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Characterization of apathy in frontotemporal dementia

by
Jennifer Merrilees

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Abstract

Characterization of apathy in frontotemporal dementia

Jennifer Merrilees

Apathy has been defined, as a deficit in drive and motivation, yet has been historically difficult to operationalize. Apathy occurs commonly in dementia and is associated with negative outcomes for both the patient and the caregiver. This study characterizes daytime activity and apathy in patients with behavioral variant (bvFTD) and semantic dementia (SD) and their family caregivers. Twenty-two patient-caregiver dyads were enrolled: 13 FTD, 9 SD and data on dementia severity, cognition, behaviors, activity, daytime sleepiness were collected. Patients and caregivers wore Actiwatches continuously for 2 weeks to record activity. Variables were examined between groups. Apathy was present in 100% of the patients with FTD and in 89% of patients with SD. Patients with FTD spent 25% of their day immobile while patients with SD spent 16% of their day inactive. FTD caregivers spent 11% of their day immobile and SD caregivers 9%. Apathy correlated with high levels of emotional distress for the caregivers in FTD, but not SD. Averages of hourly activity counts revealed the lowest amount of daytime activity was among patients with FTD followed by their caregivers, with the highest activity among SD caregivers. These results were present in patients in relatively mild disease stages. There was little evidence that factors other than apathy, for example, depression, physical impediments, or sleepiness, were contributing to the lower activity. FTD is associated with greater daytime activity disturbance (lower activity and greater numbers and duration of immobility bouts) compared to SD and the clinical manifestations of FTD produce different and more distressing impacts on the caregiver.
Results from this study provide objective data contributing to an operational definition of apathy.
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Chapter 1
Introduction and Background

Dementia is a neurodegenerative disease causing cognitive, behavioral, emotional and functional changes. It is a progressive condition leading to functional dependence and associated with significant economic and social burden (Langa et al., 2001; Moore, Zhu, & Clipp, 2001). National prevalence estimates of dementia among older adults increases with age reaching 37.4% at age 90 (Plassman et al., 2007). There are multiple etiologies of dementia, including Alzheimer’s disease (AD), vascular dementia, dementia with Lewy bodies (DLB), rapidly progressive dementias, and frontotemporal dementia (FTD). FTD is a neurodegenerative condition targeting the frontal and anterior temporal lobes of the brain. Once considered rare, it is now acknowledged that FTD accounts for 12-16% of all primary degenerative dementias (Brun, 1987; Neary et al., 1998) and is the most common cause of dementia in people under the age of 65 (Knopman, Petersen, Edland, Cha, & Rocca, 2004; Ratnavalli, Brayne, Dawson, & Hodges, 2002).

FTD refers to a spectrum of disorders characterized by symptoms that are either behavioral or aphasic in origin. The behavioral variant of FTD (bvFTD) is the most common subtype. The average age of onset of disease for FTD is 52.8-56 years (B.L. Miller et al., 1998; Ratnavalli, Brayne, Dawson, & Hodges, 2002) with a male predominance (Johnson et al., 2005; Ratnavalli, Brayne, Dawson, & Hodges, 2002). Principal symptoms in FTD include aberrant motor behaviors, apathy, hyperorality or appetite disturbance, disinhibition, and social and interpersonal misconduct (Bathgate, Snowden, Varma, Blackshaw, & Neary, 2001; Diehl & Kurz, 2002; Ikeda, Brown, Holland, Fukuhara, & Hodges, 2002; Lindau et al., 2000; Liu et al., 2004; Marczinski,
Patients with FTD have been shown to engage in socially unacceptable behaviors including traffic violations, physical assaults, and unsolicited sexual acts and typically show no remorse for their actions (Mendez, Chen, Shapira, & Miller, 2005). Patients often exhibit profound alterations in beliefs and attitudes (BL Miller et al., 2001).

FTD progresses to death more rapidly than AD and has a median survival from symptom onset of 8.7 (± 1.2) years (Roberson et al., 2005). Mean survival has been documented to be 6 (Hodges, Davies, Xuereb, Kril, & Halliday, 2003; Rascovsky et al., 2005) to 8 years (Neary, Snowden, & Mann, 2005). To date, there is no cure for FTD and treatment focuses on symptom management.

There are two aphasic subtypes of FTD. One is called semantic dementia (SD) or the temporal variant of FTD (tvFTD) and the other is progressive non-fluent aphasia (PNFA). Earliest symptoms in SD reflect the brain region affected: left anterior temporal atrophy causes deficits in semantic memory and object meaning while right temporal involvement results in behavioral and personality changes. Patients with SD will exhibit compulsivity, rigidity, and fixation on routines and constitutional complaints (W. W. Seeley et al., 2005). Left frontal lobe atrophy results in fluency deficits observed in PNFA causing effortful agrammatic speech (Gorno-Tempini et al., 2004; Rosen et al., 2002).

Pathology of FTD

Two pathologic subtypes of FTD have been identified that cause the characteristic neuronal and glial protein inclusions. The first, termed tauopathies, are associated with
accumulation of tau protein such as in Pick’s disease, corticobasal degeneration, and progressive supranuclear palsy. The other are tau-negative conditions; one associated with ubiquitin and TAR DNA-binding protein of 43 kDa (TDP-43) inclusions and one termed dementia lacking distinctive histopathology (DLDH). Inherited forms of tau positive FTD result from mutations in the MAPT gene while tau negative inheritability is related to mutations in the progranulin (PGRN) gene (Grossman et al., 2007; Johnson et al., 2005; W. Seeley, 2008). Findings from autopsy-proven cases have shown that distinct clinical profiles, functional abilities, and survival are associated with FTD neuropathology (Rascovsky et al., 2005). Tau-negative FTD has been associated with more disruption in behavior, social conduct, language, and executive dysfunction. Tau-positive FTD has a higher association with movement deficits (although the cohort contained a large number of patients with CBD) (Grossman et al., 2007).

Diagnostic criteria for FTD

Three original sets of published criteria reflect changing knowledge about FTD, concern for meeting clinical and research interests, and desire to refine definitions and terminology. There is clear need for specific criteria that will distinguish FTD from other dementia conditions: it has been demonstrated that patients with FTD easily meet diagnostic criteria for Alzheimer’s disease (Varma et al., 1999). Appendix 1 summarizes major components of diagnostic criteria for FTD. The original diagnostic criteria outlined core diagnostic, supportive, and exclusion features of FTD (Brun et al., 1994). While providing a description of behavioral and affective symptoms, the criteria has been criticized for lacking specific guidelines, timeframes, and operational definitions (Rascovsky et al., 2007). Published in 1998, Neary criteria established core and
supportive features for the three clinical subtypes of FTD (Neary et al., 1998). There are concerns that the Neary criteria is too restrictive (Mendez & Perryman, 2002), contains ambiguous and poorly operationalized terms, and is too lengthy to be of clinical utility (Rascovsky et al., 2007). In 2001, a third set of criteria was published that defined FTD in broad terms; FTD was categorized as either a behavioral or aphasia syndrome (McKhann et al., 2001), possibly a less cumbersome method but contributing to a lack of specificity. The most widely used standard in establishing a research diagnosis for FTD is the Neary criteria. However, the criteria, in its strictness and structure, may miss a proportion of patients with FTD. In a study of patients with confirmed postmortem pathology, only 58% met all of the five core features at their initial evaluation (Piguet, Hornberger, Shelley, Kipps, & Hodges, 2009). A recent publication calls for revision and simplification of bvFTD diagnostic criteria (Rascovsky et al., 2007).

The impact of behavioral symptoms on patients and families

FTD is associated with an early and profound level of behavioral disruption, critical for several reasons. Disrupted behavior is known to contribute to significant levels of stress and burden for the family members responsible for providing care (Croog, Sudilovsky, Burleson, & Baume, 2001; Dura, Stukenberg, & Kiecolt-Glaser, 1991; Gaugler, Kane, Kane, & Newcomer, 2005; Knutson, Zamboni, Tierney, & Grafman, 2008; Ory, Hoffman, Yee, Tennstedt, & Schulz, 1999; Robinson, Adkisson, & Weinrich, 2001; Rymer et al., 2002), with behavioral symptoms resulting in higher levels of emotional distress compared to cognitive symptoms (Kaufer et al., 1998). Behavioral symptoms in dementia are associated with poor health outcomes for the caregiver (Schulz, O'Brien, Bookwala, & Fleissner, 1995). Behavioral symptoms occurring early
in the disease trajectory lead to caregiver burden, depression, and more rapid institutionalization of patients (Gaugler, Kane, Kane, & Newcomer, 2005). In addition, caregiving costs increase when behavioral symptoms are present (Moore, Zhu, & Clipp, 2001).

The impact of apathy on patients and caregivers

There are consequences for patients and families associated with apathy. In patients with mild cognitive impairment, loss of interest correlates with conversion to AD (PH. Robert et al., 2008). Of all the behaviors in dementia, apathy is the most common and sustained symptom (Craig, Mirakhur, Hart, McIlroy, & Passmore, 2005). Among patients with AD, apathy has been associated with deficits in everyday life, cognitive function, and nutritional status (Benoit et al., 2008; Lechowski et al., 2009; Starkstein, Jorge, Mizrahi, & Robinson, 2006). There appears to be a unique influence of frontal symptoms (apathy, executive dysfunction, and disinhibition) on caregiver burden (Davis & Tremont, 2007; Rymer et al., 2002), showing that of all the behavioral symptoms, apathy is associated with the highest levels of emotional distress for caregivers of patients with FTD (de Vugt et al., 2006; Massimo et al., 2009).

Study Problem: Defining Apathy

Apathy incorporates cognitive, emotional, and movement features that have been historically difficult to characterize (Stuss, Van Reekum, & Murphy, 2000). The definition of apathy originated with Greek philosophers of the Stoic school as being “free from passions” and this lack of emotion was considered a positive and necessary feature to becoming a rational thinker (Starkstein & Leentjens, 2008). Dictionaries continue to refer to apathy as a lack of emotion, feeling, concern, or interest (Dictionaries, 2005) and
the current construct of apathy is a negative psychological and behavioral condition. Marin’s definition of apathy has evolved from a core problem of motivation (Marin, 1991) to a reduction of goal directed behavior (lack of effort and productivity), reduction of goal directed cognition (decreased interests, decreased concern for one’s health or functional status), and emotional components (flattened affect, emotional indifference) (Marin, 1996). On the grounds that motivation is a difficult phenomena to assess, Levy and Dubois propose that apathy be seen as a behavioral change from the individual’s baseline and measured as reduction in self-generated and purposeful activity (R. Levy & Dubois, 2006). Others have echoed concern about the problems in assessing motivation and have suggested apathy be viewed simply as a lack of self-initiated action (Stuss, Van Reekum, & Murphy, 2000). Despite these concerns, recent consensus criteria have proposed that lack of motivation is central to characterizing apathy in AD and other neuropsychiatric conditions (P. Robert et al., 2009).

A wide variety of terminology has been used to refer to apathy. These terms include: remoteness, disinterest, passivity, mental sluggishness, boredom, social withdrawal, social avoidance, lessened drive, lessened motivation, less caring, less concern, self-centeredness, loss of awareness, aspontaneity, inertia, reduction in activities of daily living, loss of interest in hobbies and leisure activities, loss of initiative, deficits in goal-directed behavior, decreased involvement in chores, decreased personal hygiene, and flattened affect. Apathy has also been described as a spectrum of deficits including conditions such as anhedonia, abulia and akinetic mutism (Bonelli & Cummings, 2007; van Reekum, Stuss, & Ostrander, 2005; Vijayaraghavan, Krishnamoorthy, Brown, & Trimble, 2002). Anhedonia has been defined as an inability to experience pleasure
Abulia is characterized as a lack of spontaneity, lack of goal-directed behavior, and paucity of speech and movement. Akinetic mutism refers to a state of profound apathy in which patients show indifference to pain, thirst, or hunger, and lack of spontaneous movement or verbalizations. Patients with akinetic mutism, despite having intact arousal systems, appear to lack the will to move (Bonelli & Cummings, 2007; van Reekum, Stuss, & Ostrander, 2005). Thus, apathy may incorporate cognitive, emotional, and movement features along a severity continuum.

Published criteria for psychological and psychiatric conditions offer little in the challenge of defining and detecting apathy. The Diagnostic and Statistical Manual of Mental Disorders (DSM) a publication by the American Psychiatric Association in its’ fourth edition provides diagnostic criteria for mental disorders. Although apathy is often referred to as a psychiatric condition or change in personality, the APA does not list apathy specifically nor does it offer a definition (American Psychiatric Association, 1994; Starkstein & Leentjens, 2008). The International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization is used throughout the world to provide codes similar to the DSM for diseases and symptoms. It is in its 10th revision (ICD-10) (World Health Organization, 1993) and there is still no mention of apathy.
Chapter 2

Literature Review

Due to the role that the frontal lobes play in governing motivation, interest, movement, and emotion, FTD is an ideal condition for the study of apathy and for guiding the development of a more operational definition of the syndrome. This paper will review literature on the association between apathy and behavioral variant (bvFTD) and a literature search was conducted for studies examining this relationship. PubMed, CINAHL, the Cochrane Library, and Digital Dissertations databases were searched using keywords: frontotemporal dementia, behavior, and apathy. Studies were limited to those with human subjects and published in English. Criteria for inclusion of studies in this review included those that utilized diagnostic criteria for dementia, an objective measure of rating for apathy, and data that could be used for analysis (means, standard deviations, significance levels, and correlations). Appendix 2 includes a summary of studies reviewed here.

The Association of Apathy with FTD

Apathy as initial symptom in FTD

Le Ber evaluated the presence of behaviors in FTD (n=68) using an informant-based 70-item inventory. For any endorsed behavior, informants were asked to recall patient’s age of onset for the behavior: 48% of patients were 3-5 years into the disease (the majority were at year 4). There was high prevalence for initial disease behaviors that the researchers termed “inertia.” These items included loss of awareness (65% of patients), reduction in activities of daily living (54%), loss of interest (54%), loss of initiative (51%), apathy (43%), social withdrawal (41%), and self-centeredness (41%).
Researchers grouped the patients into one of three categories based on the most prominent initial behavioral profile. Twenty-five percent were categorized as “inert”, 18% as disinhibited, and 57% as mixed (disinhibited and inert) (Le Ber et al., 2006).

Initial disease symptoms have been examined using comparative studies between FTD and other dementias. One study compared FTD and AD by analyzing recorded interviews and medical charts to retrospectively determine the first symptoms of dementia. Among the 52 patients meeting criteria for FTD and 101 patients with AD, researchers found that “apathy/passivity” was not only an early sign in FTD, but it discriminated between FTD and AD (p = .004). Executive dysfunction was defined as deficits in planning and carrying out daily activities, and this was also more common in FTD versus AD (Lindau et al., 2000).

The Neuropsychiatric Inventory (NPI) and informant interviews were used to compare initial symptoms in FTD, SD, and AD. The NPI is a validated, informant-based behavioral rating scale used to evaluate the presence, severity, and frequency of behaviors common in dementia (J. L. Cummings et al., 1994). The original 10-item version covered neuropsychiatric symptoms (delusions, hallucinations, agitation, depression, elation, apathy, irritability, anxiety, disinhibition, aberrant motor behavior); sleep disturbance and appetite and eating changes were incorporated at a later time. Informants are asked a screening question regarding the presence of apathy. If apathy is endorsed, eight sub-questions are asked focusing on specific features of interest, caring, concern, and engagement in activities. (While the NPI will be discussed later in greater detail, Appendix 3 contains a description of the stem and sub-questions for apathy). In this study, researchers created 4 domains: 1) change in social behavior, affection, and
daily activities, 2) cognitive decline, 3) language impairments, and 4) other abnormal symptoms, with apathy included in the first domain. The majority of patients participated at a mean of 36 months (± 24 months SD) from initial symptom. Among 36 patients with FTD, change in social behavior, affection, and daily activities was significantly more common as initial symptoms compared to the other dementia groups (62.5% of patients with FTD compared to 19 and 20% for AD and SD). The most common initial symptoms in FTD were “apathy or social withdrawal of aspontaneity” (14%) and stereotyped behavior (12.5%). These symptoms were significantly more common in FTD compared to AD (p = .0043 and .002) (Shinagawa, Ikeda, Fukuhara, & Tanabe, 2006).

Prevalence and characteristics of apathy in FTD

One study focused specifically on the association between disease severity and behavioral symptoms in FTD. Diehl used the Clinical Dementia Rating (CDR) (Morris, 1993) to group FTD patients into 2 cohorts. The CDR is a rating system of dementia severity. The CDR assesses 6 domains of function: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scripted questions are administered via interview with an informant, usually a family member. Total CDR scores range from 0 (no impairment), 0.5 (benign), 1 (mild dementia severity), 2 (moderate dementia severity), to 3 (severe dementia severity). The memory score carries influence in calculating the total CDR score. The sum of box score (the sum of the six individual domain scores) can also be reported; the range of scores being 0 to 18. The first cohort (n=21) was judged to be in the mild stage of disease (CDR of 1) and the second cohort in the moderate to severe stage (CDR of 2-3). Using data from the
NPI, it was shown that apathy was the most common of all the symptoms, occurring in 90.5% of patients with mild disease and it increased over time, occurring in 100% with moderate/severe disease (Diehl-Schmid, Pohl, Perneczky, Forstl, & Kurz, 2006).

Of eight studies that compared prevalence of behaviors in FTD with other types of dementia, four relied on the NPI. In the first, Jenner compared behaviors in FTD to AD in a cohort of patients in mild disease stages (mean CDR of 1.46 and mean MMSE score of 23.7). Apathy was significantly higher in FTD (Mann-Whitney = 408.5; p < 0.0012) and was the only behavior significantly different between the two groups (Jenner, Reali, Puopolo, & Silveri, 2006).

Liu compared behaviors between patients with frontal (n=23) and temporal variant (n=26) FTD using the NPI. Mean MMSE scores were 20.8 (± 8.7 SD) for bvFTD patients. Apathy had a higher prevalence among the frontal variant patients (96%) compared to temporal variant patients (52%) and had higher frequency by severity product scores (Liu et al., 2004).

In another study, the percentage of FTD subjects with apathy was higher (95%) than those with AD (80%) but this difference did not reach statistical significance. However, the NPI total scores (the product of frequency and severity) for apathy were significantly higher in FTD than AD (p< .01). Stepwise discriminate function analysis revealed that high scores for apathy and disinhibition in conjunction with low depression scores correctly identified FTD cases from AD in 77% of cases. Among the FTD cohort there was a negative association between apathy and disinhibition; patients tended to fall into one category or the other (M. L. Levy, Miller, Cummings, Fairbanks, & Craig, 1996).
Bozeat and colleagues (2000) used an informant questionnaire to compare behavioral features between frontal and temporal variant FTD and Alzheimer’s disease. Apathy occurred more frequently among the FTD patients, but there were no significant differences between the disease cohorts (Bozeat, Gregory, Ralph, & Hodges, 2000).

Bathgate and colleagues (2001) compared FTD, AD, and vascular dementia using the Manchester Behavioural Questionnaire (MBQ) to investigate behavioral symptoms. The MBQ is an extensive checklist of behaviors organized by domains and administered via interview with an informant. Apathy was assessed as “shows a general loss of interest in hobbies and leisure activities,” included under the Affect and Social Behavior domain. Disease duration for all three groups of patients was approximately four years and mean MMSE score was 21 for the FTD cohort (standard deviation not given). The MMSE scores were significantly lower among the AD patients (mean MMSE = 16, p = 0.006). A general loss of interest was present in 90% of patients with FTD compared to 49% of patients with AD and 56% of those with vascular disease and was one of several symptoms that increased the diagnostic odds of FTD versus AD (Bathgate, et al 2001).

Snowden and colleagues compared behaviors of 30 patients with FTD to 11 patients with SD. A 55-item questionnaire was completed with an informant who was asked to rate the presence of behavioral, emotional, and personality symptoms. Apathy was assessed with two items: “general loss of interest” and “social avoidance.” Researchers then grouped the FTD patients into one of two cohorts based on whether the predominant symptoms were apathy or disinhibition. A general loss of interest strongly differentiated FTD from SD (p = .001) and apathetic FTD patients demonstrated greater
(p = .06) social avoidance than disinhibited patients with FTD or SD (Snowden et al., 2001).

In a study examining behaviors among patients with FTD (n=29), AD (n=205), mixed dementia (n=39), and dementia with Lewy bodies (n=23), Engelborghs and colleagues (2005) utilized the Middelheim Frontality Score (MFS) and informant interviews. Apathy was assessed using the term “aspontaneity” and rated by asking about features such as loss of interest, social withdrawal, and decreased involvement with chores. Symptoms were rated as either being present or absent over the prior two weeks. There were no statistically significant differences between the cohorts based on dementia severity or MMSE scores. There was a significantly higher prevalence of aspontaneity in the FTD cohort (69%) compared to the AD cohort (29.8%) patients (p<0.001). The assessment of apathy was separated from impaired control of emotions and emotional blunting. This emotional item had a higher endorsement in FTD (93%) compared to apathy (69%) and suggests that apathy rates may have been underestimated (Engelborghs et al., 2005).

Chow and colleagues (2009) explored differences in the features of apathy between patients with FTD and AD. Researchers proposed that apathy could be divided into three domains, affective (emotional), cognitive (interest), and behavioral (activity). Using the NPI, they organized the sub-questions into three categories. For example, lack of emotions was labeled “affective”, no interest in activities of others was labeled “cognitive”, and abandonment of chores was labeled as “behavioral”. The FTD group had higher rates of apathy compared to the AD group. The groups had similar rank orders for
Inclusion of apathy in diagnostic criteria for FTD

Despite the prevalence of apathy in FTD, it has received variable attention in the three sets of published FTD consensus criteria. The Lund Manchester criteria were published in 1994 proposing clinical and neuropathological components for diagnosis of FTD. Included in the Lund Manchester is a domain “affective symptoms” incorporating items of emotional unconcern, emotional indifference, remoteness, lack of empathy, lack of sympathy, and apathy (Brun et al., 1994). Criteria developed by Neary and colleagues provide clinical diagnostic criteria that do not specifically identify apathy, but include related symptoms such as emotional blunting and decline in personal hygiene (Neary et al., 1998). In 2001, McKhann criteria delineated progressive changes in behavior and personality that modulate responses and activities. While apathy is not listed specifically in the McKhann criteria, there is acknowledgment that patients may exhibit a loss of concern for personal appearance. In addition, McKhann criteria include a statement that apathy is more pervasive in FTD compared to AD and this may reflect indifference or deficit of initiative (McKhann et al., 2001). Appendix 1 summarizes FTD diagnostic features and the inclusion of apathy within each set of criteria.

Critique of research

Research design

A critique of the literature involves a discussion of research design, methodology, and issues of validity and generalizability (Polit & Beck, 2004). Studies of apathy in FTD to date have been cross-sectional. Advantages of cross-sectional research are their ease of
conducting and relative economy. A disadvantage to cross-sectional research is the difficulty in making inferences about the findings and how apathy may change over time in the disease trajectory. Longitudinal studies collect measurements at more than one time point and are better for studying how a phenomenon changes. The risk of longitudinal research includes attrition and appropriate selection of measurement time points. FTD not only progresses more quickly than AD, but cellular mechanisms of FTD impact disease symptoms and clinical course (Forman et al., 2006). Thus, there is a risk of selecting measurement time points that will miss important disease milestones.

**Internal validity**

Internal validity refers to the strength of the association between variables; in this case does FTD cause apathy? There is strong evidence that it does. In 43-63% of patients, apathy is an initial symptom of disease. Regardless of stage of disease, apathy has been documented in 69-100% of patients. There is evidence that two distinct behavioral profiles (apathetic and disinhibited) exist in FTD (Le Ber et al., 2006) although they may converge with advancing disease (Snowden et al., 2001). Despite the high prevalence, there are several methodological concerns.

A wide array of terminology has been used to define apathy. Some researchers have referred to apathy as a single item, such as loss of interest or decreased participation in activities. Others identify apathy on the basis of two or more items, but there is no consistency on the terminology used. Most of the rating techniques ask simply whether a symptom pertaining to apathy is present or not.

Chow (2009) separated features of apathy into three major domains, cognitive, affective, and behavioral that does fit nicely with current thinking of the components of
motivation and apathy. But, it isn’t clear how easily and reliably the items fit. For instance, does a decrease in initiation of conversation fall into a cognitive/interest category or an emotional/lack of concern category or a behavioral/less verbal output category or all three?

The definition of apathy remains poorly delineated. Terms used to assess for the presence of apathy share features with other common deficits observed in the behavioral variant of FTD (bvFTD). For instance, empathy is a term defined as diminished ability to understand or to take an account of the emotional concerns of others and a lack of empathy has been documented to occur in patients with FTD (Decety & Jackson, 2004; Kipps & Hodges, 2006; Rankin, Kramer, & Miller, 2005). While deficits in empathy have been linked to the right temporal lobe (Perry et al., 2001), it may be possible that the lack of concern manifested by temporal disease has different characteristics than that of frontal disease. In addition, executive dysfunction or the impaired ability to plan and execute goal-directed tasks is a well-known cognitive deficit of FTD, yet it is not clear whether these changes represent overlap with apathy, contribute to the presence of apathy, or are distinct from the phenomena of apathy. Le Ber (2006) included “self-centeredness” within the domain of apathy, yet it isn’t clear whether being self-centered assumes less concern for others. Lindau (2000), Shinagawa (2006), and Engelborghs (2005) separated executive dysfunction symptoms from apathy. This overlap and variability in terminology raises concerns that the data either under- or over-report apathy rates in FTD.

Since the majority of behavioral assessments are conducted with caregivers and informants, confusion and overlap in terminology create a risk for misunderstanding. If
an informant conceptualizes apathy as purely a disorder of self-initiated movement, the presence of apathy may go undetected if they are questioned only about social withdrawal.

The majority of researchers relied on family informants to retrospectively identify symptoms, in many cases 3-4 years from the onset of disease. Informant-based ratings may be biased and influenced by caregiver fatigue and burden (McCurry, Gibbons, Logsdon, & Teri, 2004). It may be difficult for families to accurately recall symptoms after several years have elapsed. These concerns will be addressed in greater detail in Paper #3.

Another concern is whether changes observed in a patient with FTD reflect the presence of apathy or simply give an impression of apathetic behavior. For example, diminished verbal output and verbal fluency occur with frontal lobe dysfunction. Non-verbal demeanor and bearing often change in FTD, with patients often exhibiting prolonged staring and “fatuous” smile (Mendez, 2006). These signs may give the impression of disinterest and unconcern. Finally, deficits in daily living task performance (chores, hygiene) are functional outcomes rather than symptoms and caution should be used in assigning causality.

Diminished levels of spontaneous movement and activity are considered signs of apathy. Yet, movement can be disrupted in FTD for a variety of reasons, including age-related changes, concomitant Parkinson’s disease, and environmental constraints. Selective Serotonin Reuptake Inhibitors (SSRIs), the mainstay of symptomatic treatment in FTD (Huey, Putnam, & Grafman, 2006; Perry & Miller, 2001), are associated with
side effects of apathy, anhedonia, akathesia, and somnolence. Few studies addressed these factors in their analysis.

Apathy and depression share similar features and can be challenging to differentiate. DSM-IV criteria treat apathy as a potential component of depression by including items such as diminished interest or pleasure in activities and slowing of movement (American Psychiatric Association, 1994). Yet, apathy does not always accompany depression (Starkstein, Ingram, Garau, & Mizrahi, 2005). And, while there is evidence that depression may be present in some patients with FTD (Chow, Miller, Boone, Mishkin, & Cummings, 2002), the overlap in clinical features make it challenging to distinguish.

Finally, there is a potential for misdiagnosis of FTD. The diagnosis of dementia is a clinical one and 100% accuracy is obtained only with pathological confirmation. Post-mortem study has revealed that not only can dementia be incorrectly diagnosed, but that patients often have evidence of two or more types of dementia (Kovacs et al., 2008). Therefore, it is likely that different etiologies were represented in the study cohorts and the possibility exists that non-demented subjects were included in demented samples. Better delineation of disease features and pathological confirmation will continue to improve the diagnostic accuracy of FTD.

External validity

External validity refers to the generalizability of the findings to other FTD samples and the studies reviewed here were published only in English and represent cross-cultural samples ranging from the United States, Japan, Germany, France and Belgium. There are several issues of concern. First, dementia is a progressive condition
lasting years whose associated features are expected to change over time. In order to generalize findings, it is necessary to make linkages between symptoms and disease severity.

Most researchers relied on the Mini-Mental State Examination (MMSE), a brief screen of cognitive function (Folstein, Folstein, & McHugh, 1975). In AD, it has been suggested that MMSE scores correspond to disease severity (early: MMSE 24-30; mild: MMSE 15-23; moderate: MMSE 8-14; moderately severe: MMSE 4-7; severe: MMSE 0-3) (Kraemer, Taylor, Tinklenberg, & Yesavage, 1998). Yet, MMSE standards for FTD have not been established, and there is evidence that FTD patients score differently than AD patients on cognitive tests. For instance, the MMSE focuses predominantly on memory and language abilities, and FTD patients typically score well on these tests. Also, patients with FTD may demonstrate understanding of cognitive tests, yet may perform poorly, suggesting that they are able to complete the task, but will not opt not to (Snowden et al., 2003). When compared to disinhibited FTD patients, apathetic FTD patients scored lower on the MMSE. Researchers cited the poor effort by apathetic patients and the greater tendency to respond, “I don’t know” to questions (Snowden et al., 2001).

Another concern involves sensitivity of the measures to change over time. The rate of change in MMSE scores appear to be different, with FTD declining at a faster rate than AD (6.7 point for FTD versus 2.3 points for AD (Rascovsky et al., 2005). Thus, FTD patients with high MMSE scores could therefore be falsely perceived as being in mild disease stages. Finally, the MMSE has bias for multiple socioeconomic issues that may influence performance and scores including ethnic factors (Espino, Lichtenstein,
Another way to make comparisons between studies is by a measure of dementia severity. The CDR was developed for use in AD and is used widely in dementia research as a method for staging disease severity (Morris et al., 1997), and has good reliability and validity in this population. However, the influence of the memory score on the total score carries a risk of underestimation of dementia severity in FTD patients. Diehl provides a starting point for this issue by dividing her FTD cohort into two groups using both CDR and MMSE scores (Diehl-Schmid, Pohl, Perneczky, Forstl, & Kurz, 2006).

The first group, considered to have mild dementia severity had CDR scores of 1 and MMSE scores of 23.2 ± 5.8. The second cohort was judged to be moderately to severely advanced with CDR scores of 2-3 and MMSE scores of 15.4 ± 6.9. Researchers showed that apathy severity increased with advancing disease. Further study will help to clarify appropriate dementia staging criteria for FTD.

Issues in sampling and a risk for selection bias affect generalizability of the data. It is widely accepted that the dementias are heterogeneous disorders with great variability in disease manifestation. A small sample size risks omission of unique findings, while a larger sample size risks diluting those unique experiences. Patients with certain types of dementia may be less likely to consent for research. Neuropsychiatric symptoms are common in dementia and the presence of irritability, compulsive behaviors, agitation, and apathy may influence study participation.
Summary of Literature Review

There is evidence that apathy is an early and common symptom of FTD. Apathy not only occurs with greater severity when compared to other types of dementia, its presence helps to discriminate FTD from other dementia conditions. There is some support that two behavioral profiles exist in FTD, one of apathy and one of disinhibition, although patients may show features of both. Differences in study design, mechanisms for staging dementia severity, and the lack of consensus regarding the definition of apathy limit our understanding of whether these two profiles are distinct at the very earliest stages of FTD. Studies to date have focused primarily on whether apathy is present or not, limiting our understanding of how apathy may change with advancing disease. Abulia and akinetic mutism refer to profound states of apathy, yet are rarely used in the literature to describe FTD patients. The identification of discrete components of apathy and exploration of neuroanatomical correlates should further our understanding of how best to define and measure apathy. Future characterization of behavioral symptoms, including apathy, will necessitate incorporation of pathological determinants.

As mentioned earlier, recent consensus criteria have been proposed for apathy in AD and other neuropsychiatric disorders. A deficit in motivation is the core feature of the proposed criteria, and patients must meet criteria in two of three domains involving interest, emotional, or movement deficits (P. Robert et al., 2009). One of the bigger challenges is the view that apathy is a deficit in drive and motivation, phenomena that are difficult to assess and difficult to assign causality. It may be possible that drive and motivational deficits can be inferred, but mechanisms for making this inference are lacking.
In addition, better clarity is needed regarding apathy and the impact on patient’s functional abilities. Deficits in self-care and decreased interest and participation in activities have been described as indications of apathy. Yet, these are functional outcomes rather than symptoms, and caution should be used in assigning cause for these deficits. A decrease in task skill level and productivity may give the appearance of apathy, but could be the result of other cognitive, motor, and behavioral problems. FTD patients often have concomitant deficits in judgment, problem-solving, executive planning, and interpersonal and social conduct that can impact functional abilities. Caution should be taken in assuming that apathy is the primary etiology for functional impairment.

Behavioral symptoms, apathy in particular, are associated with emotional distress for FTD caregivers. Apathy produces varying degrees of functional dependence with greater reliance on caregivers for assuming tasks and responsibilities. Yet, it is unclear whether specific aspects of apathy create distress. For instance, is it more distressful for caregivers to observe inertia or to have a spouse show little interest in them? If apathy symptoms change over time, how do these changes affect the caregiver? What influence does other behavioral, personality, and affective symptoms have in how the caregiver experiences apathy?

It has been suggested that apathy is amenable to treatment (Hastak, Gorawara, & Mishra, 2005; Marin, Fogel, Hawkins, Duffy, & Krupp, 1995). There is mild support that psychosocial interventions with apathetic patients are beneficial in minimizing the negative behaviors (Verkaik, van Weert, & Francke, 2005). Better clarity on an
operational definition for apathy would facilitate development of assessment and measurement techniques needed to monitor efficacy of interventions.

In conclusion, there are many intriguing issues to explore in regard to apathy in bvFTD. There is no clear operational definition and it has not been fully characterized according to severity and how it may change over time. Apathy has been largely viewed as a symptom associated with disease; it may be more fruitful to view it as a syndrome, encompassing several distinct aspects of cognitive, affective, and behavioral features. Due to the prominent role the frontal lobes play in governing drive and motivation, FTD is an excellent condition in which to examine apathy.

Conceptual Framework

It has been established that specific areas of the brain make unique and critical contributions to an individual’s behavior. One of the most well known reports is of a railroad worker, Phineas Gage, who suffered damage to the frontal lobes of his brain when a steel rod was driven through his head. Before the accident, terms to describe Gage included “active, temperate habits, and efficient”, and afterwards as “capricious and vacillating about his plans, and grossly profane”. It was thus suggested that the frontal lobes contribute to aspects of an individual’s drive and social behavior (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Macmillan, 2008). The frontal cortex is now considered to be an important mediator of executive abilities, the organization of movement, and motivation (Fuster, 1991; B. L Miller & Cummings, 2007).

Apathy has been defined primarily as a disorder of motivation (P. Robert et al., 2009); therefore an understanding of what constitutes motivation is warranted (Marin, 1996). Motivation is the force (cognitive, affective, and behavioral) that modulates goal-
directed behavior (Dictionaries., 2005; Marin, 1991), activity that is voluntary and purposeful. Atkinson and Birch (1978) state that motivation requires an appreciation for the “direction, vigor, and persistence of an individual’s actions” (page 4) (Atkinson & Birch, 1978), thus helping to conceptualize motivation as encompassing overt behavior, sustained interest, and emotional commitment. Motivation also requires the ability to set goals, plan action, generate activity, and evaluate outcomes. There exists a voluminous number of theories regarding the underpinnings of motivation ranging from the power of reinforcement, the threat of punishment, hierarchy of needs, and drive reduction. On a basic level, it has been suggested that motivation is influenced by the pursuit of reward, factors that are either intrinsic or extrinsic to the individual. An intrinsic factor might be the personal enjoyment gained from an activity while an extrinsic factor could be a monetary reward for an activity. Figure 1 depicts the general processes involved in goal-directed behavior.
A diminution in motivation (or apathy) results in a behavioral state of diminished goal-directed activity, is a change from the individual’s baseline, is not due solely to environmental or physical constraints, and is measurable (R. Levy & Dubois, 2006). FTD typically involves deficits in the ability to plan and generate actions (Hornberger, Piguet, Kipps, & Hodges, 2008). FTD also changes one’s ability to respond to factors involving reward (Viskontas, Possin, & Miller, 2007). FTD is also noteworthy for it’s dismantling of empathy and emotional reactivity (Kipps & Hodges, 2006; Rankin, Kramer, & Miller, 2005). Therefore, the mechanism or etiology of diminished motivation in bvFTD may be quite unique and encompass multiple factors.
Over the years, models of frontal-subcortical circuitry have been proposed to explain how linkages between the frontal cortex and subcortical structures contribute to drive and motivation (G. E. Alexander, DeLong, & Strick, 1986; J. L. Cummings, 1993). Despite certain limitations, brain-imaging studies have offered clarification of the role that distinct regions in the brain have on behavior. The discovery of multiple pathological mechanisms of FTD, suggests greater heterogeneity in features of the disease (Whitwell et al., 2007). This paper will use the frontal-subcortical circuitry model to explore the phenomena of apathy in the behavioral variant of frontotemporal dementia (bvFTD). Neuroimaging studies examining regional associations for behavior, specifically apathy, in FTD will be reviewed. From a critique of these studies, gaps in knowledge and directions for future research will be identified.

**Neuroanatomy of Apathy**

Research focused on neurodegeneration and damage in the brain has helped clarify the role of the frontal cortex in the development of apathetic states and also suggests that unique aspects of apathy are mediated by different structures. Frontal lobotomies, a procedure once used for psychiatric disturbances induced passivity. White matter in the frontal lobes has been linked to the development of apathy (Poncet & Habib, 1994). Akinetic mutism (a state of profound apathy) has been associated with lesions in the frontal lobe (M. S. Mega & Cohenour, 1997; Tengvar, Johansson, & Sorensen, 2004). The anterior cingulate cortex is involved in drive (Benson, 1993), focus and problem-solving (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). Plaque burden in the anterior cingulate cortex (ACC) has been correlated with apathy in Alzheimer’s disease (AD) (Tekin et al., 2001) and in another study, had a significant association with the
right ACC (Apostolova et al., 2007; Benoit, Clairet, Koulibaly, Darcourt, & Robert, 2004; Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2006; P. H. Robert et al., 2006). Figure 2A &B depict frontal cortex structures.

Figure 2. A & B. Frontal cortex regions.

Subcortical areas have also been implicated in drive and motivation (Carota, Staub, & Bogousslavsky, 2002; Kumral, Bayulkem, Evyapan, & Yunten, 2002; R. Levy & Dubois, 2006; Stuss, Van Reekum, & Murphy, 2000). The basal ganglia, containing the amygdala, globus pallidus, and striatum, play a role in coordinating movement. The amygdala has a specific part in processing the emotional salience of events. The substantia
nigra refers to a group of cells with a functional role in reward and movement. The putamen has a unique role in moderation of self-initiated action (Francois-Brosseau et al., 2009; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). The thalamus influences arousal, wake, and sleep processes. Basal ganglia structures are depicted in Figure 3.

![Basal ganglia structures](image)

Figure 3. Basal ganglia structures.

Aspontaneity has been reported following localized damage to the basal ganglia (M. P. Alexander, Naeser, & Palumbo, 1987; Yamagata, Yamaguchi, & Kobayashi, 2004) and the dorsomedial thalamic nucleus (McGilchrist, Goldstein, Jadresic, & Fenwick, 1993). In an extensive review of the literature, apathy was identified as the most common behavioral symptom following lesions to the caudate (Bhatia & Marsden, 1994). Abulia has been described following lesions to the thalamus and globus pallidus (R. Levy & Dubois, 2006; Strub, 1989). Cases of akinetic mutism have resulted from conditions involving sections of the basal ganglia and the medial thalamus (M. S. Mega &
Cohenour, 1997). Using the Apathy Inventory, discrete aspects of apathy (lack of interest and lack of initiative) in patients with AD correlated significantly with lowered perfusion in the right frontal and inferior temporal regions of the brain (Benoit, Clairet, Koulibaly, Darcourt, & Robert, 2004; P. H. Robert et al., 2006) while emotional aspects of apathy (emotional blunting) negatively correlated with perfusion in the left dorsolateral prefrontal cortex (Benoit, Clairet, Koulibaly, Darcourt, & Robert, 2004).

Frontal sub-cortical circuitry

Five circuits link the frontal lobes with subcortical structures and are associated with distinct behavioral profiles and motor activity (G. E. Alexander, DeLong, & Strick, 1986; J. L. Cummings, 1993; M.S. Mega & Cummings, 1994; B. L Miller & Cummings, 2007). All five circuits involve connections between the frontal lobe, striatal structures (putamen and caudate nucleus), globus pallidus, substantia nigra, and the thalamic nuclei, thus linking the frontal cortex with the basal ganglia and the thalamus. Dysfunction within the frontal sub-cortical circuits have been referred to as “disorders of action” due to a primary role with behavioral output versus perception or stimulus integration (M.S. Mega & Cummings, 1994).

Of the five frontal-subcortical circuits, two influence motor function while three are related to behavior and cognition. Of these three behavioral circuits (see Figure 4), motivation, drive and initiation is linked to the circuit originating in the anterior cingulate cortex (ACC) located in the medial prefrontal cortex (PFC), Brodmann’s area 24. Referred to as either the medial frontal circuit or the anterior cingulate circuit, direct pathways travel from the ACC to the ventral or limbic striatum (comprised of the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle).
From there, projections pass to the rostromedial globus pallidus, ventral pallidium, and rostrodorsal substantia nigra. The ventral pallidium communicates with the ventral anterior nucleus of the thalamus, and returns to the ACC. Damage to this circuit is associated with apathy (Bonelli & Cummings, 2007; J. L. Cummings, 1993).

The dorsolateral prefrontal circuit (DLPFC) is recognized as an important moderator of executive function: the ability to set goals, anticipate and plan for the future, and generate motor activity (Kirshner, 2002). The DLPFC originates in Brodmann’s area 9 and 10 with projections to the dorsolateral head of the caudate nucleus, globus pallidus, thalamus, and return to the prefrontal cortex. Damage results in executive dysfunction (Bonelli & Cummings, 2007).

The third behavioral circuit is the orbitofrontal circuit (OFC) important in modulation of personality, socially appropriate behavior, and empathy. The circuit originates in Brodmann’s area 10 and 11 and projects to the ventromedial caudate. Pathways continue to the globus pallidus, substantia nigra, lateral subthalamic nucleus, thalamus, and return to the prefrontal cortex. Damage to this circuit causes disinhibition, irritability, emotional lability (Bonelli & Cummings, 2007), and diminishes an individual’s sensitivity to the emotions of others (as measured by performance on cognitive tests of empathy) (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). Figure 4 is an illustration of the three behavioral and cognitive circuits.
The two motor circuits linking frontal cortex with subcortical structures are an oculomotor and a motor circuit. The oculomotor circuit modulates frontal eye fields and movement while the motor circuit links the supplementary motor area and cortex. Sections of the frontal lobes (primary motor cortex, medial frontal, and premotor areas) are the site of planning and coordination of movement. Information is sent via Brodmann’s area 6 to the primary motor cortex (Brodmann’s area 4) that activates muscles via motor neurons in the spinal cord. Lesions in the medial frontal area cause disorders of voluntary movement and damage to the supplementary motor circuit results in decreased verbal fluency and verbal output (M. P. Alexander, Benson, & Stuss, 1989).

Connections within the frontal-subcortical circuits are mediated via excitatory (glutamate) and inhibitory (y-aminobutyric acid or GABA) fibers. The frontal cortex processes information from the internal and external environment. The neural signals are sent to the basal ganglia for processing and refinement. Direct and indirect pathways...
carry input to the thalamus: damage within the direct pathway causes thalamic inhibition while damage to the indirect pathway results in thalamic over-activity. Signals are transferred back to the frontal cortex, ultimately modifying behavioral output. Damage of one structure carries influence over the entire circuit in the capacity to select, initiate, and maintain behavior (Tekin & Cummings, 2002).

Frontal Lobe Neurotransmitters

Neurotransmitters have important functionality with regard to behavior (Tekin & Cummings, 2002). Dopamine and serotonin both project from the cortex to subcortical structures. Serotonin (5-hydroxytryptamine, 5-HT) is found in high concentrations particularly the cingulate cortex, and motor and premotor areas. 5-HT receptors control the release of many of the neurotransmitters and hormones that modulate a wide variety of normal and abnormal behaviors including mood, movement, compulsions, and appetite.

Dopamine, found in high concentrations in the nucleus accumbens and prefrontal cortex, modulates mood, emotion, and thinking. Dopamine appears to play a role in reward and attention-based learning (R. Levy & Dubois, 2006) and associated with linking pleasure to motivation to perform activities. Dopamine is implicated in control of movement, with depletion in the midbrain being a critical feature of Parkinson’s disease (Arias-Carrion, Poppel, 2007). Medications that block dopaminergic activity cause a decline in motivation and a lowered feeling of well-being.

The blockade of dopaminergic and serotonergic neurons between the frontal cortex and sub-cortical structures and excessive GABA are linked to diminished drive (Tekin & Cummings, 2002). Serotonin and dopaminergic deficits have been identified in
FTD (Huey, Putnam, & Grafman, 2006) and specific regions in the brain have been implicated. Post-mortem studies of FTD patients identified a reduction of serotonin neurons in the frontal cortex and temporal cortex (Procter, Qurne, 1999), the nucleus centralis superior and nucleus raphe dorsalis (Yang, Schmitt, 2001). Franceschi et al (2005) found marked reductions of 5-HT receptor densities in frontal and cingulate cortex regions (Franceschi et al., 2005). Dopamine depletion in the striatum, caudate nucleus, and putamen has been associated with extrapyramidal symptoms in patients with FTD, with scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) negatively correlated with radiotracer uptake (Rinne et al., 2002; Sedaghat et al., 2007).

**Neurodegeneration in FTD**

*Neuroimaging techniques*

Neuroimaging studies provide data on the neural mechanisms for brain and behavior in dementia (Hodges, 1992; Williams, Nestor, 2005; Edwards-Lee, 1997). Imaging techniques are designed to highlight areas of atrophy or metabolic underactivity. Brain imaging has become increasingly important in the evaluation, care, and study of patients with suspected neurodegenerative diseases. Serial imaging has been used to measure atrophy and disease progression over time, and has become an accepted biomarker for outcome measurements in clinical trials of treatments for dementia (O'Brien, 2007). Magnetic resonance imaging (MRI) has the ability to detect structural damage and atrophy patterns characteristic of different types of dementia via visual inspection and measurements of regions of interest (Whitwell, 2009). Voxel-based morphometry (VBM) of MRI data is a technique for analyzing focal differences in brain structures and facilitates statistical comparisons of gray matter concentration. The
technique permits large numbers of MRI scans to be evaluated together allowing for
group analysis (Ashburner & Friston, 2000; Good et al., 2001; Whitwell & Jack, 2005). Techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are aimed at measuring cerebral perfusion within the brain through the use of injected radionuclides. Diffusion tensor imaging (DTI) is used primarily for analysis of white matter (Whitwell, 2005). Arterial spin labeled MRI (ASL-MRI) is a non-invasive method for quantifying cerebral perfusion (Detre, Wang, Wang, & Rao, 2009).

*Neuroimaging and FTD*

Behavioral variant FTD (bvFTD) essentially targets all frontal-subcortical circuits with damage to the frontal (dorsolateral, orbital, and medial) lobes and these atrophy patterns help to distinguish FTD from AD (Bocti, Rockel, Roy, Gao, & Black, 2006; Rabinovici et al., 2007). The right frontal, frontoinsular, anterior cingulate, and orbitofrontal cortex have been implicated as early and primary sites of degeneration in FTD (Boccardi et al., 2005; Perry et al., 2006; Rosen et al., 2002; W. W. Seeley et al., 2008; W. W. Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Hypoperfusion has been documented in the frontotemporal regions among patients with FTD; these patterns of reduced glucose uptake help to differentiate FTD from AD (B. L. Miller et al., 1991; Salmon et al., 2003). In a comparison study between FTD (n=21), AD (n=24), and normal controls (n=25), ASL-MRI was used to detect differences in hypoperfusion patterns. FTD was associated with bilateral hypoperfusion in the middle and right frontal cortex while AD was associated with posterior hypoperfusion (parietal and posterior cingulate) (Du et al., 2006).
VBM was utilized in 2 studies examining volume changes in the caudate nucleus and putamen among patients with dementia. The study cohorts consisted of patients with bvFTD (n=12), semantic dementia (n=13), progressive non-fluent aphasia (n=9), Alzheimer’s disease (n=19), and normal controls (n=19). Mini-mental status examination scores and disease duration (in years) were used to stage dementia severity. In the first volumetric study, the caudate nucleus was significantly smaller among the FTD subtypes compared to both controls and patients with AD. Mean volumes among the dementia cohorts were lowest in the bvFTD group (75%) compared to AD (93%). Volume loss was weakly associated with MMSE scores (Looi et al., 2008). In a volumetric examination of the putamen among the same study cohorts, volume in the right putamen was lower among the dementia cohorts compared to normal controls, but there were no volume differences found in the left putamen (Looi et al., 2009).

Recent work has highlighted the presence of network degeneration uniquely tied to different dementia etiologies (Schroeter, Raczka, Neumann, & Yves von Cramon, 2007). Using VBM of MRI’s of patients early in disease (with a Clinical Dementia Rating score of 1 or less), Seeley et al (2009) demonstrated that bvFTD, semantic dementia, corticobasal syndrome, progressive non-fluent aphasia, and Alzheimer’s disease had dissociable atrophy patterns that followed distinct functional neural networks. For example, an episodic memory network correlated to patients with AD, while patients with bvFTD mirrored a frontoinsular and emotional salience network. These atrophy patterns were unique to each diagnostic group (W. W. Seeley, Crawford, Zhou, Miller, & Greicius, 2009).
It has been suggested that Von Economo neurons (VENs) serve as the locus for earliest degeneration in FTD. VENs are located in the ACC and the frontoinsular (FI) cortex of humans, certain chimpanzees, gorillas (Nimchinsky et al., 1999), elephants (Hakeem et al., 2009), dolphins (Butti, Sherwood, Hakeem, Allman, & Hof, 2009), and whales (Hof & Van der Gucht, 2007), all creatures capable of varying levels of sophisticated social and emotional function. Seeley et al (2006) compared features and amounts of VENs in tissue from the anterior cingulate cortex of patients with FTD and AD. Researchers documented a 69% reduction in VENs in the FTD samples compared to AD, where the number of VENs remained unchanged with disease. In addition, VEN shape was often dysmorphic and contained abnormal amounts of tau inclusions in FTD samples (W. W. Seeley et al., 2006). These findings may help to explain the early and profound devastation in social, behavioral, and cognitive abilities observed in FTD.

**FTD and apathy**

The following studies were selected for review due to their focus on associations between tissue loss or hypometabolism in the brain and apathy among patients with FTD. Studies were selected for review if they were published after 2001, the date of the most recent consensus criteria for FTD (McKhann et al., 2001); this date was selected as a way of increasing diagnostic accuracy in the study cohorts.

*Neuroimaging studies of apathy in FTD*

Rosen and colleagues (2005) utilized voxel-base morphometry (VBM) of magnetic resonance imaging (MRI) data to explore correlations between behaviors and tissue loss in the brain. The study group consisted of a combined cohort of dementia patients (n=148); diagnoses included FTD, semantic dementia, progressive non-fluent
aphasia, corticobasal degeneration, progressive supranuclear palsy, and AD. Dementia severity was rated using the Clinical Dementia Rating (CDR) scale with a mean of 0.9 (± 0.6 SD) and the Mini-Mental State Examination (MMSE) with a mean of 21 (± 7.7 SD). The relationship between voxel values and Neuropsychiatric Inventory (NPI) (J. Cummings, 1997) total scores of 12 neuropsychiatric symptoms were analyzed. The NPI is administered via interview with a person knowledgeable about the patient and a person trained in how to administer it. For each endorsed behavior, a score is obtained by rating the frequency and severity of that behavior. A total score is the sum of the products of the frequency and severity. Four behaviors correlated with tissue loss; apathy, disinhibition, eating disorders, and aberrant motor behavior. The most common behavior was apathy (62% of patients). Among the patients with FTD, apathy was one of four behaviors that showed significant correlation between NPI score and tissue loss. These regions were within the right hemisphere and included the ventral ACC, ventral medial superior frontal gyrus, posterior ventromedial prefrontal cortex, the middle frontal gyrus, caudate head, the orbitofrontal cortex, and anterior insula. There was sizeable overlap between all four behaviors and these seven regions, although there was a unique effect (p<0.05) for apathy and tissue loss in the ventral medial superior frontal gyrus (Rosen et al., 2005).

Zamboni and colleagues (2008) used VBM and apathy scores from the Frontal Systems Behavior Scale (FrSBe) to analyze correlations between behavior scores and volume loss in the brain. The FrSBe is a 46-item scale designed to quantify behaviors associated with frontal lobe damage. Items fit into three subscales: apathy, disinhibition, and executive dysfunction (Malloy, Tremont, Grace, & Frakey, 2007). Forty-eight
patients meeting criteria for FTD were compared with 14 patients with aphasic presentation and 14 age-matched normal controls. The Mattis-Dementia Rating Scale (DRS) and MMSE scores were obtained but not reported, although other demographic values (age, disease duration, and MMSE score) were not statistically different among the groups. In the right hemisphere there was a significant correlation between volume loss and severity scores for both apathy and disinhibition. Apathy scores correlated with volume loss in the bilateral dorsolateral prefrontal cortex (DLPFC), right lateral OFC, right temporoparietal junction, ACC, and right putamen (p uncorrected < 0.001).

Regression analysis demonstrated that 32.7% of the variance in FrSBe Apathy scale scores was explained by values in the right and left DLPFC and the Mattis-DRS. Items pertaining to executive function were reportedly associated with the DLPFC as well, although data were not reported (Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008).

Massimo and colleagues (2009) utilized VBM to investigate the relationship between volume loss and distressing behaviors for caregivers of FTD patients. While the focus of this study was caregiver distress, the neuroanatomical findings are of interest. Two FTD cohorts were compared; one with a behavioral/executive profile (n=26) and the other with an aphasic profile (n=14). Neary criteria were used to establish diagnosis and dementia severity was based on MMSE scores with mean scores of 21.8 (± 9.1 SD) for the behavioral/executive cohort and 26.2 (± 3.1 SD) for the aphasic cohort. Symptoms associated with the highest levels of caregiver distress were apathy and disinhibition (p < 0.005), with apathy causing the highest level of distress for both the behavioral/executive and aphasic cohorts. Apathy significantly correlated with atrophy in the dorsal anterior cingulate cortex and right dorsolateral prefrontal cortex regions (Massimo et al., 2009).
A comparison of two groups of FTD patients (one with apathy and one without) did not find an association between apathy and changes in the basal ganglia (Links et al., 2009). Regional volumetric information of the striatum and thalamus was calculated. Of the 21 patients with FTD, 15 had evidence of apathy according to caregiver rating on the NPI. Researchers used the MMSE and disease duration in years to stage dementia severity. Apathetic patients had slightly higher mean MMSE scores than non-apathetic patients (23.7 ± 6.3 versus 20.8 ± 8.8 respectively) although disease duration was longer (4.6 years ± 3 versus 2.9 ± 2 respectively). Researchers found no differences in subcortical volume between the apathetic and non-apathetic patients (Links et al., 2009).

Peters et al (2006) studied 41 bvFTD patients using positron emission tomography and the [18] fluorodeoxyglucose method (FTD-PET). This method of measuring sugar uptake in the brain is used as a measure of metabolic activity. The apathy subscale of the NPI was used to dichotomize patients into two groups, one with apathy (NPI apathy score over 8, n= 13) and one without apathy (NPI apathy score below 4, n=12). Dementia severity was staged using the Clinical Dementia Rating scale (CDR) and duration of illness in months. FTD patients had a mean CDR score of 1.5 (± 0.8 SD) and mean disease duration of 38.9 months (± 27.3 months SD). Hypometabolism in the gyrus rectus of the orbitofrontal cortex was identified in the apathetic, and not the non-apathetic cohort, although this was not a statistically significant difference (Peters et al., 2006).

Franceschi et al (2005) examined associations between apathy and disinhibition in 18 bvFTD patients and cerebral glucose uptake in the brain. A measure of function, the Instrumental Activities of Daily Living and disease duration in months were used to stage
dementia severity. Apathetic patients had mean disease duration of 28 months (ranging from 12-72 months). All bvFTD patients showed reduction in glucose uptake in the orbitofrontal cortex, frontal cortex, anterior cingulate cortex, dorsolateral cortex, temporal medial cortex, basal ganglia, and thalamus. Apathy showed a unique association with reduction of FDG uptake in the dorsolateral frontal cortex (Franceschi et al., 2005).

**Discussion**

*Apathy and frontal-subcortical circuitry*

The frontal-subcortical model links apathy to the anterior cingulate/medial frontal circuit; the majority of studies, while confirming this relationship, suggest involvement of additional regions. Massimo (2009) and Zamboni (2008) both found an association between apathy and the DLPFC (a site implicated in executive functioning). Massimo et al (2009) found a correlation between the right DLPFC and apathy, while the left side correlated with disinhibition. Zamboni et al (2008) found a correlation between apathy and bilateral atrophy of the DLPFC. Massimo et al (2009) also found correlations between apathy and regions of the temporal lobe. Zamboni et al (2008) also found an association between apathy and the OFC, a site implicated in emotional processing. Rosen and colleagues (2005) found an association between apathy and the vmSFG, an area also implicated in emotions. The metabolic studies also revealed associations with apathy and regions beyond the anterior cingulate/medial frontal circuit. Peters (2006) identified the orbitofrontal cortex and Franceschi (2005), while showing evidence of involvement of all three circuits, also found a unique association with the dorsolateral cortex. Links (2009) did not find an association between apathy and basal ganglia
structures, even though these structures appear to be affected in FTD (Franceschi et al., 2005; Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008).

There are several potential explanations for the discrepancies between these research findings. Apathy in bvFTD probably reflects damage that extends beyond the anterior cingulate/medial frontal circuit. It has been suggested that while each of the five frontal-subcortical circuits is composed of dedicated neurons, openings exist within the circuits that link with other regions in the brain (M.S. Mega & Cummings, 1994). Due to these openings and the proximity of the circuits to one another, damage to one may cause damage to another (M.P. Alexander & Stuss, 2000).

Alternatively, the assessments may be identifying phenomena not specific to apathy and it may be fair to ask, “What is being studied?” All of the studies assessed the presence of apathy using measures that incorporate varying degrees of cognitive, emotional, and movement features. The NPI, used by Massimo (2009), Rosen (2005), Peters (2006), and Franceschi (2005) in assessing apathy, asks a stem question focused on whether the patient’s interest in activities or others has diminished in the past three months. Not only does this focus primarily on a cognitive aspect of apathy, “interest” is a difficult state to assess. The NPI apathy stem question and sub-questions are outlined in Appendix 3. The FrBSe used by Zamboni et al (2008), is organized around three domains (apathy, executive dysfunction, and disinhibition) and contains 14 items related to apathy. There is potential overlap between executive dysfunction and apathy. A reduction in goal-directed activity could be attributed to problems with planning, problems with initiation, or problems with both. Additionally, patients with bvFTD can have damage to the left frontal lobe resulting in lowered verbal output. A patient who
doesn’t engage in conversation or is quiet may give the appearance of apathy. Thus, occurrence or prevalence rates of apathy may be either under or over-reported.

There is mixed evidence regarding the contribution of the basal ganglia in the development of apathy in bvFTD. The lack of consistent findings could be attributed to small sample size (Links, 2009) or due to problems discussed earlier relating to structural imaging, dementia severity ratings, and/or difficulties studying patients in the earliest stages of disease.

**Gaps in Knowledge**

**Study cohorts**

Not all studies used a pure bvFTD cohort. A limitation of Massimo (2009) and Rosen (2005) was the constitution of their samples. By grouping behavioral and dysexecutive patients into one cohort, Massimo et al (2009) may have found associations with structures contributing to both executive dysfunction and apathy. Rosen et al (2005) grouped FTD and semantic dementia patients together into one cohort, although it has been shown in earlier work that patients with frontal versus temporal disease have more severe apathy (Liu et al., 2004; Snowden et al., 2001). In addition, patients with right temporal disease often exhibit self-centeredness, a factor that might influence an informant’s rating of apathy.

**Dementia severity**

The lack of a valid and standard method for staging dementia severity in FTD limits interpretation of the findings. In order to stage dementia severity, Rosen (2005), Massimo (2009), and Peters (2006) utilized the CDR, Zamboni (2009) used the Mattis-Dementia Rating Scale (DRS), and Franceschi (2005) used an activities of daily living
tool originally developed for use in older adults (Lawton & Brody, 1969). Many of these measures were developed for use with AD and have not been validated in FTD, a conflict in making comparisons between these types of dementia. Several of the researchers used disease duration as a method for staging the study cohorts, but they did not state how this was derived. For instance, was onset of disease timed from initial symptom(s) or time of diagnosis? There are often delays for FTD patients in obtaining the appropriate diagnosis (Pijnenburg, Gillissen, Jonker, & Scheltens, 2004), therefore clarification of how onset of disease is defined is critical. A consistent method for rating severity in bvFTD would facilitate comparisons between studies. None of the studies evaluated apathy longitudinally, leaving gaps in our knowledge of how apathy manifests over the course of the disease. Better methods of staging dementia severity could help facilitate the characterization of apathy through the disease trajectory.

**Operational definition of apathy**

Another limitation of these studies is the lack of a standardized and operational definition for apathy. This problem in definition does suggest that apathy assessments may be identifying features of other cognitive, behavioral, and emotional phenomena. It also suggests that important aspects of apathy are not being assessed adequately, a conflict that could hamper the identification of salient neuroanatomical circuits and networks that are impaired in apathetic patients with bvFTD.

**Neuroimaging**

There are limitations in using brain imaging techniques in the study of behavioral symptoms in dementia. Behavioral symptoms of the disease can precede detectable atrophy on brain imaging (Perry et al., 2006) and by the time atrophy is detectable,
symptoms may have progressed. It should be noted that frontal and temporal atrophy are only supportive features of FTD (McKhann et al., 2001; Neary et al., 1998) and the diagnosis can be made in the absence of atrophy. Also, FTD patients manifest with heterogeneous patterns of brain atrophy and disease progression (Davies et al., 2006). For example, FTD patients with progranulin (PGRN) mutations showed more widespread atrophy involving frontal, temporal, and parietal lobes compared to patients without the mutation (Whitwell et al., 2007). Therefore results may not be generalizable to all patients with FTD.

Links et al (2009) showed evidence that the basal ganglia is not more atrophied in patients with apathy and suggested that structural neuroimaging may not be the ideal method for capturing regional dysfunction. When comparing cerebral blood flow data against autopsy findings, SPECT had a sensitivity of 80% and specificity of 65% in distinguishing between AD and FTD (McNeill et al., 2007). Yet, it has been proposed that metabolic studies reveal deficits in glucose uptake in the absence of detectable tissue atrophy from structural imaging (Franceschi, 2005).

There are validity and reliability issues concerning VBM. Processing MRIs for VBM analysis is a multi-stage process. These processes include spatial matching of the scans (called spatial normalization), portioning the scans according to white matter, gray matter, and cerebrospinal fluid, and smoothing the scans (the intensity of each voxel is replaced by the average of the surrounding voxels). Each step carries the risk of error and increased variability. Smoothing may increase the sensitivity to detect change within the group of scans, but may diminish specificity in identification of discrete localization of damage in the brain (Ashburner & Friston, 2000).
Gaps in Research

Operational definition of apathy

While the core deficit in apathy is diminished motivation, most definitions also include aspects of cognitive (interest) and affective (emotion) change. Yet, these are difficult phenomena to define, and therefore, difficult to assess. Studies to date evaluating the presence of apathy in bvFTD have relied primarily on the NPI, a tool guided by an initial question focusing on diminished interest. This problem in definition contributes to an uneven perspective of what constitutes apathy in bvFTD. The use of a standard and accepted definition of apathy would facilitate its’ characterization across the disease trajectory of bvFTD. A standard definition would also help in the identification of specific structures and processes implicated in apathetic conditions.

Characterization of apathy over different disease trajectories

The existence of different pathological mechanisms for bvFTD implies a varying manifestation of the disease and associated symptoms. The neurodegenerative process of bvFTD appears to affect an interconnected system, responsible for behavior, cognitive processes, and emotion. Perhaps patterns and features of apathy are influenced by dementia type, cellular and pathological etiologies, and genetic versus sporadic causes for disease.

Objective measurement of apathy

Interest and concern are psychological constructs, subjective in nature, and difficult to measure. The behavioral component of apathy may prove more fruitful to measure. Showing initiative, participation in activity, and the ability to engage and generate goal-directed tasks are examples of behavioral output that could be the focus of
objective measurement. This objective, or functional perspective of apathy might also link with future strategies aimed at treating apathetic conditions.

Summary

Frontal-subcortical circuitry provides a framework for understanding apathy in bvFTD. Patients in the early stages of bvFTD often present with profound deficits in drive and initiative: these symptoms are the result of damage to multiple structures within the frontal-subcortical circuits. The effect of this damage likely influences a cascade of changes due not only to neuronal death and tissue loss, but to perturbations in neurotransmitter functions (serotonin and dopamine) that influence motivation, affect, and other aspects of social and personal regulation.

The studies reviewed here show evidence that circuits beyond the anterior-cingulate cortex are implicated in apathy among patients with bvFTD: damage to the dorsolateral and orbitofrontal circuits appear to be involved as well. The dorsolateral circuit helps an individual with planning goals and activities while the orbitofrontal circuit aids in the identification of emotional saliency. It has been suggested that dementia symptoms may be the result of damage to larger networks of brain regions, and that damage in one area in conjunction with damage elsewhere could result in a more profound and severe form of apathetic behavior (Rosen et al., 2005). The identification of different pathological mechanisms for FTD and potential differences in genetic versus sporadic forms of disease suggest heterogeneity in disease progression and symptom severity, and may also explain some of the inconsistencies regarding regions affected by apathy.
There is need for a consistent and standard definition for apathy. Studies on apathy to date have relied exclusively on the NPI, and this rating tool may or may not adequately capture salient aspects of apathy. Behavioral variant FTD (bvFTD) is an excellent model for this focus of study, and could help to clarify an objective measurement of diminished drive and motivation.

Aims of This Study

This study proposes to characterize the movement aspect of apathy. The approach used will be a comparison between two cohorts of patients, one with behavioral variant FTD (bvFTD) and one with Semantic dementia (SD) using actigraphic data of movement and informant ratings of behavior and emotional distress. The working hypothesis is that patients with FTD will have ratings of apathy that correspond to low measures of daytime activity. A second aim is to describe the impact of apathy on the family caregiver. The working hypothesis is that apathy will be associated with emotional distress for the caregiver. Findings from this study will contribute to a more precise definition of apathy and to our knowledge of the impact that apathy has on the movement of patients with FTD and their caregivers.
Chapter 3
Methodology

Research design

This is a descriptive cross-sectional study of daytime activity and behavior of patients with FTD. Two groups of patients along with their primary family caregivers were included, one bvFTD and the other SD.

Research setting and sample

Patients were recruited using a convenience sample approach. Patients and their family caregiver were recruited from an ongoing NIH-funded Program Project Grant (PPG) examining FTD at the University of California, San Francisco Memory and Aging Center entitled “Genes, Images and Emotions.” Consent for participation in the study on rest-activity was obtained according to approved Institutional Review Board guidelines. We enrolled 22 patient-caregiver dyads from the bvFTD and SD subgroups: 13 FTD and 9 SD. All patients resided at home with their caregivers. Clinical diagnoses were established by consensus agreement of a panel of experts consisting of a neurologist, neuropsychologist, and a clinical nurse specialist. Neary criteria were used to establish the diagnosis of FTD (Neary et al., 1998).

Due to the description nature of this project, a power analysis was not calculated. However, prior research on rest-activity patterns in dementia has been conducted on sample sizes as small as 5 per diagnostic category (Harper et al., 2001) to as high as 110 (Nagels et al., 2006).

Data collection methods

1. Techniques
Activity and movement data was collected using actigraphy. Semi-structured interviews and surveys were conducted with family caregivers to collect data on behavioral symptoms, sleepiness, dementia severity, and demographics. Caregivers also maintained a “sleep diary” or record of sleep/wake habits for both the patient and themselves and these were used to validate the scoring of the actograms. Cognitive status of the patients was obtained via testing by a neuropsychologist.

II. Description of instruments and apparatus:

Rest-activity data were collected using MiniMitter Actiwatch monitors (AW-64). Actiwatches are wristwatch size devices that use an accelerometer to monitor the occurrence, degree and speed of motion. Actigraphy is movement-based monitoring used widely in sleep and circadian rhythm research based on the premise that activity is more prominent during wake periods and less prominent during sleep (Ancoli-Israel et al., 2003; Morgenthaler et al., 2007). Actigraphy provides objective movement data that it used to make inferences about a person’s activity patterns. A signal reflecting magnitude and duration of motion is generated, amplified and digitized by an on-board circuit. This information is stored in memory as activity counts. The Actiwatches were programmed to collect data at one-minute epochs continuously over the 2-week data collection period. Data were analyzed for daytime (from “lights on” in the morning to “lights off” at bedtime), bedtime (from ”lights off” to “lights on”), and the sleep interval that lies within the bedtime interval (the period between sleep start and sleep end).

Daytime activity outcome variables included:

a) Length of the daytime interval

b) Average activity counts per minute
c) Percentage immobile (percentage of time without activity during the day)

d) Number of hours spent immobile

e) Number of daytime immobility bouts

f) Immobility bout duration (in minutes)

The NPI, a structured interview with established reliability and validity, assesses 12 neurobehavioral domains and the severity of caregiver’s distress. Clinical Nurse Specialists trained in the administration of the NPI completed the ratings with family caregivers. The behavioral domains include: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and eating/appetite. There is a yes or no screening question for each domain. If respondents answer affirmatively, further questions are asked in order to rate the behavior in terms of frequency, severity and caregiver distress. Frequency is scored as 1=less than once per week, 2=about once per week, 3=several times per week, 4=very frequently. Severity is scored as 1=mild, 2=moderate, 3=marked. Caregiver’s distress is rated for each endorsed behavior and is scored as: 1=minimal, 2=mild, 3=moderate, 4=severe, and 5=very severe. The behavioral domain score is the product of the frequency and severity. A total scale score is calculated by adding the domain scores. The total caregiver distress score is the sum of each domain rating.

Adjunctive data is necessary in clarifying the inferences made about activity derived from actigraphy. Subjective data about patients’ daytime sleepiness (Epworth Sleepiness Scale) was collected from the caregiver. The ESS is an 8-item questionnaire measuring general level of daytime sleepiness and tendency to doze during passive activities (Johns, 1991). Scores range from 0-24, with a score of 10 or more indicating
excessive sleepiness. An example of the ESS is included as Appendix 4. Depression is rated using ratings by the caregiver on the NPI. The Barthel Index (BI) is a measure of performance and ability in self-care and mobility (Mahoney & Barthel, 1965). The ten variables assessed by the BI are bowel and bladder control, personal hygiene, transfers, walking, and stair climbing. Scores range from 5-10 per variable with 100 as the highest possible score. In this study, completion of the BI is via a semi-structured interview by the clinical nurse specialist and the caregiver. For the purpose of this study, data from the BI is used to assess whether patients have restricted mobility. An example of the BI is included as Appendix 5.

Supplemental logs or diaries are considered fundamental for the verification of scoring the sleep and activity intervals (Berger et al., 2008; Murphy, 2009), for estimating typical behavior patterns, and thus critical to enhancement of the reliability of actigraphy data.

The CDR and MMSE are used to provide a measure of the severity of the patient’s dementia. The CDR was developed for use in AD and is used widely in dementia research as a method for staging disease severity (Morris et al., 1997), and has good reliability and validity in this population. The Mini-Mental State Examination (MMSE), a brief screen of cognitive function (Folstein, Folstein, & McHugh, 1975) has been used in many studies as a method of staging disease severity.

III. Reliability and Validity

Staff training is required for all aspects of the study protocol. Staff completed the Institutional Review Board (IRB) certification program. Study staff attended periodic research meetings to discuss issues and concerns with study protocol. Staff administering
the CDR completed required certification and standard training from the UCSF Memory
and Aging Center’s nursing staff for administration of the NPI. Questions regarding
appropriate scoring of the actigraphy data were decided by consensus of study staff
trained in the scoring and application of actigraphy.

Developed in the early 1970’s, actigraphy has become an accepted method for
studying the rest-activity rhythm in patients with dementia (Ancoli-Israel et al., 2003;
Littner et al., 2003). Research and practice parameters developed for actigraphy have
focused on sleep and circadian rhythm disorders (Ancoli-Israel et al., 2003; Littner et al.,
2003; Morgenthaler et al., 2007); its use in movement disorders has not been as well-
defined.

The Neuropsychiatric Inventory (NPI) (J. L. Cummings et al., 1994) is ubiquitous,
has established reliability and validity (J. Cummings, 1997), and has been validated in
multiple racial and ethnic populations among patients with dementia.

The ESS is able to discriminate normal subjects from those with a variety of sleep
disorders and has high internal consistency (Cronbach’s alpha = .88) and high inter-rater
reliability (r = .82) (Johns, 1992).

The BI has been used extensively among patients undergoing rehabilitation from
stroke and has demonstrated good reliability and validity (Sainsbury, Seebass, Bansal, &
Young, 2005; Wyller, Sveen, & Bautz-Holter, 1995).

Procedure

Demographic information, the CDR, NPI, and MMSE were collected at the
patients’ annual PPG visits and patients and their caregivers were informed about the
rest-activity study. After consenting to participate in the study, patients and their primary
family caregivers were fitted with an actiwatch and received verbal and written instructions including research staff contact information. Subjects were instructed to affix the actiwatches to their non-dominant wrist on the following Monday afternoon and to wear them for 2 weeks. At the end of the 2-week data collection period, the watches, diaries and questionnaires were returned to study staff in a self-addressed, pre-paid mailer and the data was subsequently downloaded and scored.

Data analysis

Actigraphy records were analyzed for both patient and caregiver dyads at the medium sensitivity setting. Areas of validated “watch off” time were deleted from analysis as well as any periods greater than 2 hours when there was no recorded activity, indicating the watch was most likely off the wrist. Records for both members of each dyad were “matched” by deleting identical periods on both records to ensure accuracy in comparison. For example if the patient had removed the watch one night, the data for both patient and caregiver were excluded on that night. To facilitate visual comparison, the actogram activity scale was calibrated to be the same for both data sets. Raw actigraphy data were subjected to a scoring algorithm in the Actiware software. Bed and rise times were interpreted by the analyst based on diary entries and the raw data. Actiware and Statistical Package for the Social Sciences (SPSS) software were used for data analyses. For all variables, nonparametric independent samples were employed to compare patients with FTD to SD, and FTD caregivers to SD caregivers and to compare the FTD and SD patient groups with their respective caregiver groups.
Chapter 4

Results

Means, standard deviations, and frequencies of subject demographics are summarized in Table 1. Mini Mental State Examination (MMSE) scores were significantly lower among the patients with SD compared to FTD (p=.03). Clinical Dementia Rating (CDR) scores were higher (indicating greater dementia severity) for the patients with FTD compared to SD (1.6 versus 1.0) (p=.034). Average Epworth Sleepiness Scale (ESS) scores were 7.38 (7.44) for FTD and 6.00 (2.5) for SD with a range of 23 and 6.5 respectively. Four patients with FTD and one patient with SD had ESS scores greater than 10 indicating a propensity for daytime sleepiness. The Barthel Index (BI) scores demonstrate greater physical impairment among the patients with FTD compared to SD, although this reflected need for assistance with personal care and hygiene and not problems with independent movement. Only one patient with FTD required minor help with walking; all other patients were rated as independent in transfers, mobility, and stair climbing.

Means and standard deviations for daytime variables were calculated and are summarized in Table 2. In all measures of daytime activity, patients with FTD were less mobile than their caregivers. Mean daytime activity count was significantly lower (p=.009) in patients with FTD compared to caregivers. Patients were immobile 25% of the daytime hours while their caregivers were immobile 11% of the daytime interval (p=.005). For the average FTD patient with a daytime period length of 14.24 hours, 3.49 hours were spent immobile. Although patients with SD had similar characteristics (lower activity counts, higher percentage of time immobile) compared to their caregivers, these
differences did not reach statistical significance. A Spearman rho correlation coefficient was calculated for the relationship between the patients total apathy score and number of immobility bouts and their duration. A strong positive correlation was found ($\rho (11) = .756, p = .01$), indicating a significant relationship between apathy score and number of immobility bouts among patients with FTD but not SD: apathetic patients with FTD had greater number of immobility bouts. Both groups of caregivers had daytime intervals that were longer than the patients.

Apathy was endorsed by all of FTD caregivers who also rated it as occurring very frequently. Apathy was endorsed by all but one SD caregiver, with four rating it as occurring frequently and three as very frequently. Of the 12 behavioral domains assessed by the NPI, apathy was significantly correlated with distress for caregivers of both FTD and SD patients. There was no evidence of depression among the patients with bvFTD as rated by their caregivers. Three patients (33%) with SD were rated by their caregivers as having depression occasionally ($n=1$) or often ($n=2$). Total NPI score correlated significantly with caregiver distress for both FTD and SD. Table 3 summarizes scoring for the 12 behavioral domains along with correlation coefficients.

Averages of hourly activity scores for the patients and caregivers are shown in Figure 5. Upon visual inspection, the lowest amount of daytime activity was found in the FTD patient group followed by the patients with SD. The caregivers of both groups are relatively similar. Both show overall greater activity than the patient groups, yet activity in the FTD caregiver group is lower during the afternoon hours compared to the SD caregivers.
Chapter 5

Discussion

The results from this exploratory study provide objective data on activity and behavior in FTD and SD that can be applied toward a definition of apathy. Of note, the results reflect activity and behavior in a cohort of patients in the relatively mild stages of disease as characterized by their CDR ratings and MMSE scores. Daytime activity was lower in both patient groups, and patients with FTD demonstrated the lowest activity compared to patients with SD patients and both groups of caregivers. Both groups of patients spent less time in the daytime interval compared to their caregivers. This diminished activity was associated with high apathy scores (as measured by the NPI) particularly among the patients with FTD. Apathy has been defined as a deficit of drive and motivation (R. Levy & Dubois, 2006; Marin, 1991), yet it has been acknowledged that these are phenomena difficult to measure objectively. This data supports the effect that diminished drive has on actual movement. Similar results have been found in two other studies exploring movement and apathy. In a study measuring movement over a two-year interval of a patient with FTD, an increase in the patient’s apathy occurred in conjunction with lowered levels of daytime activity (Merrilees, Hubbard, Mastick, Miller, & Dowling, 2009). Muller (2006) compared levels of apathy between adult patients with brain damage (n=24) and normal controls. The high apathy group recorded lower daytime activity, shorter episodes of daytime activity, and increased number of naps (Muller, Czynnemek, Thone-Otto, & Von Cramon, 2006). Since the frontal lobes are considered a primary site in the modulation of motivation and purposeful activity, apathy in bvFTD is
not a surprising finding. Yet, our data, like Muller’s helps to characterize apathy as encompassing a measurable effect on movement and activity.

In addition, these results describe the impact of apathy on family caregivers. As shown in previous research, apathy in bvFTD is associated with high levels of emotional distress for the caregiver. Our data confirms this relationship, yet the SD caregivers had a higher correlation between apathy and emotional distress compared to FTD caregivers. It may be that patients with SD exhibit more cognitive or emotional aspects of apathy that is perhaps more distressful than the movement aspects of apathy. Patients with SD may exhibit apathy for some things while developing obsessive interests in other areas and this may result in different levels of distress for the caregiver. This study did not explore these factors.

It would appear that the lower levels of activity of the patients with FTD might have an associated effect of lowered activity in the afternoon by their caregivers, phenomena unique to FTD and not SD. There are a number of potential reasons for this relationship. FTD caregivers may find it too difficult to engage the patient in activity, and due to the need to provide patient supervision, are unable to engage in activity themselves. It is also possible that the FTD caregivers are depressed, a condition noted for an association with diminished activity, or have conditions impeding their activity. Our study did not explore these factors.

Perhaps the biggest challenge of actigraphy research concerns the ability to distinguish types of activity. Actigraphy analysis involves application of scoring algorithms in order to make inferences about activity, but it does not give information about what the person is doing. Apathy, a deficit in drive and motivation, influences
purposeful and goal-directed behavior. Yet, some activities can be sedentary and purposeful, for example watching television, talking on the telephone, or working at a computer. Conversely, periods of high activity can be due to psychomotor agitation or compulsive routines, movement that could be mistaken for goal-directed and purposeful activity. Inactivity can also be a manifestation of motor impairment or anything that blocks the ability to move. It could also be argued that periods of lower activity are an indication that the person is depressed, sitting quietly, is drowsy, or sleeping. In this study, adjunctive measures show no compelling evidence that lower patient activity is associated with these factors. There was no evidence of depression among the patients with FTD as rated by their caregivers. Three patients with SD were rated as having depression. Scores from the BI, while overall suggesting problems with independent function, actually support that all but one patient with FTD had full independent movement: one FTD patient required minor assistance with walking. ESS scores were below 10 for the majority of patients, thus there was little evidence of propensity for daytime sleepiness as subjectively assessed by the caregiver.

Both patient groups spent less time in the daytime interval than their caregivers. In the author’s clinical experience, caregivers often describe that while patients may go to bed early in the evening, they are often observed to be lying quietly not sleeping. Some researchers have concluded that actigraphy overestimates sleep by misinterpreting nocturnal wakefulness as sleep (Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001). This study did not include information about nighttime or sleep patterns.

Terms to define apathy have been historically difficult to operationalize. Despite the high prevalence of apathy in FTD, three sets of diagnostic criteria provide only vague
references to the condition. While current consensus criteria recommends that apathy been conceptualized as a disorder of drive and motivation (P. Robert et al., 2009), there remains the continuing problem of what that means. This study sought to characterize apathy by analyzing movement variables and provides evidence that patients with apathy have decreased activity and greater immobility during the daytime.

Of all the daytime variables analyzed, immobility may be the most salient and direct term. Patients with bvFTD, all of who had apathy, spent more time immobile compared to patients with SD and all caregivers. Activity counts provide a numerical value that can be used to compare cohorts, but the values are perhaps difficult to apply to real life situations. A multitude of terms have been used in assessing the movement aspect of apathy including: decreased involvement in chores, social withdrawal, inertia, aspontaneity, deficits in goal-directed behavior, reduction in ADLs, and lessened drive and motivation. These terms are problematic because they are vague, can mean different things to different people, and several are functional outcomes that could be due to conditions other than apathy. Immobility is a more precise term, is relatively easy to observe, and may be fruitful to include in the assessment of apathy.

There are limitations to this study. The inclusion of actigraphy data from age-matched normal controls would contribute to the characterization of activity for both the patient and caregiver cohorts. There is evidence that neuropathology influences functional and clinical outcomes in FTD (Rascovsky et al., 2005). This study did not include pathology data, and future research could help in characterizing whether pathological determinants carry influence on the nature of apathy in FTD. In addition, there are limitations in how apathy and depression were assessed. This study relied on
caregiver ratings using the NPI. In making an assessment of apathy, caregivers are asked a stem question focused primarily on the cognitive aspect of apathy that could potentially miss those patients exhibiting emotional and movement features associated with apathy. Depression is assessed by asking the caregiver if the patient appears sad or depressed, features that can be easily mistaken for apathy. Finally, a limitation to actigraphy is that while it provides a measure of activity, it cannot provide information about the person’s behavior. For example, low counts of activity can be inferred as sleep when the person may in fact be sitting quietly. For this reason, rather than focusing on scoring algorhythms, we explored associations between the raw actigraphy data and adjunctive measures such as informant reports and mobility ratings.

**Conclusions**

Apathy is a deficit in drive and motivation, concepts difficult to measure. The measurement of activity and movement among patients with FTD shows an association between apathy and lowered levels of activity and greater immobility during the daytime interval. Immobility may be a more precise term to use in the assessment of apathy. Apathy is a distressful condition for caregivers, although reasons for this deserve further study. Choosing to measure features of both the patient and caregiver dyad holds promise as a method for accurately assessing behavioral outputs and the functional impact of disease.
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Table 1. Demographic data for patients and caregivers

<table>
<thead>
<tr>
<th></th>
<th>FTD pts n=13</th>
<th>FTD caregivers n=13</th>
<th>SD pts n=9</th>
<th>SD caregivers n=9</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.5 (5.9)</td>
<td>59.9 (9.1)</td>
<td>66.2 (8.9)</td>
<td>63.0 (10.8)</td>
</tr>
<tr>
<td>MMSE</td>
<td>24.5 (3.8)</td>
<td>16.4 (9.1)</td>
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<td></td>
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<tr>
<td>CDR</td>
<td>1.6 (0.6)</td>
<td>1.0 (0.6)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>69%</td>
<td>31%</td>
<td>56%</td>
<td>44%</td>
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<tr>
<td>ESS</td>
<td>7.38 (7.44)</td>
<td>6.00 (2.50)</td>
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<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td>80.76 (22.15)</td>
<td>94.44 (9.82)</td>
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<td></td>
</tr>
</tbody>
</table>

MMSE -Mini Mental State Exam, range 0-30; CDR - Dementia Rating Scale, range 0-3; ESS –Epworth Sleepiness Scale;
^ FTD and SD patients p = .030
∠ FTD and SD patients p = .034

Table 2. Daytime variables

<table>
<thead>
<tr>
<th></th>
<th>FTD n=13</th>
<th>FTD CG n=13</th>
<th>SD n=9</th>
<th>SD CG n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of daytime interval in hours</td>
<td>14.16 (1.6)</td>
<td>15.34 (.92)</td>
<td>13.85 (1.36)</td>
<td>15.71 (.65)</td>
</tr>
<tr>
<td>Activity counts per minute *</td>
<td>201.07(148.95)</td>
<td>316.67 (102.45)</td>
<td>247.81 (112.07)</td>
<td>332.55 (110.62)</td>
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<tr>
<td>Percent immobile **</td>
<td>24.71 (17.74)</td>
<td>11.22 (6.85)</td>
<td>15.75 (13.69)</td>
<td>9.08 (5.26)</td>
</tr>
<tr>
<td>Number of hours spent immobile</td>
<td>3.49 (.28)</td>
<td>1.72 (.06)</td>
<td>2.18 (.18)</td>
<td>1.42 (.03)</td>
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<tr>
<td>Number of immobility bouts</td>
<td>67.58 (31.60)</td>
<td>48.88 (24.70)</td>
<td>50.58 (24.63)</td>
<td>41.00 (21.90)</td>
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<tr>
<td>Immobility bout duration (in minutes)</td>
<td>2.78 (1.10)</td>
<td>2.176 (0.69)</td>
<td>2.37 (1.14)</td>
<td>2.01 (0.43)</td>
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</table>

* FTD pt and FTD CG = .009
** FTD pt and FTD CG = .005
Table 3. Neuropsychiatric Inventory Results and Correlation Coefficients for total scores with emotional distress.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Presence of Behavior</th>
<th>Total Score</th>
<th>Frequency</th>
<th>Emotional Distress</th>
<th>Spearman Rank</th>
<th>Very Frequent</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valid % n</td>
<td>M (SD)</td>
<td>Occasional</td>
<td>Frequent</td>
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<tr>
<td>Delusions</td>
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</tr>
<tr>
<td>FTQ</td>
<td>16.4 2</td>
<td>6.0 (2.8)</td>
<td>1</td>
<td></td>
<td>2</td>
<td>2.0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>22.2 2</td>
<td>3.5 (3.5)</td>
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<td>1</td>
<td>2.0 (0.0)</td>
<td>-</td>
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<td>Hallucinations</td>
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<tr>
<td>FTQ</td>
<td>16.4 1</td>
<td>3.0 (1.4)</td>
<td>1</td>
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<td>1</td>
<td>2.0 (1.4)</td>
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<td>SD</td>
<td>11.1 1</td>
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<td>1</td>
<td>2.0 (0.0)</td>
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<tr>
<td>Agitation/Aggression</td>
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<td></td>
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<tr>
<td>FTQ</td>
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<td>4.2 (4.0)</td>
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<td>3</td>
<td>1</td>
<td>2.7 (1.5)</td>
<td>68</td>
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<td>SD</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>2.3 (1.9)</td>
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<td>Depression/Dysphoria</td>
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<td>1.7 (0.6)</td>
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<td>Anxiety</td>
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<td>SD</td>
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<td>2.0 (1.4)</td>
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<td>Delusions</td>
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<tr>
<td>FTQ</td>
<td>46.2 6</td>
<td>3.2 (0.8)</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2.0 (0.0)</td>
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<tr>
<td>SD</td>
<td>22.2 2</td>
<td>5.0 (4.2)</td>
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<td>2.5 (0.7)</td>
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<tr>
<td>Apathy/Inattention</td>
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</tr>
<tr>
<td>FTQ</td>
<td>100 13</td>
<td>8.3 (3.0)</td>
<td>1</td>
<td>15</td>
<td>3.5 (1.1)</td>
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<td></td>
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<td>SD</td>
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<td>4</td>
<td>2.5 (1.3)</td>
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<td>3</td>
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<td>SD</td>
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<td>5.3 (6.9)</td>
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<td>1</td>
<td>2.7 (1.5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Impulsivity/Lability</td>
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<tr>
<td>FTQ</td>
<td>30.8 4</td>
<td>7.5 (3.4)</td>
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<td>SD</td>
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<td>2.0 (1.0)</td>
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<td></td>
</tr>
<tr>
<td>Aberrant Mental Behavior</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FTQ</td>
<td>92.3 12</td>
<td>8.7 (4.0)</td>
<td>2</td>
<td>10</td>
<td>2.9 (1.3)</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>SD</td>
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<td>4.5 (2.1)</td>
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<td>2.5 (0.8)</td>
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<tr>
<td>Nighttime Behavior</td>
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</tr>
<tr>
<td>FTQ</td>
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<td>5.5 (2.8)</td>
<td>2</td>
<td>8</td>
<td>2.1 (1.2)</td>
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</tr>
<tr>
<td>SD</td>
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<td>1</td>
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<td>2.7 (1.2)</td>
<td>50</td>
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<tr>
<td>Appetite/Feeding Disorders</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FTQ</td>
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<td>7.8 (3.3)</td>
<td>3</td>
<td>10</td>
<td>2.0 (1.4)</td>
<td>34</td>
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<tr>
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<td>70</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTQ</td>
<td>45.1 (45.6)</td>
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<td></td>
<td></td>
<td>18.7 (8.1)</td>
<td>85 *</td>
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<tr>
<td>SD</td>
<td>20.9 (24.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.8 (6.4)</td>
<td>97 **</td>
</tr>
</tbody>
</table>
Figure 5. Hourly activity scores for patients and caregivers.
# Appendices

## Appendix 1. Diagnostic criteria for FTD

<table>
<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
<th>Major Symptoms</th>
<th>Inclusion of apathy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund Manchester, Published 1994</td>
<td>Clinical and neuropathological criteria</td>
<td>Establishes FTD as a behavioral disorder with the following core features: insidious onset, slow progression, mental rigidity/inflexibility, hyperorality, stereotyped/preservative behavior, utilization behavior, distractibility, impulsivity, and early loss of personal awareness &amp; disinhibition. Includes affective, speech, and physical symptoms. Includes supportive features. Includes multiple exclusion features.</td>
<td>Under the domain “Affective Symptoms” in a category called emotional unconcern (which also lists emotional indifference, remoteness, lack of empathy and sympathy, apathy)</td>
</tr>
<tr>
<td>Neary, Published 1998</td>
<td>Clinical diagnostic criteria</td>
<td>Core features include: insidious onset &amp; early decline in social interpersonal conduct, regulation of personal conduct, insight, and emotional blunting. Multiple supportive features encompassing behavioral, language, speech, and physical symptoms.</td>
<td>Impaired personal conduct, emotional blunting, loss of insight, decline in personal hygiene, but does not list apathy specifically</td>
</tr>
<tr>
<td>McKhann, Published 2001</td>
<td>Clinical and pathological criteria</td>
<td>Clinical criteria: development of behavioral or cognitive deficits that are either: a. early progressive change in personality, difficulty modulating behavior (social and personal misconduct), often resulting in inappropriate responses or activities or b. language changes.</td>
<td>Behavioral presentation does not describe apathy specifically except an acknowledgment that patients may have a loss of concern for their personal appearance, and that apathy is more pervasive in FTD compared to AD and may reflect indifference or generalized lack of initiative</td>
</tr>
</tbody>
</table>
## Appendix 2. Studies of apathy in FTD

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Purpose</th>
<th>Diagnostic criteria</th>
<th>Sample/Stage</th>
<th>Methods/Analysis</th>
<th>Salient Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy, 1996</td>
<td>Compare behaviors between FTD and AD</td>
<td>Lund-Manchester SPECT MRI</td>
<td>N=22 (FTD) N=30 (AD) MMSE FTD=14.9 AD=17.5</td>
<td>NPI (10 items)</td>
<td>Disinhib, apathy, depr identified pt diagnosis in 77% of cases. Total NPI score significantly different: FTD=23.2, AD=15.7 (p&lt;.05). FTD had higher levels of apathy and disinhibition, and lower depr. (p&lt;.01) Disinhibited pts were less apathetic; pts without disinhibition had higher apathy.</td>
<td>Grouped fv and tvFTD together</td>
</tr>
<tr>
<td>Bozeat, 2000</td>
<td>Distinguishing features between fvFTD, tvFTD, and AD</td>
<td>None, but did comprehensive evaluation NINCDS-ADRDA for AD.</td>
<td>N=13 (fv)MMSE-24.3 N=20 (tv)MMSE-16.4 N=37 (AD)MMSE-19.2 Moderate to advanced based on MMSE and CDR scores</td>
<td>Informant questionnaire focused on frequency of behaviors.</td>
<td>Apathy more freq in FTD, but not a signif, difference. Aberrant motor behaviors occurred with same freq among 3 groups. Weakest factor (#4) accounted for 5.6% of variance included social w/drawal, diminished conversation.</td>
<td>No diagnostic criteria used for FTD</td>
</tr>
<tr>
<td>Lindau, 2000</td>
<td>Identification of earliest symptoms in FTD and AD And delineate symptoms associated with focal atrophy</td>
<td>Lund-Manchester SPECT used for visual identification of hypoperfusion in order to classify pts as right, left or bilateral.</td>
<td>MMSE (moderately advanced) FTD R-sided=19.7 FTD L-sided=14.8 Bilateral =21.3</td>
<td>Recorded interviews (inductive and explorative) and chart reviews. Factor analysis</td>
<td>Apathy/passivity was early sign in FTD, presence was signif. greater in FTD vs. AD (discriminated between FTD and AD (p=0.0004). Apathy higher in unilateral left and right-sided groups. Decreased exec. Fucn significantly greater in bilateral FTD (p=0.0000).</td>
<td>Symptoms classified: 1. Behavioral: included apathy/passivity 2. Exec. Func: decreased planning, decreased ability to execute daily activities</td>
</tr>
</tbody>
</table>
| Bathgate, 2001 | Features that distinguish FTD from AD | Neary | N=30(FTD)  
N=75(AD)  
N=34(CVD)  
Severity: illness duration/MMSE  
FTD=4.2 yrs/21  
AD=4.7 yrs/16  
CVD=4.3 yrs/21  
Manchester Behaviour Quest.  
High inter-rater reliability, mean Kappa stat. = 0.97  | Symptoms that increased diagnostic odds of FTD=  
loss of interest hobbies, leisure activities, pacing and pacing fixed route, wandering, simple and complex repetitive behaviors  | Pacing listed under both vegetative and repetitive domains on the Manchester  |
|———|———|———|———|———|———|
| Snowden, 2001 | Compare behaviors between FTD and SD | Neary  
Lund-Manchester | N=30 (FTD)  
N=11 (SD)  
Illness duration/MMSE  
FTD-apathetic=4 yrs and 10/30  
FTD-disinh=4 yrs and 21/30  
SD = 5 yrs and 21/30  
Questionnaire with informant that defined apathy as “general loss of interest and social avoidance”  
FTD grouped into 2 cohorts based on predominant symptoms:  
FTD-A (apathy)  
FTD-D (disinh)  
FTD-A dorsolateral and more widespread.  
More likely to engage in simple repetitive behaviors.  
And more likely to avoid social contacts  
FTD-D purposeless overactivity, orbitomedial frontal  
General loss of interest strongly differentiated FTD and SD (p = .001)  
Pacing fixed route significantly diff. between both FTDs and SD  | Illness duration matched but MMSE scores disparate=  
FTD-A showed less effort and more “I don’t know” answers.  
Trend for FTD-A to be older than FTD-D (p=.06)  
FTD-A less aggressive than FTD-D (p=.06)  |
| Liu, 2004 | Compare features of tv and fv FTD. Compare behaviors and associated regional volumes | Neary | N=26 (tv)  
N=23(fv)  
MMSE  
fv=20.8  
tv=24.1  
AD=20.9  
NPI 12 items  
Higher apathy in bvFTD  
96%  
Sleep higher in tvFTD  
52%  | Not necessarily at same dementia stage.  |
| Engelborghs, 2005 | Behavioral profile in AD, FTD, mixed, DLB | Neary | N=205(AD)  
N=29 (FTD)  
N=39(mixed)  
N=23(DLB)  
Staged with GDS: FTD = 4.9, stat. lower than other groups, i.e. FTD less impaired, but still  
Middelheim Frontality Score (MFS) for the past 2 weeks/although changes from pts baseline are scored as present: 0 = absent and 1=present for total score of 10  
FTD had higher MFS scores than AD.  
Prevalence of aspontaneity was highest in FTD (60% of pts) compared to AD (30%) (p<0.001).  | MFS: Apathy defined as “aspontaneity”, interview with informant includes descriptive questions that delves into loss of interest, social  |
| Le Ber, 2006 | Describe behaviors in fvFTD and compare brain perfusion SPECT between fvFTD and normal controls | Lund-Manchester, Neary MMSE, Mattis Dementia Rating Scale, Frontal Assessment Battery (Dubois), Free and Cued Recall test | N=61 (FTD in clinical study) N=68 (includes the 61 in clinical plus 7 additional FTD in SPECT) Disease duration: majority (48%) were at 3-5 years. Majority included in this study at 4 yrs +/- 3.5 Mean Mattis score=109 +/- 17.5 Mean MMSE was 21.4 +/- 5.4 Pts moderately advanced | 70-item behavioral inventory, informant-based interview and for each endorsed behavior, informant asked to recall age of onset for behavior. Neurologis then grouped pts according to the most prominent initial profile 1)disinhibited 2) inert 3)mixed Analysis: students test to compare demographics. Fisher exact and Wilcoxon to compare small groups | Most frequent signs at disease onset were Affect/emotion and Inertia: Loss of awareness(65%), *Reduction in ADLS (54%), *Loss of interest (54%), *Loss of initiative (51%), Lack of empathy/indifference to others (49%), *Apathy (43%), Logopenia (42%), *Social withdrawal (41%), *self-centeredness (41%), decreased attention(41%). *Symptoms of inertia. Other symptoms were listed in domain called Affect/Emotion and withdrew, less involved with chores. Some incorporate “emotional blunting” as part of apathy; this is item 7 in the MFS (so maybe apathy is underestimated here?) GDS relies on cognitive ratings to make functional severity staging. BEHAVE-AD lists Activity Disturbance, but not clear if this could by hypo or hyperactivity. Informant recall after several years could be questioned. Shorter survival associated with hypoperfusion on brainstem. Posterior involvement (parietal-occipital) that was also reported by Diehl-Schmid, 2006). |
| Diehl-Schmid, 2006 | Characterize prevalence and intensity of FTD behaviors according to dementia severity | Lund-Manchester | CDR of 1, MMSE 23.2 (n = 21)  
CDR or 2-3, MMSE 15.4 (n = 19) | NPI  
Mann-Whitney U test to analyze differences in mean scores on the NPI | Mild FTD=apathy most common symptom at 90.5%  
Mod/severe=apathy at 100%  
Aberrant motor behaviors increased from mild to mod,  
Discusses limitations of the CDR in FTD |

Attn/Executive.

Grouping at disease onset:
Mixed=57%  
Inert=25%  
Disinhibited=18%

At 4 yrs into disease, behaviors had moved to mixed or inert profile. There were no variables that distinguished the groups (i.e. they are the same disease)

Behaviors that progressed over time were relating to hyperorality, language, OCDs.

Age at onset was associated with differences in brain perfusion: age-at-onset before 65 had more severe hypoperfusion in the medial and dorsolateral frontal and cingular cortices.

Inertia associated with medial frontal and cingulated hypoperfusions. Disinhibited had hypoperfusion in ventromedial prefrontal and temporal.

Mixed had features of both.
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Participants</th>
<th>Methods</th>
<th>Results</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Jenner, 2006</td>
<td>Differentiate behaviors in fvFTD and AD</td>
<td>McKhann, Neary, Lund-Manchester</td>
<td>N=24(fvFTD) N=22(AD) CDR (mean 1.46) ADL (mean 5.12) IADL (mean 4.29) MMSE (mean 23.7)</td>
<td>NPI Mann-Whitney U with Bonferroni correction. Fisher exact test. Spearman. Multivariate logistic regression with stepwise forward procedure. Total NPI score higher in fvFTD but not statistically significant. Apathy only significant difference between the 2 groups (Mann-Whitney = 408.5; p&lt;0.0012). CDR correlated signif with behavior severity in fvFTD.</td>
<td>Mean age of fvFTD was 73.4 (SD = 8.45)</td>
</tr>
<tr>
<td>Shinagawa et al, 2006</td>
<td>Initial symptoms FTD, SD, AD</td>
<td>Neary</td>
<td>N=36(FTD) N=17(SD) N=52(AD) CDR MMSE</td>
<td>NPI Caregiver ratings on initial symptoms: 1st domain included change in social behavior, affect, and daily activities= loss of personal awareness, disinhibition, apathy or social withdrawal or aspontaneity, stereotyped behaviors, oral. Apathy (14%)and stereotyped behaviors (12.5%) most common initial symptoms in FTD. The 1st domain was significantly more common in FTD than SD or AD (p&lt;0.01). Apathy had 25% sensitivity and 92% specificity for the differentiation between the 3 groups.</td>
<td>Does not help to determine causality for reduction in daily activities</td>
</tr>
<tr>
<td>Chow et al, 2009</td>
<td>Compare features of apathy between FTD and AD</td>
<td></td>
<td>NPI apathy sub-questions were put into categories: affective, cognitive, or behavioral</td>
<td>Higher apathy rates in FTD. Similar rank orders for frequencies of the sub-questions. Subjective categorization, e.g. diminished conversation cognitive, affective, behavioral (less verbal output), or all 3?</td>
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Appendix 3. Apathy assessment of the Neuropsychiatric Inventory (NPI)

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<td>Has the patient lost interest in the world around him/her? Has he/she lost</td>
<td>- Has the patient lost interest in the world around him/her? Has</td>
</tr>
<tr>
<td>interest in doing things or does he/she lack motivation for starting new</td>
<td>he/she lost interest in doing things or does he/she lack</td>
</tr>
<tr>
<td>activities? Is he/she more difficult to engage in conversation or in doing</td>
<td>motivation for starting new activities? Is he/she more difficult</td>
</tr>
<tr>
<td>chores? Is the patient apathetic or indifferent?</td>
<td>to engage in conversation or in doing chores? Is the patient</td>
</tr>
<tr>
<td></td>
<td>apathetic or indifferent?</td>
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<table>
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<th>Sub-questions</th>
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<tr>
<td>1. Does the patient seem less spontaneous and less active than usual?</td>
<td>1. Does the patient seem less spontaneous and less active than</td>
</tr>
<tr>
<td></td>
<td>usual?</td>
</tr>
<tr>
<td>2. Is the patient less likely to initiate a conversation?</td>
<td>2. Is the patient less likely to initiate a conversation?</td>
</tr>
<tr>
<td>3. Is the patient less affectionate or lacking in emotions when compared to</td>
<td>3. Is the patient less affectionate or lacking in emotions when</td>
</tr>
<tr>
<td>his/her usual self?</td>
<td>compared to his/her usual self?</td>
</tr>
<tr>
<td>4. Does the patient contribute less to household chores?</td>
<td>4. Does the patient contribute less to household chores?</td>
</tr>
<tr>
<td>5. Does the patient seem less interested in the activities and plans of</td>
<td>5. Does the patient seem less interested in the activities and</td>
</tr>
<tr>
<td>others?</td>
<td>plans of others?</td>
</tr>
<tr>
<td>6. Has the patient lost interest in friends and family members?</td>
<td>6. Has the patient lost interest in friends and family members?</td>
</tr>
<tr>
<td>7. Is the patient less enthusiastic about his/her usual interests?</td>
<td>7. Is the patient less enthusiastic about his/her usual interests?</td>
</tr>
<tr>
<td>8. Does the patient show any other signs that he/she doesn’t care about</td>
<td>8. Does the patient show any other signs that he/she doesn’t</td>
</tr>
<tr>
<td>doing new things?</td>
<td>care about doing new things?</td>
</tr>
</tbody>
</table>
Appendix 4. Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation - Chance of dozing

Sitting and reading ..................................................
Watching TV ..........................................................
Sitting, inactive in a public place (e.g. a theatre or a meeting) ....
As a passenger in a car for an hour without a break ............
Lying down to rest in the afternoon when circumstances permit ...
Sitting and talking with someone ..................................
Sitting quietly after a lunch without alcohol ......................
In a car, while stopped for a few minutes in traffic ..............
Total (add the numbers for each situation) .......................

Appendix 5. The Barthel Index

FEEDING
0 = unable
5 = needs help cutting, spreading butter, etc., or requires modified diet
10 = independent

BATHING
0 = dependent
5 = independent (or in shower)

GROOMING
0 = needs to help with personal care
5 = independent face/hair/teeth/shaving (implements provided)

DRESSING
0 = dependent
5 = needs help but can do about half unaided
10 = independent (including buttons, zips, laces, etc.)
**BOWELS**
0 = incontinent (or needs to be given enemas)
5 = occasional accident
10 = continent

**BLADDER**
0 = incontinent, or catheterized and unable to manage alone
5 = occasional accident
10 = continent

**TOILET USE**
0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping)

**TRANSFERS (BED TO CHAIR AND BACK)**
0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent

**MOBILITY (ON LEVEL SURFACES)**
0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards

**STAIRS**
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent

**TOTAL SCORE** = _____________

The Barthel Index: Guidelines
1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.
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