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The Cognitive and Neural Basis for Apathy in Frontotemporal Degeneration

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Abstract
The syndrome of apathy, defined as a reduction in goal-directed behavior (GDB), has profound consequences for morbidity and mortality in the patient and for family-caregiver burden. Apathy is one of the primary neuropsychiatric syndromes associated with the disruption of the frontal-striatal system, but the behavioral and biological mechanisms underlying apathy are not well understood. Apathy is especially prevalent in behavioral variant frontotemporal degeneration (bvFTD). In a sample of 20 apathetic adults with bvFTD and 17 normal controls (NC), impairments in three components of GDB--initiation, planning and motivation--were examined using a novel computerized reaction time test. Employing structural neuroimaging techniques, I then examined the neural basis of GDB in these apathetic bvFTD participants. I found evidence that apathy is associated with an impairment in any of the three GDB components. Initiation, planning, and motivation each map onto three distinct brain regions in the frontal lobe that work together in a large-scale neural network. Furthermore, I was able to identify participants with specific subtypes of apathy, depending on the impaired GDB mechanism. I developed and submitted a proposal for continued study of the phenomenon; the proposal was awarded. The long-term potential impact of this beginning program of research is profound for patients with neurodegenerative disease, their caregivers, and families. Current treatment of apathy has been hindered due to poor understanding of the mechanisms underlying this condition. This work will lead to a better understanding of these mechanisms and structures fundamental to the behavior, and, with this knowledge, tailored interventions can be designed and implemented by professional and lay caregivers. Thus, a more precise characterization of apathy will allow providers to implement the most appropriate therapy for a given patient.

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THE COGNITIVE AND NEURAL BASIS FOR APATHY IN FRONTOTEMPORAL DEGENERATION

DEDICATION

For Betty and Dolores

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ABSTRACT

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The syndrome of apathy, defined as a reduction in goal-directed behavior (GDB), has profound consequences for morbidity and mortality in the patient and for family-caregiver burden. Apathy is one of the primary neuropsychiatric syndromes associated with the disruption of the frontal-striatal system, but the behavioral and biological mechanisms underlying apathy are not well understood. Apathy is especially prevalent in behavioral variant frontotemporal degeneration (bvFTD). In a sample of 20 apathetic adults with bvFTD and 17 normal controls (NC), impairments in three components of GDB—initiation, planning and motivation—were examined using a novel computerized reaction time test. Employing structural neuroimaging techniques, I then examined the neural basis of GDB in these apathetic bvFTD participants. I found evidence that apathy is associated with an impairment in any of the three GDB components. Initiation, planning, and motivation each map onto three distinct brain regions in the frontal lobe that work together in a large-scale neural network. Furthermore, I was able to identify participants with specific subtypes of apathy, depending on the impaired GDB mechanism. I developed and submitted a proposal for continued study of the phenomenon; the proposal was awarded. The long-term potential impact of this beginning program of research is profound for patients with neurodegenerative disease, their caregivers, and families. Current treatment of apathy has been hindered due to poor

understanding of the mechanisms underlying this condition. This work will lead to a better understanding of these mechanisms and structures fundamental to the behavior, and, with this knowledge, tailored interventions can be designed and implemented by professional and lay caregivers. Thus, a more precise characterization of apathy will allow providers to implement the most appropriate therapy for a given patient.

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LIST OF ACRONYMS

AAL	automated anatomical labeling
ACC	anterior cingulate cortex
AD	Alzheimer's disease
AES	Apathy Evaluation Scale
ANTS	advanced normalization tools
bvFTD	behavioral variant frontotemporal degeneration
CC	corpus callosum
CfN	Center for Functional Neuroimaging
dlPFC	dorsolateral prefrontal cortex
DT	diffusion tensor
DTI	diffusion tensor imaging
DWI	diffusion-weighted images
fMRI	functional MRI
FA	fractional anisotropy
FDR	false discovery rate
FWHM	full width at half maximum
FxS	frequency by severity
FTD	frontotemporal degeneration
GDB	goal-directed behavior
GMP	grey matter probability
IRB	Institutional Review Board
LEQ	Lifetime of Experiences Questionnaire
MMSE	Mini-Mental State Exam

MNI	Montreal Neurological Institute
MPRAGE	magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo
MRI	magnetic resonance imaging
MSS	multisensory stimulation
MT	midtemporal
NC	normal controls
ND	neurodegenerative disease
NPI	Neuropsychiatric Inventory
OFC	orbital-frontal cortex
PACT	Philadelphia Apathy Computerized Test
PD	Parkinson's disease
PET	positron emission tomography
PSP	progressive supranuclear palsy
ROI	regions of interest
RT	reaction time
SLF	superior longitudinal fasciculus
UNC	uncinate
UPHS	University of Pennsylvania Health System
VBM	voxel brain morphometry
vmPFC	ventromedial prefrontal cortex

CHAPTER 1: INTRODUCTION

The syndrome of apathy, defined as a reduction in self-generated or voluntary behavior (Levy & Dubois, 2006), has profound consequences for morbidity and mortality in patients with neurodegenerative disease (ND) and contributes significantly to family caregiver burden (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Chio et al., 2010; Karttunen et al., 2010). Apathy is especially prevalent in behavioral variant Frontotemporal degeneration (bvFTD), where it is reported in up to 90.5% of mild-stage patients (Diehl-Schmid, Pohl, Perneczky, Forstl, & Kurz, 2006).

FTD is the second most common young-onset ND (Ratnavalli, Brayne, Dawson, & Hodges, 2002; Rosso et al., 2003). Neuronal loss in the frontal and temporal lobes of the brain results in difficulty regulating social behavior (Massimo & Grossman, 2008). In the field of ND, abnormal social behavior includes a wide range of neuropsychiatric symptoms that are disruptive to social interaction (Massimo, Evans, & Benner, 2013). Abnormal social behavior is the hallmark symptom of bvFTD, with the syndrome of apathy being the most common, evident pervasively throughout the duration of the disease (Le Ber et al., 2006; Mendez, Lauterbach, & Sampson, 2008). Although apathy in bvFTD is a very common and significant problem, the mechanisms contributing to this behavior rarely have been studied. At present, no proven effective treatments exist for apathy, in part because the underlying dysfunction is not fully understood (Chase, 2011). Thus, the purpose of this study was to advance understanding of mechanisms contributing to apathy to improve outcomes for those suffering its consequences.

The concept of goal-directed behavior (GDB) provides a useful model for examining the mechanisms underlying apathy. In neuroscience, GDB is used to

operationalize a broad spectrum of purposeful actions and their determinants (Brown & Pluck, 2000), related to the belief that when action *a* is taken, goal *x* may be obtained as a result. The GDB model was proposed by Levy and Dubois (2006) to improve understanding of the mechanisms that contribute to the loss of self-initiated behavior referred to as "apathy." Despite urging from caregivers, pain, and risk of death, patients with apathy do not initiate GDB.

Three distinct components of GDB are initiation, planning, and motivation (Brown & Pluck, 2000). Each component of GDB is supported by a distinct anatomic circuit centered on a specific portion of the prefrontal cortex. Apathy is hypothesized to emerge where there is dysfunction of any one of these components (Levy & Dubois, 2006). Using neurobiological tools, such as quantitative brain imaging, to study patients with apathy strongly suggests an anatomic basis for the mechanisms contributing to apathy (Massimo et al., 2009; Rosen et al., 2005; Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008). Therefore, I proposed to use the GDB model to examine the brain-behavior relationships underlying apathy in bvFTD. Specifically, I conducted an empirical study that quantified difficulty with each component of GDB using a novel computerized reaction-time test, examined the distinct prefrontal neuroanatomical substrates of these impairments in an apathetic bvFTD sample using regression, and then related specific apathetic behaviors to grey matter atrophy and white matter integrity, quantified by magnetic resonance imaging (MRI).

Study Significance

The following case captures the problem this research addressed:

> BJ is a 58-year-old female with FTD. Her husband notes that "it is impossible to get her going." She sits and watches static on the television all day long and her husband rarely sees her move spontaneously. She has developed pressure ulcers because of her lack of movement: Neither urgent prompts from her husband nor the pressure ulcer associated pain has been successful in compelling her to move. Her husband is very distressed about his wife's behavior and wants to know, "Why does she just sit there?" Of note, her Mini-Mental State Exam (MMSE) score is 28 of 30 ("no impairment").

BJ's case demonstrates the significant problems that can occur when someone is apathetic. The goal of this research was to help answer questions about why apathy occurs in individuals with bvFTD. Apathy is a very common neuropsychiatric syndrome negatively affecting patient and caregiver outcomes (Chio et al., 2010; Karttunen et al., 2010) including increased patient mortality (Vilalta-Franch, Calvo-Perxas, Garre-Olmo, Turro-Garriga, & Lopez-Pousa, 2013). Apathy is associated with a variety of undesirable consequences in patients, such as poor insight and poor cognitive performance (Chase, 2011; Ishii, Weintraub, & Mervis, 2009; Pedersen, Alves, Aarsland, & Larsen, 2009; Pluck & Brown, 2002). The deficits observed in apathetic patients such as poor planning, poor motivation, and the inability to initiate even the simplest self-care activities contribute to functional deterioration (Pedersen, Alves, et al., 2009). These findings suggest that apathy contributes significantly to global decline and mortality, and support the need for its identification and proper management in at-risk patient populations.

Caring for a person with apathy is challenging. The physical and emotional demands associated with performing many activities for persons with apathy are profound. High levels of depression, burden, and stress have been reported in caregivers of apathetic patients (Chio et al., 2010; Massimo et al., 2009).

Apathetic bvFTD patients, in particular, lack insight into their social difficulties and are unaware of the consequences of their behavior (Eslinger et al., 2005; Massimo, Libon, et al., 2013). Their caregivers often misinterpret apathy as a sign of oppositional or volitional behavior, leading to dissatisfaction with caregiving (Landes, Sperry, Strauss, & Geldmacher, 2001; Massimo, Evans, et al., 2013). A study of 53 spousal caregivers demonstrated that apathetic behavior had the greatest impact on the decline of the marital relationship (de Vugt et al., 2006). This impact has significant implications for caregiver burnout because it is the bond between caregiver and care recipient that sustains caregiving under adverse conditions (Wrubel & Folkman, 1997).

Treatments for apathy have heretofore been ineffective. In a recent systematic review of pharmacological treatments, there was insufficient evidence to support the use of medications for the improvement of apathy in ND (Drijgers, Dujardin, Reijnders, Defebvre, & Leentjens, 2010). One reason for these failures may be the way apathy is currently conceptualized. That is, apathy is viewed homogeneously, as if derived simply from a lack of motivation (Marin, 1996). There is evidence to suggest several different mechanisms contribute to apathy, including deficits in initiation and planning, as well as motivation (Chow et al., 2009; Eslinger, Moore, Antani, Anderson, & Grossman, 2012; Levy & Dubois, 2006; Massimo et al., 2009). Additionally, there is neuroanatomical evidence to support a multicomponent approach to apathy. Several neuroimaging studies associate apathy with numerous regions in the frontal cortex (Massimo et al., 2009; Rosen et al., 2005; Zamboni et al., 2008). Mechanisms underlying apathy are qualitatively different**,** and, thus, may require distinct interventions. Knowledge of distinct subtypes of apathy would help explain treatment failures that may be due, at least

in part, to the attempt to treat all apathy with a single approach. For example, when apathy emerges in response to planning difficulties, there is benefit to be gained from structuring the activity in a simple way for the patient. For patients with impaired goal-selection, modifications such as amplified lighting in a room may increase the reward potential of the environment (Ishii et al., 2009). Last, multisensory stimulation (MSS), a therapeutic approach that provides visual, auditory, tactile, and olfactory stimulation, may be helpful for patients with initiation difficulty (Baker et al., 2001); the use of MSS in a patient with planning difficulty, however, may worsen rather than improve apathy. Additionally, apathy is often ignored by clinicians because of patients' lack of apparent distress (Butterfield et al., 2010). One of the primary obstacles in furthering the research in this area has been the absence of an empirically-based approach that can elucidate the mechanisms contributing to apathy. This research, thus, aimed to fill this gap by applying a model of GDB in persons with bvFTD where apathy is highly prevalent. This work, which attempted to understand the cognitive and neural basis for apathy, represents the first step to support the development of rational treatment for patients with various subtypes of apathy.

The potential long-term impact of this work is significant. This research holds promise for changing the way in which nurses and other health professionals currently view, evaluate, and treat apathy in patients with ND, as well as in other neuropsychiatric conditions. The pathophysiological model resulting from this work, revealing several mechanisms contributing to apathy, may lead to improved treatment using tailored biobehavioral interventions that target the impairments in GDB. In addition to direct

clinical benefits, the knowledge gained from this work will advance neurocognitive models of social behavior. Thus, The aims of this study were:

Specific Aims

Aim 1: To relate impairments in GDB (initiation, planning, and motivation) in bvFTD to distinct neuroanatomic regions in the prefrontal cortex.

H1: Poor initiation is related to grey matter atrophy in the anterior cingulate cortex (ACC) and to reduced white matter integrity in the cingulum.

H2: Poor planning is related to grey matter atrophy in the dorsolateral prefrontal cortex (dlPFC) and to reduced white matter integrity in the superior longitudinal fasciculus.

H3: Poor motivation is related to grey matter atrophy in the orbital-frontal cortex (OFC) and to reduced white matter integrity in the uncinate fasciculus.

Aim 2: To differentiate three apathetic subtypes based on impaired components of GDB in bvFTD using a novel computerized reaction time test (Philadelphia Apathy Computerized Test [PACT]) and to examine regional grey matter volume underlying these impairments.

H1: Participants with bvFTD will have greater difficulty with initiation than normal controls (NC). Moreover, I will identify a subtype of bvFTD participants with a specific deficit of initiation who will have significantly slower initiation times on the simple condition of the PACT compared to NC. Participants with initiation difficulty will have significantly reduced ACC grey matter values compared to a control brain region.

H2: Participants with bvFTD will have greater difficulty with planning than NC. Moreover, I will identify a subtype of bvFTD participants with a specific planning deficit who will have significantly greater slowing on the complex planning condition, contrasted with the simpler planning condition of the PACT compared to NC. Participants with planning difficulty will have significantly reduced dlPFC grey matter values compared to a control brain region.

H3: Participants with bvFTD will have greater difficulty with motivation than NC. Moreover, I will identify a subtype of bvFTD participants with a specific deficit of motivation who will fail to respond to penalizing motivators in the simple condition compared to NC. Participants with motivation difficulty will have significantly reduced OFC grey matter values compared to a control brain region.

Aim 3: To develop a proposal, based on findings from Aims 1 and 2, which will improve understanding of apathy by examining mechanisms of longitudinal decline and neural compensation**.**

GDB allows people to be independent in everyday task performance. This research advances models of social neuroscience by examining cognitive and neural bases to understand a key aspect of human behavior. Moreover, the results will help change the paradigm to assess and treat apathy in ND, leading to improved diagnostic accuracy and effective interventions. This outcome will greatly improve the ability of families, nurses, and other health professionals to manage a pervasive feature of ND.

Background

Definition of apathy. The word *apathy* derives from the Greek word *pathos* or passion. It describes a state of indifference or inertia (Robert et al., 2009). Over time the concept of apathy has undergone changes in meaning, and remains vaguely defined and broadly applied (Chase, 2011). Sometimes described as a symptom of other disorders such as depression, Marin (1990) clarified the concept of apathy for medical purposes by proposing its definition as a lack of motivation. Marin suggested that apathy is a syndrome or dimension of behavior that results from psychiatric, neurologic, or medical disorders. One problem with Marin's definition is that lack of motivation is not the only mechanism that contributes to apathetic behavior; "lack of motivation" is not easily quantifiable. In 2006, Levy and DuBois (2006) proposed to define apathy as the quantitative reduction of self-generated voluntary and purposeful GDB. Their definition informed the current study. From this perspective, it is possible to observe and measure the various mechanisms contributing to apathy. Furthermore, it may be possible to operationalize these underlying mechanisms and postulate "subtypes" of apathy based on impaired GDB.

A new consensus for the clinical diagnosis of apathy in neurodegenerative conditions has been proposed by an international task force (Robert et al., 2009). To meet criteria, the patient must meet the following requirements: the core feature of diminished motivation must be present for at least 4 weeks, there must be a reduction in two of three domains, and there must be a functional impairment attributed to the behavior. Domain 1 refers to reduced GDB, describing the loss of self-initiated behavior (e.g., starting a conversation) and loss of environment-stimulated behavior (e.g., responding to

conversation). Domain 2 refers to a reduction in goal-directed cognitive behavior, describing a loss of ideas and curiosity for new routines (e.g., recent news or social opportunities). Domain 3 refers to a reduction in emotion, describing a loss of spontaneous emotion or loss of emotional responsiveness to positive or negative stimuli (e.g., little reaction to exciting news). A reliable clinical diagnosis of apathy is necessary to identify its presence and to distinguish it from other clinical syndromes such as depression. These criteria, however, focus solely on clinical presentation of apathy. This dissertation goes beyond providing a clinical description of apathy; the intent is to understand the different mechanisms that underlie apathy so that meaningful treatment, based on specific impaired mechanisms, can be pursued.

Thus, in this dissertation, I examined the GDB model, applied to apathy, to identify the underlying mechanisms (Aim 1), and I operationalized the underlying mechanisms to postulate "subtypes" of apathy (Aim 2). Last, the findings from Aims 1 and 2 informed a proposal for future work in which I intend to examine the trajectory of apathy and identify factors that moderate the progression of this devastating neuropsychiatric syndrome (Aim 3). The literature for this chapter was selected from search results using CINAHL, EMBASE, Medline, PubMed, PsycINFO, Cochrane Reviews, and a hand search of the reference lists from articles. Selected articles included randomized-controlled trials, descriptive studies, and reviews. Although it may be useful to investigate neurochemistry as it relates to apathy, this area of inquiry was beyond the scope of this dissertation study.

Hypothesized model of apathy. Apathy can be explained and examined as part of the concept of GDB. GDB is operationalized as a "broad spectrum of purposeful

actions and their determinants, from the simplest movement to the most complex patterns of behavior" (Brown & Pluck, 2000, p. 416). This is related to the belief that when action *a* is taken, goal *x* may be obtained as a result. Central to GDB is the integration of the processes that influence a person to act (intention). According to the model, three processes (initiation, planning, and motivation) influence the intention to act. Although each step is necessary to achieve GDB, clinical observations of patients with ND suggest that these processes may not be sequential. In the hypothesized model, apathy arises when any one of these three processes is impaired. For example, patients who have profound impairments in the executive abilities needed to design and carry out plans of action may be motivated to engage in GDB, but their planning impairments make it difficult to engage in GDB. Therefore, it is likely that each process is independent and, when compromised, contributes to apathy.

These three processes of GDB map onto three distinct networks of brain regions. In particular, neuroimaging studies in patients have linked apathy to specific regions in the prefrontal cortex, anterior cingulate, and basal ganglia. G. E. Alexander, DeLong, and Strick (1986) were first to describe the five circuits (two motor and three behavioral) linking the basal ganglia and frontal cortex. The three functional neuroanatomic loops in the frontal area (anterior cingulate circuit, dorsolateral prefrontal circuit, and orbitofrontal circuit) capture the information from internal and external environments needed to make a decision about possible actions to be performed, likely important to GDB. Each circuit is functionally separate and mediates in its own way. This dissertation study focused on the three functional neuroanatomic loops—anterior cingulate circuit, dlPFC circuit, and orbitofrontal circuit—and their relationship to initiation, planning, and motivation.

Frontotemporal degeneration. FTD is an ND that mainly affects the frontal and temporal lobes of the brain. This condition affects individuals at a young age, typically presenting in the fifth or sixth decade of life (Massimo & Grossman, 2008; Rosso et al., 2003). FTD is recognized as the most common young onset dementia with prevalence ranging from 15–22 per 100,000 cases per year (Knopman & Roberts, 2011). These numbers are likely to be an underestimate, as the disorder is difficult to diagnose and requires a level of expertise in behavioral neurology. Clinically, bvFTD presents with difficulty regulating social behaviors such as disinhibition and apathy and a profound loss of insight (Rascovsky et al., 2011). One large autopsy-confirmed study demonstrated the frequency of behavioral symptoms in bvFTD to be between 59% to 84%, with apathy most frequent (Rascovsky et al., 2011). These behaviors significantly impact everyday functions and contribute to caregiver distress (Massimo et al., 2009; Mioshi & Hodges, 2009). Thus, it is important to understand apathy for the optimal management of patients.

Apathy in neurodegenerative disease. In addition to FTD, apathy is also common in other neurodegenerative disorders such as Alzheimer's disease (AD), FTD, Lewy Body Disease, and Parkinson's disease (PD; Clarke et al., 2008; Mega, Cummings, Fiorello, & Gornbein, 1996). In the AD population, the prevalence rate is between 51 and 80% (Aharon-Peretz, Kliot, & Tomer, 2000; Di Iulio et al., 2010; Kaufer et al., 1998). The frequency of apathy in PD may also be substantial, as estimates of prevalence range from 12 to 70% (Aarsland et al., 2009; Pedersen, Larsen, Alves, & Aarsland, 2009; Starkstein et al., 1992).

Abnormal social behavior is a hallmark of FTD. In particular, it has been suggested that apathy is the most prevalent behavior in FTD, occurring in up to 90.5% of

mild-stage patients and up to 100% of moderate and severe-stage patients in one study that evaluated the prevalence of behavioral disturbances in FTD (Diehl-Schmid et al., 2006). Other authors also reported apathy to be the most common neuropsychiatric behavior in FTD (Massimo et al., 2009; Peters et al., 2006). Although apathy is often referenced as a behavior or symptom, this study examines apathy as a syndrome, which acknowledges heterogeneous behavioral processes and neuroanatomical mechanisms contributing to the clinical phenomenology.

Evidence from previously reported work suggests that impairments in GDB are also present in bvFTD patients. Poor motivation may occur in these patients because they have decreased reactivity to positive and negative signals in social situations. Grossman and colleagues (2010) recently examined decreased reactivity by asking bvFTD patients to judge the acceptability of social situations. They found that bvFTD patients were particularly insensitive to the interpretation of negatively valenced features. Impaired executive function, a common finding in bvFTD, has also been associated with apathy in this group (Eslinger, Moore, Anderson, & Grossman, 2011; Eslinger et al., 2012). Impaired executive function may contribute to apathy because of the inability to carry out plans of action. Last, although poor initiation has not been explicitly examined in bvFTD, the anterior cingulate—an area that has been hypothesized to contribute to the loss of self-initiated thoughts or actions (Levy & Dubois, 2006)—is compromised in apathetic patients (Massimo et al., 2009).

Depression and apathy are two distinct syndromes that are often confused. Symptoms that are common to both apathy and depression include hypersomnia and fatigue (Landes et al., 2001; Mega et al., 1996). Starkstein, Ingram, Garau, and Mizrahi

(2005) examined the differentiation of apathy and depression using factor analysis of the Hamilton Depression Scale. They found that dysphoric symptoms such as sad mood, guilt, suicidal ideation, anxiety, and insomnia loaded as sadness factors, suggesting these were more commonly found in a depressed patients. Other symptoms such as self-criticism and negative thoughts about the future were common in depressed patients, but were absent in apathetic patients who tended to show a lack of concern (Marin, 1996). This is consistent with similar findings suggesting that apathy is a discrete syndrome separate from depression (Landes et al., 2001). Because apathy is so common in ND, efforts to distinguish this syndrome from depression are imperative for clinicians, especially in guiding treatment decisions.

Voxel-based morphometry. The study of the neuroanatomy of apathy is of scientific interest because its study can validate the contribution of an impairment of the three components of GDB to apathy in bvFTD. A large-scale neural network is thought to support the mechanisms (initiation, planning, and motivation) contributing to apathy by involving brain regions specific to each process (Levy & Dubois, 2006). By using neurobiological tools such as voxel brain morphometry (VBM) to study patients with apathy, the nature and anatomic localization of the mechanisms contributing to apathy can be identified. Imaging of apathetic patients, thus, allows for the dissociation of clinical constructs into specific processes (i.e., impairments in initiation, planning, and motivation) that contribute to behavior like apathy (Nader, Bechara, & van der Kooy, 1997). From this mechanistic perspective, I hypothesized that the physiopathology of apathy would not be reduced to a single entity, but rather that multiple processes would

be shown to contribute to apathy. An investigation of each process would directly link to neuronal mechanisms known to underlie GDB.

Morphometry analysis is a common tool used to measure structural differences in a group or across groups (Savio et al., 2011). Voxel values are modulated by Jacobian determinants derived from spatial normalization, which occurs after tissue classes are segmented (cerebrospinal fluid, grey matter, white matter). When pathology in the brain structures occurs, there is an impact on the fine morphology of the grey matter and atrophy, or tissue loss, results. White matter is also susceptible to pathological damage in bvFTD (Lu et al., 2013). By measuring directional changes in water diffusivity, diffusion tensor (DT) provides information about the microstructural tissue integrity of white matter tracts (Whitwell et al., 2010).

Components of goal-directed behavior.

Initiation component. The failure to execute behavior leads to apathy when processing is unable to generate a signal significant enough to initiate a response. Difficulty with initiation has been reported in patients with focal lesions in either the ACC or the basal ganglia. It is important to note that there are interconnections between the two regions. ACC projects to the striatum (equipped with mechanisms for behavior selection) and the subthalamic nucleus, both of which are input zones of the basal ganglia (Hikosaka & Isoda, 2010); then there is a final loop back to the ACC to form a closed circuit. The failure of the basal ganglia to activate the cortex or the impaired activation of the motor system following ACC damage can cause difficulties with initiation (Kotchoubey, Schneck, Lang, & Birbaumer, 2003).

For example, the akinetic mute state is a medical term describing patients who tend to sit quietly in the same position all day without speaking or talking. It has been specifically related to ACC damage (Mega & Cohenour, 1997). Another related term, abulia, describes a loss of initiative and of spontaneous thought associated with damage to the basal ganglia (Bhatia & Marsden, 1994). Although these symptoms are thought to originate from two distinct anatomic structures, they are both symptoms of a failure to initiate or activate GDB.

The ACC has been well studied in dementia and neuroimaging evaluations have linked the ACC region to apathy in various groups. Low grey matter density in the cingulate gyrus was associated with increased severity measures of apathy in PD (Reijnders et al., 2010). Others have implicated this region in apathetic bvFTD patients (Massimo et al., 2009; Zamboni et al., 2008). Previous diffusion tensor imaging (DTI) studies investigating white matter disease and apathy have an association with the cingulum (Hahn et al., 2013; J. W. Kim et al., 2011; Ota, Sato, Nakata, Arima, & Uno, 2012). Although disease in the ACC and related white matter tracts contributes to apathy in patients, there have been few evaluations that describe the relationship in initiation of GDB.

Planning component. The ability to execute an action is highly dependent on the cognitive processes needed to formulate and carry out goals. Apathy related to "cognitive inertia" results from impairments in executive functions such as planning, working memory, and task switching (Levy & Dubois, 2006). These cognitive processes are needed to organize and structure GDB. The loss of these abilities will quantitatively reduce behavior.

Multitasking is an important aspect of executive function, referencing the ability to carry out several separate tasks concurrently while keeping the goals of each task in mind. The cognitive demand of multitasking includes selecting, organizing, and executing numerous tasks in a given time period (Burgess, 2000). Esposito et al. (2010) recently examined the aspect of multitasking related to apathy in AD patients. They found that an inability to perform several tasks (measured by rule breaks) was predictive of a lack of initiative (motivation). This outcome suggests that when patients are faced with complex problems that are cognitively demanding, they may become overwhelmed and, thus, less likely to engage in activities. An alternative hypothesis, in contrast to the findings of Espositio and colleagues, may be that patients perform more poorly because of other processes like impaired judgment or poor working-memory performance. Although there seems to be a relationship between apathy and deficits in multitasking, further studies are needed to determine the exact role of planning in apathy.

Weintraub and colleagues (2005) examined the dimension of executive function as it relates to apathy in PD patients. They found that poor planning, measured by standardized tests of planning, was associated with increased severity of apathy. An important issue that was not addressed by Weintraub et al., however, is the relative complexity of the plan needed to engage in GDB. Consideration should be given to the total complexity of a task and the amount of executive resources it demands as it relates to apathy severity.

The anatomic basis of executive dysfunction has been linked to dorsolateral portions of prefrontal cortex (dlPFC; Miller & Cohen, 2001). This region has been shown to play a critical role in planning and working memory. Several investigations have

demonstrated that working memory is associated with dlPFC (Champod & Petrides, 2007; Funahashi, 2001; Yun, Krystal, & Mathalon, 2010). Garavan, Ross, Li, and Stein (2000) evaluated the role of working memory by manipulating allocation of attentional resources in working memory tasks. This technique was used to disentangle working memory from other executive processes, allowing for a pure analysis of working memory. Using functional MRI (fMRI) technique, they found that working memory-demanding tasks activated dlPFC in healthy controls.

Other work also suggested the importance of dlPFC for planning (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011). The planning process can be assessed with measures like the Tower of London task where participants are asked to preplan mentally a sequence of moves to match a set goal. Event-related fMRI techniques are employed to capture planning demands in NC. Using this technique, several studies have demonstrated the activation of dlPFC in planning tasks (Newman, Carpenter, Varma, & Just, 2003; Rowe, Owen, Johnsrude, & Passingham, 2001; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004).

Studies suggested an association between apathy and poor executive function in bvFTD (Zamboni et al., 2008). Imaging studies of patients with ND have linked apathy to tissue loss in dlPFC and related white matter tracts including the superior longitudinal fasciculus (Cacciari et al., 2010; Massimo et al., 2009; Zamboni et al., 2008). Patients who suffered from dysfunction in these circuits failed to elaborate, manipulate, and integrate important information needed for behavior that was goal-directed.

Motivation component. Finally, apathy may result from a lack of responsiveness to either reward or negative-consequence feedback, thereby making goal selection

difficult (Levy & Dubois, 2006; Rosen et al., 2002). Because rewards and avoidance of negative consequences constitute basic goals of behavior, motivational functions are based partly on the processing of reward information (Schultz, Tremblay, & Hollerman, 2000).

Evidence from healthy-subject MRI studies suggested that the OFC is important to determine information regarding interpretation of reward (Hare, Camerer, Knoepfle, & Rangel, 2010; Kable & Glimcher, 2007). In an fMRI study of reward processing in healthy controls, Smith and colleagues (2010) found that the ventromedial prefrontal cortex (vmPFC) is highly specialized in the way it processes rewards. In particular, they found that, in vmPFC, the anterior portion experienced value for social and monetary rewards, whereas the posterior vmPFC tracked the decision value between these two reward categories. Together, these findings suggest that multiple value signals exist simultaneously in the anterior and posterior vmPFC, each playing a distinct role in reward processing.

This region also may mediate the inhibition of inappropriate responses while facilitating appropriate responses for goal completion (Gill, Castaneda, & Janak, 2010). This is important to apathy because the inability to suppress the response evoked by a stimulus in the immediate environment prevents a patient from selecting an appropriate action plan. Thus, the behavior is controlled by the emotional impact of the stimulus at hand. Bechara, Damasio, and Damasio (2000) tested this hypothesis in patients with lesions of vmPFC. Patients participated in a gambling task. Compared to controls, patients with vmPFC lesions preferred decks with a high immediate reward, even though the decks with smaller reward were advantageous in the long term. They also preferred

decks with low immediate punishment to those with higher immediate punishment, although the higher immediate punishment was more advantageous in the long run. Their results reinforced the notion that decisions made by patients with vmPFC lesions are largely based on the immediate prospects and do not consider the severity of future adverse consequences (Bechara et al., 2000).

Persons with bvFTD have been examined extensively in reward processing because they have an early degeneration of the associated frontal circuit in comparison to other neurodegenerative conditions (Rabinovici et al., 2007). Grossman and colleagues (2010) examined the interpretation of positive and negative situations in bvFTD. They found bvFTD participants were particularly impaired in interpreting negative consequences of a social situation (e.g., "Rolling through a red light at 2am when there is a police car at the intersection"). Their insensitivity to negative consequences may underlie reduced motivation.

The study of reward processing and resultant apathetic behavior in the bvFTD population offers essential insights into the functions of the OFC. Experimental evidence using imaging techniques in patients with bvFTD has emphasized the link between orbitofrontal regions and apathetic behaviors. Comparison of brain activity between apathetic and nonapathetic bvFTD participants using positron emission tomography (PET) data revealed patients have decreased activity in the OFC of apathetic participants (Peters et al., 2006). Rosen and colleagues (2005) examined apathy, measured by the Neuropsychiatric Inventory (NPI), and found apathy scores to be independently associated with atrophy in the ventromedial frontal gyrus. The uncinate (UNC) is a major tract connecting the anterior temporal lobe with the medial and lateral prefrontal cortex

(Papagno et al., 2011), areas known to be important for GDB (Kable & Glimcher, 2007). DTI studies performed in patients with AD and progressive supranuclear palsy (PSP) implicated UNC in apathy (Hahn et al., 2013; Kvickstrom et al., 2011). The conclusions from these imaging studies suggested that the OFC and related white matter tracts have a relationship to apathy, although distinct areas of this region may have specific roles.

Summary of Key Points

Apathy can be viewed as the quantitative reduction of GDB and is a common behavior in neurodegenerative conditions, especially bvFTD. Studies of the frontal-subcortical circuits contributed to explaining its phenomenological presentation. In support of this view, and using the above definition, I hypothesized that three impaired GDB mechanisms (initiation, planning, and motivation) contribute to subtypes of apathy. The first subtype of apathy is related to an initiation difficulty. This subtype of apathy can be seen in patients with disease in the ACC. The second subtype is due to impaired planning, which results from disease in the dlPFC. The third subtype of apathy is related to related to impaired goal selection and motivation that occurs when disease affects areas in the OFC.

Research Design and Methods

Overview of research design. In Aim 1, structural MRIs in bvFTD participants were compared to NC, and regression analyses related apathy scores (see Table 1) to grey matter structures and associated white matter tracts. In Aim 2, results on a computerized task, the PACT, were analyzed for apathy subtypes in bvFTD using the PACT measures, and regional grey matter volume was then assessed for each impaired GDB component.

In Aim 3, findings from Aims 1 and 2 were used to support the development of a research proposal to examine mechanisms of longitudinal decline and neural compensation**.**

Table 1

Sample Criteria

Inclusion	Exclusion
Diagnosis of bvFTD (Rascovsky et al., 2011) or NC.	Other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorder such as depression or psychosis, or systemic illness that could interfere with cognitive functioning.
Mild disease stage (measured by Mini-Mental State Exam ≥ 20).	Mini-Mental State Exam ≤ 19 to minimize confounding factors related to cognitive impairment by excluding persons with moderate or severe dementia.
No depression as determined by Geriatric Depression Scale Short Form score of ≤5.	Depressed patients (Geriatric Depression Scale-Short form score >5) since apathy is often clinically confused with depression and could confound interpretation of the data.
Modest doses of SSRI or antipsychotic medication may have been needed for treatment as clinically indicated, and, thus, were allowed. A stable dose (no change in 3 months) was necessary to minimize potential confound because these medications can contribute to apathy (Benoit et al., 2008).	Patients taking regular doses of benzodiazepines and other soporific medications because of the sedating effects of these drugs.
A reliable caregiver who had frequent contact with the patient (>3 times/week for ≥1 hour).	Patients who do not have caregiver contact to ensure accurate proxy ratings of the patient's behavior, since patients with bvFTD typically have poor insight into their deficits (Eslinger et al., 2005).
Neuropsychiatric Inventory apathy subscale frequency by severity score ≥1.	Captures bvFTD patients with higher likelihood of having apathy syndrome.
Ability to speak and understand English language sufficient to complete the questionnaires.	Patients with English language skills insufficient to complete questionnaires.

Participants and setting. Participants with bvFTD and age- and education-matched NC who were enrolled in the ongoing longitudinal study, "Cognitive and Neural Impairment in Frontotemporal Dementia" (P01-AG17586) at the University of Pennsylvania were selected for the proposed research. These participants had available

neuropsychological, neuroimaging, and biomarker data. I focused particularly on bvFTD because apathy is very common in this condition, these patients do not have physical limitations that can confound the quantitative assessment of reduced GDB, and there are no language or visuospatial deficits that can potentially limit the interpretation of bvFTD patient performance. Participation was limited to those with apathy, determined by scores on the NPI to increase the likelihood of capturing the phenomenon of interest.

Power Analysis. To conservatively estimate the power required to detect a significant difference on the PACT between NC and bvFTD participants, I used the PACT measure with the smallest difference between controls and bvFTD participants found in our pilot data (Initiation score: bvFTD = 522ms ± 224.17 vs. NC = 375ms ± 69.46). With reasonable assumptions of 1.0 *SD* difference in performance between groups and a beta of 0.8, a power analysis suggested that 18 participants were required in each group to achieve a difference that is significant at the .05 level using Wilcoxon rank-sum test. For the VBM imaging study, a minimum of 20 participants were required in each group to detect a 1mm (equivalent to 1 voxel) change in grey matter at the $p < .05$ (corrected) level with a beta of 0.15 (power =. 85; Lerch & Evans, 2005; see Table 2).

Table 2

Power Analysis

SD diff	β = 0.8	β = 0.9
0.5	68	91
0.75	31	41
1.0	18	24
1.5	9	12
2.0	6	8

Note. *Sample size needed to detect a mean difference between two groups from Wilcoxon rank-sum test; alpha = .05.

Procedures. As previously described, this dissertation study was part of a larger, ongoing longitudinal study entitled "Cognitive and Neural Impairment in Frontotemporal Dementia" (P01-AG17586; PI: Virginia Lee, PhD, Clinical Core Leader: Murray Grossman, MD). This study included individuals from the parent study who were diagnosed with bvFTD and NC. University of Pennsylvania Institutional Review Board (IRB) approval was initially obtained for P01-AG17586 in January 1999 and the most recent continuing review approval from the IRB in September 2013 encompassed the MRI procedures and the battery of neuropsychological testing that included the PACT.

I met with Dr. Grossman on a weekly basis to determine whether any newly eligible patients had been entered into the abovementioned study. If so, the neurologist or clinical coordinator asked the patient and caregiver if they were interested in hearing more about the dissertation study. If so, I met the patient and caregiver to give an overview and confirm their intention to participate.

Ideally, I would collect the PACT data, neuropsychological data and MRI data on the same day. To maximize recruitment, retention, and convenience to participants, the

patients and caregivers had the option to request that PACT and neuropsychological data be collected during a follow-up in-home visit. In any case, I collected the MRI and PACT data in the same 6-month period. Given the rate of brain volume change in bvFTD, 6 months is a widely accepted time frame in neuroscience research (Whitwell et al., 2008).

Data collection. I obtained the data for this study, including that generated from the PACT, neuroimaging, and neuropsychological tests, from each participant in the ongoing study (P01-AG17586). I administered the PACT which took approximately 45 minutes to complete. The neuroimaging sequence, completed by Department of Radiology technicians, generally took 30 minutes to complete. The neuropsychological tests were conducted by trained research technicians and took approximately 60 minutes to complete.

I collected data in the Cognitive Neurology Clinic and in the Department of Radiology at the Hospital of the University of Pennsylvania. I conducted the PACT and neuropsychological tests in a quiet room in the Department of Neurology. Alternatively, if the patient and caregiver desired, I collected the PACT and neuropsychological testing during an in-home visit.

Instrumentation.

The Philadelphia Apathy Computerized Test (PACT). Experimental computer tests examining the basis for a social behavior are useful in studying the mechanisms contributing to the behavior. Moreover, they are quantitatively rigorous. The PACT was intended to measure three components of GDB—initiation, planning, and motivation. The PACT was developed based on a review of experimental paradigms in the scientific literature and clinical observations (Elliott, Agnew, & Deakin, 2010; Jenkins, Jahanshahi,

Jueptner, Passingham, & Brooks, 2000; Ruh, Cooper, & Mareschal, 2010). In all experimental conditions, a trial began when the participant depressed a computer "start" key with one finger. Reaction time (RT) to lift this finger from the start key in response to a signal (RT1) and then RT to depress the target key once lifted from the start key (RT2) were each measured. A practice block, in which participants received instructions about task performance and 12 practice trials, preceded each of three experimental conditions described below.

Initiation refers to one's ability to self-generate or activate actions (Levy & Dubois, 2006). In the simplest condition designed to measure initiation, the participant began a trial by depressing the start key; a central stimulus appeared on the computer screen, and a fixed central target key was then depressed in response to this stimulus; over 48 trials, the signal occurred on average 1,250msec (range 500–5000msec) after depressing the start key. Initiation was assessed by RT1 in this condition.

Planning refers to the ability to elaborate plans of action (Levy & Dubois, 2006). Thus, assessing the *planning* component required a resource-demanding task that depended on the integration of strategies to meet the challenges of the condition (Sorel & Pennequin, 2008; Toglia & Berg, 2013). In the second condition, designed to assess the planning component of GDB, two levels of task difficulty were assessed. In the first level (simple planning), after depressing the start key, participants were signaled by randomly ordered lateralized visual stimuli to press a left or right target key (stimulus appears on left, then go left; stimulus appears on right, then go right). In the second, more complex level, one of two lateralized keys is pressed contingent on the combination of patterns in a central visual stimulus (if the stimulus is blue or has horizontal stripes, the key on the

left is correct; if the stimulus is orange or contains vertical stripes, the key on the right is correct). To assure that planning could be assessed specifically, we minimized the influence of working memory confounds by making the patterns visually available to participants during performance. We assessed two measures of planning: total latency in the complex planning condition and the difference in response times between the two levels of difficulty.

Motivation refers to the ability to associate affective signals (positive or negative) with value in order to perform actions (Levy & Dubois, 2006). In the third condition, designed to assess motivation, the simple condition was repeated with an explicit monetary incentive using a point system (monetary units) to reward participants for responding correctly and more rapidly. Participants received feedback on the computer screen about their response speed after each trial. Sensitivity to negative consequence was assessed by having a "penalty" condition. In this "penalty" condition, we gave participants a number of monetary units at the beginning of each task, and took away monetary units if they did not respond correctly and more rapidly. I used the penalty condition measure to assess motivation because previous work has shown that bvFTD patients are particularly insensitive to negative feedback (Grossman et al., 2010). I used a point system involving "monetary units" and monetary units were "converted" to actual money in a manner that allowed all participants to receive the same total payment at the end of the study.

I obtained 48 experimental trials during each condition. I measured RT1, RT2, total latency (RT1 + RT2) and errors. Average RTs for initiation, planning, and

motivation (see Table 3) were each generated from the conditions described above and used in the regression analyses (Aim 1).

Table 3

Scores Generated From the PACT

Score	Measure
Initiation score	Average Reaction Time 1 in simple condition
Planning score	Average total latency in complex planning condition
Motivation score	Average total latency in simple penalty condition

Structural MRI. I obtained MRI data with the support of P01-AG17586 (PI: Virginia Lee, PhD; Clinical Core Leader: Murray Grossman, MD). Three-dimensional T1-weighted structural MRI provided 1 mm^3 resolution for assessing grey matter-volume loss, and we used spoiled gradient-echo imaging (MPRAGE on our Siemens Trio) with an inversion preparation to increase grey/white matter contrast at high field. We used three dimensional spoiled gradient echo imaging parameters as follows: *TR* = 1620ms, *TI* = 950ms, *TE* = 3ms, flip angle = 15°, 160 contiguous slices 1.0 mm thick, in-plane resolution 0.9×0.9 mm, *FOV* = 192x256mm^2, matrix = 192 X 256, 1NEX with a total scan time of 6 min for the entire volume. We repeated this sequence twice, allowing signal-to-noise ratio to be increased by signal averaging following realignment, or one volume could be discarded if excessive motion (> 3mm in any axis) occurred. We acquired diffusion-weighted images (DWI) using a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (*FOV* = 245mm; matrix size = 128 × 128; number of slices = 57; voxel size = 2.2mm isotropic; *TR* = 6,700ms; *TE* = 85ms; fat saturation). In total, we acquired 31 volumes along 30 noncollinear directions per subject,

one without diffusion weighting (b = 0 s/mm^2) and 30 with diffusion weighting (b = 1,000 s/mm^2).

Neuropsychological tests. Researchers collected neuropsychological data shown in Table 4 for the parent study and made them available to me. Researchers use neuropsychology test results to help to improve characterization of apathy in bvFTD, because preliminary data associate apathy with executive and social deficits (Chow et al., 2009; Eslinger et al., 2011; Eslinger et al., 2012; Eslinger et al., 2007; Girardi, Macpherson, & Abrahams, 2011). The overall guiding principle for the parent study was that the neuropsychological battery was comprehensive in its scope, and included measures with good psychometric properties that were well normed for a broad age range, yet administrable in a reasonable amount of time (in our experience, about 60 minutes). I used two of the available measures to execute the inclusion/exclusion criteria, and, although no measures specific to components of GDB (initiation, planning, and motivation) were included in the database, several tests or items sampled some aspects of these components, thereby potentially providing auxiliary support for the PACT.

Data management. I managed data using web-based, intranet data management. The database server was Microsoft SQL Server 2005 with front end application developed in PHP dynamic web language, hosted via Microsoft IIS 6.0 web server. The database, located on the University of Pennsylvania Health System (UPHS) network, was protected from the Internet via the UPHSnet firewall. The servers were part of the UPHS enterprise backup system. Backups were performed daily by the UPHS backup administrators. MRI data were archived onto compact disk (CD) from the scanner immediately following data acquisition. Data were loaded onto a workstation, stripped of

identifying information, and transferred via secure ftp to a specific account for this project on the Center for Functional Neuroimaging (CfN) web server at the University of Pennsylvania. Data stored on the CfN cluster were backed up weekly using SDLT tape, and daily interim backups were performed onto external firewire hard drives. All data entered were cleaned, transformed and analyzed using the statistical software package SPSS 21.0 for Mac.

Table 4

Neuropsychological Data

Name of test	Time	Brief description	Use in study
Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975)	10 minutes	A screen for dementia. Determines cognitive impairment using a cutoff of 23. The instrument has a sensitivity of 82% and specificity of 99% for determining cognitive impairment with this cutoff (Tangalos et al., 1996).	Mini-Mental State Exam assessed severity of cognitive dysfunction to determine inclusion/exclusion.
Geriatric Depression Scale Short Form (Sheikh & Yesavage, 1980)	10 minutes	Measures depression briefly in elderly and in persons with dementia where a longer form may be burdensome (Burke, Roccaforte, & Wengel, 1991; Lach, Chang, & Edwards, 2010). This instrument has sensitivity and specificity of 87% and 83% respectively. The Geriatric Depression Scale was chosen because it ascertains affective symptom ratings of depression.	Identified depressed patients who were then excluded from the study.
Neuropsychiatric Inventory (Cummings, 1994)	15 minutes	Evaluates 12 neuropsychiatric disturbances, including apathy, as rated by caregivers, each with a frequency by severity score. Content validity, concurrent validity, interrater reliability and test–retest reliability of the Neuropsychiatric Inventory were established by past work (Cummings et al.,1994).	Confirmed caregiver-perceived presence of apathy for inclusion in the study, and measured associated caregiver distress.
Apathy Evaluation Scale-Informant Rated (AES-I) (Marin, Biedrzycki, & Firinciogullari, 1991)	10 minutes	An 18-item caregiver-completed scale that is commonly used to quantify global apathy. Responses to items were recorded on a 4-point Likert-type scale with the following categories: Not *at All True, Slightly True, Somewhat True,* and *Very True.* A higher score represents greater apathy severity. Response to the single item, "He/she has motivation," was used to determine the subject's level of motivation.	Assessed caregivers' perceptions of the patient's level of motivation.
Digit Span Backward	3 minutes	Digits are repeated in the reverse. Assesses mental manipulation and planning.	Assessed planning.
Trail Making	5 minutes	An alternating pattern is traced between numbers and letters.	Assessed planning.
Letter Guided Fluency	5 minutes	Name words beginning with the letters F, A, and S in 60 seconds each; first quartile fluency assesses initiation (Lamar, Zonderman, & Resnick, 2002).	Assessed planning, initiation.

Overall plan for analysis. I described the overall sample demographically and according to continuous measures of the PACT and relevant scores on the neuropsychiatric measures using means, standard deviations, and interquartile ranges. For categorical data, I used frequencies and percentages.

Analysis Aim 1.

Grey matter imaging. I used VBM to quantify significant grey matter changes in the bvFTD sample acquired with high resolution volumetric T1 MPRAGE images. All images were preprocessed using PipeDream (Sourceforge, 2014) and advanced normalization tools (ANTS, Penn Image Computing Science Lab, 2014) to perform the most stable and reliable multivariate normalization and structure-specific processing currently available (Avants, Epstein, Grossman, & Gee, 2008). PipeDream deforms each individual dataset into a standard local template space in a canonical stereotactic coordinate system. Core processing involved mapping T1 structural MRI to a population-specific template consisting of an unbiased average-shape and average-appearance image derived from a representative population of 25 healthy seniors and 25 patients with FTD (J. Kim et al., 2008). This procedure provided superior representations of variable anatomy as occurs in distinct populations such as in the examination of a healthy population and those with a neurodegenerative condition (Avants & Gee, 2004). I used a diffeomorphic deformation for registration that is symmetric so that it is not biased toward the reference space (for computing the mappings) and preserves topology to capture the large deformation necessary to aggregate images in a common space. These algorithms allowed template-based priors to guide cortical segmentation and compute grey matter atrophy (Das, Avants, Grossman, & Gee, 2009). We used SPM8 to smooth images using a 4mmFWHM Gaussian kernel and to compare patients to matched controls using a two-sample *t*-test. We accepted clusters containing a peak voxel that survived a $p < .001$ (FDR-corrected) height threshold and a 50 adjacent-voxel extent. We then used the regression module in SPM8 to identify the relationship between performance on each

PACT score (see Table 3) and grey matter density. To constrain the interpretation of the regression analysis to areas of known disease in participants, we used an atrophy mask generated from the *t*-test contrasts of bvFTD relative to NC. For each regression, we entered a single PACT score (average RTs over 48 trials) for each condition (see Table 3) for each patient. For the regression analyses, we accepted that a cluster was related to behavior if it contained a peak voxel which survived a $p < .005$ height threshold and a 30 adjacent-voxel extent.

White matter imaging. DWIs were preprocessed with PipeDream and ANTS, as above. We removed motion and distortion artifacts by affine coregistration of each DWI to the unweighted ($b = 0$) image. We computed DTs using a linear least squares algorithm (Salvador, Suckling, Schwarzbauer, & Bullmore, 2005) implemented in Camino (Cook et al., 2006), and tensors were reoriented using the preservation of principal directions algorithm (D. C. Alexander, Pierpaoli, Basser, & Gee, 2001). We computed fractional anisotropy (FA) from the DT image for each subject and corrected distortion between T1 and DT images by registering the FA image to the T1 image. We warped each participant's T1 image to the template via the symmetric diffeomorphic procedure in ANTS; then warped the FA image to template space by applying the T1-to-template warps.

We smoothed FA images using a 4mm full width at half maximum (FWHM) isotropic Gaussian kernel. I performed DTI analyses of FA in SPM8 using the two-samples *t*-test module and analyzed DTI volumes using an explicit mask ($FA \geq 0.25$) to constrain comparisons to regions of white matter. Comparisons of bvFTD participants to matched controls used a $p < .005$ (false discovery rate [FDR]-corrected) height threshold

and a 200-voxel extent. I constrained regression analyses to white matter tracts with reduced FA using an explicit mask generated from the results of the direct comparison with NC. Using a deterministic tractography procedure in Camino (Cook et al., 2006), I tracked white matter fibers in a healthy-subject template generated using the DTI sequence described above. I retained fiber tracts that passed through voxels of reduced FA to define the mask for regression analyses. I accepted a significant cluster with a volume of 150 adjacent voxels and a peak voxel Z-score > 3.3 (equivalent to $p < .0005$).

Analysis Aim 2.

Behavioral data. I described the sample according to the proposed apathetic subtype of initiation, planning, and motivation (see Table 5) using means, standard deviations, and z-scores. Shapiro–Wilks tests were used to assess normality in the data. I examined differences on scores on each task (initiation score, planning score, and motivation score) between bvFTD and NC groups using independent samples t-tests. Because the data were not normally distributed, I assessed differences between subject groups using nonparametric tests such as the Mann–Whitney U statistic. I calculated correlations with neuropsychiatric tests (see Table 4) using Spearman's rho. I expected initiation measures to be significantly associated with first quartile letter-guided fluency. I expected planning measures would be significantly associated with performance in the overall score on the digit span backward, trail making, and letter-guided fluency. Last, I expected a significant association between motivation measures and score (1–4) on the single AES-I item, "He/she has motivation."

I hypothesized specific apathy profiles as well, and described the number of participants in each subtype according to predetermined criteria (see Table 5). I generated

individual *z*-scores relative to NC. I designated participants as a specific subtype if the *z*-score was ≥ 2.0 for one profile criteria, but within the range of normal (i.e., *z*-score ≤ 2.0, $p \leq .05$) for the remainder of the tasks.

Table 5

Behavioral Criteria for Apathy Subtypes

Subtype profile	Criteria
Initiation	Significantly slow Reaction Time 1 in simple condition
	Does not have slowed latencies for complex condition
	Able to improve performance on the simple condition in response to penalty
Planning	Significantly slowed on complex planning condition and, for those with multiple impairments, significant slowing on the complex planning condition compared to the simpler planning condition
	Does not have slowed initiation for simple condition
	Able to improve performance on the simpler planning condition in response to penalty
Motivation	Significantly slowed on simple penalty condition and fails to improve performance with penalizing motivators
	Does not have slowed initiation for simple condition
	Does not have slowed latencies for complex condition

Grey matter imaging. I obtained a priori defined regions of interest (ROI) for ACC, dlPFC, and OFC. I selected these ROIs based on literature suggesting that poor initiation is related to disease in ACC (Kotchoubey et al., 2003; Reijnders et al., 2010), poor executive function is related to disease in dlPFC (Kaller et al., 2011; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004; van den Heuvel et al., 2005) and reduced motivation is related to disease in OFC (Diekhof, Falkai, & Gruber, 2011; Sescousse, Redoute, & Dreher, 2010). I used the standardized automated anatomical labeling (AAL) and parcellation method (Tzourio-Mazoyer et al., 2002) to label the following ROIs. The first ROI (e.g., initiation) was centered on the ACC (AAL label = ACIN). The second (e.g.,

planning) ROI was centered on the middle frontal gyrus portion of the dlPFC (AAL label = F2). The last ROI (e.g., motivation) was composed of the orbital regions of the middle and superior frontal gyri (AAL labels = F10, F20). Additionally, I assigned a control ROI in the midtemporal (MT) region (AAL label = T2). I chose this region because it is an area implicated in bvFTD (Brettschneider et al., 2014), but is not hypothesized to contribute to GDB. For all ROIs, I computed the mean grey matter probability (GMP) value, divided by the subject's individual average whole-brain GMP value. I used this ratio to examine relative differences in regional composition of grey matter in frontal areas thought to underlie GDB impairments and the control region in the lateral temporal lobe.

Anticipated Study Difficulties and Alternative Approaches Used to Achieve Aims.

Prior to initiating this study, I anticipated potential difficulties and identified alternative approaches to achieve the aims:

Interpretation and potential problems, Aim 1. I predicted that apathetic bvFTD participants would have significant atrophy in the frontal lobe. Further, PACT initiation scores would be related to significant ACC atrophy and associated white matter tracts; PACT planning scores would be related to atrophy in dlPFC and associated white matter tracts, and PACT motivation scores would be related to atrophy in OFC and associated white matter tracts. These predictions were made based on the literature suggesting that poor initiation is related to ACC disease (Kotchoubey et al., 2003; Reijnders et al., 2010), poor executive function is related to disease in dlPFC (Kaller et al., 2011; Unterrainer,

Rahm, Kaller, Ruff, et al., 2004), and reduced motivation is related to disease in OFC (Diekhof et al., 2011; Sescousse et al., 2010).

Anticipating that the regression analyses might not detect a distinct relationship between grey matter density and behavioral performance, I planned to use cortical thinning rather than grey matter density. It was possible I would find atrophy related to the striatum, given the observation of apathy in Parkinson's patients with striatal disease (Drapier et al., 2006), strong frontal-striatal connections (Bonelli & Cummings, 2007) and the observation of histopathological disease in the striatum of bvFTD (Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011; Whitwell et al., 2009). Anticipating the possibility that participants with long disease duration would have diffuse, nonspecific atrophy, I examined only participants with mild cognitive impairment. I expected some difficulty obtaining imaging in some participants because of time restriction, medical contraindication (e.g., claustrophobia or pacemakers) and participant preferences. If that were the case, I still planned to ask subjects to participate in the PACT assessment, using *t*-tests to confirm no significant differences between those with and without imaging data.

Interpretation and potential problems, Aim 2. I expected differences in PACT scores between bvFTD and NC groups. I predicted each apathetic subtype would show a distinct performance profile on the PACT. The initiation subtype would have slow RT1 across all conditions in the PACT. Once initiated, tasks would be performed slowly (RT2) but accurately. Participants would not have slowed latencies for complex conditions and would be able to improve their total latency times in response to incentives. The planning subtype would have significantly slow total latency on the complex planning condition, but participants would not have significantly slowed

initiation. They would also improve their time in response to incentive. The motivational subtype would improve less in response (measured by total latency) to financial incentive—and particularly the penalty condition—than the initiation and planning patients under the simpler planning condition, but would not have slowed initiation times, and would not have disproportionally slowed performance for the complex planning condition. This insensitivity to penalty is supported by previous studies that show bvFTD patients are insensitive to negative consequences but respond to a reward (Farag et al., 2010; Grossman et al., 2010; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009).

I acknowledged that my data might not support clear distinctions between the apathy subtypes; in this case, I planned to adjust my subtype criteria, which might include more stringent inclusion criteria for one or more of the subtypes.

Human subjects.

Human subjects involvement and characteristics. This dissertation study was part of a larger ongoing longitudinal study entitled "Cognitive and Neural Impairment in Frontotemporal Dementia" (P01-AG17586; PI: Virginia Lee, PhD, Clinical Core Leader: Murray Grossman, MD). For the purpose of this study, we offered participation to subjects diagnosed with bvFTD and NC. See Table 1 for a description of inclusion and exclusion criteria. I selected a total sample of 37 subjects (20 bvFTD and 17 NC).

Primary study approval. University of Pennsylvania IRB approval was initially obtained for P01-AG17586 in January 1999 from the University of Pennsylvania. Most recently (September 2013), the University of Pennsylvania IRB awarded the P01 continuing approval for a protocol that included neuropsychological testing including the

PACT, questionnaires, and MRI procedures. For the dissertation study, I obtained IRB approval to amend the parent study (P01-AG17586) to include the above analyses on July 25, 2012.

Source of materials. I obtained the materials for this study, including data generated from the PACT, neuroimaging, and neuropsychological tests (including the NPI), from participants in the parent study. The PACT took approximately 45 minutes to complete. The neuroimaging sequence generally took 30 minutes to complete. The neuropsychological tests took approximately 60 minutes to complete.

I collected data in the Cognitive Neurology Clinic and in the Department of Radiology at the Hospital of the University of Pennsylvania. If the subject and caregiver desired, I collected the PACT and neuropsychological testing during an in-home visit. I entered the raw data, which included subject and caregiver demographics, directly into a Web-based data-management system. I anonymized data through the use of alpha numeric identification numbers, and kept the key for the identification in a separate password-protected site. The server was log-in accessible only to the investigators and key study personnel. Data and all analyses for this study were kept on this server. After the data were entered, I stored the raw data in the Department of Neurology in a secured file cabinet and will keep it for 6 years to satisfy university policy.

I archived all MRI data from the scanner onto compact disk immediately following data acquisition. I loaded data onto a workstation, stripped them of identifying information, and transferred them via secure ftp to a specific account for this project on the CfN web server at the University of Pennsylvania. I backed up data stored on the CfN

cluster weekly using SDLT tape, and made daily interim backups onto external firewire hard drives.

Potential risks and adequacy of protection against risks.

Informed consent and assent. Informed consent and assent for the parent study were obtained from the caregiver and patient in accordance with the University of Pennsylvania IRB approved procedures. Participants were recruited from a pool of patients and their caregivers in the Cognitive Neurology Clinic at the Hospital of the University of Pennsylvania. After participants were evaluated for inclusion/exclusion by a cognitive neurologist (MG), they were provided a written and verbal explanation of the purpose, protocol, risks, and benefits of the study. At all times during the informed-consent process, potential study participants were reminded that participation was voluntary and withdrawal was an acceptable alternative to participation. After participants/caregivers had an opportunity to ask questions, fully informed written/assent was obtained from patient and caregiver.

Assessing each individual's capacity was an important step in the informed-consent process, because cognitively impaired individuals, such as those with bvFTD, may not have been able to understand relevant information or may not have been able to reason about the alternatives available to them. Previous research has shown that ND patients with preserved awareness of their diagnosis, symptoms, and prognosis are likely to retain the capacity to make decisions about their care (Karlawish, 2008). Because judgment and insight are lost early in bvFTD patients (Piguet, Hornberger, Mioshi, & Hodges, 2011), we did not assume capacity to consent even with "mildly impaired" scores on the MMSE. To our knowledge, no studies addressed the decision-making

capacity of bvFTD patients. Capacity assessment remains a clinical assessment performed by the cognitive neurologist (MG). If patients did not have sufficient capacity to consent, then assent was obtained. At minimum, assent from the patient and proxy consent were obtained for all participants. Potential risks for patients and caregivers who participated in this study were related to subject burden and distress as well as administration of testing materials. A list of the potential risks in this study and the protections against risks are addressed below.

Risk associated with PACT and/or neuropsychological testing for patients. Patients took no physical risks by performing the PACT and answering questions associated with the neuropsychological tests. Some participants may have become fatigued or felt anxious while performing these tests.

Protection against risk. The testing was divided into several small sections, thereby providing frequent rest periods, and the testing may have continued during a follow-up session, as appropriate. Participants could request additional rest periods at any time. Prior to each task, we discussed the nature of the task. Because participation in the study was voluntary, participants could choose not to answer any question and had the right to withdraw if desired.

Risks associated with MRI. There is little risk associated with MRI studies. Many participants have been safely studied in MRI research. The technique uses no radiation, so it can be repeated with no known adverse effects (Cogbill & Ziegelbein, 2011). The measurement is painless, but it is noisy inside the magnet. The magnetic field is not harmful in itself, but implanted devices (e.g., pacemaker) that contain metal may malfunction during the MRI. In addition, a metallic object may fly through the air toward

the magnet and hit the patient. Last, participants may experience claustrophobia in the machine; thus, we excluded participants with a known history of claustrophobia from the MRI portion of the study.

Protection against risk. We gave participants earplugs to decrease the noise level while in the scanner. Because of the strong magnetic field, we excluded patients with pacemakers or other metallic implants from this component of the study. Participants and caregivers completed an MRI screening form with study personnel before entering the MRI room. The purpose of the form was to identify known metallic implants that would be a contraindication for MRI. We required participants to remove all metal from their person and clothing, including metal objects in their pockets before entering the MRI room. Last, we gave participants a call bell to squeeze if they became uncomfortable or claustrophobic, and the MRI study was stopped at that point.

Risks associated with caregiver questionnaires. We held some concern for psychological distress for the family caregivers when we administered the NPI and AES-I. Neuropsychiatric features in dementia can be a sensitive topic and some caregivers were at risk for becoming upset. Similar research studies involving interviews with spousal caregivers, however, found that the experience afforded them a positive opportunity to share their experience and contribute to scientific knowledge (Hellstrom, Nolan, Nordenfelt, & Lundh, 2007; Mastwyk, Ritchie, LoGiudice, Sullivan, & Macfarlane, 2002).

Protection against risk. In the event that a negative emotional response occurred, we reminded caregivers that they did not have to answer any question with which they felt uncomfortable and they were provided a break. Additionally, we provided caregivers

with support-group information. The name and contact information for a licensed psychologist who has experience working with caregivers of persons with dementia was also available.

Ethics of participant payment. We paid participants $35 for the burden associated with the MRI procedure of the parent study. Also, we paid participants an additional $10 for participating in the PACT. This test asked participants to make decisions about picture stimuli on a computer screen. The experimental hypothesis tested whether participants were able to improve their times in return for positive feedback. In the PACT, points were awarded for appropriate responses or deducted for inappropriate responses. We told all participants that the number of points they accumulated would be converted into a monetary award at the end of the experiment. We constructed a conversion scale so that we paid all participants $10 for their participation, regardless of the points they earned. To calculate reimbursement, we used the wage-payment model. This payment model operates on the notion that research participation requires little skill, but does require time and effort (Dickert & Grady, 1999). We chose this model because it standardizes the payment process so that all participants were paid equally.

Potential benefits of the proposed research to human subjects and others. We informed participants that they would have no additional risk and receive no additional benefits from analysis of data in this study. It is possible that although these results may benefit patients and caregivers in the future, participants in this study would not realize an immediate or direct benefit from participating. Given the minimal risks associated with this study, and the general benefits to the patients and families with ND and the research community, the overall risk-to-benefit ratio was favorable. Further, we found

research studies that suggested there are altruistic benefits to participating in dementia research, even if the subject is not directly benefited (Law, Russ, & Connelly, 2013; Lynoe, Sandlund, & Jacobsson, 1998).

Importance of knowledge to be gained. The overall goal of this innovative research project was to identify the neural mechanisms that contribute to apathy in patients with a certain type of ND. By identifying three distinct impairments in GDB, interventions can be explored based on an individual's pathology profile. Interventions may help the apathetic patient engage in activity, but the interventions must be tailored to the subtype of apathy. To facilitate this research, researchers need an objective evaluation that is able to differentiate subtypes of apathy by neuroanatomical mechanisms. Then a systematic evaluation of existing interventions for apathy will be warranted, followed by the testing of interventions designed by apathetic subtype. These studies are necessary to improve patient and caregiver quality of life.

Inclusion of women and minorities. The sample included both male and female adults. FTD affects slightly more men than women (Johnson et al., 2005), and to date, the parent study tended to recruit slightly more male than female patients. In the case of an imbalanced enrollment, I planned to query the database to find a representative sample.

Recruitment, selection, and enrollment were not discriminatory regarding race or gender; however, an unequal number of minorities were enrolled in the parent study. Recent research suggested that members of minority populations are less likely to participate in dementia research because, relative to their Caucasian counterparts, they are often diagnosed later, and thus do not receive specialized dementia care (Cooper, Tandy, Balamurali, & Livingston, 2010). Ongoing efforts to engage a community of

minorities included a monthly educational series at community centers in Philadelphia and surrounding areas. Researchers used these efforts to aggressively increase and retain minority-group representation.

Inclusion of children. The participants in this study were adults age 21 and older. We excluded children, as this research relates to adults with ND.

CHAPTER 2: NEUROANATOMY OF GOAL-DIRECTED BEHAVIOR IN FRONTOTEMPORAL DEGENERATION

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Abstract

Apathy, the major manifestation of impaired GDB, is the most common neuropsychiatric syndrome associated with bvFTD. The behavioral and biological mechanisms of apathy, however, are not well understood. To improve understanding of apathy, we examined the neural basis of GDB in bvFTD. Eighteen apathetic bvFTD participants and 17 healthy controls completed the PACT. This test quantifies each of three components of GDB—initiation, planning, and motivation—hypothesized to contribute to apathy. We then analyzed the association between PACT scores with grey matter atrophy and reduced white matter FA in bvFTD. Compared to controls, bvFTD participants demonstrated significant impairments in the three hypothesized components of GDB that contribute to apathy. Regression analyses related each component to disease in specific grey matter

structures and associated white matter tracts. Poor initiation related to grey matter atrophy in anterior cingulate and reduced FA in cingulum. Planning impairment related to grey matter atrophy in dlPFC and reduced FA in superior longitudinal fasciculus. Poor motivation related to grey matter atrophy in orbitofrontal cortex and reduced FA in uncinate fasciculus. bvFTD patients have difficulty with initiation, planning, and motivation components of GDB. These findings are consistent with the hypotheses that GDB encompasses three processes, that these are supported by a large-scale neural network in specific portions of the frontal lobe, and that degradation of any one of these prefrontal regions in bvFTD may contribute to apathy.

Introduction

Apathy is among the most common behavioral manifestations that contribute to bvFTD (Diehl-Schmid et al., 2006). However, the mechanisms that contribute to apathy are poorly characterized. We hypothesize that apathy can be operationalized as an impairment in GDB that is essential to daily human functioning. GDB defined as "broad spectrum of purposeful actions, from the simplest movement to the most complex patterns of behavior" (Brown & Pluck, 2000, p. 416)—includes mechanisms such as initiation, planning, and motivation, which allow a person to direct purposeful behavior toward a desirable goal or away from an undesirable outcome (Geurts & de Wit, 2013). In this study, we examined dissociable behavioral and neuroanatomic components of GDB in bvFTD in an effort to improve understanding of apathetic behavior.

Most studies of bvFTD assumed that apathy is a single, undifferentiated behavioral phenomenon. Using a unitary model, researchers have linked apathy in bvFTD to several prefrontal areas, including dorsolateral, anterior cingulate, and orbital

regions (Massimo et al., 2009; Zamboni et al., 2008). Heterogeneous findings such as these may reflect that apathy is multifactorial, consistent with the GDB model, and that each of these anatomic regions supports one component of a large-scale network that may be compromised in bvFTD patients who display apathy. In the present study, we used a novel RT test that directly ascertains each of three components thought to play a role in GDB, and we relate patterns of impairment for each component to MRI regions of grey matter atrophy and white matter integrity in bvFTD.

Methods

Participants. Eighteen bvFTD patients (five women) were recruited from the outpatient clinic of the Department of Neurology, University of Pennsylvania and evaluated by experienced cognitive neurologists (DJI, MG) using published consensus criteria (Rascovsky et al., 2011). All patients had mild disease (MMSE $\geq$ 20) to minimize potential confounding factors related to severe cognitive impairment. Medical and psychiatric causes of dementia were excluded by clinical examination and blood- and brain-imaging tests. We also excluded individuals with depression using the Geriatric Depression Scale-Short Form (Sheikh & Yesavage, 1980) scores > 5, as depression can be confused with apathy, and we excluded participants taking benzodiazepines and other soporific medications because of their sedating side effects. All participants had apathy, determined by the NPI (Cummings et al., 1994) FxS score $\geq$1. The FxS score is rated on the basis of scripted questions administered to the patient's caregiver, yielding a maximum score of 12. Caregiver also rate their own levels of distress for each domain. Seventeen healthy seniors served as a control group for the behavioral measure. Control participants were demographically-comparable to bvFTD participants for age and

education and self-reported a negative neurological or psychiatric history. See Table 6 for a summary of demographic characteristics. All participants and responsible caregivers for patients participated in an informed-consent procedure approved by the University of Pennsylvania IRB.

Table 6

Mean (±S.D.) Demographic and Clinical Features of Patients with Behavioral Variant Frontotemporal Degeneration and Healthy Controls

	Controls (*n* = 17)	bvFTD (*n* = 18)
Age (Years)	67.12±10.82	61.00± 5.2
Education (Years)	15.35±2.91	17.00± 3.1
Disease duration (Years)	na	3.70±1.63
Mini-Mental State Exam (max score=30)	29.47±0.87	27.33±2 .2

Behavioral measures.

The Philadelphia Apathy Computerized Test (PACT). The PACT was developed to quantify components of GDB that are compromised in patients with apathy. It was developed based on a review of experimental paradigms in the literature and clinical observations of apathy (Jenkins et al., 2000; Ruh et al., 2010). Briefly, a computerized RT was obtained to assess initiation, planning, and motivation components of GDB. Participants had a brief practice period of several trials for each of the measures described below, and all participants appeared to understand the tasks.

To assess the *initiation* component, participants began a trial by depressing the "start" key, then a central visual stimulus (triangle) appeared on the computer screen (latency ranging pseudorandomly 500–1,200msec); finally, another fixed central target

key must be depressed in response to this stimulus for 48 trials. To obtain an *initiation score,* we measured the latency for the subject to lift the finger off of the start key in response to the stimulus on the screen.

Assessing the *planning* component required a resource-demanding task that depended on the integration of strategies to meet the challenges of the condition (Sorel & Pennequin, 2008; Toglia & Berg, 2013). Here, participants must correctly press one of two pseudorandomly lateralized keys, contingent on the combination of two features of a central visual-pattern stimulus: if the stimulus is blue or has horizontal stripes, the key on the left is correct; if the stimulus is orange or contains vertical stripes, the key on the right is correct. To assure that planning could be assessed specifically, we minimized the influence of working memory confounds by making the patterns visually available to participants during performance. A *planning* score was generated by averaging the total latencies on correct trials of the planning task described above.

To assess the *motivation* component, the participant performed the initiation task described above; here, we gave participants an additional amount of money in the form of monetary units at the beginning of the task, and money was taken away as a "penalty" if they did not respond more rapidly to a stimulus relative to their previous performance, obtained during the initiation task described above. Participants received verbal and visual feedback (a bank of points appeared on the screen) about their response speed after each trial on the computer screen, compared to their prior RT, and we told participants that monetary units would be converted to money at the end of the study. Participants also performed a "reward" condition where they receive points for responding more rapidly than during the initiation condition (reward and penalty conditions were

administered in a randomly ordered manner across participants, but we used the penalty condition to obtain a *motivation score* because previous work has shown that bvFTD patients are particularly insensitive to negative feedback (Grossman et al., 2010).

Neuroimaging data. Structural MRI data were available for all bvFTD participants with PACT scores (n = 18), and DTI data from the same scan session were also available for a subset of these participants (n = 15). We acquired high-resolution T1-weighted 3-dimensional spoiled gradient echo images on a Siemens 3.0T Trio scanner with an 8-channel coil (repetition time = 1,620msec, echo time = 3msec, slice thickness = 1.0mm, flip angle = 15°, matrix = 192 × 256, and in-plane resolution = 0.9 × 0.9mm). We acquired DWI using a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (FOV = 245mm; matrix size = 128 × 128; number of slices = 57; voxel size = 2.2mm isotropic; TR = 6,700ms; TE = 85ms; fat saturation). In total, we acquired 31 volumes per subject, one without diffusion weighting (b = 0 s/mm^2) and 30 with diffusion weighting (b = 1,000 s/mm^2) along 30 noncollinear directions. For comparison, we selected a standardized sample of 24 controls with existing MRI and DTI. Two sample t-tests confirmed that patients and controls [mean age = 60.71 years (SD = 6.9); mean education = 15.79 years (SD = 1.9)] were demographically comparable (age, education, and gender, all $p > .1$). To ensure our imaging control cohort was representative of the behavioral control cohort, we performed two-sample t-tests and confirmed that these groups were demographically comparable (age, education, and gender, all $p > .1$).

Grey matter imaging data. Before normalization, we segmented each individual's structural image into tissue classes using *Atropos,* a voxel-based segmentation tool that segments the brain into grey matter, white matter, and cerebrospinal fluid (Avants,

Tustison, Wu, Cook, & Gee, 2011). We preprocessed all images using PipeDream (Sourceforge, 2014) and ANTS (Penn Image Computing & Science Lab. 2014) to perform multivariate normalization. Researchers demonstrated that this method accurately normalizes large-scale data in studies of patients with ND (Avants et al., 2008; Avants, Tustison, Song, et al., 2011). We used a diffeomorphic deformation for registration that is symmetric so it is not biased toward the reference space for computing the mappings (Avants, Tustison, Song, et al., 2011). Processing involved mapping T1 structural MRI to an unbiased average-shape and average-appearance template derived from a representative population consisting of 25 healthy seniors and 25 patients with FTD (J. Kim et al., 2008) This diffeomorphic method for registration and normalization avoids the need to use identical participants in the local template. Grey matter probability images were calculated as a quantitative measure of grey matter density. We then transformed grey matter probability images into Montreal Neurological Institute space for statistical analysis and down-sampled to $2mm^3$ resolution to attain a more anatomically relevant voxel size.

We used SPM8 (SPM, 2014) to smooth grey matter images using a 5mmFWHM Gaussian kernel. We conducted a whole-brain analysis: First, we compared grey matter density in bvFTD and 24 healthy seniors using a two-sample *t*-test with a voxel level threshold of $p < .001$ (FDR-corrected) and extent threshold of 50 voxels. In the second analysis, we performed regressions to relate grey matter density in bvFTD directly to the scores (initiation, planning, and motivation) on the PACT. We restricted regression analyses to evaluate only potential relationships between PACT performance and regions demonstrated to be atrophied in our bvFTD sample in an effort to constrain our

interpretations of the regression analyses to those brain regions known to be significantly atrophic and highly likely to have disease. For example, a significant correlation between a nonatrophied area and a PACT score could otherwise be attributed to factors that are independent from disease and instead related to nonspecific factors such as age. The height threshold for the regression analyses was set at $p < .005$ (uncorrected). The threshold was set at $p < .05$ for the planning regression due to limited variance in planning scores. We accepted as significant a cluster with a volume of 30 adjacent voxels and a peak voxel Z-score > 3.09 (equivalent to $p < .001$).

White matter imaging. DWIs were preprocessed with PipeDream and ANTS, as above. We removed motion and distortion artifacts by affine coregistration of each DWI to the unweighted ($b = 0$) image. We computed DTs using a linear least squares algorithm (Salvador et al., 2005) implemented in Camino (Cook et al., 2006), and reoriented tensors using the preservation-of-principal-directions algorithm (D. C. Alexander et al., 2001). We computed FA from the DT image for each subject, correcting distortion between T1 and DT images by registering the FA image to the T1 image. We warped each participant's T1 image to the template via the symmetric diffeomorphic procedure in ANTS; then warped the FA image to template space by applying the T1-to-template warps.

We smoothed FA images using a 4mm FWHM isotropic Gaussian kernel. We performed DTI analyses of FA in SPM8 using the two-samples t-test module. We analyzed DTI volumes using an explicit mask (FA > 0.25) to constrain comparisons to regions of white matter. To compare bvFTD participants to healthy seniors, we used a $p < .005$ (FDR-corrected) height threshold and a 200-voxel extent. We constrained

regression analyses to white matter tracts with reduced FA using an explicit mask generated from the results of the direct comparison with healthy seniors. We limited our analyses to white matter tracts with significant disease, as above, to constrain our interpretation to disease-specific neuroanatomical regions. Using a deterministic tractography procedure in Camino (Cook et al., 2006) we tracked white matter fibers in a healthy elderly template generated using the DTI sequence described above. We retained fiber tracts that passed through voxels of reduced FA to define the mask for regression analyses and accepted as significant a cluster with a volume of 150 adjacent voxels and a peak voxel *Z*-score > 3.3 (equivalent to $p < .0005$).

Results

Behavioral data results. Mean apathy FxS score on the NPI for the bvFTD group was 5.27 ± 3.3. Mean caregiver distress associated with apathy was 2.77 ± 1.4. Caregiver distress scores and FxS scores were moderately correlated (rho = 0.53; $p = .03$).

Table 7 summarizes the performance on the PACT measures. Between-group comparisons revealed that apathetic bvFTD participants had slower latencies than NC on all three measures of GDB: initiation ($t[33] = 2.26$, $p = .03$; planning ($t[33] = 4.79$, $p < .001$; and motivation ($t[33] = 2.17$, $p = .03$).

Table 7

Mean (S.D.) Reaction Time Scores for PACT Performance

PACT score	Control ($n = 17$)	bvFTD ($n = 18$)	*p*-value
Initiation	364.2ms ± 54.0	587.50ms ± 404.3	.03
Planning	1023.76ms ± 139.9	1754ms ± 612.5	< .001
Motivation	522.31ms ± 113.6	916ms ± 715.5	.03

Imaging results.

Grey matter imaging. Figure 1 illustrates widespread reduction in grey matter density (green) in lateral (Panel A) and medial (Panel B) frontal and temporal regions in bvFTD compared to controls. Table 8 summarizes the location of peak voxels in significantly atrophic clusters.

The results of the regression analysis relating PACT performance to reduced grey matter density are also summarized in Table 8. Initiation performance was related to ACC (Figure , Panel C, purple). Planning performance was related to dlPFC (Figure 1, Panel D, red). Motivation performance was related to OFC (Figure 1, Panel E, blue).

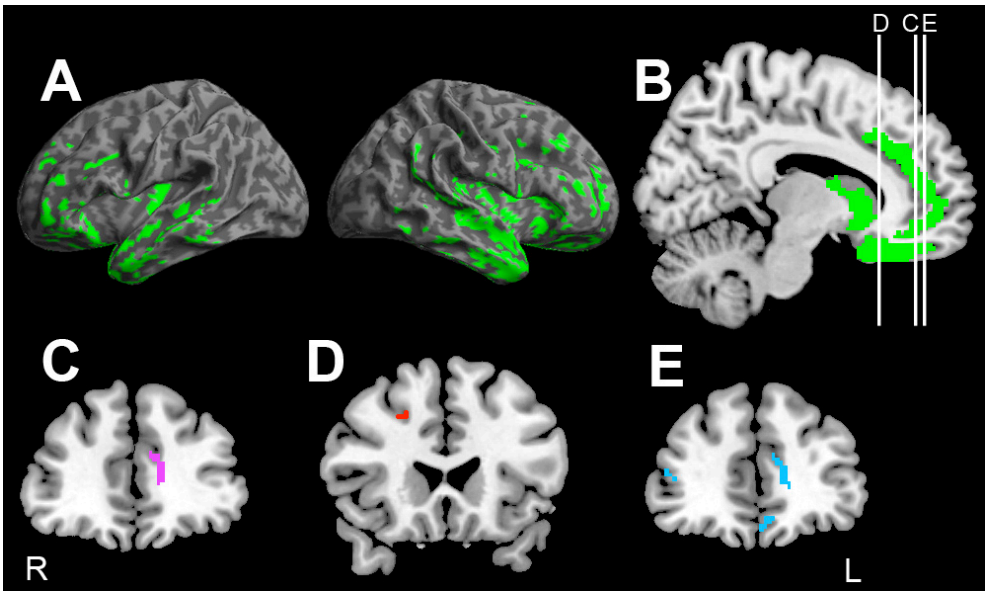

Figure 1. Significant atrophy in behavioral variant frontotemporal degeneration, and regressions relating Philadelphia Apathy Computerized Test performance to grey matter density (n = 18)[1].
Note: **1. Panel A and B**: Anatomic distribution of significant grey matter atrophy in participants with behavioral variant frontotemporal degeneration (green). **Panel C:** Significant regressions relating initiation performance to cortical atrophy in anterior cingulate (purple) at y = 40. **Panel D:** Significant regressions relating planning performance to cortical atrophy in dorsolateral prefrontal cortex (red) at y = 22. **Panel E:** Significant regressions relating motivation performance to cortical atrophy in orbitofrontal cortex (blue) at y = 42. See text and Table 8 for details.

Table 8***

Anatomic Locus of Peak Voxels in Clusters Relating PACT Scores to Grey Matter Atrophy (n = 18) and White Matter Integrity in bvFTD (n = 15)

Anatomic locus (BRODMANNAREA)[1]	MNI coordinates[2]			*Z*-score of peak voxel	Cluster size (voxels)
	X	Y	Z		
behavioral variant frontotemporal degeneration < Eld (grey matter atrophy)					
L superior frontal gyrus (10)	-22	46	26	4.65	96
R rostral prefrontal (11)	22	52	4	5.17	362
R middle frontal gyrus (9)	20	26	38	5.06	106
R inferior frontal gyrus (44)	40	8	28	5.84	401
L insula	-22	20	-6	4.69	194
R subcallosal gyrus (25)	16	18	-8	5.24	524
R parahippocampal gyrus (27)	18	-34	-2	6.25	14067
R fusiform gyrus (20)	40	-34	-20	4.51	99
R middle temporal gyrus (20)	58	-32	-18	4.70	94
R inferior temporal gyrus (37)	54	-52	-10	4.90	149
R inferior parietal lobule (40)	34	-34	38	5.10	64
behavioral variant frontotemporal degeneration Initiation Regression (grey matter)					
R dorsal anterior cingulate gyrus (32)	22	16	42	4.87	52
L dorsal anterior cingulate gyrus (32)	-14	42	14	4.30	74
behavioral variant frontotemporal degeneration (grey matter)					
R middle frontal gyrus (9)	22	14	44	3.28	56
L middle frontal gyrus (11)	-20	40	-22	3.10	104
behavioral variant frontotemporal degeneration Motivation Regression (grey matter)					
L medial orbital frontal gyrus (11)	-4	44	-16	4.61	42
R inferior frontal gyrus (46)	40	38	10	3.90	42
R inferior frontal gyrus (47)	34	34	2	3.17	78
L inferior frontal gyrus (47)	-48	24	-6	3.52	34
R cingulate gyrus (32)	22	18	40	5.41	63
L cingulate gyrus (32)	-14	42	14	4.16	77
behavioral variant frontotemporal degeneration < Eld (reduced fractional anisotropy)					
L uncinate fasciculus	-33	2	-9	6.30	13222
R uncinate fasciculus	38	7	-28	5.15	1388
L inferior frontal gyrus white matter	-34	14	22	5.87	7623

Anatomic locus (BRODMANNAREA)[1]	MNI coordinates[2]			*Z*-score of peak voxel	Cluster size (voxels)
	X	Y	Z		
R cingulum	3	-21	30	4.60	355
R anterior corona radiata	11	34	-13	4.54	1244
Body of corpus callosum	-7	6	25	4.44	1546
R column and body of fornix	3	-8	16	6.42	541
L posterior limb of internal capsule	-18	-8	5	4.17	347
L crus of fornix or striaterminalis	-14	-30	13	4.76	261
Splenium of corpus callosum	12	-33	11	5.15	1220
R inferior temporal gyrus white matter	47	-48	-13	5.10	335
behavioral variant frontotemporal degeneration Initiation Regression (fractional anisotropy)					
L cingulum	-7	30	15	3.43	1693
Body of corpus callosum	2	8	25	3.52	Same cluster as cingulum
Genu of corpus callosum	13	52	14	4.03	1056
Genu of corpus callosum	-12	53	23	3.39	382
R uncinate fasciculus	16	39	-16	4.84	2587
L medial orbital gyrus white matter	-14	32	-16	4.29	4609
behavioral variant frontotemporal degeneration Planning Regression (fractional anisotropy)					
R superior longitudinal fasciculus	25	-40	34	3.47	191
L inferior frontal gyrus white matter	-49	31	5	3.54	217
R inferior frontal occipital fasciculus	18	25	-3	5.10	1092
Genu of corpus callosum	12	47	26	4.23	650
Body of corpus callosum	15	15	42	3.82	533
Body of corpus callosum	10	6	58	3.74	162
R posterior corona radiata	20	-26	37	3.93	258
L superior corona radiata	-20	-14	38	3.54	269
L. cingulum	-5	-8	37	3.45	239
behavioral variant frontotemporal degeneration Motivation Regression (fractional anisotropy)					
R uncinate fasciculus	16	39	-16	4.67	2537
L medial orbital gyrus white matter	-13	33	-16	3.98	1678
Genu of corpus callosum	16	51	15	3.92	1091
Genu of corpus callosum	2	25	7	3.77	2593

Note. 1. The corresponding Brodmann area is indicated by the figure in parentheses. L = left; R = right. 2. Peak locus of these clusters are derived from MNI (= Montreal Neurological Institute) space converted to Talairach space using Montreal Neurological Institute.

White matter imaging. bvFTD showed widespread reductions in FA in bilateral frontal and temporal white matter relative to controls (Figure 2, Panel A, green). Peak voxels in clusters of significantly reduced FA, and regressions of FA with PACT scores are summarized in Table 8. Initiation performance was related to FA in cingulum, UNC fasciculus, inferior longitudinal fasciculus, and corpus callosum (CC) (Figure 2, Panel B, purple). Planning performance was related to FA in superior longitudinal fasciculus (SLF), right inferior frontal-occipital fasciculus, rostral frontal corona radiata, and CC, as well as posterior thalamic radiations (Figure 2, Panel C, red). Finally, motivation performance was related to FA in UNC as well as CC, corona radiata , and inferior longitudinal fasciculus (Figure 2, Panel D, blue).

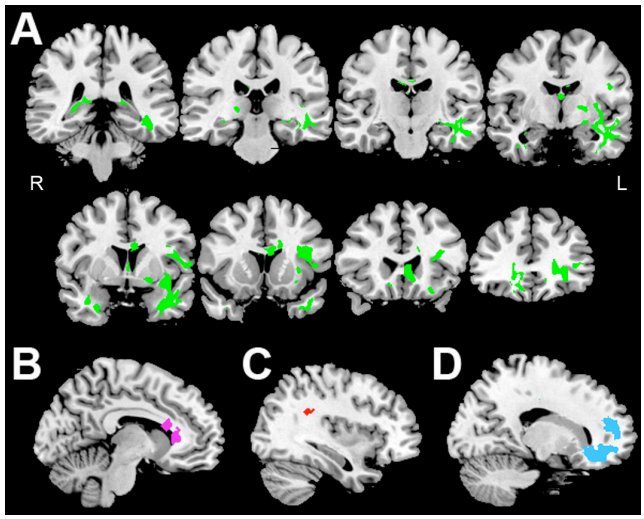

Figure 2. Reduced white matter integrity in behavioral variant frontotemporal degeneration, and regressions relating Philadelphia Apathy Computerized Test performance to reduced fractional anisotropy (n = 15)[1].
Note: **1. Panel A:** Anatomic distribution of reduced fractional anisotropy in participants with behavioral variant frontotemporal degeneration (green). **Panel B:** Significant regressions relating initiation performance to reduced fractional anisotropy including cingulum (purple). **Panel C:** Significant regressions relating planning performance to reduced fractional anisotropy including right superior longitudinal fasciculus (red). **Panel D:** Significant regressions relating motivation performance to reduced fractional anisotropy in uncinate fasciculus (blue). See text and Table 2.3 for details.

Discussion

This study investigated the behavioral and neural basis of GDB by examining bvFTD patients who display prominent apathy. We found that apathetic bvFTD patients are impaired on each of the three processes thought to contribute to apathy due to deficits in GDB: initiation, planning, and motivation. These three GDB processes were associated with disease in three distinct frontal grey matter regions and in white matter projections between these regions and other brain areas. Specifically, initiation difficulty related to atrophy in the ACC and to disease in the cingulum, poor planning related to atrophy in dlPFC and disruption in SLF and frontal corona radiata, and impoverished motivation related to atrophy in OFC and UNC disease. These findings are consistent with a three-component model of GDB that can contribute to apathy in bvFTD.

The PACT identified impairment in the three components of GDB: initiation, planning and motivation. A deficit in any one of these can contribute to apathy in bvFTD. Moreover, each of these deficits was associated with selective disruption of a large-scale neuroanatomic network important for GDB. Consider first a deficit in initiating a behavior that is related to ACC and white matter tracts including the cingulum. Considerable work has suggested that the ACC is important to initiate a behavior (Tekin & Cummings, 2002). Researchers previously implicated the ACC in processes that influence action initiation in healthy adult studies (Mulert, Gallinat, Dorn, Herrmann, & Winterer, 2003). Others implicated the ACC in initiation difficulty in those with frontal lobe injury. For example, the *akinetic mute state* is a medical term describing patients who tend to sit quietly in the same position all day without speaking or talking, and researchers related this specifically to ACC damage (Mega & Cohenour, 1997). The ACC

has been well studied in dementia, and neuroimaging evaluations have linked the ACC region to apathy in various groups. Researchers associated reduced grey matter density in the cingulate gyrus with apathy in patients with bvFTD (Massimo et al., 2009; Zamboni et al., 2008) and PD (Reijnders et al., 2010). Previous DTI studies investigating white matter disease and apathy showed an association with the cingulum, which has reciprocal connections between ACC and the medial orbitofrontal region that is important for motivation (Hahn et al., 2013; Ota et al., 2012). In healthy adults, ACC and dlPFC structures work in concert during complex tasks that require attentional control, likely to be mediated through the cingulum (Silton et al., 2010). Therefore, disease in ACC and interruption of projections between ACC and other structures important for GDB may contribute to apathetic behavior.

Researchers associated deficits in the planning component of GDB with atrophy in the dlPFC and reduced FA in related white matter tracts, including SLF and frontal corona radiata. fMRI studies of healthy adults suggested that dlPFC contributes to planning and working memory (Di, Rypma, & Biswal, 2013). Patients who suffer from dysfunction in these circuits failed to elaborate, manipulate, and integrate important information needed for behavior that is goal-directed. Studies suggested a relationship between apathy and poor executive function in bvFTD (Eslinger et al., 2012; Zamboni et al., 2008). Eslinger and colleagues (2012) found caregiver apathy scores were significantly correlated with executive-function measures, suggesting that apathy emanates in part from difficulty manipulating and integrating elements of a plan to achieve a goal (Eslinger et al., 2012). Imaging studies of patients with FTD and AD have linked apathetic behavior to atrophy in dlPFC as well (Massimo et al., 2009; Zamboni et

al., 2008). In addition, a previous study of patients with amnestic mild cognitive impairment revealed a relationship between reduced FA in the SLF and apathy (Cacciari et al., 2010). The SLF is a prominent white matter tract interconnecting the frontal, temporal, and parietal lobes, and this tract has been implicated in the integration of these diverse regions involved in planning (Genova, DeLuca, Chiaravalloti, & Wylie, 2013).

We found that difficulty with the motivation component of GDB is associated with atrophy in the OFC and related white matter tracts, including UNC. Evidence from healthy subject fMRI studies suggested that the OFC plays a role in interpreting value and reward-related information (Hare et al., 2010). Researchers have examined deficits in processing value and reward extensively in patients with FTD because they appear to have early degeneration of this frontal circuit in comparison to other neurodegenerative conditions (Rabinovici et al., 2007). Poor motivation can occur in these patients because they have decreased reactivity to positive "reward" and negative "punishment" signals, thereby making goal-selection difficult (Levy & Dubois, 2006). Experimental evidence, however, emphasized that patients with bvFTD and other diseases affecting OFC have the greatest difficulty interpreting "punishment" signals (Grossman et al., 2010). Imaging evidence from patients with bvFTD emphasized the link between OFC and apathetic behavior (Massimo et al., 2009). Fludeoxylucose PET brain activity is decreased in OFC in bvFTD patients with apathetic compared to nonapathetic patients (Peters et al., 2006). UNC is a major tract connecting the anterior temporal lobe with the medial and lateral prefrontal cortex areas known to be important for GDB (Kable & Glimcher, 2007). DTI studies performed in AD and PSP implicated UNC in apathy (Hahn et al., 2013) and our findings extend this to bvFTD.

Although we suggest specific contributions of neural mechanisms to distinct components of GDB, we do observe some overlap across measures. For example, our grey matter observations suggested that the cingulate may contribute to both initiation and motivation. In fact, post hoc correlation analyses of PACT measures revealed a significant correlation between initiation and motivation performance (rho = .78; $p < .001$). Post hoc correlations, however, are not significant between other PACT measures (all $p > .05$, Bonferroni corrected) and we otherwise observed distinct neuroanatomical regions contributing to components of GDB. It will be important for future work to identify quantitative measures of initiation and motivation that are not interdependent.

This is the first study using the impaired GDB model to help explain apathy in ND, and our findings have potentially important implications for its treatment. Prior measures to manage apathy have not been effective (Mizrahi & Starkstein, 2007). One reason for this failure may be the way apathy is conceptualized. That is, apathy is currently viewed homogeneously, as if derived from a single source; our findings suggest that each of three components of GDB contribute to apathetic behavior. Treatments, thus, have tended to focus on improving the initiation component of GDB, often with stimulants (Devos et al., 2013), even though apathy may be due to a deficit in one of the other components of GDB.

Some limitations should be kept in mind when considering our findings. Although our sample was larger than in prior investigations of apathy, we nevertheless studied a small number of patients and power in the imaging studies may have been insufficient to detect every anatomic region associated with apathy. Because floor effects in performing

the planning measure limited variance, we were forced to use a liberal threshold for our hypothesis-driven grey matter analyses. Last, we do not have neuropathological confirmation of the diagnoses of these patients.

With these caveats in mind, we conclude that apathetic behavior in bvFTD can be characterized as an impairment in GDB that is a multicomponent process including initiation, planning, and motivation. These three processes are supported by a large-scale neural network constituting the neuroanatomic basis for GDB, including distinct grey matter regions in the frontal lobe and related white matter projections.

CHAPTER 3: DIFFERENTIATING IMPAIRMENTS IN GOAL-DIRECTED BEHAVIOR: APATHY IN FRONTOTEMPORAL DEGENERATION

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Abstract

Apathy involves a reduction in GDB. In the current study, we sought to identify three subtypes of apathy in bvFTD by differentiating impairments in GDB. Twenty patients with bvFTD and 17 matched healthy controls participated in this study. We measured RTs using a novel computerized procedure—PACT—to quantify performance for each of three components of GDB—initiation, planning, and motivation—and to derive individualized patient-apathy profiles. We explored neuroanatomical associations of these performance profiles using a region of interest volumetric analysis. We found isolated deficits in each component of GDB in 12 (60%) bvFTD participants, including two (10%) with an isolated initiation impairment, eight (40%) with an isolated planning impairment, and two (10%) with an isolated motivation impairment. An additional eight (40%) participants were impaired on multiple components of the PACT. Voxel-based

morphometry revealed that those participants with reduced initiation had ACC atrophy; those with impaired planning had atrophy in dlPFC, and those with poor motivation had OFC atrophy. Apathy is a complex, multicomponent syndrome, and we found quantitative reduction in each of the three processes contributing to apathy in bvFTD.

Introduction

GDB describes a set of related processes that support independent, goal-obtaining action in everyday activities (Brown & Pluck, 2000). Core components of GDB include initiation, planning, and motivation. We adopted the perspective that apathy is a reduction in GDB which arises when one or more GDB processes are compromised (Levy & Dubois, 2006). We developed a quantitative measure to directly assess the behavioral and neuroanatomic basis for apathy in bvFTD.

Apathy is reported to be the most common initial behavioral syndrome in bvFTD, occurring in up to 90.5% of patients (Diehl-Schmid et al., 2006). Researchers associated akinetic mutism and abulia that emphasize a lack of initiation with apathy (Starkstein & Leentjens, 2008). Further, others related apathy to executive deficits that limit planning needed for goal-obtaining actions (Eslinger et al., 2012). Still others have broadly defined apathy as reduced motivation (Marin, 1996). Each of these characteristic behaviors can be seen in apathetic bvFTD patients. We assessed initiation, planning, and motivation components of GDB using a novel computerized RT test—PACT—in apathetic patients with bvFTD.

Researchers think apathy arises following degeneration of frontal-subcortical circuits (Levy & Dubois, 2006). Consistent with the view that a single-component model may be insufficient to explain apathy, neuroimaging studies associate apathy with several

frontal regions (Massimo et al., 2009; Rosen et al., 2005; Zamboni et al., 2008). Previous imaging studies in persons without apathy suggested that poor initiation relates to ACC disease, (Kotchoubey et al., 2003; Reijnders et al., 2010); poor planning relates to disease in dlPFC, (Kaller et al., 2011; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004; van den Heuvel et al., 2005), and reduced motivation relates to disease in OFC (Diekhof et al., 2011; Sescousse et al., 2010). A specific process of GDB suffers when one of these frontal areas is compromised, resulting in apathetic behavior. We hypothesized that patients with bvFTD have differentiated profiles of apathy, and that these relate in part to patients' neuroanatomic distribution of disease.

Methods

Participants. We examined 20 apathetic patients with bvFTD (female = 5) and 17 demographically matched healthy controls (NC). Experienced cognitive neurologists from the Department of Neurology, University of Pennsylvania (MG, DJI) evaluated and recruited all patients. bvFTD patients were diagnosed using published criteria (Rascovsky et al., 2011). Neurologists assessed patients as having apathy based on the apathy subscale of the NPI using an FxS score ≥ 1. As summarized in Table 9, we included only participants with mild disease (MMSE ≥ 20) to minimize confounding factors related to severity of cognitive impairment. Geriatric Depression Scale-Short Form (Sheikh & Yesavage, 1980) scores ≤ 5 demonstrated that participants were not depressed, as depression also could confound our findings. All subjects and responsible caregivers participated in an informed-consent procedure approved by the University of Pennsylvania IRB.

Table 9

Mean (S.D.) Demographic Features of Participants

	NC (*n* = 17)	bvFTD (*n* = 20)
Age (YEARS)	67.12±10.82	63.1±5.88
Education (Years)	15.35±2.91	16.65±2.79
Mini-Mental State Exam (max score = 30)	29.47±0.87	26.45±2.48
Disease duration (Years)	na	3.4±1.64
Mean Neuropsychiatric Inventory Apathy frequency by severity (max score = 12)	na	5.54±3.1

The initial clinical diagnosis of bvFTD was consistent with results of serum studies, structural imaging such as MRI or CT, studies of cerebrospinal fluid, and functional neuroimaging studies such as single-photon emission computerized tomography or PET (when available). Exclusion criteria included the presence of other neurological conditions such as stroke, closed-head trauma, or hydrocephalus; primary psychiatric disorders such as depression or psychosis; a systemic illness that can interfere with cognitive functioning; or use of soporific medications because of their sedating side-effects. Patients may have been taking a fixed dosage of a cholinesterase inhibitor (e.g., donepezil, rivastigmine, or galantamine) or memantine, or a low dosage of a nonsedating antidepressant (e.g., serotonin-specific reuptake inhibitors such as sertraline) or an atypical neuroleptic agent (e.g., quetiapine), indicated clinically.

The Philadelphia Apathy Computerized Test (PACT). The PACT is a novel computerized RT test designed to quantify each core component of GDB: initiation, planning, and motivation. The PACT was developed based on a review of experimental paradigms and clinical observations (Elliott et al., 2010; Jenkins et al., 2000; Ruh et al.,

2010). There are 48 trials in each of the three conditions, one for each GDB component. A practice block, in which participants receive instructions about task performance and 12 practice trials, precedes each experimental condition.

In each condition, a trial begins when the subject depresses a computer "start" key with the index finger. In response to a signal, RT1 is the latency for a participant to lift the finger from the start key, and RT2 is measured as the time to depress the target key after lifted from the start key. Total latency is the sum of RT1 and RT2. We counterbalanced all stimuli and randomly distributed them in each condition.

In the simplest condition, designed to measure the initiation component, a participant begins a trial by depressing the start key; when a stimulus appears centrally on the computer screen, the participant lifts the finger from the start key, then depresses a fixed central target key in response to this stimulus; the signal occurs on average 1,250msec (range 500–2,000msec) after depressing the start key. Initiation is assessed by measuring RT1.

To measure the planning component, we administered two levels of task difficulty. In the first level, participants depress the start key and then are presented with randomly ordered lateralized visual stimuli on the computer screen. Participants are instructed to press a left or right target key (stimulus appears on the left, then go left; stimulus appears on right, then go right. In the second, more complex level, one of two lateralized keys is pressed contingent on the combination of patterns in a central visual stimulus (stimulus appears on the left, then go left; stimulus appears on right, then go right). These patterns are visually available to participants during performance to minimize task-related working memory confounds. We used two measures to identify a planning deficit: total

latency in the complex planning condition and the difference in response times between these two levels of difficulty.

To assess motivation, we repeated the simplest condition with an explicit monetary reward incentive; a system of "monetary units," was exchanged for actual money at the end of the study, for responding correctly and more rapidly than during the simple task. Participants see their response speed during the unrewarded condition on the computer screen, and receive feedback about their "rewarded" response speed on the computer screen after each trial. Sensitivity to negative consequences is also assessed with a "penalty" condition. In this "penalty" condition, participants are given a number of monetary units at the beginning of the task. If they do not respond correctly and more rapidly, they lose units. We use the total latency in the penalty condition to assess motivation because previous work has shown that bvFTD patients appear to be relatively insensitive to negative feedback (Grossman et al., 2010). The point system was adjusted, without knowledge of the participant, so that each participant received the same total actual payment at the end of the study.

Behavioral criteria for developing apathy subtypes. We developed performance profiles according to predetermined criteria that correspond to each of the components of GDB, and these were ascertained in individuals using latency means and standard deviations over 48 trials in each of the three experimental conditions (see Table 10). Individual participant *z*-scores were generated for NC performance for each condition. Significant impairments were defined as a *z*-score ≥ 2 for each component. Most participants with impairments in initiation and/or motivation also had a planning impairment, consistent with the dysexecutive profile typically seen in bvFTD (Rascovsky

et al., 2011). For participants whose impairment was limited to planning, we assumed this component was the sole contributor to apathy. To better distinguish which components contributed most to apathy in those with multiple impairments, we implemented the application of the planning criteria in a stepwise fashion. Thus, we subjected planning-impaired participants who also had deficits in initiation and/or motivation to a second level review; we only classified those participants who also had greater slowing on the complex planning condition compared to the simpler planning condition in the planning-impairment subtype.

Table 10

Behavioral Criteria for Apathy Subtypes

Subtype profile	Criteria
Initiation	Significantly slow Reaction Time 1 in simple condition
	Does not have slowed latencies for complex condition
	Able to improve performance on the simple condition in response to penalty.
Planning	Significantly slowed on complex planning condition and, for those with multiple impairments, significant slowing on the complex planning condition compared to the simpler planning condition
	Does not have slowed initiation for simple condition
	Able to improve performance on the simpler planning condition in response to reward or "penalty."
Motivation	Significantly slowed on simple penalty condition and fails to improve performance with penalizing motivators
	Does not have slowed initiation for simple condition
	Does not have slowed latencies for complex condition.

Neuroimaging data. High-resolution T1-weighted 3-dimensional spoiled gradient echo images were acquired on a Siemens 3.0T Trio scanner with an 8-channel coil (repetition time = 1,620msec, echo time = 3msec, slice thickness = 1.0mm, flip angle = 15°, matrix = 192 × 256, and in-plane resolution = 1.0 × 1.0mm). Before

normalization, each participant's structural image was segmented into tissue classes using *Atropos,* a voxel-based segmentation tool that segments the brain into grey matter, white matter, and cerebrospinal fluid (Avants, Tustison, Wu, et al., 2011). We preprocessed all images processed using PipeDream (Sourceforge, 2014) and ANTS (Penn Image Computing & Science Lab, 2014). Researchers previously demonstrated the ability of this method to accurately normalize large-scale data as in studies of patients with ND (Avants et al., 2008; Avants, Tustison, Song, et al., 2011). We used a symmetric diffeomorphic deformation for registration to avoid bias toward the reference space for computing the mappings (Avants, Tustison, Song, et al., 2011). Processing involved mapping T1-weighted structural MRI to an unbiased average-shape and average-appearance template derived from a representative population consisting of 25 healthy seniors and 25 patients with FTD (J. Kim et al., 2008). This diffeomorphic method for registration and normalization avoids the need to use identical participants in the local template (Avants & Gee, 2004). Images were then warped to Montreal Neurological Institute space for analysis. We calculated grey matter probability images as a quantitative measure of grey matter density.

Structural MRI data were available for 19 bvFTD participants who completed the PACT. We obtained a priori defined ROI for ACC, dlPFC, and OFC. These ROIs were selected based on literature suggesting that poor initiation relates to disease in ACC (Kotchoubey et al., 2003; Reijnders et al., 2010), poor executive function relates to disease in dlPFC (Kaller et al., 2011; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004; van den Heuvel et al., 2005), and reduced motivation relates to disease in OFC (Diekhof et al., 2011; Sescousse et al., 2010). We used a standardized AAL and parcellation

method (Tzourio-Mazoyer et al., 2002) to label the following ROIs. The first ROI (e.g., initiation) was centered on the ACC (AAL label = ACIN). The second (e.g., planning) ROI was centered on the middle frontal gyrus portion of the dlPFC (AAL label = F2). The last ROI (e.g., motivation) was composed of the orbital regions of the middle and superior frontal gyri (AAL labels = F10, F20). Additionally, we used a control ROI in the MT region (AAL label = T2). We chose this region because it is an area implicated in bvFTD (Brettschneider et al., 2014), but we did not hypothesize it to contribute to GDB.

For all ROIs, we computer the mean GMP value and divided it by the subject's individual average whole-brain GMP value. Using this ratio, we examined relative differences in regional composition of grey matter in frontal areas thought to underlie GDB impairments and the control region in the lateral temporal lobe.

Results

Behavioral results. Mean (*SD*) NPI apathy FxS score for the bvFTD group was 5.54 ± 3.1, which suggests moderate levels of global apathy. Table 11 summarizes mean group performance on PACT measures. Between-group comparisons found that apathetic bvFTD participants have significantly slower latencies than NC on each GDB measure: Initiation ($t[35] = 2.35$, $p = .03$; Planning ($t[35] = 5.58$, $p < .001$; Motivation ($t[35] = 2.60$, $p = .01$). Although caregiver distress scores were correlated with NPI FxS scores for apathy, PACT scores did not correlate with either caregiver distress scores or NPI apathy scores.

Table 11

Mean (SD) Latencies for each PACT Score in all Participants

PACT score	Control (*n* = 17)	bvFTD (*n* = 20)	*p*-value
Initiation	364.31ms ±54.06	584.03ms ±381.60	.03
Planning (complex condition)	1023.79ms ±140.01	1845.75ms ±592.89	< .001
Motivation (penalty condition)	522.22ms ±113.54	967.67ms ±675.15	.01

Note. PACT = Philadelphia Apathy Computerized Test; bvFTD = behavioral variant frontotemporal degeneration.

Inspection of individual patient *z*-score profiles identified 12 patients (60%) with an impairment on a single GDB component. As summarized in Table 12, two (10%) had an initiation deficit, eight (40%) had a planning deficit, and two (10%) had a motivation deficit. Four patients (20%) had an initiation impairment combined with impaired planning or motivation, and four (20%) were impaired across all three GDB components. There were no differences in any demographic variables between participants with impairments in single or multiple components of GDB.

Table 12

Number of bvFTD Participants According to Apathetic Subtype (N = 20)

Subtype	N (%)
Single component	12 (60%)
Initiation	2 (10%)
Planning	8 (40%)
Motivation	2 (10%)
Multicomponent	8 (40%)
Initiation and planning	3 (15%)
Initiation and motivation	1 (5%)
Initiation, planning, and motivation	4 (20%)

Neuroimaging results. We examined differences in regional GMP in bvFTD participants with MRI data (n = 19) based on PACT performance. Paired samples t-tests were conducted to compare GMP in a priori ROIs to the control ROI in the MT region. Participants with any initiation deficit (n = 9) showed significantly reduced grey matter in the ACC region (M = 1.03, SD = 0.10) compared to the MT region (M = 1.19, SD = 0.02); $t(8) = 3.59$, $p = .007$). Participants with any planning deficit (n=13) showed reduced grey matter in the dlPFC (M = 0.99, SD = 0.04) compared to the MT region (M = 1.17, SD = 0.03); $t(12) = 8.05$, $p \leq .001$). Last, participants with any motivation deficit (n = 10) showed reduced grey matter in the OFC (M = 1.07, SD = 0.05) compared to the MT region (M = 1.17, SD = 0.04), $t(9) = 3.20$, $p = .01$).

We confirmed these findings in every participants with a single apathy deficit. Thus, we evaluated the specificity of these imaging results with a post hoc assessment of GMP in each participant with a single deficit in each apathy component. Although the small number of participants with single impairments precluded statistical analysis, we confirmed that participants with a single impairment in initiation (n = 2) had reduced grey matter density in the ACC compared to the MT region, participants with a single impairment in planning (n = 7) had reduced grey matter density in the dlPFC compared to the MT region, and participants with a single impairment in motivation (n = 2) had reduced grey matter density in the OFC compared to the MT region (see Figure 3).

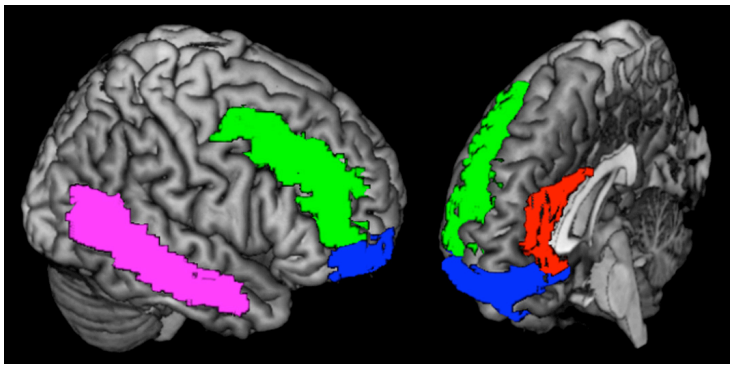

Figure 3. Regions of interest selected from the automated anatomical labeling template. *Note:* Three parcellated gyral-based regions of interest (lateral and medial view of the right hemisphere). Red = anterior cingulate cortex (initiation); green = dorsolateral prefrontal cortex (planning); blue = orbitalfrontal cortex (motivation); magenta = midtemporal (control region).

Discussion

This study examined differentiated impairments in GDB in bvFTD patients who displayed prominent apathy. We identified three components of apathy based on impaired GDB processes defined by performance on an objective behavioral instrument: impairment of initiation, planning, and motivation. Our observations support that apathy is a multicomponent syndrome, and specific deficits in initiation, planning, and motivation are associated with discrete regions of the frontal lobe.

Understanding the precise nature of the mechanisms that contribute to apathy is of clinical and theoretical importance. At present, no one has identified effective treatments for apathy (Drijgers, Aalten, Winogrodzka, Verhey, & Leentjens, 2009). This may be due, at least in part, to consideration of apathy as a single, undifferentiated phenomenon when, in fact, specific components may be differentially compromised. From this perspective, treatment of an initiation deficit may not benefit an individual with impaired motivation. A crucial step toward improving management of apathy, thus, may involve improving understanding of the mechanisms that contribute to apathy. According to a GDB model,

at least three core processes—initiation, planning, and motivation—must be functional to translate an idea into a goal-obtaining action (Brown & Pluck, 2000). Impaired initiation limits spontaneous action and results from difficulty activating cognitive and motor functions to initiate an act or thought. Plans of action often consist of multiple mental steps, and compromised planning may limit the ability to manipulate the components of a task mentally in order to execute an action. Impaired motivation compromises the ability to process the internal and external determinants that augment the rewarding value or help avoid the negative consequences associated with the intention to act (Levy & Dubois, 2006). The present study used the GDB model to demonstrate differentiated deficits in these three components of apathy in bvFTD.

An international task force proposed criteria for the clinical diagnosis of apathy in neurodegenerative conditions, drawing a distinction between behavioral, cognitive, and emotional domains (Robert et al., 2009). These correspond in part to the initiation, planning, and motivation components of apathy suggested by the GDB model. One of the primary obstacles to advancing knowledge in this area has been the absence of a quantitative method that directly measures specific mechanisms contributing to apathy. Although several global apathy-assessment tools exist for the cognitively impaired population, there is a lack of agreement on the interpretability of the data from these measures (Clarke et al., 2011). This lack of consensus may be due in part to the fact that traditional instruments to ascertain apathy commonly use proxy report. This approach is subject to caregiver confounds such as burden and strain that may impact the evaluation. Indeed, we did find the ascertainment of apathy by proxy report was biased by caregiver stress. Caregiver distress scores and FxS scores were correlated ($r = .47$; $p = .04$),

suggesting that estimated symptom severity in bvFTD was likely biased by caregiver distress.

Further, beyond confirming the presence of apathy, current instruments such as the NPI are ineffective in identifying different subtypes of apathy (Chow et al., 2009). One goal of the present study was to quantify components of GDB in apathetic participants in an objective manner, minimally confounded by proxy report. In a series of bvFTD patients with apathy, we identified individuals who demonstrated single deficits in each of the hypothesized components of GDB, providing some validation for this approach. Additional work is needed to examine these components in larger groups of participants with bvFTD and other neurodegenerative conditions.

The failure to initiate behavior leads to a subtype of apathy such that an individual is unable to generate a signal significant enough to begin a response. The akinetic-mute state describes individuals who sit quietly in the same position all day without speaking, due to anterior cingulate damage (Mega & Cohenour, 1997). Abulia is the loss of initiative and spontaneous thought, and external stimulation is needed to start mental activity or speech (Quaranta, Marra, Rossi, Gainotti, & Masullo, 2012). The initiation condition of the PACT assesses this GDB component quantitatively by measuring the latency to initiate a movement in response to a visual signal. We found that some apathetic bvFTD individuals are significantly impaired only on this component of GDB. Moreover, this impairment was associated with anterior cingulate atrophy.

Initiation difficulty is not the only basis for apathetic behavior. The ability to execute an action is also highly dependent on the cognitive processes needed to plan, organize, and carry out goals. Apathy related to “cognitive inertia” can result from

impairments in executive functions such as planning, working memory, and task-switching (Burgess, 2000; Levy & DuBois, 2006). Apathy in AD has been related to difficulty performing several tasks interchangeably (Esposito et al., 2010). In PD, performance on standardized tests of planning was associated with severity of apathy (Weintraub et al., 2005). Poor planning was the most prevalent single component of apathy found to be impaired in our bvFTD sample. This is not surprising, given that a dysexecutive neuropsychological profile is a common finding in bvFTD (Rascovsky et al., 2011). Moreover, we found that this subtype of apathy is associated with lateral prefrontal atrophy. Other work has associated executive difficulty in bvFTD with lateral prefrontal atrophy (Huey et al., 2009).

Another component of GDB is motivation, that is, responsiveness to external and internal drives that may be positive or negative. Apathy may result from a lack of responsiveness to reward or risk, thereby making goal-selection difficult (Levy & Dubois, 2006; Rosen et al., 2002; Schultz et al., 2000). Likewise, reduced ability to assess and interpret consequences of actions, whether positive or negative, can limit motivation (Zamboni et al., 2008). Patients with bvFTD typically have a greater desire for certain rewards such as money and social praise, but tend to show less sensitivity to negative consequences (Grossman et al., 2010; D. C. Perry, Sturm, Wood, Miller, & Kramer, 2013). We found that patients performed faster on the reward condition (compared to the simple condition without incentive), suggesting they were motivated by a monetary incentive. Their performance pattern did not change, however, when we took away monetary units for not performing faster, thereby suggesting relative insensitivity to negative consequences. In our sample of bvFTD participants, we identified some

individuals with insensitivity to the motivational component of GDB, associated with OFC atrophy. Other work has associated limited motivation with ventral frontal atrophy in bvFTD (Grossman et al., 2010).

Although each of the three components we assessed may contribute to GDB, clinical observations suggest that deficits in initiation, planning, and motivation may not be sequential, as some have hypothesized (Levy & Dubois, 2006). Instead, apathy may arise when any one of these three processes is impaired. For example, patients who have profound impairments in planning an action may be able to initiate an action and may be motivated to achieve a goal, but their planning impairments alone may make it difficult to engage in GDB. Our findings suggest that initiation, planning, and motivation processes are relatively independent and, when compromised, may each contribute to apathy. Additional work is needed to confirm these profiles in a longitudinal cohort. Nevertheless, we found several individuals who appeared to be impaired with multiple components of GDB. That is, some patients with initiation difficulty also had limitations in planning, motivation, or both. Although consideration may be given to the possibility that a deficit in initiation may also lead to additional difficulty in other GDB components, the observation of independent deficits in each GDB component makes this less likely. Compared to individuals displaying a multicomponent subtype of apathy, those with a single GDB deficit did not differ by age, disease duration, and MMSE (all $p > .05$). This outcome suggests that variations in apathetic profiles are not easily attributable to variability in the underlying disease process, but instead are related, at least in part, to anatomical distribution of disease.

Our findings need to be interpreted in light of several limitations. Our findings require confirmation in a larger sample of participants. We studied patients with relatively mild disease, and it would be valuable to extend assessment to more severely impaired patients. We studied bvFTD particularly because apathy is very common in this condition, these patients do not have motor limitations such as weakness or involuntary movements that can confound the quantitative assessment of reduced GDB, and there are no language or visuospatial deficits that can potentially limit the interpretation of impaired performance. Nevertheless, it would be important to investigate GDB in apathetic patients with other neurodegenerative conditions such as AD or PD who also display apathy.

With these caveats in mind, we identified three components of GDB, using a novel computerized RT test that may show independently impaired results in apathetic patients with bvFTD. There appear to be at least three distinct sources of apathy, including a deficit in initiation, planning, or motivation, and these appear to depend in part on regions in the frontal lobe that support GDB. Impairment in any one or combination of these components—initiation, planning, or motivation—may emerge as apathy.

CHAPTER 4: THE NEURAL BASIS OF APATHY IN FRONTOTEMPORAL DEGENERATION: A LONGITUDINAL STUDY[1]

Specific Aims

Apathy, a reduction in GDB (Levy & Dubois, 2006), affects 90% of people with bvFTD (Diehl-Schmid et al., 2006), a common cause of early onset ND (Vilalta-Franch et al., 2013). The cognitive and neural impairments associated with apathy make it difficult to initiate, plan, and motivate activities toward a specific goal, such as dressing or bathing. These impairments are associated with significant decline in functional ability, caregiver burden, and increased cost of care due to early institutionalization (Butterfield et al., 2010; Lechowski et al., 2009; Massimo et al., 2009; Okura et al., 2011). Caregivers struggle to provide care without hope of relief because current treatments are ineffective (Mizrahi & Starkstein, 2007). In this interdisciplinary research training grant, I propose innovative methods to advance understanding of the longitudinal course of apathy, a clinical manifestation of brain pathology in persons with bvFTD. My long-term goal is to design tailored interventions targeting reduction and management of apathy and the poor-health outcomes that accrue to affected individuals and their caregivers. This work will also serve as a training venue to help me attain my professional goal to become an independent researcher by developing expertise with new measures of moderators (environmental factors and genetics), as well as new statistical (longitudinal analysis) and imaging techniques (diffusion-tensor imaging).

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[1] This chapter was submitted as a National Research Service Award for Individual Post-Doctoral Fellows (F32). It appears here as it does in the submitted application.

In my dissertation work, funded by an Individual Predoctoral National Research Service Award (F31NR013306), I used empirical methods to identify three subtypes of apathy in bvFTD that interfere with GDB: impairments in initiation, planning, and motivation. Each of these deficits was associated with selective disruption of a large-scale neuroanatomic network underlying GDB. Specifically, initiation subtype was related to atrophy in ACC, the planning subtype was related to atrophy in dlPFC, and the motivation subtype was related to atrophy in OFC. My preliminary longitudinal data revealed that decline is restricted to the subtype of initial impairment and does not generalize to the other subtypes. These distinct types of apathy may benefit from interventions tailored to mediate each compromised mechanism, but I must first understand the natural history of these impairments and the biological and environmental factors that influence the rate of decline. Cognitive-reserve theory is a framework for understanding these brain–behavior relationships. Using cognitive-reserve theory, I posit that environmental factors (education, occupation, and leisure activities) are related to neural connectivity and cognitive strategies that support brain functioning in the face of ND, and thereby play a moderating role in the rate of longitudinal decline (Steffener & Stern, 2012). Biological factors that impact longitudinal decline include focal changes in grey matter and associated white matter tracts and genetic factors such as Apolipoprotein E (ApoE) and tau haplotype (Morley et al., 2012a; Van Gerven, Van Boxtel, Ausems, Bekers, & Jolles, 2012; Whitwell et al., 2008). I will examine both types of factors in this study.

The identification of factors that moderate the clinical expression of disease, in this case apathy, is an important consideration for identifying persons “at risk” for more

rapid decline and optimizing interventions for all persons with apathy associated with ND. This research training proposal is a longitudinal investigation of impaired GDB using resources from an ongoing program project, "Cognitive and Neural Impairment in Frontotemporal Dementia" (P01-AG17586), which includes longitudinal clinical, neuropsychological, neuroimaging, and genetic data.

The goals of this research proposal will be achieved through three aims:

Aim 1. Examine longitudinal changes in subtypes of apathy in bvFTD compared to NC.

H1: Based on preliminary longitudinal data, I hypothesize that apathy will worsen in bvFTD, and that decline will be restricted to the subtype of initial impairment.

Aim 2. Determine the effect of environmental factors (education, occupation, and leisure activities) and genetic factors (ApoE status and tau haplotype) as moderators of annualized rate of change in apathy subtypes.

H1: I hypothesize slowed annualized worsening in apathy in bvFTD individuals with higher education and occupational attainment and greater leisure activities.

H2: A more rapid rate of worsening in apathy will be associated with the presence of ApoE e4 allele and tau H1H1 haplotype in bvFTD.

Aim 3. Relate changes in apathy subtypes in bvFTD to annualized grey matter thinning and reduced FA on DT imaging studies of white matter; and I will explore the impact of moderating environmental and genetic factors on rates of grey matter and white matter change in anatomic structures related to each apathy subtype.

H1: Change in each bvFTD apathy subtype will be related to progressive grey matter thinning of specific frontal brain regions and to reduction in FA in related white matter tracts.

The results from this proposed research will improve understanding of apathy by providing insights into mechanisms of longitudinal decline and neural compensation. Optimized interventions for apathy can be designed based on an understanding of these mechanisms. For example, knowledge of the progression of apathy will give direction for designing tailored interventions that target problems with initiation, planning, and motivation, and the optimal timing of their implementation. This work will also allow us to assess the effectiveness of these interventions based on a comparison with the natural trajectory of change in bvFTD-related apathy. This work supports the National Institute of Nursing Research strategic plan and will further my career goal to become an independent researcher.

Significance

Apathy is extraordinarily common in ND, contributing to poor patient and caregiver outcomes. Deficits observed in apathetic persons, such as poor planning, poor motivation, and inability to initiate even the simplest self-care activities, contribute to deteriorating function and greatly reduced quality of life (Pedersen, Alves, et al., 2009). Apathy is also associated with other undesirable features, such as poor insight and impaired cognitive performance (Chase, 2011; Ishii et al., 2009; Pedersen, Alves, et al., 2009; Pluck & Brown, 2002). These features have strong implications for noncompliance with therapeutic interventions and further exacerbate disability (Chow, Pio, & Rockwood, 2011). Furthermore, apathy appears to be an independent predictor of earlier risk for

mortality (Brown & Pluck, 2000; Holtta et al., 2012; Vilalta-Franch et al., 2013). The societal costs associated with caring for people with ND are enormous. The annual global burden cost of dementia is estimated at $315 billion (Dartigues, 2009). Long-term care is a significant driver of costs and rates of institutionalization are higher in apathetic persons because of the significant strain placed on caregivers (Bakker et al., 2012).

Caring for a person with apathy is extremely challenging. The physical and emotional demands associated with the need to perform the simplest activities for those with apathy are profound, and high levels of depression, burden, and stress are reported in caregivers of apathetic persons (Chio et al., 2010; Massimo et al., 2009). Caregivers misinterpret apathy as a sign of volitional opposition and poor cooperation (Bakker et al., 2012; Massimo, Evans, et al., 2013), leading to dissatisfaction with caregiving (Landes et al., 2001). Thus, it is important to optimize management of apathy. Additionally, caregivers often want to know what to expect behaviorally from the patient over the course of their disease (Chow et al., 2012). Insight into the trajectory of apathetic behavior is important to prepare caregivers for the changes in the affected person. Findings from this study will be used to inform caregivers about what to anticipate as the disease progresses. Prognostic information can be used as a decision aid to determine resources for support.

Currently there are no effective treatments for apathy because of a poor understanding of the mechanisms underlying this condition. Treatments for apathy can best be developed in a context where behavioral and anatomic substrates of apathy are understood. My preliminary dissertation work shows that there are distinct subtypes of apathy associated with distinct anatomic substrates (Massimo, Evans, Morgan, Powers,

Grossman, 2012; Massimo, Morgan et al., 2012). An approach accepted for a wide variety of circumstances to manage apathy, thus, appears to be inappropriate, and tailored interventions focusing on a specific apathy subtype are more likely to be successful. Researchers assume that apathy worsens over time (Chow et al., 2012; Turro-Garriga et al., 2009), yet do not know if these distinct apathy subtypes persist or change longitudinally. Knowledge of the natural history of apathy is essential in the development of treatment trials for apathy. This knowledge will contribute critical information to the design of interventions and inform selection of end-points in treatment trials. In the proposed work, I will examine how persons with apathy worsen over time (Aim 1) and identify the influence of environmental, genetic (Aim 2) and anatomic (Aim 3) factors on the rate of change in apathetic persons. The proposed work will fill a crucial gap and will be used to develop treatment strategies and evaluate the effectiveness of tailored interventions.

Conceptual framework. Disturbances of GDB in ND represent a significant problem that is understudied. In neuroscience, GDB is used to operationalize a broad spectrum of purposeful actions and their determinants (Brown & Pluck, 2000). GDB is related to the belief that when action *a* is taken, *x* may be obtained as a result. The GDB model has been proposed to improve understanding of the mechanisms that contribute to the loss of self-initiated action (Levy & Dubois, 2006); a behavior referred to as "apathy." According to the model, three processes—initiation, planning, and motivation—influence the intention to act. Apathy arises when any one of these three processes is impaired (Massimo, Evans et al. 2012; Massimo, Morgan et al., 2012).

These three GDB processes map onto three distinct brain regions that work together in a large-scale neural network associated with apathy. In particular, three functional neuroanatomic loops underlying GDB in the frontal area (anterior cingulate circuit, dorsolateral prefrontal circuit, orbitofrontal circuit) appear to capture the information from internal and external environments needed for GDBs and possible actions to be performed. Each circuit is functionally separate in supporting initiation, planning, and motivation, but interacts with the others to mediate overall GDB. Previous imaging studies in persons without apathy, and my dissertation data on apathetic persons, suggest that poor initiation is related to ACC disease, (Kotchoubey et al., 2003; Reijnders et al., 2010), poor planning is related to disease in dlPFC (Kaller et al., 2011; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004; van den Heuvel et al., 2005), and reduced motivation is related to disease in OFC (Diekhof et al., 2011; Sescousse et al., 2010). A specific process of GDB suffers when one of these frontal areas is compromised, resulting in apathetic behavior. The proposed research will extend my cross-sectional dissertation data. First, I will study longitudinal changes in behavior and neuroanatomy following an impairment of each process of GDB. Second, I will examine the influence of environmental, genetic, and anatomic factors. A more complete understanding of apathy will lead to the development of treatments for persons with specific subtypes of apathy.

Few studies have examined longitudinal decline in bvFTD, a disorder of social comportment and executive dysfunction related to frontal and temporal degeneration. Researchers previously reported that neuropsychological impairments in bvFTD remain distinct over the duration of illness rather than converging in a common undifferentiated

state (Libon et al., 2009). This outcome suggests the brain is highly organized around specific cognitive functions involving large-scale neural networks. These neural networks allow individuals to implement compensatory cognitive strategies, thereby maintaining relatively distinct patterns of impairment well into the disease course (Gigi, Babai, Penker, Hendler, & Korczyn, 2010). Compensatory brain-reserve mechanisms have been assessed in only two studies of bvFTD, revealing that reserve mechanisms may be moderated by factors such as education, occupation, and leisure activities (Borroni et al., 2009; Y. Liu et al., 2012; Premi et al., 2012; Stern, 2006). Moreover, genetic factors such as ApoE status and tau haplotype may influence the presence of neuropsychiatric symptoms (Panza et al., 2012), including apathy (D'Onofrio et al., 2011; Monastero et al., 2006) and genetic markers such as the presence of the e4 allele have been associated with faster decline in ND, although this has not been assessed in bvFTD. This research proposes to examine the influence of environmental factors and genetics on a common neuropsychiatric syndrome in well-characterized persons with bvFTD to gain a better understanding of reserve mechanisms and their relationship to behavioral functions such as apathy to determine who may be "at risk" for faster decline. Finally, brain atrophy is progressive in a small number of bvFTD studies, (Frings et al., 2012; Gordon et al., 2010; Whitwell et al., 2008) but the neuroanatomic basis for longitudinal worsening of apathy has not been examined.

Preliminary studies.

Although several apathy assessment tools exist for the cognitively impaired population, current instruments such as the NPI are ineffective in identifying subtypes of apathy (Chow et al., 2009) and may be confounded by caregiver stress (Boyer, Novella,

Morrone, Jolly, & Blanchard, 2004). Moreover, caregiver-completed surveys do not assess apathy directly through patient performance**.** Therefore, as part of my dissertation work, I developed the PACT, a novel behavioral instrument, based on the GDB model, a review of experimental paradigms in the scientific literature and clinical observations (Elliott et al. 2010; Jenkins et al., 2000; Ruh et al., 2010). PACT is used to capture subtypes of apathy based on impairments in GDB (initiation, planning, and motivation). A trial begins with a start key depressed. In response to a signal, RT1 is measured when a participant lifts their finger from the start key; RT2 is the time needed to depress the target key. Total latency is the sum of RT1 and RT2. *Initiation* is assessed by measuring RT1 to a single visual stimulus. To measure the *planning* component of GDB, two levels of task difficulty are assessed. To assess *motivation*, the "simple" planning level is repeated with a monetary incentive (reward and penalty conditions) using a point system of "monetary units." Three scores (see Table 13) are generated from these times in the conditions described below for the proposed analysis. Below is a detailed description of the PACT.

Table 13

Scores Generated from the PACT

Score	Measure
Initiation	Reaction Time 1 in initiation condition
Planning	Total latency in "complex" planning level minus Total latency in "simple" planning level
Motivation	Total latency in reward or penalty condition minus Total latency in "simple" level from Planning condition

Preliminary Study 1. My dissertation work examined performance on the PACT for 19 persons with bvFTD (see Table 13). Participants with an *initiation* impairment (*N* = 5/19) demonstrated significantly slowed time to initiate a response (RT1). Imaging data showed atrophy in the ACC in this group (see Figure 4, Panel B blue). The *planning* impaired group (*N* = 8/19) had significantly slowed latencies and made errors on the complex measure of the PACT. Imaging data showed dlPFC atrophy in this group (see Figure 4, Panel A green). Participants in the third group with impaired *motivation* (*N* = 6/19) were not motivated to perform faster in response to the penalty condition in the PACT. This group showed significant atrophy in OFC (see Figure 4, Panel A yellow).

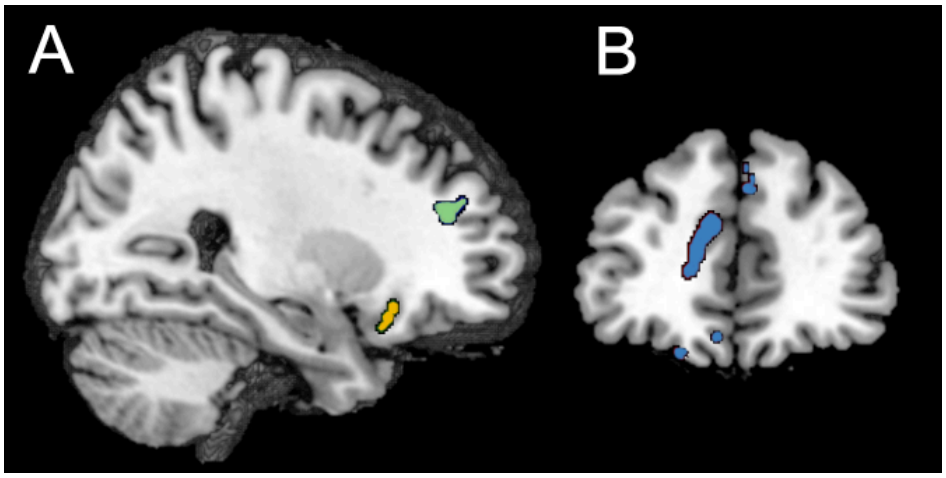

Figure 4. Significant regressions of apathy subtypes using PACT measures. Blue = initiation (anterior cingulate cortex); Green = planning (dorsolateral prefrontal cortex); Yellow = motivation (orbitalfrontal cortex).

Preliminary Study 2. I collected longitudinal data (mean follow up = 12months) in 7 bvFTD participants (see Figure 5). Two participants had initiation subtype at Time 1. Both participants showed more slowing on the initiation measure at Time 2 (slowed by an average of 162.71msec), but not on the planning or motivation measure (see Figure 5, Panel A). Three participants met criteria for the planning subtype at Time 1. Times

slowed for two of three participants (by an average of 108.60msec) on the planning measure, but not on the initiation or motivation measure (see Figure 5, Panel B). Two participants met criteria for the motivation subtype at Time 1. At Time 2, only one participant had additional slowing (555.15msec) on the motivation measure of the PACT. There were no additional worsening on initiation or planning measures (see Figure 5, Panel C). In sum, five of seven participants showed worsening that was restricted to the domain of initial impairment. Two of the seven participants mentioned above did not show slowing at Time 2. It is possible that these participants have cognitive reserve that slows the rate of apathy worsening, and I will examine this factor in the proposed study.

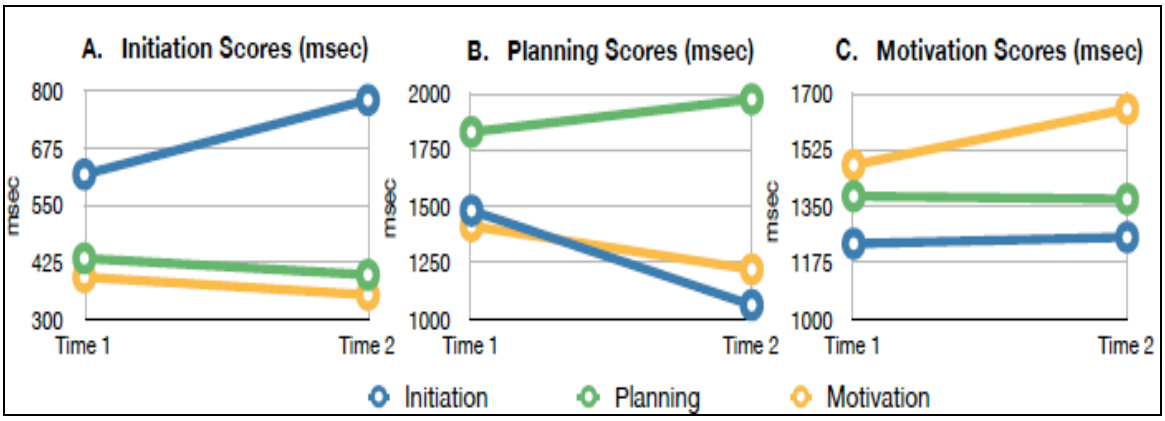

Figure 5. Longitudinal worsening in apathy subtypes on PACT measures.

Preliminary Study 3. To explore the effect of cognitive reserve on the longitudinal trajectory of bvFTD, I performed a retrospective chart review of autopsy confirmed bvFTD (n = 63). I found that environmental factors like higher occupational attainment, a proxy for cognitive reserve, were associated with longer survival time in bvFTD (F = 6.31, p = .0006) (Massimo et al., 2013). In the proposed study, I will

examine the moderating effect of cognitive reserve on annualized rate of change in the profile of apathy subtypes.

Research Strategy

A longitudinal case-control research design will be employed to conduct this study. I chose to compare normal and diseased populations (bvFTD) to elucidate mechanisms contributing to apathy subtypes. I focus particularly on bvFTD because apathy is very common in this condition and my dissertation data demonstrated the presence of each apathy subtype in bvFTD. These individuals do not have physical limitations that can confound the quantitative assessment of reduced GDB, and have no language or visuospatial deficits that can potentially limit the interpretation of bvFTD patient performance during the study. I have the opportunity to integrate my aims and instruments to collect prospective data on NC and bvFTD participants, as they are newly enrolled in the cosponsor's ongoing study, "Cognitive and Neural Impairment in Frontotemporal Dementia" (P01-AG017586, PI: Virginia Lee, PhD; Clinical Core Leader: Murray Grossman, MD). The purpose of Dr. Grossman's longitudinal study is to collect neuropsychological, neuroimaging, cerebrospinal fluid and genetic data to better understand the neural basis of impairments in this population, and relate these data to findings at autopsy. Potential participants are recruited from Dr. Grossman's FTD clinic (University of Pennsylvania Center for Frontotemporal Degeneration) in Philadelphia, PA. Consented participants are assessed at baseline and then 6–12 months following baseline (see Table 14). Qualifying individuals are invited to enroll. All participants meet enrollment criteria listed in Table 15.

Table 14

Schedule of Data Collection

Time 1 **initial visit** **(Day 1–2)**	Clinical diagnosis and demographics
	Mini-Mental State Exam
	Neuropsychiatric Inventory
	Geriatric Depression Scale Short Form
	Genetic Data
	Neuroimaging
	Philadelphia Apathy Computerized Test
	Lifetime of Experiences Questionnaire
Time 2 **follow-up visit** **(6–12 months after initial visit)**	Mini-Mental State Exam
	Neuropsychiatric Inventory
	Geriatric Depression Scale Short Form
	Neuroimaging
	Philadelphia Apathy Computerized Test

I will have full access to these data, including neuroimaging and genetic data, for my own analyses. The proposed study extends the parent study by prospectively collecting the PACT and Lifetime of Experiences Questionnaire (LEQ) for eligible participants coinciding with the first two data-collection points (Times 1 and 2). Table 14 explicates the data-collection schedule for each participant; measures added for the proposed study are bolded. Currently 54 participants with bvFTD are being followed longitudinally and we have successfully collected full sets of multimodal data (neuropsychology, DNA, grey matter imaging, and white matter imaging) for 43 of these. The setting is a reliable source of well-characterized clinical patients because four new bvFTD patients are diagnosed each month and > 80% of these patients agree to participate in Dr. Grossman's research program (see Table 15, Enrollment Criteria for

Proposed Study). NCs are recruited from the surrounding community and screened prior to entry in the parent study.

Table 15

Enrollment Criteria for the Proposed Study

Inclusion	Exclusion
Individuals diagnosed with bvFTD (Rascovsky et al., 2011) or NC	Persons with other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorder such as depression of psychosis, or systemic illness that could interfere with cognitive functioning.
Mild impairment (measured by Mini-Mental State Exam ≥ 20) at initial visit	Mini-Mental State Exam ≤ 19 to exclude moderate or severe dementia to minimize confounding factors related to severe cognitive impairment.
Participants who are not depressed as determined by Geriatric Depression Scale Short Form score of ≤5 at initial visit.	Individuals with depression (Geriatric Depression Scale-Short Form score > 5) are excluded because depression is confused with apathy and can confound interpretation of the data. I will exclude participants in the rare event that participants become depressed during follow up.
Modest doses of selective serotonin reuptake inhibitors or antipsychotic medication may be needed for clinical management, and thus are allowed. Moreover, a stable dose (no change during follow-up study period) is necessary to minimize potential confounding effects because these medications can contribute to apathy (Benoit et al., 2008).	Participants taking regular doses of benzodiazepines and other soporific medications will be excluded because of their sedative effects.
A reliable caregiver who has frequent contact with the participant (> 3 times/week for ≥ 1 hour).	Participants who do not have caregiver contact. Frequent contact with patient is needed to accurately rate the patient's behavior, because patients with bvFTD often have poor insight into their own deficits (Massimo, Libon et al., 2013).
Speak and understand English to complete the questionnaires.	Insufficient English to complete questionnaires.

In Aim 1, a standard apathy scale from the NPI will be administered to identify participants with apathy. The PACT will be administered to ascertain initiation, planning, and motivation subtypes of apathy in bvFTD. The PACT will be collected again 6–12 months after the initial visit to examine longitudinal change. I will specifically monitor

whether participants with all subtypes of apathy, regardless of their initial presentation, maintain their distinct subtype profile of apathy longitudinally or accumulate additional subtype features to converge on a single apathy phenotype over time.

In Aim 2, potential moderating environmental factors (education, occupation, and leisure activities) and genetic factors (ApoE status and tau haplotype) will be related to changes in apathy subtypes over time. From the perspective of the model of longitudinal change known as "cognitive reserve," factors such as education, occupation, and leisure activities may moderate the rate of longitudinal decline (Bartres-Faz & Arenaza-Urquijo, 2011). Thus, I propose to monitor the ways these environmental and genetic factors moderate the rates of clinical progression (Stern, 2002). Importantly, this knowledge will provide insight into potential responses of participants to planned cognitive interventions for apathy (Simon, Yokomizo, & Bottino, 2012).

In Aim 3, MRI obtained at initial and follow-up assessments in apathetic participants will be compared to NC, and regression analyses will relate apathy subtype scores (see Table 13) to cortical thinning and FA of white matter tractography. Biological factors such as grey matter volume and white matter tractography must be considered to understand the neuroanatomic basis of change in apathy subtypes. During longitudinal monitoring of apathy, progression restricted to a specific subtype should continue to involve primarily a specific neuroanatomic circuit; by comparison, progression involving additional apathy subtypes may incorporate additional disease involving other brain regions associated with apathy and/or white matter tracts. I will also explore whether environmental and genetic factors impact longitudinal MRI changes in areas related to apathy subtypes.

Instrumentation for Aim 1: Examine longitudinal changes in subtypes of apathy.

The PACT is a novel, quantitatively rigorous computerized RT test designed to quantify each GDB process. In my preliminary dissertation data, the PACT is able to identify apathy subtypes according to distinct behavioral response patterns (Massimo, Evans et al., 2012; Massimo, Morgan et al., 2012). In all conditions, a trial begins when the participant depresses a computer "start" key with one finger. The PACT measures RT to lift this finger from the start key in response to a signal (RT1) and then RT to depress the target key (RT2).

Initiation refers to one's ability to self-generate or activate actions (Levy & Dubois, 2006). In the simplest condition designed to measure initiation, the participant begins a trial by depressing the start key, then a central stimulus on the computer screen appears. A fixed central target key must be depressed in response to this stimulus; the stimulus occurs on average 1,250msec (range 500–2000msec) after depressing the start key. Initiation is assessed by measuring RT1.

Planning refers to the ability to elaborate plans of action (Levy & Dubois, 2006). In the second condition, designed to assess the planning process of GDB, two levels of task difficulty are assessed. In the first, "simple" level, after depressing the start key, participants are signaled by randomly-ordered lateralized visual stimuli to press a left or right target key (stimulus appears on the left, then go left; stimulus appears on right, then go right). In the second, "complex" level, one of two lateralized keys is pressed contingent on the combination of patterns in a central visual stimulus (stimulus appears

on the left, then go left; stimulus appears on right, then go right). Planning is assessed by measuring the RT difference between these two levels of difficulty.

Motivation refers to the ability to associate affective signals (positive or negative) with value in order to perform actions (Levy & Dubois, 2006). In the third condition designed to assess motivation, the "simple" level from the planning condition is repeated with an explicit monetary incentive using a point system (monetary units) to reward participants for responding correctly and more rapidly. Participants receive feedback about their response speed after each trial on the computer screen. I also assess the sensitivity to negative consequence by having a "penalty" condition, where participants are given monetary units at the beginning of each task, and monetary units are taken away if they do not respond correctly and more rapidly. (Unbeknownst to participants, all receive the same final amount for participation by adjusting the dollar value of a monetary unit.)

I obtain 48 trials during each condition. A practice block precedes each experimental condition where participants get instructions on the task and 12 practice trials. The PACT measures RT1, RT2, total latency (RT1 + RT2) and errors. In our experience, the PACT takes approximately 45 minutes to complete.

Instrumentation for Aim 2: Determine the effect of environmental factors (education, occupation, and leisure activities) and genetic factors (ApoE status and tau haplotype) as moderators of annualized rate of change in the profile of apathy subtypes in bvFTD.

Environmental factors. The LEQ (Bartres-Faz & Arenaza-Urquijo, 2011) is a reliable and valid instrument that assesses cognitive lifestyle, a proxy for cognitive

reserve. The LEQ will be obtained by interviewing a knowledgeable informant for educational, occupational, and leisure activities that are protective against cognitive decline. The LEQ consists of 42 items constructed around two dimensions: three life stages (young, mid, and late adulthood) and specific versus nonspecific mental activity in each stage. Scores are calculated for each stage and then summed for a total LEQ score. Higher scores indicate higher lifetime mental activity. The LEQ has an overall internal consistency of .66 and test–retest reliability of .98, and it discriminates between older adults with high and low mental-activity levels. Healthy older adults with higher LEQ scores have shown less cognitive decline over 18 months than those with low scores, independent of covariates (Bartres-Faz & Arenaza-Urquijo, 2011).

Genetic factors. DNA is extracted from frozen blood using a previously reported procedure (Van Deerlin et al., 2010). DNA samples will be evaluated for purity by spectrophotometric analysis (NanoDrop) and for degradation by 1% agarose gel electrophoresis (Invitrogen). Genetic analysis for bvFTD includes sequence analysis of ApoE genotype and tau haplotype. ApoE genotyping will be performed by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism. Tau haplotypes will be determined by either DNA sequence analysis or by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism of Exon 9 using the following intronic primers: forward 5'acctgcctaacccagtggtg-3' and reverse 5'gaggggactggggtgttatg- 3'. The amplified fragment will be digested with HpaII and HpyCH4IV and the resulting fragments analyzed by agarose gel electrophoresis to determine the haplotype based on three known polymorphisms of Exon 9 that segregate with the known major haplotypes.

Instrumentation for Aim 3: Relate changes in apathy subtypes in bvFTD to annualized grey matter thinning and reduced FA on DT imaging studies of white matter tractography.

Volumetric MRI. T1-weighted MRI scans will be collected using a research-dedicated Siemens Trio 3.0T scanner with 1-mm slice thickness, in-plane resolution = .9766 x .9766, and a 195 x 256 matrix using an magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MPRAGE) protocol (*TR* = 1,620ms, *TE* = 3ms, flip angle = 15°).

Diffusion weighted image (DWI). DWI images are collected using the following parameters: FOV = 240mm; matrix size = 128 x 128; number of slices = 70; imaging resolution = 1.9 x 1.9 x 2 mm; *TR* = 8,000ms; *TE* = 82ms; fat saturation. In total, 34 volumes will be acquired per subject, four volumes without diffusion weighting (*b* = 0 s/mm2) interleaved within 30 volumes with diffusion weighting (*b* = 1,000s/mm2) along 30 noncollinear directions.

Analyses.

Analyses Aim 1: Examine longitudinal changes in subtypes of apathy. The overall sample will be described demographically and according to continuous measures of the PACT using means, standard deviations, median, and interquartile ranges. Additionally the sample will be described according to the apathetic subtype of initiation, planning, and motivation (see criteria below) using means, standard deviations, and *z*-scores. I established the criteria shown in Table 16 to partition participants into subtypes using PACT observations (Elliott et al. 2010; Jenkins et al., 2000; Ruh et al., 2010).

Table 16

Criteria for Apathy Subtypes

Subtype	Criteria
Initiation	Significantly slow RT1 in initiation condition; does not have slowed latencies for "complex" level of planning condition; able to improve performance on the "simple" planning level in response to "reward" or "penalty."
Planning	Significantly greater slowing on the "complex" planning level compared to the "simple" planning level; does not have slowed initiation for all conditions; able to improve performance on the "simple" planning level in response to "reward" or "penalty."
Motivation	Fails to respond to "reward" or "penalty" motivators in "simple" level of planning condition; does not have slowed initiation for all conditions; does not have slowed latencies for "complex" level of planning condition.

Individual *z*-scores will be used to define subtypes. These will be based on the entire patient population. Participants will be designated as a specific subtype if the *z*-score is > 1.96 for one condition, but within the range of the remainder of the population (i.e., *z*-score 1.96) for the remainder of the conditions. I will use a linear mixed-effects model (Laird & Ware, 1982) to assess longitudinal change in each subtype. Linear mixed-effects models account for within-subject correlations over time and accommodate both variable length of follow-up for different subjects and variation in the interval between assessments. In the analysis, the intercept and regression coefficients for the follow-up time will be treated as random effects, such that each individual would have a unique intercept and regression coefficient for the follow-up time. Population mean coefficients for the follow-up time will be obtained by averaging the participants' specific regression coefficients for follow-up time. The population mean regression coefficient for the follow-up time estimates the annual change in PACT scores over time

and accounts for differences in baseline PACT scores. I will also confirm subtype worsening relative to NC.

Analyses Aim 2: Determine the effect of environmental factors (education, occupational attainment, and leisure activities) and genetic factors (ApoE status and tau haplotype) as modulators of annualized rate of change in the profile of apathy subtypes in bvFTD. Environmental factors such as education, occupation, and leisure activities data will be scored according to the LEQ, as described above**.** The patient group will be dichotomized based on the following genotypes: **(**a) ApoE e4 carrier versus not; (b) microtubule-associated protein tau genotype H1/H1 versus not. Linear mixed-effects models will be used to test for associations between environmental factors, different genotypes and changes in apathy subtypes.

Analyses Aim 3: Relate changes in apathy subtypes in bvFTD to annualized grey matter thinning and reduced FA on DT imaging studies of white matter tractography.

Volumetric MRI. High-resolution volumetric ($1mm^3$) images will be segmented and normalized to a common space using Pipedream and ANTs (Avants, Tustison, Song, et al., 2011; Avants et al., 2008), as previously reported. Briefly, this procedure provides the newest ideas and most current features (Harris, Adams, Zubatsky, & White, 2011): unbiased diffeomorphic and symmetric registration of MRI volumes into local template space. MRI volumes are then segmented into three tissue classes using probabilistic information and template priors (Avants, Tustison, Wu, et al., 2011) and from these images I will compute grey matter density and cortical thickness (Das et al., 2009). I will use the multiple-regression module in SPM8 to identify the relationship between

performance on each PACT score (see Table 13) and cortical thinning. To constrain the interpretation of the regression analysis to areas of known disease in bvFTD, I will use an atrophy mask generated from a *t*-test contrast of all apathetic bvFTD participants relative to NC. I will also evaluate atrophy in each apathy subtype defined according to behavioral performance on the PACT. I will evaluate longitudinal change in grey matter by generating a single volume reflecting longitudinal change (Time 2 - Time 1/months), and compare this to longitudinal change in NC. The regression module in SPM8 will be used to relate longitudinal imaging change to change in PACT scores. To determine the relative contribution to the variance of environmental and genetics factors, I will also perform a stepwise multiple-regression analysis.

DTI. DWI images will be preprocessed using ANTs (Avants, Tustison, Song, et al., 2011) and Camino (J. Perry, 2002). Motion and distortion artifacts will be removed by affine coregistration of each DWI to the unweighted ($b = 0$) image in the diffusion imaging sequence. DT will be computed using a linear least squares algorithm implemented in Camino. The distortion between the participant's T1 and DT images will be corrected by registering FA in the DT image to the T1 image. The DT image will be warped to template space by applying intrasubject (FA - > T1) and intersubject (T1 - > template) warps. A general linear-model module in SPM8 will be used to compare FA in bvFTD to NC. I will calculate mean FA in each apathy subtype defined by behavioral performance (see Section B.7.1). I will also use logistic regression to evaluate the relationship between apathy subtypes and FA. I will evaluate longitudinal change in FA by generating a single volume reflecting longitudinal change (Time 2 - Time 1/months). The regression module in SPM8 will be used to relate longitudinal imaging change to

change in PACT scores. To determine the contribution of environmental and genetic factors, I will perform stepwise multiple-regression analysis.

Power analyses. Sample-size estimates and power calculations are based on the minimum detectable slope (rate of decline) difference between two groups (e.g., NC and bvFTD) over time using a mixed-effect model, with an $\alpha = .05$. I assume moderate correlations between repeated measures ($r = .5$) and one follow-up after baseline. Table 17 lists sample size needed per group to detect a slope difference between two groups. With 16 participants per group, we will have 80% power to detect a slope difference of 1.0 *SD* of an outcome measure (e.g., PACT scores). The detectable effect size (1.0 *SD*) is larger than what was observed (0.3 *SD*) in pilot data. However, the current study allows me to generate important pilot data for a larger scale study in the future. For the imaging studies, a minimum of 20 participants are required in each group to detect a 1mm (equivalent to 1 voxel) change at the $p < .05$ (corrected) level with a beta of 0.15 (power = .85). The final sample size, accounting for a 10% attrition rate will be 44 participants (NC and bvFTD).

Table 17

Sample Size to Detect Difference Between Two Groups

SD diff	β = 0.8	β = 0.9
0.5	63	84
0.75	28	37
1.0	16	21
1.5	7	9

Potential Challenges

Interpretation and potential problems Aim 1. I predict that the profile of apathetic subtypes will be maintained over the course of the disease trajectory, (Libon et al., 2009), although additional deficits may accrue over a longer duration. If I see slowed RTs for more than one PACT measure in a subtype, I will look for additional evidence for generalized cognitive worsening using neuropsychological measures (collected by the cosponsor's ongoing longitudinal study), as previously reported in my cross-sectional dissertation study, and covary PACT performance for these general cognitive deficits. There may not be worsening in a subtype, and this may be due to not enough time between Time 1 and Time 2. I will also assess cognitive reserve factors that may minimize or slow worsening (see Aim 2).

Interpretation and potential problems Aim 2. I predict that the rate of change in apathy will be moderated by environmental and genetic factors. There may be too much variation in occupation and leisure activity so I may have to categorize these variables according to level of cognitive stimulation the activity provides, as previously reported (Foubert-Samier et al., 2012). I expect participants with e4 alleles and H1H1 haplotypes will have faster rates of worsening in apathy than those without these genetic markers (Di Maria et al., 2010; Morley et al., 2012). If I do not detect an effect on the trajectory of apathy due to limited impact of genetics on apathy, I will look for additional evidence of moderating effects in other cognitive domains using longitudinal neuropsychological (collected under the cosponsor's ongoing longitudinal study). I may also look at the influence of the number of e4 alleles on apathy worsening (additive model) rather than the proposed dominant method (e4 present or not). Rather than

affecting the slope of decline, factors such as education and leisure activities may delay the point at which worsening begins; likewise, the presence of genetic risk factors may hasten the onset of worsening rather than steepen the slope. These alternatives can be assessed statistically.

Interpretation and potential problems Aim 3. I predict that apathetic participants will have significant cortical thinning and loss of white matter integrity in the frontal lobe (Diekhof et al., 2011; Kaller et al., 2011; Kotchoubey et al., 2003; Reijnders et al., 2010; Sescousse et al., 2010; Unterrainer, Rahm, Kaller, Leonhart, et al., 2004). If unable to detect longitudinal change in the proposed imaging regression, I will obtain mean grey matter thickness values at Time 1 and Time 2 and compare with *t*-tests. I can also evaluate DTI using tract-specific analysis, which minimizes "crossing-fibers" and enables the analysis of individual white matter structures (Wimo, Jonsson, Bond, Prince, & Winblad, 2013). I will also evaluate whether white matter disease is related to grey matter disease or independent from grey matter disease by investigating the residuals of white matter atrophy in a linear regression that includes areas of grey matter atrophy as nuisance covariates, and vice versa.

It is also possible that participants with long disease duration will have diffuse, nonspecific atrophy, and I propose to examine participants who are mild at initial visit. I will also evaluate whether disease duration and age contribute to group-level difference by including these as nuisance covariates. It may be difficult to obtain imaging in some participants because of time restriction, medical contraindication (e.g., claustrophobia and pacemakers) and participant preferences. If this is the case, participants will still be asked to participate in the PACT assessment and I will assess the dataset to ensure those

who are imaged are representative of the entire data set by performing *t*-tests to ensure there are no significant differences between those who are imaged and those who do not have imaging data.

The MRI may not have been collected on the same day the PACT was administered; however all images will be collected within 6 months of the PACT. Given the rate of brain volume change in bvFTD, 6 months is a widely accepted timeframe (Whitwell et al., 2008). Despite these caveats, the results from this research will extend my dissertation work by providing an understanding of the trajectory of apathy as well as the identification of factors that moderate the progression of this devastating neuropsychiatric symptom. With this knowledge, tailored interventions that target problems with initiation, planning, and motivation can be appropriately designed and implemented.

CHAPTER 5: DISCUSSION

Introduction

Apathy, a reduction in GDB (Levy & Dubois, 2006), profoundly limits a person's ability to engage in self-care activities. Apathy affects 90% of people with bvFTD (Diehl-Schmid et al., 2006), a common cause of early onset ND. Researchers hypothesized that apathy emerges where there is dysfunction at the level of GDB (Levy & Dubois, 2006). Therefore, I proposed to use the GDB model to examine the brain-behavior relationships underlying apathy in bvFTD. Specifically, I conducted an empirical study that quantified difficulty with each component of GDB using a novel computerized RT test, examined the distinct prefrontal neuroanatomical substrates of these impairments in an apathetic bvFTD sample using regression, and related specific apathetic behaviors to grey matter atrophy and white matter integrity, quantified by MRI. This study used a novel RT test and neuroimaging to examine three dissociable behavioral and neuroanatomical components of GDB—initiation, planning, and motivation—in a sample of 20 apathetic adults with bvFTD and 17 normal older adults. Impairment in each of these components was associated with selective disruption of a large-scale neuroanatomic network underlying GDB. Specifically, impaired initiation was related to disease in the ACC, impaired planning was related to disease in the dlPFC and impaired motivation was related to disease in the OFC. Moreover, some participants with bvFTD were found to have specific subtypes of apathy, depending on the impaired GDB mechanism, whereas others had more global impairments. Together, these findings demonstrate that apathy is not simply a unitary phenomenon, but rather has multiple components related to impairments in GDB. In this chapter, I elucidate these findings: (a) how initiation,

planning, and motivation are supported by a large-scale neural network constituting the neuroanatomic basis for GDB, including distinct grey matter regions in the frontal lobe and related white matter projections, and (b) how, when compromised, impairments in these mechanisms contribute to apathy in bvFTD. This discussion concludes with implications for clinical practice and social neuroscience research.

Summary and Discussion of Principal Findings

GDB is supported by a large-scale neural network in distinct specific portions of the prefrontal cortex (AIM 1, see Chapter 2). The integration of three processes that influence the intention to act are central to the model of GDB is (Levy & Dubois, 2006). *Initiation* refers to one's ability to self-generate or activate actions. *Planning* is the ability to elaborate plans of action. *Motivation* refers to the ability to associate affective signals (positive or negative) with value in order to perform actions. I found that apathetic bvFTD participants are impaired in one or more of these three processes. Further, impairments in these three GDB processes were associated with disease in three distinct frontal grey matter regions and in white matter projections between these regions and other brain areas.

I found that difficulty in initiating a behavior is related to reduced grey matter in the ACC and white matter tracts including the cingulum (H1). Considerable published work has suggested that the ACC is important for initiating a behavior (Tekin & Cummings, 2002), and the ACC has previously been implicated in processes that influence action initiation in studies with healthy adults (Mulert et al., 2003). For example, fMRI studies have demonstrated the role of the ACC in processing "action"-related signals such as movement selection (e.g., simple finger tapping) and timing of movement initiation (e.g.,

selecting the moment of when; Hoffstaedter, Grefkes, Caspers, et al., 2013; Hoffstaedter, Grefkes, Zilles, & Eickhoff, 2013). Additionally, the ACC is functionally linked to important motor systems such as premotor areas and the basal ganglia, suggesting a core network of brain structures, important for implementation of intentional motor control (Beckmann, Johansen-Berg, & Rushworth, 2009; Hoffstaedter, Grefkes, Caspers, et al., 2013).

The ACC is also implicated in initiation difficulty in those with frontal-lobe injury. For example, the *akinetic mute state*—a medical term describing patients who tend to sit quietly in the same position all day without speaking or talking—has been specifically related to ACC damage (Mega & Cohenour, 1997). The ACC has been well studied in dementia, and neuroimaging evaluations have linked the ACC region to apathy in various groups. Specifically, reduced grey matter density in the cingulate gyrus was associated with apathy in persons with bvFTD (Massimo et al., 2009; Zamboni et al., 2008) and PD (Reijnders et al., 2010). Previous DTI studies investigating white matter disease and apathy have shown associations among the three frontal areas important for GDB. That is, the cingulum has reciprocal connections between ACC and the medial orbitofrontal region that is important for motivation (Hahn et al., 2013; J. W. Kim et al., 2011; Ota et al., 2012). In healthy adults, ACC and dlPFC structures work in concert during complex tasks that require attentional control, and this is likely mediated through the cingulum (Silton et al., 2010). These prior findings provided support for the notion that disease in ACC and interruption of projections between ACC and other structures important for GDB may contribute to apathetic behavior, and were further supported in this study.

I found that deficits in the planning component of GDB were associated with atrophy in the dlPFC and reduced FA in related white matter tracts, including SLF and frontal corona radiata (H2). fMRI studies of healthy adults suggested that the dlPFC supports planning and working memory (Di et al., 2013; Miller & Cohen, 2001). In addition, some studies demonstrated hemispheric specialization or differential effects of right and left dlPFC in planning tasks. For example, researchers thought the left dlPFC analyzes propositional information such as task parameters, whereas the right dlPFC manipulates and integrates information into a sequence (Huey et al., 2009; Ruh, Rahm, Unterrainer, Weiller, & Kaller, 2012). Thus, it is likely that patients who suffer from dysfunction in these circuits fail to elaborate, manipulate, and integrate important information needed for behavior that is goal directed. Studies have suggested a relationship between apathy and poor executive function in bvFTD (Eslinger et al., 2012; Zamboni et al., 2008). Eslinger and colleagues (2012) found caregiver apathy scores were significantly correlated with executive-function measures, suggesting that apathy emanates in part from difficulty manipulating and integrating elements of a plan to achieve a goal. Imaging studies of persons with FTD and AD have linked apathetic behavior to atrophy in dlPFC (Massimo et al., 2009; Zamboni et al., 2008). In addition, a previous study of persons with amnestic mild cognitive impairment revealed a relationship between reduced FA in the SLF and apathy (Cacciari et al., 2010). The SLF is a prominent white matter tract interconnecting the frontal, temporal, and parietal lobes; this tract has been implicated in the integration of these diverse regions involved in planning (Genova et al., 2013). Thus, my findings are congruent with previous work.

I found that difficulty with the motivation component of GDB is associated with atrophy in the OFC and related white matter tracts, including UNC (H3). Evidence from healthy subject fMRI studies suggests that the OFC plays a role in interpreting value- and reward-related information (Hare et al., 2010). In particular, evidence suggests that the medial OFC is more sensitive to reward signals and the lateral OFC is more sensitive to punishment signals (X. Liu, Hairston, Schrier, & Fan, 2011). Thus, the OFC encodes and assigns the relative value of reward for future decisions on avoidance or acquisition of the stimulus (S. I. Kim, 2013). Deficits in processing value and reward have been examined extensively in persons with FTD because they appear to have early degeneration of this frontal circuit in comparison to persons with other neurodegenerative conditions (Rabinovici et al., 2007).

Poor motivation can occur in these individuals because they may have decreased reactivity to positive "reward" and negative "punishment" signals, thereby making goal-selection difficult (Levy & Dubois, 2006). Experimental evidence, however, has emphasized that persons with bvFTD and other diseases affecting OFC have the greater difficulty interpreting "punishment" rather than "reward" signals (Grossman et al., 2010; Noonan, Kolling, Walton, & Rushworth, 2012). Imaging evidence from persons with bvFTD has emphasized the link between OFC and apathetic behavior (Massimo et al., 2009). fludeoxyglucose PET brain activity is decreased in OFC in bvFTD patients with apathetic compared to nonapathetic patients (Peters et al., 2006). Apathy scores from the NPI have been associated with atrophy in ventromedial frontal regions (Rosen et al., 2005). UNC is a major tract connecting the anterior temporal lobe with the medial and lateral prefrontal cortex (Papagno et al., 2011), areas known to be important for GDB

(Kable & Glimcher, 2007). DTI studies performed in AD and PSP implicated UNC in apathy (Hahn et al., 2013; Kvickstrom et al., 2011), and my results extend this finding to bvFTD.

Three subtypes of apathy, based on differentiated impairments in GDB, exist in bvFTD (AIM 2, see Chapter 3). Consistent with the definition of apathy as the pathology of GDB, I studied a sample of apathetic bvFTD participants and identified individuals who demonstrated impairments on one or more components of GDB. Consider first the failure to *initiate* behavior, which leads to a subtype of apathy when processing is unable to generate a signal significant enough to begin a response. The initiation condition of the PACT assessed this GDB component quantitatively by measuring latency to initiate a movement in response to a visual signal. I found that some apathetic bvFTD participants were significantly impaired only on this component of GDB (H1).

Initiation difficulty, however, was not the only basis for apathetic behavior. The ability to execute an action is also highly dependent on the cognitive processes needed to plan, organize, and carry out goals. Apathy related to "cognitive inertia" can result from impairments in executive functions such as *planning*, working memory, and task-switching (Burgess, 2000; Levy & DuBois, 2006). I assessed two levels of task difficulty in the planning condition of the PACT. In the first level (simple planning condition), after depressing the start key, participants were signaled by randomly-ordered lateralized visual stimuli to press a left or right target key. In the second, more complex level, one of two lateralized keys were pressed, contingent on the combination of patterns in a central visual stimulus (blue and horizontal stripes go left, orange and vertical stripes go right). I

found that some apathetic participants were significantly impaired only on the planning condition (H2). Moreover, poor planning was the most prevalent single component of GDB found to be impaired in this bvFTD sample. This is not surprising, given that a dysexecutive neuropsychological profile is a common finding in bvFTD (Rascovsky et al., 2011). Another component of GDB is *motivation*, that is, responsiveness to external and internal drives that may be perceived as positive or negative. Apathy may result from a lack of responsiveness to reward or risk, thereby making goal-selection difficult (Levy & Dubois, 2006; Rosen et al., 2002; Schultz et al., 2000). Likewise, reduced ability to assess and interpret consequences of actions, whether positive or negative, can limit motivation (Zamboni et al., 2008). Patients with bvFTD typically have a greater desire for certain rewards such as money, but tend to show insensitivity to negative consequences (Grossman et al., 2010; D. C. Perry et al., 2013). Therefore, I used a penalty condition (negative consequence) to assess impaired motivation. I found that participants performed faster on the simple reward condition (compared to the simple condition without incentive), suggesting they were motivated by the monetary incentive. Their performance pattern did not change, however, when I removed monetary units in response to not performing faster, suggesting an insensitivity to negative consequences. In my sample of bvFTD participants, I identified some individuals with single impairment in the motivational component of GDB (H3). Thus, the results support the presence of differentiated sources of apathy, including deficits in initiation, planning, and motivation that work together to limit GDB.

Together, the analyses of Aims 1 and 2 support the model of apathy as a complex behavioral syndrome comprised of three distinct mechanisms related to

impairments in GDB, each with its own neuroanatomical basis. Using this model opens new avenues of approaches to managing or treating apathy. Most researchers of bvFTD have assumed that apathy is a single, undifferentiated behavioral phenomenon (Rosen et al., 2005, Zamboni et al., 2008). One early approach proposed defining an undifferentiated form of apathy as a lack of motivation (Marin, 1990), although lack of motivation does not appear to be the only mechanism that contributes to apathetic behavior. Others have suggested that apathy is related to impairment of other single processes such as difficulty with initiation (Tekin & Cummings, 2002). Subsequently, investigators proposed to define apathy as "the quantitative reduction of self-generated voluntary and purposeful behavior" (Levy & Dubois, 2006, 916). The model of GDB includes initiation, planning, and motivation (Brown & Pluck, 2000), which allow a person to direct purposeful behavior toward a desirable goal or away from an undesirable outcome (Geurts & de Wit, 2013). Although each process is necessary to achieve GDB, my research findings suggest these processes are, in fact, dissociable. For example, I found that apathetic bvFTD patients are impaired on one or more of the three processes thought to contribute to GDB: initiation, planning, and motivation. These three GDB processes were associated with disease in three distinct frontal grey matter regions and in white matter projections between these regions and other brain areas. Moreover, I found apathetic participants who demonstrated single deficits in only one of the three components of GDB. Indeed, apathy arises when any one of these three processes is impaired. For example, patients who have impairments in executive abilities needed to carry out plans of action may not find it difficult to initiate GDB or lack motivation, but their planning impairment may overwhelm their ability to develop plans of action that are

complex. My findings, thus, suggest that each GDB process is relatively independent and, when compromised, likely contributes to apathy.

Implications for Practice

This study examined a pathophysiological model of GDB, which revealed three distinct mechanisms likely contributing to apathy: impairments in initiation, planning, and motivation. A future goal is to optimize interventions for apathy subtypes based on an understanding of these mechanisms. The assessment of the efficacy of treatments for apathy has heretofore been hindered because of methodological failures in trials where apathetic patients are viewed homogeneously, for example solely as displaying a "lack of motivation." I found that lack of motivation is not the only process that contributes to apathy. Based on my work, future treatments for apathy would more appropriately be tailored to the specific component(s) of GDB that is (are) compromised in an individual. Interventions should be explored based on the structural anatomic features of each of the three impairments in GDB. For example, when apathy emerges in response to *planning* difficulties, benefit may be gained from restructuring a complex activity into simple components for the patient. For patients with impaired goal-selection (*motivation*), modifications such as amplified lighting in a room or onto a specific activity or object may increase the reward potential of the environment (Ishii et al., 2009). Last, MSS—a therapeutic approach that provides visual, auditory, tactile and olfactory stimulation—may be helpful for patients with *initiation* difficulty (Baker et al., 2001). The use of MSS in a patient with planning difficulty, however, may worsen rather than improve apathy because it can cause distractibility. To facilitate research, a systemic evaluation of existing interventions for apathy is warranted, followed by the categorization and testing

of interventions designed for specific subtypes. These studies are important to improve patient and caregiver quality of life.

Recognizing and making a reliable diagnosis of apathy is essential to initiate treatment. Healthcare practitioners may overlook patients with apathy because of their lack of apparent distress (Butterfield et al., 2010). Although several apathy-assessment tools exist for the cognitively impaired population, researchers lack agreement on the interpretability of the data from these measures (Clarke et al., 2011). Traditional instruments to ascertain the presence of apathy commonly rely on proxy report. Unfortunately, this approach is subject to caregiver confounds such as burden and strain that may impact the evaluation. This dissertation study, along with others (Boyer et al., 2004), has found that this approach is biased by caregiver stress. One goal of the present study was to identify subtypes of apathy in an objective manner, minimally confounded by proxy report. This study furthers the research in this area because I used an empirically-based approach that elucidated mechanisms contributing to apathy. This work is the first step in the development of an instrument that would be based on objective, empirical measurements of impairments of each of the components of GDB that contribute to apathy. Such an instrument would improve on the current instruments because of its objective basis and would increase the likelihood of detection and targeted treatment of specific subtypes of apathy.

Implications for Social Neuroscience

I propose, in short, that the syndrome of apathy is complex, consisting of impairments in at least one GDB process. As discussed above, these processes are largely independent of each other, rather than sequential or hierarchical, as has been suggested

by others (Dezfouli & Balleine, 2013; Levy & Dubois, 2006). My findings support the view that apathy is a conceptually heterogeneous syndrome, explained in part by underlying dysfunction at the neuroanatomical level. Figure 6 presents an illustration of my hypothesized model of apathy, adapted from Levy and DuBois (2006).

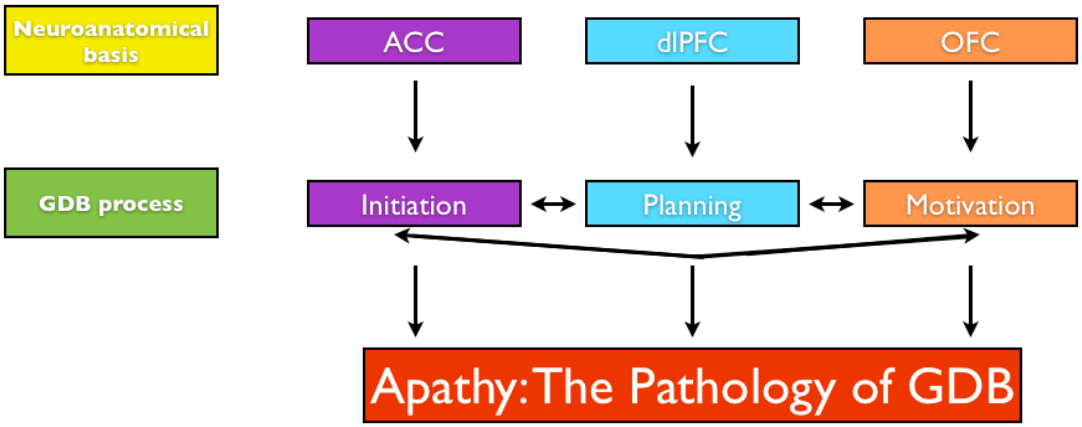

Figure 6. Model of apathy as the pathology of goal-directed behavior in behavioral variant frontotemporal degeneration.
Note. Adapted from "Apathy and the Functional Anatomy of the Prefrontal Cortex-Basal Ganglia Circuits," by R. Levy & B. Dubois, 2006, *Cerebral Cortex, 16,* 918. doi:10.1093/cercor/bhj043

Study Strengths

Although apathy is a significant problem that is commonly observed in persons with bvFTD and has a pervasive impact on their caregivers, current understanding of apathy is based on observational data. This dissertation is the first study to examine apathy using the GDB model to guide direct, empirical assessments of behavior and interpretation of results. Overwhelmingly, the most common way to assess apathy has been through caregiver questionnaires. Caregiver surveys, however, do not assess apathy by directly ascertaining patient performance, thereby limiting their validity and reliability**.** Moreover, ascertainment of patient apathy solely from a caregiver's perspective is likely to be confounded

by caregiver stress (Boyer et al., 2004). Indeed, I found a correlation between apathy symptom FxS scores and caregiver-distress scores on the NPI. Currently available instruments, such as the NPI, are less than optimal because they are also insensitive to subtypes of apathy (Chow et al., 2009). The PACT was developed as an alternate measure that provides a direct, independent assessment of GDB components contributing to apathy that is not biased by the subjectivity of caregiver-rated questionnaires.

The method used in this dissertation, thus, offers several advantages over traditional, questionnaire-based approaches to measuring apathy because I directly ascertained participant performance without the intervening factor of a caregiver's impression. Moreover, I assessed several different components of GDB that are believed to contribute to apathy. Although not a primary aim of the study, the study data served to provide validation for the PACT with a neuroanatomical model of apathy. I used VBM to quantify significant grey matter changes in this bvFTD sample and I related these changes to PACT performance. Based on previous literature reports in ND and lesion studies, I hypothesized that poor *initiation* was related to ACC disease (Kotchoubey et al., 2003; Reijnders et al., 2010), poor executive function (*planning*) was related to disease in dlPFC (Kaller et al., 2011; Unterrainer, Rahm, Kaller, Ruff, et al., 2004), and reduced *motivation* was related to disease in the orbital and medial prefrontal cortex (Diekhof et al., 2011; Sescousse et al., 2010). These earlier findings were replicated in my dissertation data. My hypothesized anatomic model of apathy falls in the broad area in the frontal lobe that I had previously correlated with NPI FxS apathy scores (Massimo et al., 2009). Moreover, my assessment of white matter disease was the first to examine apathy in bvFTD comprehensively. The availability of both grey matter and white matter

neuroimaging data allowed me to investigate a large-scale neural network that subserves a complex behavior. This allowed me to develop a framework that captured the complex associations of impaired GDB encompassing the various subtypes of apathy and their associated neuroanatomic substrates, and to examine the ways the breakdown of this network can lead to the clinical syndrome of apathy.

Study Limitations

Several potential limitations should be kept in mind when considering these findings. Although the sample was larger than in prior investigations of apathy, I nevertheless studied a small number of participants; power in the imaging studies may not have been sufficient to detect every anatomic region associated with apathy. In addition, as anticipated, the participant sample was not diverse and querying the database to find a representative sample did not reveal additional women or diverse racial/ethnic participants. Because floor effects in performing the planning measure limited variance, I was forced to use a higher threshold for the grey matter analyses in Chapter 2. In addition, I had to adjust my planning subtype criteria in Chapter 3. Most participants with impairments in initiation and/or motivation also had a planning impairment, consistent with the dysexecutive profile typically seen in bvFTD (Rascovsky et al., 2011). To better classify participants with impaired planning, I implemented the application of the planning criteria for those with multiple impairments in a stepwise fashion. That is, I subjected planning-impaired participants who also had deficits in initiation and/or motivation to a second level review; I only classified participants who also had greater slowing on the complex planning condition compared to the simpler planning condition into the planning-impairment subtype.

Based on these considerations, however, it will be important in future studies to make the planning condition less complex by giving participants only two contingencies. Four participants with an isolated planning subtype were mildly impaired on the complex-planning condition (mean *z*-score = 2.52), but their difference score on the simpler planning condition compared to complex planning condition did not quite attain significance. Thus, it will be important in the future to study more patients with mild apathy to better characterize early behavioral changes. Additionally, I studied participants with mild ND (defined by MMSE score), and it would be valuable to extend assessment to participants with greater cognitive impairments. It would also be important to follow participants longitudinally to see if apathetic profiles are maintained throughout the duration of disease (see Aim 3, Chapter 4). I studied apathy in bvFTD particularly because it is very common in this condition; these patients do not have physical limitations that can confound the quantitative assessment of reduced GDB, and there are no language or visuospatial deficits that can potentially limit the interpretation of impaired performance. Nevertheless, it is important to investigate GDB in apathetic participants with other ND, like AD or PD, who also display apathy.

Areas for Further Research

This dissertation research study found that three distinct mechanisms, related to impairments in GDB, likely contribute to subtypes of apathy in bvFTD. As previously described, conceptualizing distinct subtypes of apathy may benefit the development of interventions tailored to mediate each compromised mechanism, but I must first understand the natural history of these impairments and the biological and environmental factors that influence the rate of their decline. The identification of factors that moderate

the clinical expression of disease, in this case apathy, is an important consideration for identifying persons "at risk" for more rapid decline and optimizing interventions for all persons with apathy associated with ND. Thus, my next research projects will examine how GDB impairments in apathetic bvFTD patients worsen over time (Aim 3, see Chapter 4). I plan to identify the influence of cognitive reserve factors such as environmental, genetic and anatomic influence on the rate of change in GDB impairments in apathetic persons with bvFTD. This will help me gain a better understanding of reserve mechanisms and their relationship to apathy, to determine who may be "at risk" for faster decline. With support from my Ruth L. Kirschstein National Research Service Award for Individual Postdoctoral Fellowships (F32; see Appendix B), this work will fill a crucial gap and will be used to develop treatment strategies and evaluate the effectiveness of tailored interventions.

A number of participants (40%) were impaired on multiple components of GDB. Compared to individuals displaying a multicomponent subtype of apathy, those with a single GDB deficit did not differ by age, disease duration, MMSE or NPI FxS score (all $p > .05$), suggesting that I cannot easily attribute variations in apathetic difficulty to variability in the underlying disease process, but instead can relate them, in part, to anatomical distribution of disease. Additional work is needed to confirm this with larger groups of participants.

A questionnaire instrument that measures each component of GDB, quantified by the PACT, may provide further validation for my hypothesized GDB model. As previously described, beyond confirming the presence of apathy, current instruments such as the NPI are ineffective in identifying different subtypes of apathy (Chow et al., 2009).

In fact, I did not find correlations between PACT scores (individual or composite) with either NPI caregiver-distress scores or NPI FxS apathy scores. This lack of finding provides support for the notion that the NPI assesses global apathy whereas the PACT assesses component of GDB that contribute to apathy.

A necessary step is the development of an instrument that is based on my empirical measurements of impaired GDB. This type of instrument would increase the likelihood of detection and treatment of subtypes of apathy and, being specific to each component of GDB, may invite less respondent bias than do existing more general measures. Other instrumentation such as neuropsychological measures may also provide validation for my hypothesized model. I did not find significant correlations between the neuropsychological data available for my study and initiation and motivation measures from the PACT. This may be due, in part, to the lack of specificity for initiation and motivation constructs in currently available measures.

I did observe some overlap across behavioral and neuroanatomical measures. For example, my grey matter observations suggested that the ACC may contribute to both initiation and motivation. In fact, post hoc correlation analyses of PACT measures revealed a significant correlation between initiation and motivation performance (rho = .78; $p < .001$). Post hoc correlations, however, are not significant between other PACT measures (all $p > .05$ Bonferroni corrected) and I otherwise observed distinct neuroanatomical regions contributing to components of GDB. It will be important for future work to identify quantitative measures of initiation and motivation that are not interdependent.

This study investigated the neural basis for apathy from a structural neuroanatomical viewpoint. Although voxel-based morphometry is the most commonly used approach to examine the anatomical basis of behavioral syndromes in ND, the measurement of brain activation using functional neuroimaging (fMRI) may be a complementary way of validating and increasing understanding of the GDB model. My findings suggest that GDB is supported by a large-scale neural network in distinct specific portions of the prefrontal cortex. A functional investigation of apathy may provide additional information regarding how each process of GDB interacts with another. Other technologies that measure function such as transcranial magnetic stimulation or actigraphy may be helpful in confirming the interaction of GDB processes. This can be done by examining distinctive patterns of cortical excitability or locomotive activity. In sum, apathy is a complex behavioral syndrome and multimodal methods should be adopted in future research to provide insight into the dynamic interrelationships between structure and function (Carey & Seitz, 2007).

Conclusion

GDB is a multicomponent process that involves initiation, planning, and motivation. These three GDB processes map onto three distinct brain regions that work together in a large-scale neural network. This network captures the information from internal and external environments needed for GDBs. Each frontal region is functionally separate in supporting initiation, planning, and motivation, but interacts with the others to mediate overall GDB. A specific GDB process suffers when one of these frontal areas is compromised, and is associated with behavior currently referenced as apathy. Presently, apathy is viewed as a unitary concept. This research has supported the view that apathy is a

multicomponent phenomenon—a complex behavioral syndrome that emerges when there is dysfunction in any GDB component. Thus, it is likely that the pathophysiology is not a single mechanism, but rather multifaceted, depending on which specific GDB process is impaired. Furthermore, it is possible to identify single impairments in GDB that may contribute to different clinical profiles or subtypes of apathy. GDB allows people to be independent in everyday task performance. This work will change the paradigm for assessing and treating apathy, leading to improved diagnostic accuracy and effective interventions to improve the ability of families, nurses, and other health professionals to manage a pervasive feature of ND.

APPENDIX A: NEUROPSYCHIATRIC INVENTORY APATHY SUBSCALE

How emotionally distressful is this behavior to the family? 0 - not at all 1 - minimally 2 - mildly 3 - moderately 4 - severely 5 – extremely

Section 5: Apathy/ Indifference - Has your family member lost interest in the world around him or her? Has your family member lost interest in doing things or lacks the motivation to start new activities? Is your family member more difficult to engage in conversation or in doing chores? Has your family member become rather apathetic or indifferent?

		How Often Do These Behaviors Occur				
9 please check (ɪ) the box if apathy *is not* present and go to the next section		occasionally (1) (less once/ week)	often (2) (about once/ week)	frequently (3) (several times/ week, less than every day	very frequently (4) (once or more per day)	
1.	Does the patient seem less spontaneous and less active than usual?	____	____	____	____	
2.	Is the patient less likely to initiate a conversation?	____	____	____	____	
3.	Is the patient less affectionate or lacking in emotions when compared to his/ her usual self?	____	____	____	____	
4.	Does the patient contribute less to household chores?	____	____	____	____	
5.	Does the patient seem less interested in the activities and plans of others?	____	____	____	____	
6.	Has the patient lost interest in friends and family members?	____	____	____	____	
7.	Is the patient less enthusiastic about his/her usual interests?	____	____	____	____	
8.	Does the patient show any other signs that he/she doesn't care about doing new things?	____	____	____	____	/32

Apathy/ Indifference: Please rate the severity of these problems

____ 1. Mild - apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.

____ 2. Moderate - apathy is very evident; may be overcome by the care giver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.

____ 3. Marked - apathy is very evident and usually fails to respond to any encouragement or external events. ____**total score**

APPENDIX B: NOTICE OF GRANT AWARD

Notice of Research Fellowship Award

NATIONAL RESEARCH SERVICE AWARD **Issue Date:** 09/26/2013
Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF NURSING RESEARCH

Grant Number: 1F32NR014777-01

Principal Investigator(s):
Lauren M Massimo, MSN

Project Title: The Neural Basis of Apathy in Frontotemporal Degeneration: A Longitudinal Study

Mr. Itinger, Jerome R
The Pennsylvania State University
110 Technology Center Building
university park, PA 168027000

Award e-mailed to: osp@psu.edu

Latest Activation Date: 03/28/2014

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $49,814 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to PENNSYLVANIA STATE UNIVERSITY-UNIV PARK in support of the above referenced project. This award is pursuant to the authority of 42 USC 288 42 CFR 66 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Nursing Research of the National Institutes of Health under Award Number F32NR014777. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with 42 CFR Part 50 Subpart F. Subsequent to the compliance date of the 2011 revised FCOI regulation (i.e., on or before August 24, 2012), Awardees must be in compliance with all aspects of the 2011 revised regulation; until then, Awardees must comply with the 1995 regulation. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Kelli Oster

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