our sample of nfvPPAs have begun to progress toward a more characteristic behavioral FTD presentation, as is typical for nfvPPA disease progression (Le Rhun et al., 2005). Future research should attempt to better characterize emotion functioning in nfvPPA.

Diagnostic criteria for PSP also does not include deficits of socioemotional functioning, and instead describe primarily motor problems, specifically with eye movements and axial rigidity (Litvan et al, 1996a). While socioemotional changes are commonly noted by clinicians, literature examining emotional functioning in PSPs is somewhat mixed. Ghosh et al. (2008)

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found that, while PSPs showed some deficits in emotion recognition, their impairments were correlated with severity of other cognitive deficits and did not occur in isolation. Other reports describe a heterogeneous PSP population, with overlapping symptoms of FTD such as social and emotional cognition and behavior (Bak, Crawford, Berrios, & Hodges, 2010; Kobylecki et al., 2015; Yatabe et al., 2011). The prominence of apathy observed in PSP is hypothesized to result from a disconnection between frontal (anterior cingulate, insula and orbitofrontal cortex) and subcortical (pulvinar, dorsomedial and anterior nuclei of the thalamus, and superior and inferior colliculum) brain regions (Boxer et al., 2006). It is possible that social deficits are also a result of this disconnection, specifically given the importance of the insula and anterior cingulate in emotion functioning. Our results add to the growing literature on PSPs and emotional functioning, and future research should attempt to better characterize emotion cognition in this disease.

Distinct Characteristics of Right Temporal FTD

rtFTD patients performed quantitatively worse on the DART and another dynamic affect naming test (TASIT-EET), with bvFTD and svPPA groups also performing significantly worse than controls, but quantitatively better than rtFTDs. These findings support literature indicating syndromic differences in FTD presentations depending on temporal lobe involvement and laterality (Chan et al., 2012; Coon et al., 2012; Edwards-lee et al., 1997; Gorno-Tempini et al., 2004b; Henry et al., 2014; Josephs et al., 2009; Miller et al., 1993; Mychack et al., 2001; Perry et al., 2001; Rankin et al., 2006; Rosen et al., 2002, 2006; Seeley et al., 2005; Snowden et al., 2001; Thompson et al., 2003). More specifically, patients with left hemisphere degeneration present with language deficits (i.e., frank object knowledge loss), while right hemisphere loss is associated with significant personality and social functioning changes (i.e., lack of interpersonal

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warmth and empathy, social awkwardness, rigidity and compulsiveness). There is a paucity of literature that includes rtFTD as a distinct diagnosis separate from bvFTD and/or svPPA. This tendency to group rtFTD with other subtypes is likely due to the similarities in presentations, as well as the and the fact that rtFTD is not listed as a separate FTD subtype in the consensus diagnostic criteria (Rascovsky et al., 2011). Our finding showing disproportionate deficits between svPPA and rtFTD groups is consistent with literature indicating the importance of the temporal lobes in emotion processing, particularly the right side (e.g., Adolphs, 2003; Mesulam, 1998; Perry et al., 2001; Rankin et al., 2006). Ranasinghe, et al. (*under review*) found that frontotemporal patients (labeled as rtFTD patient group in our study) were significantly worse at emotion naming using a dynamic measure (TASIT-EET) than frontal-predominant patients (labeled as bvFTD patient group in our study), although both groups showed deficits.

The DART versus Other Measures of Emotion Reading

As noted above, we found that the DART strongly correlated with an already-established and frequently used dynamic measure of affect naming (TASIT-EET). This, in conjunction with the differences in disease group performance, suggests that the DART is a dynamic measure of emotion naming that is as good as the commercially available tests.

The DART moderately correlated with an affect naming measure that uses static images (CATS), and only one disease group (bvFTD) performed significantly worse than healthy controls on the static measure. Meanwhile, the rtFTD and svPPA groups were not significantly different from healthy controls, which is inconsistent with the real-life emotional functioning of these groups. This further supports previous literature suggesting that dynamic measures, such as the DART, are a better approximation of real-world affect recognition processes.

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The TASIT-EET, like the DART, is a dynamic measure that has advantages over static assessments. However, the TASIT-EET has possible limitations in its use with dementia patients. For example, it is somewhat lengthy for a screening measure (28 items in its standard form, or 14 items for abbreviated test), and may seem tiring for an impaired individual. Further, the task is relatively complex given that the video depicts an interaction between multiple actors. This requires the viewer to track and retain information (including name and identity) in order to facilitate accurate test response. The measure was developed in Australia. Hence, the actors have Australian accents, which could reduce comprehension for American patients, particularly those with dementia who are prone to distraction. Finally, patients respond via pencil and paper multiple choice answer sheets, which adds to the task complexity. The DART attempts to remedy some of these issues by shortening the task (12 20-second video clips), simplifying the scene in each video (i.e., one actor in front of a simple background with few environmental distractions), and utilizing actors with American accents. For this study, participants watched video clips on a computer and either physically indicated their responses (touching, pointing), or verbally reported their response to the examiner. The most recent version of the DART is completely tablet-based (e.g., IPad), further simplifying the task by decreasing the demand on the individual to shift back and forth between modalities. Finally, the DART is open-sourced and freely available, essentially eliminating many costs.

The results of the ROC analysis indicated that the DART is performing as well as the current measures of affect naming in terms of discriminating deficits across patient groups. We expected to see a greater difference between the dynamic (DART and TASIT-EET) and static measures (CATS). Our sample group was overall mildly impaired (inclusion criteria included an MMSE score of 7 or above; mild CDR scores (e.g., AD: 0.9, bvFTD: 1.3, rtFTD:

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1.0; svPPA: 0.5)). It is possible that in patient groups that are more impaired, we may start to see ADs fail on static tests and remain intact on dynamic measures. However, it is beyond the scope of the current project to make any conclusions with confidence.

A cut score of 9/12 had average sensitivity and specificity across group comparisons, while a cut score of 8/12 increased specificity with somewhat decreased sensitivity in across all groups except bvFTD (sensitivity was slightly increased with an 8/12 cut score in this group). We expected to see that the DART was more discriminating across dementia types. The test appears to be most useful as a screening tool for general deficits in language and emotion systems consistent with these diseases. Information gained from DART performance, in conjunction with information collected as part of a standard clinical evaluation, may aid in the diagnostic process within a research and/or clinic setting.

Limitations and Future Directions

There are some important limitations to this study that should be considered. This study was designed to evaluate the use of the DART with neurodegenerative disease groups, some of which are fairly rare. As such, some group sizes were small. While this was a clear limitation, the observed effect sizes in the sample were moderate to large, suggesting that the study design allowed adequate power. The patient groups included in this study were clinically diagnosed. Subjects' diagnoses have not yet been pathologically-confirmed and thus, remained classified as "probable" under research criteria. Thus, there remains the possibility that upon post-mortem pathology evaluation, diagnoses may change and alter the results of this study. Finally, structural voxel-based morphometry has limitations, despite its quantitative specificity in analyzing structural MRI scans across large sample sizes with focal atrophy. Sollberger et al. (2009) highlight some of these limitations, including issues associated with variability of brain anatomy

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across subjects, questions of generalizability beyond study subjects, and issues with whole-brain analysis. More specifically, the authors describe issues associated with the inter-subject spatial normalization process that aligns subjects' corresponding brain anatomy used to correct for inter-individual variances in brain shape. The diversity in neuroanatomy across subjects does not allow for exact overlying of the corresponding anatomy. This variability causes issues with localization of clusters of neuroanatomical structures. The authors also note that VBM is a method that is based on an atrophy model and that the clinically-defined subjects within groups have variable atrophy patterns, possibly limiting the degree to which results can be generalized beyond the study subjects. Finally, the authors detail restrictions by whole-brain analysis. There is possible loss of statistical power to detect brain-behavior relationships in some important brain regions if only a small number of subjects display atrophy. The current study mediates the potential loss of statistical power by providing a large, diverse sample that includes patients with diseases that impact a broad range of cortical structures. It will be important to re-examine our patient groups once a definitive pathology-confirmed diagnosis has been made to further validate the DART's accuracy in differentiating neurodegenerative disease groups. The most recent version of the DART is tablet-based, which would allow for increased qualitative data collection, such as response time and response patterns (e.g., perseverations related to choice of emotion or spatial position of answer choice on the screen). Clinically, this qualitative data could help provide important information related to a diagnostic criterion (preservation, stereotyped, or compulsive behavior) beyond changes in empathy (Rascovsky et al., 2011). Some research has examined emotion expressive behavior, such as facial mimicry, in neurodegenerative disease populations (e.g., Henry et al., 2009; Sturm et al., 2008; Werner et al., 2007). A possible modification to future versions of the DART in its tablet-form include a video-recording feature

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so as to evaluate examinee's facial mimicry when completing the task. The DART was designed to be clinically useful, and thus brevity was a goal, with two video vignettes per emotion. However, a longer version of the DART with an increased number of vignettes per emotion could allow for investigation of any differences between diseases groups' reading of specific emotions. Currently, the findings related to group differences in ability to read specific emotions are mixed (e.g., Calder et al., 2003; Fernandez-Duque & Black, 2005; Kessels et al., 2007; Kipps et al., 2009; Rosen et al., 2004). Kumfor et al. (2011) described the importance of intensity of emotional expression in evaluating affect naming. The authors found that some FTD patients have improved facial affects recognition with enhanced emotional intensity. In future versions of the DART, it may be useful to alter the vignettes in terms of intensity of the displayed emotion expression to further investigate this construct.

Conclusion

Tests allowing fast but valid evaluation of emotion reading deficits at the bedside via ecologically-realistic modalities are an essential component of a comprehensive neuropsychological evaluation of neurodegenerative disease. We have validated the Dynamic Affect Recognition Test (DART), a quick, novel video-based test, as an assessment of affect naming. This test was designed with the intention to help remedy FTD diagnostic difficulties by improving measurement of social emotional functioning through assessing affect naming. We have shown that the DART is as accurate of a measure of emotion naming as the current commercially available dynamic assessment in differentiating neurodegenerative disease groups, especially those that are often difficult to distinguish (i.e., AD and FTD). The DART may project a more realistic sensory emotional experience than traditional static measures, which might allow for individuals without real-world impairment to distinguish emotions more

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accurately. The DART attempts to remedy some limitations of other dynamic tests with dementia populations by simplifying stimuli and shortening the test. Further, the DART essentially eliminates many costs in that it is open sourced and freely available.

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