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Prosocial Behavior and Neurodegenerative Disease

by

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Abstract

Prosocial Behavior and Neurodegenerative Disease

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Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterized by progressive and dramatic changes in behavior and emotional responses. In particular, patients with bvFTD have deficits in empathy, including the ability to relate and respond to the emotions of others. These deficits are important precursors for prosocial behaviors – actions intended to benefit people other than oneself – and were thus hypothesized to be impaired in patients with bvFTD. Thus far, no known studies have utilized objective laboratory tests to examine patients' prosocial behaviors. The present study addressed these gaps by using objective laboratory measures (i.e., a donation paradigm) and a multi-method approach by studying the neural and emotional responses (i.e., autonomic and somatic peripheral physiology, facial expressions) associated with prosocial behavior across a sample of patients with neurodegenerative diseases and non-symptomatic aging caregivers. In the present study, 88 participants (17 with bvFTD, 12 with Alzheimer's disease, and 59 non-symptomatic caregivers) viewed a film of others in distress. Participants were then given the option to donate their own money as a measure of prosocial behavior. Results revealed that patients with bvFTD donated significantly less money than non-symptomatic caregivers, while patients with Alzheimer's disease and non-symptomatic caregivers donated comparable amounts. When examining emotional responses and regions of neural degeneration as potential mediators of the relationship between diagnosis and prosocial behavior, neither emotional responses nor neural regions were found to mediate the findings with one exception: lower ventral striatum volume was significantly associated with lower levels of prosocial behavior. This finding aligns with research that suggests that the ventral striatum plays a central role in the reward network of the brain, and how evolutionarily, feeling reward when engaging in prosocial behaviors likely conferred benefits in the context of interpersonal relationships. The study extends our understanding of a neurodegenerative disease that profoundly impacts the lives of patients and their families and contributes important new information to the literature on prosocial behavior.

Prosocial Behavior and Neurodegenerative Disease

The philosopher Hobbes described life as “nasty, brutish, and short,” but despite this we still find people helping one another every day. These helping, or prosocial, behaviors—actions intended to benefit people other than oneself (Batson & Powell, 2003; Batson, 1998)—are an essential component of successful and meaningful social interactions. For example, prosocial behaviors shown by teachers can lead students to develop into more educated, informed, and helpful citizens, and prosocial acts by world leaders such as Mahatma Gandhi, Nelson Mandela, and Thich Nhat Hanh can lead to social justice, equality, and freedom. Responsiveness to the distress of others and the ability to mobilize helping behaviors is thus socially valued, and can have far-reaching consequences on individuals’ social lives, long-term relationships, and well-being.

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterized by a progressive change in social behavior, personality, and emotional responses, with one of the core deficits being a lack of empathy (Neary et al., 1998; Rascovsky et al., 2011). In particular, research has indicated that patients with bvFTD show diminished care and warmth towards others (Hsieh, Irish, Daveson, Hodges, & Piguet, 2013; Rankin et al., 2006; Rankin, Kramer, & Miller, 2005) and have trouble responding appropriately to the emotions of others (Eckart, Sturm, Miller, & Levenson, 2012). Although no research to our knowledge has examined prosocial behavior in patients with bvFTD, deficits are hypothesized because the capacity to be empathic and respond to the emotions of another is an important precursor for engaging in helping behaviors. This dissertation examined how prosocial behavior is affected by neurodegenerative disease, and examined the emotional responses and neural regions that may mediate these hypothesized deficits.

In the sections to follow, the measurement of prosocial behavior is discussed, followed by what we currently know about the neural, physiological, and facial behavioral underpinnings of prosocial behavior. Our current understanding of the lifespan development of prosocial behavior, included in both healthy aging and neurodegenerative disease, is also reviewed. Finally, an outline of the present study, including the gaps in the literature that it aimed to address, is presented.

Prosocial Behavior – Measurement

Prosocial behavior is a term that encompasses behaviors in which one person responds to the needs of another instrumentally (e.g., with money or time) or emotionally (e.g., providing comfort or sympathy; Batson & Powell, 2003; Dunfield, Kuhlmeier, O’Connell, & Kelley, 2011). The motivation behind the action is often unspecified, meaning that it can be altruistic, selfish, or both (Eisenberg, 1982). Laboratory research has often examined prosocial behavior by measuring how much someone is willing to donate their time or money to help another. For example, prosocial behavior in children has often been measured by their willingness to point to the location of a dropped item, or to help an experimenter pick up a dropped item (Sommerville, Schmidt, Yun, & Burns, 2013; Warneken, Hare, Melis, Hanus, & Tomasello, 2007; Warneken & Tomasello, 2007). Some studies have examined children’s willingness to give up recess time or donate money to someone in distress (Eisenberg et al., 1989). In adults, prosocial behaviors are often measured through self-reported measures, such as daily accounts of helping behaviors (Hein, Silani, Preuschoff, Batson, & Singer, 2010; Rameson, Morelli, & Lieberman, 2012) or reported willingness to donate time and money to help someone (Mathur, Harada, Lipke, & Chiao, 2010). Other studies have directly examined prosocial behaviors by asking participants to

view images, films, or stories about people in distress and then examining the amount of money participants were willing to donate as the behavioral outcome (Moll et al., 2006; Sze, Gyurak, Goodkind, & Levenson, 2012; Twenge, Baumeister, DeWall, Ciarocco, & Bartels, 2007). Economic fairness tasks such as the Dictator Game, where a participant is given money and then the option to share some (if any) of that money with another participant, have also been used in imaging studies to examine prosocial behavior and affiliated behaviors such as cooperation and fairness (Harbaugh, Mayr, & Burghart, 2007; Rilling et al., 2002; Zaki & Mitchell, 2011).

Physiological Underpinnings of Prosocial Behavior

Neural Underpinnings

The brain consists of multiple neural networks, which connect different neural regions to each other to enable the sharing and integration of information. For example, the so-called “salience network” links the orbital frontoinsula and anterior cingulate cortices to subcortical and limbic structures (Seeley, Allman, et al., 2007; Seeley, Menon, et al., 2007). This network is activated in response to emotionally salient stimuli, such as when one needs to recognize and respond to the emotions of another (Seeley, Menon, et al., 2007; Seeley, Zhou, & Kim, 2012). The salience network is of particular relevance to the focus here—namely, prosocial behavior—because of its critical role in processing personally salient emotional information. Our survey of the literature focuses on particular regions comprising the salience network rather than the network itself because most past research examining prosocial behavior has taken a modular approach (i.e., examining specific brain regions rather than the connections between regions); research examining neural network connectivity (using functional connectivity magnetic resonance imaging) and prosocial behavior is scarce.

Frontal regions. The orbital frontal and lateral frontal regions have been found in past research to be crucial to our ability to experience empathy and engage in prosocial behavior. In a study comparing participants who were required to make a charitable donation with those who could volunteer a charitable donation, the latter group showed the greatest activation in the ventromedial PFC, which includes the anterior cingulate and medial orbitofrontal cortex (OFC; Hare, Camerer, Knoepfle, O'Doherty, & Rangel, 2010). This association of the OFC with prosocial behavior is not surprising given that the OFC is activated in facial and vocal emotion recognition (Adolphs et al., 1999; Decety & Jackson, 2004; Eslinger, 1998; Hornak et al., 2003; Kipps, Nestor, Acosta-Cabrero, Arnold, & Hodges, 2009); when people respond appropriately in social contexts (Beer, John, Scabini, & Knight, 2006); and in understanding how another person is feeling (Decety & Jackson, 2004; Eslinger, 1998; Hornak et al., 2003; Hynes, Baird, & Grafton, 2006; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). The OFC plays a role in evaluating external stimuli as positive or negative (Davidson, 2004) and uses this information to produce beneficial outcomes (Beer et al., 2006; Decety & Jackson, 2004; Schoenbaum, Takahashi, Liu, & McDannald, 2011). From a social standpoint, a beneficial outcome in this context would encompass prosocial behaviors because they help build strong social bonds.

The medial PFC region, which includes the subgenual cingulate, is activated when people choose to donate charitably, but not when they refrain from doing so or receive a monetary reward (Moll et al., 2006). Activation of the dorsal medial PFC has also been found to be a reliable predictor of which participants would later donate money, or spend the most time completing a cognitive task to help another (Waytz, Zaki, & Mitchell, 2012). Research using high-frequency transcranial magnetic stimulation to stimulate the dorsal lateral PFC (dlPFC) has also found this intervention to increase participants' self-reported decisions to act in prosocial

ways (Balconi & Canavesio, 2014).

Medial regions. Medial neural regions consist of the anterior insula, anterior cingulate, and frontal pole (Rosen, Gorno-Tempini, et al., 2002; Schroeter, Raczka, Neumann, & Von Cramon, 2008; Seeley et al., 2012). Both the anterior insula and the anterior cingulate are crucial for processing emotion because they integrate information from other regions associated with subjective experience and visceral sensations (Craig, 2009; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). As such, both regions play an important role in our ability to experience and respond to the emotions of others (Jabbi, Swart, & Keysers, 2007; Jackson, Brunet, Meltzoff, & Decety, 2006; Wicker et al., 2003), which are integral to prosocial behavior. Greater anterior insula activity has been associated with a greater reported willingness to alleviate a rival's physical pain (Hein et al., 2010) and cooperative behavior (King-Casas et al., 2008), including the willingness to donate time and money to helping ingroup members (Mathur et al., 2010). Along with the medial PFC, activity in the anterior insula has been associated with participants sending more prosocial or comforting emails to a person being socially rejected (Masten, Morelli, & Eisenberger, 2011), as well as with the reported frequency with which people help friends in their daily life (Rameson et al., 2012). These medial regions also appear to be important for experiencing the emotions of another (Jabbi, Swart, & Keysers, 2007). In conjunction with temporal cortex regions, the medial regions have also been associated with empathic responses (Singer et al., 2004; Singer et al., 2006), prosocial and cooperative behavior (Harbaugh et al., 2007; King-Casas et al., 2008; Tankersley, Stowe, & Huettel, 2007), and the ability to shift attention away from oneself in order to attend to others (Saxe & Kanwisher, 2003). Notably, the medial regions of the PFC also contain von Economo neurons (VENs), which reside in layer V of the anterior insula and anterior cingulate. These large cells which have extensive axons that extend into multiple neural regions, are hypothesized to play a role in our ability to build social bonds (Allman et al., 2010), and have thus far only been found in highly social non-human animals such as apes and elephants that need to process and integrate social, cultural, and emotional information the way humans do.

Subcortical. Areas of the striatum (which consists of the caudate, putamen, and nucleus accumbens/ventral striatum) have also been associated with greater prosocial behavior. Research has found these areas to be activated when people provide support to loved ones receiving small electric shocks (Inagaki & Eisenberger, 2012) and when they complete economic fairness tasks such as the Dictator Game, where a participant is given the option to share money with another (Harbaugh et al., 2007; Rilling et al., 2002; Zaki & Mitchell, 2011). Similarly, increased nucleus accumbens activation has been found to occur immediately before people make charitable donations, with levels of activation being positively linked to the amount of money donated. This association not found for the insula and amygdala (Genevsky, Västfjäll, Slovic, & Knutson, 2013). Additionally, when comparing neural activity in participants who were either volunteering to donate charitably or required to donate charitably, volunteering to donate charitably was associated with greater activation in the ventral striatum and the vmPFC (Harbaugh et al., 2007; Moll et al., 2006), suggesting that subcortical and cortical structures both play an important role in prosocial behavior. Given the central role the nucleus accumbens plays in the reward network of the brain (Haber & Knutson, 2010), this link between prosocial behavior and the ventral striatum suggests that people may find prosocial acts to be a rewarding experience.

Limitations. Research on the neural correlates of prosocial behavior has elucidated the regions of the brain associated with this behavior in young adults. However, no studies to date

have examined neural correlates of prosocial behavior in older adults, limiting the generalizability of these findings. Furthermore, most studies rely on self-report measures, such as asking people to state how often or how likely they are to help someone (Hein et al., 2010; Mathur et al., 2010; Morelli et al., 2014; Rameson et al., 2012), or to report how prosocial someone appears as they provide a stranger with comfort (Masten et al., 2011). Although helpful, self-report measures can be prone to bias or social desirability effects (Arnold & Feldman, 1981; Paulhus & Reid, 1991; Van de Mortel, 2008). This may especially be the case with prosocial behavior (which is by definition socially desirable), and thus could benefit from being examined using objective, behavioral measures.

Autonomic and Somatic Underpinnings

Autonomic physiological responses play an integral role in our emotional experiences, as they communicate information from our viscera and help coordinate behaviors that allow us to express how we feel (Levenson, 2003, 2014). Research examining autonomic nervous system correlates of prosocial behavior has largely focused on heart rate acceleration and deceleration. Specifically, researchers tended to examine whether the average heart rate during the most intense periods of sadness emotion-induction tasks differed from the average heart rate at the beginning of the task. Because heart rate can be influenced by many factors, such as attention and orienting (Bradley, 2009; Libby, Lacey, & Lacey, 1973), and motor activity (Obrist, Webb, Sutterer, & Howard, 1970), it is not surprising that the relationships observed between heart rate acceleration/deceleration and prosocial behaviors are mixed. For example, when responding to a sadness film, preschool children who had higher heart rates throughout the film and greater heart rate deceleration during the most intense point in the film were also the children who displayed the most prosocial behaviors later when they were given the opportunity to help someone (Zahn-Waxler, Cole, Welsh, & Fox, 1995), a finding that has been replicated in different samples of children (Eisenberg et al., 1989; Eisenberg et al., 1988) and adults (Barraza, Alexander, Beavin, Terris, & Zak, 2015; Eisenberg et al., 1989). These findings suggest that heart rate deceleration when seeing another person in distress may be an important indicator of whether someone will engage in prosocial behavior later. This pattern is theorized to result from empathy being an “other-oriented” emotion where one needs to gather and attend to external information about another (Eisenberg et al., 1988), as such behaviors have been associated with heart rate deceleration (Cacioppo & Sandman, 1978; Lacey, Kagan, Lacey, & Moss, 1963). Furthermore, heart rate deceleration is regulated by the vagus nerve, which has been linked to prosocial behavior (Barraza et al., 2015; Miller, Kahle, & Hastings, 2015) and other affiliative behaviors such as compassion (Stellar, Cohen, Oveis, & Keltner, 2015).

In contrast, other research has found that patterns of heart rate acceleration may be associated with the recognition that someone is clearly in need of immediate help, likely because the body is preparing to take action (Gaertner & Dovidio, 1977; Sterling & Gaertner, 1984). Similarly, one of the few studies to examine prosocial behavior in aging adults found that greater cardiac activity, a measure created by averaging multiple measures of heart rate, was associated with older adults being more likely to take action and donate charitably to people in need (Sze et al., 2012). Although the direction of these findings on heart rate acceleration/deceleration have been somewhat mixed, generally speaking, heart rate reactivity has been found to be linked with prosocial behaviors and affiliative tendencies important for prosocial behavior, such as feeling sympathy and distress (Eisenberg et al., 1990; Eisenberg et al., 1989; Eisenberg & Miller, 1987; Fabes, Eisenberg, & Eisenbud, 1993), trait empathy (Eisenberg et al., 1988), and attending to

others (Batson, 1987; Eisenberg & Fabes, 1990; Eisenberg, Fabes, Schaller, Carlo, & Miller, 1991).

Facial Expressions

Facial expressions are an essential method of communication between conspecifics. For prosocial behavior, it may be particularly relevant, as facial expressions can signal that help is needed, or that care will be provided. Research examining facial correlates of prosocial behavior is scarce however, and the few extant studies have focused primarily on children. Several studies have found that children who display sadness behaviors (i.e., upturned eyebrows, downturned lip corners) or empathic concern/interest-worry (i.e., eyebrows lowered and drawn towards each other, eyes squinted or widened, mouths sometimes opened) (Eisenberg et al., 1989; Eisenberg et al., 1988; Fink, Heathers, & de Rosnay, 2015) when viewing another person in distress are more likely to engage in prosocial behavior (Eisenberg et al., 1989) and to report higher levels of sympathy (Eisenberg et al., 1988). Interestingly, previously mentioned research that used high frequency (10Hz) rTMS to stimulate the dorsal lateral PFC (dlPFC) reported that this stimulation led to greater engagement in prosocial behavior, and that this intervention was associated with increased zygomaticus (i.e., AU6 or smiling) and corrugator (i.e., AU4 or brow furrowing) activity, suggesting that greater facial activity and facial mimicry may be correlated with making prosocial decisions (Balconi & Canavesio, 2014).

Prosocial Behavior Change in Healthy Aging

Many theorists have suggested that prosocial behavior is an evolutionarily inherited trait present from early infancy (Hamlin, Wynn, & Bloom, 2007; Preston & De Waal, 2002; Warneken & Tomasello, 2007). In the past, the idea of prosocial behavior having phylogenetic origins in our primate ancestors was quite controversial. For example, researchers originally thought that chimpanzees were incapable of altruism, because observational studies found time and again that chimps would not move a tray of food towards a conspecific if doing so did not personally benefit them (Jensen, Hare, Call, & Tomasello, 2006; Vonk et al., 2008). However, more recent research has noted that in many of those studies the conspecific did not signal the need for assistance (e.g., by displaying a struggle to reach the food). Without that incentive, chimps may not have recognized the need to take action. Using food may also bias behaviors, as chimps are particularly competitive about food. Indeed, when an unfamiliar experimenter or a genetically unrelated conspecific exhibits the need for assistance when reaching for an object, young wild-born chimps do engage in prosocial behaviors, regardless of whether or not they receive a reward for doing so (Warneken et al., 2007). Similarly, when given the option of a large reward that is paired with a conspecific being shocked or a small reward that brings no shock, the majority of chimps act in a prosocial manner by preferring the small reward. These prosocial behaviors increase if the chimps themselves experience the shock or are familiar with the conspecific being shocked (Preston & De Waal, 2002). Prosocial behavior has also been found in other species, such as rats and pigeons (Bartal, Decety, & Mason, 2011; Church, 1959; Watanabe & Ono, 1986), with theorists suggesting that this behavior came from maternal caregiving. Theorists also believe this behavior was selected for in evolution because being attuned to the emotions of conspecifics and recognizing which conspecifics are helpful likely conveyed a fitness benefit (De Waal, 2012; Hamlin et al., 2007; Preston & De Waal, 2002).

Prosociality has also been found in young infant humans. At 6-10 months old, infants are more likely to prefer animated objects that helped rather than hindered a climber in a previously viewed film (Hamlin et al., 2007). Similarly, 12-month old infants appear to cry in sympathy

when another infant cries (Decety & Jackson, 2004; Eisenberg, Fabes, & Spinrad, 1998; Radke-Yarrow, Zahn-Waxler, & Chapman, 1983), and by 14 months, infants will spontaneously help others (e.g., open a cabinet for an experimenter whose hands are full) and offer experimenters with helpful information (e.g., pointing to a dropped object) even without being signaled or rewarded for doing so (Warneken et al., 2007; Warneken & Tomasello, 2006, 2007). Thus, recognizing the needs of others, along with spontaneous cooperative and prosocial behaviors, appears early in infancy (Brownell & Carriger, 1990; Eckerman & Whitehead, 1999).

Although present in infancy, empathy also increases with age through learning, and appears to align with age-specific goals. For example, although young adulthood is often focused on career building, it is also a time when many adults begin building their families and caring for children (Havighurst, 1948). As individuals enter middle age and late life, many become increasingly concerned with generativity, or the desire to guide and provide for the welfare of future generations (Erikson, Erikson, & Kivnick, 1986). Generativity is often expressed through parenting and grandparenting, as such roles lead many to focus on future generations and the world their grandchildren will inherit. Older adults are also likely to be involved in providing care for significant others, including spouses and children (Alliance, 2001; Medicine, 2008) and are more likely than their younger counterparts to provide assistance to strangers in need (Midlarsky & Hannah, 1989; Sze et al., 2012). Interestingly, when compared to young and middle-aged adults, older adults are also more likely to donate charitably even when controlling for factors such as socioeconomic status, income, and trait empathy (Beadle, Sheehan, Dahlben, & Gutchess, 2015; Sze et al., 2012). Thus, the present literature suggests that prosocial behavior and empathy increase with age. Very little research however, has examined whether prosocial behavior changes with abnormal aging (e.g., aging adults with neurodegenerative diseases, or physical illnesses).

Prosocial Behavior and Neurodegenerative Disease

Behavioral variant Frontotemporal Dementia

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterized by progressive, dramatic changes in social behavior, personality, and emotional responses but relative preservation of many cognitive abilities (e.g., memory, visuospatial abilities; Snowden, Neary, & Mann, 2002). Of particular relevance to the focus of this proposal on prosocial behavior are the deficits in empathy characterizing this disease, including the ability to relate and respond to the emotions of others (Neary et al., 1998; Rascovsky et al., 2011). Such deficits often have a devastating effect on close loved ones in the affected person's life, as they impair the patient's ability to express social warmth and maintain meaningful social relationships, increasing the feelings of loneliness, frustration, and sadness experienced by caregiving spouses and other loved ones. Below, the known empathic deficits found in patients with bvFTD are discussed, and how these deficits may be relevant to our hypothesis that patients with bvFTD will exhibit deficits in prosocial behavior is explained. These deficits will then be compared to another group of patients (those with Alzheimer's disease) to examine whether any observed deficits in prosocial behavior among patients with bvFTD are specific to the disease or reflect neurodegenerative conditions more broadly.

Past research on empathic deficits in bvFTD has focused primarily on patients' ability to recognize the emotions of others. Patients with bvFTD have been found to struggle with recognizing emotions (Goodkind et al., 2015; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; Lough et al., 2006; Rosen, Perry, et al., 2002; Werner et al., 2007), even when stimuli are

presented with more context to aid recognition (Goodkind et al., 2015; Kipps et al., 2009; Lough et al., 2006; Werner et al., 2007). Less research has been conducted to examine patients' deficits in their ability to generate and respond to the emotions of others. Studies examining caregiver reports of patients' abilities to relate to and care about how others feel have found that patients have diminished responses (Lough et al., 2006; Rankin et al., 2005). These findings have been supported by laboratory assessments which have revealed diminished disgust and self-conscious responses in patients with bvFTD (Eckart et al., 2012; Sturm, 2006; Sturm, Ascher, Miller, & Levenson, 2008), and align with caregiver reports that patients with bvFTD become increasingly apathetic; most patients care less about others and show diminished motivation for goal-directed behavior (Merrilees et al., 2013; Quaranta, Marra, Rossi, Gainotti, & Masullo, 2012). These deficits across multiple areas of empathy are not surprising given the pattern of neurodegeneration that characterizes bvFTD.

Early stages of degeneration in bvFTD tend to begin focally in medial regions of the brain such as the anterior cingulate, frontoinsula cortex, medial PFC, and striatum (Rosen, Gorno-Tempini, et al., 2002; Schroeter et al., 2008; Seeley et al., 2012). As discussed earlier, these neural regions are important for recognizing and understanding the emotions of others (Botvinick et al., 2005; Jabbi et al., 2007; Jackson et al., 2006; Jackson, Meltzoff, & Decety, 2005; Mathur et al., 2010; Singer, 2006; Singer et al., 2004; Singer et al., 2006), and for engaging in prosocial behavior (Hein et al., 2010; Mathur et al., 2010; Morelli, Rameson, & Lieberman, 2014; Rameson et al., 2012). Also mentioned previously, Von Economo neurons (VENs), which are important for integrating social and emotional information, are particularly vulnerable to loss in patients with bvFTD (Kim et al., 2012; Seeley et al., 2006). As bvFTD progresses, neural degeneration spreads medially into frontal regions, such as the orbital and dorsolateral frontal regions (Seeley, 2008; Seeley et al., 2012) and subcortically into regions such as the septal area (Broe et al., 2003; Rosen, Gorno-Tempini, et al., 2002; Schroeter et al., 2008; Seeley et al., 2012), targeting more regions of the brain that are crucial for the ability to experience empathy and engage in prosocial behaviors.

Alzheimer's Disease

To examine whether possible deficits of prosocial behavior in patients with bvFTD are specific to the patterns of neural degeneration in this disease, patients with bvFTD were compared to patients with Alzheimer's disease, in whom there is also neurodegeneration but in areas primarily outside of the salience network. Specifically, patients with AD show degeneration in the "default mode network," which consists of medial temporal structures such as the hippocampus, posterior cingulate, precuneus, and lateral parietal regions important for forming and recalling memories (Seeley, Allman, et al., 2007). From a behavioral standpoint, AD patients typically have cognitive problems such as memory loss (McKhann et al., 1984), but otherwise present as warm, socially appropriate people (Sturm et al., 2010; Zhou et al., 2010) who do not show significant impairments in the ability to recognize (Kipps et al., 2009) or feel what others feel (Rankin et al., 2006). Indeed, recent research suggests that patients with AD may report experiencing even higher levels of distress in social situations than healthy controls (Sturm et al., 2013). The present study compared patients with bvFTD and AD to non-symptomatic caregivers.

Neurodegenerative Disease as a Model for Studying Prosocial Behavior

Studying neural correlates of behavior can be achieved through multiple methods. Many studies examining the neural correlates of prosocial behavior in healthy young adults utilize

functional magnetic resonance imaging (fMRI), a technique that uses change in blood flow to measure neural activity while participants view films or complete tasks as they lie in a scanner. This approach has allowed researchers to deepen our understanding of neuroanatomy and map the neural regions involved across a variety of cognitive and emotion tasks. However, this methodology has limitations. Using fMRI provides information about the neural regions recruited for, but perhaps not essential to, completing a prosocial task. Furthermore, fMRI approaches are often constrained by less effective emotion-eliciting stimuli, as fMRI scanners are loud and people must lie still in a confined space. If a powerful emotion were to be induced, the facial and perhaps physical movements generated by the emotion would lead to signal artifacts (Levenson, Sturm, & Haase, 2014).

The neurodegenerative disease approach can also be effective for studying neural correlates of behavior. Patients with neurodegenerative disease have known regions or circuits of neural damage, and correlating neural damage to behavioral symptoms allows researchers to conduct laboratory studies that are not constrained by technology or motion artifact restrictions. Although patients can have significantly different levels of cognitive functioning that need to be controlled for, and this method cannot capture the temporal dynamics of brain-behavior relationships, it enables researchers to elicit and investigate emotion in a more ecologically valid manner. Allowing patients to respond naturally and complete a wider range of tasks can lead to important insights that track more closely with patients' everyday behaviors. This in turn, can improve our understanding of patient symptoms and deficits. In using the neurodegenerative disease approach, the study aimed to identify the neural regions that are essential for prosocial behavior through the use of a strong emotion induction in a controlled laboratory setting. The physiological responses and behaviors expressed by patients in this more naturalistic setting were then examined as mediators of the relationship between patient diagnosis and prosocial behavior. Patients with bvFTD are particularly ideal candidates for this test as there are clear overlaps between the neural regions associated with prosocial behaviors and those specifically affected by the disease.

The Present Study

Although interest and research in prosocial behavior has increased dramatically in the past decade (Zaki & Ochsner, 2012), there are still gaps in our understanding of the neural, physiological, and facial behavioral correlates of prosocial behavior. The developmental literature has used multi-modal approaches by assessing both self-reported and behavioral measures of prosocial behavior (e.g., Eisenberg et al., 1989; Warneken et al., 2007; Warneken & Tomasello, 2007), but few developmental studies have examined the neural correlates underlying these behaviors. Neural correlates of prosocial behavior have been studied in young adults, but limitations in the adult literature stem from the reliance on self-reported prosocial behavior (Hein et al., 2010; Mathur et al., 2010; Morelli et al., 2014; Rameson et al., 2012). Very few studies with adults have examined prosocial behavior directly with behavioral measures. The present study addressed these gaps by examining the neural correlates associated with a direct and objective measure of prosocial behavior.

Another major limitation of the research in prosocial behavior is that most of the existing studies focus exclusively on young adults or children (Eisenberg et al., 1989; Eisenberg et al., 1988; Genevsky et al., 2013; Morelli et al., 2014; Waytz et al., 2012; Zaki, Davis, & Ochsner, 2012), leaving open the question of whether these findings generalize across the lifespan and in abnormal aging. Some research has found that older adults are more likely to show prosocial

behaviors than young or middle-aged adults, and have theorized that these changes occur due to age-related changes in goals and motivations (Beadle et al., 2015; Sze et al., 2012). In patients with neurodegenerative disease, no known studies have utilized objective laboratory tests to examine patients' prosocial behaviors or the neural correlates associated with these behaviors. Deficits are hypothesized for patients with bvFTD, because the ability to share and respond to the emotions of others—i.e., empathy, a capacity in which this patient group has shown deficits—are important precursors for engaging in helping behaviors (Batson, 1987; Decety & Jackson, 2004; Eisenberg & Miller, 1987). The present study addressed these gaps by using objective laboratory measures (i.e., a donation paradigm) and a multi-method approach by studying the neural, peripheral physiological, and facial correlates of prosocial behavior across a sample of patients with neurodegenerative diseases and non-symptomatic aging caregivers.

Understanding the brain regions important for prosocial behavior will allow us to both better understand the emotional impairments patients with bvFTD suffer and shed light on the neural mechanisms that enable us to be caring, prosocial people. Increasing our understanding of bvFTD and AD also have broader implications for clinicians, as it would allow medical providers to give caregivers more information about their loved one's deficits and strengths, and the tools they may need to manage them.

Methods

Participants

82 participants (15 with bvFTD, 10 with Alzheimer's disease, and 57 non-symptomatic caregivers) were recruited from the Memory and Aging Center at UC San Francisco. All patients with neurodegenerative disease underwent standard neurological and psychological assessments in which information on cognitive, behavioral, and emotional symptoms were collected. Patients were diagnosed based on their neuropsychological assessment results in conjunction with neuroimaging data collected from structural MRI scans. For patients to meet the diagnostic criteria for bvFTD they needed to display three of the six potential behavioral or cognitive symptoms (i.e. behavioral disinhibition, apathy, loss of sympathy, hyperorality, stereotyped behaviors, and executive dysfunction with spared memory and visuospatial abilities; Neary et al., 1998; Rascovsky et al., 2011). To meet the diagnostic criteria for Alzheimer's disease, patients must have displayed significant memory and cognitive impairments (McKhann et al., 1984). Non-symptomatic caregivers were comparable to patients in socioeconomic status, age, race, and sex, making them an ideal control group. Because caregivers can experience negative outcomes as a result of caregiving burden, we limited our sample to caregivers who reported minimal to no symptoms of depression and anxiety [Center for Epidemiologic Studies – Depression scale (CES-D) score <15 and Beck Anxiety Inventory (BAI) < 9]. Non-symptomatic caregivers did not have structural scans collected.

In terms of ethnicity, 63% of participants were Caucasian, 24% African American, 5% Asian American, 2% Hispanic, 6% Other. Participants reported their annual income using the following income brackets (0= "unsure"; 1= <\$20,000, 2= \$20,001-\$35,000; 3=\$35,001 - \$50,000; 4=\$50,001-\$75,000; 5=\$75,001-\$100,000; 6=\$100,001-\$150,000; 7=<\$150,000), but no significant income differences were revealed. All participants were paid \$30 in addition to any transportation costs they incurred. See Table 1 for demographic variables.

Procedure

Participants visited the Berkeley Psychophysiology Laboratory on the Berkeley campus for the laboratory session. Upon arrival, they were informed that they were participating in a

study of emotion, during which their physiological and self-reported responses would be recorded and their behavior videotaped. Prior to the start of the laboratory session, patients had non-invasive physiological sensors attached to their bodies to record peripheral physiology responses (see below). During the laboratory session, participants' upper body and face were filmed with a partially concealed video camera. The experimental protocol includes a number of laboratory tasks (e.g., tasks on emotion reactivity and recognition) that were designed to measure different aspects of emotional functioning (Levenson, 2007). This dissertation examined the experimental trial during which participants viewed a film depicting individuals in need (see below) and then had an opportunity to contribute to a charity associated with the film. The trial began with a one-minute baseline period, during which participants were asked to clear their mind, relax, and focus on an X in the center of the video screen. Following the baseline period, a written message appeared above the X indicating that the film was about to start. The 117 second film (described below) was then shown. The film was followed by one minute resting period. Afterwards, a research assistant entered the room to remove the physiological sensors. The experimenter returned afterwards to give the participant ten \$1 bills and said: *"As an added thank you, we are going to give you an extra \$10 in addition to the compensation you will receive today. If you are interested, we periodically donate to a charity that assists the people in the film you just viewed. If you would also like to donate, there is a donation box in this corner that you can put money into. If you choose to donate, however, please wait until I leave the room, as we would like this donation to be anonymous and voluntary – we are no longer videotaping. Once you are done, please meet me outside to complete your consents and receive feedback about the day."* After participants completed the task, they returned to an adjacent waiting room to complete their consent forms regarding the use of their video recording. When participants left the laboratory, the research assistant opened the donation box and logged the amount donated to the charity. Consistent with what participants were told, all contributions were donated to the Darfur charity "Not On Our Watch."

Film. The film began with a brief introduction to the Darfur crisis followed by a sequence of still images showing the people of Darfur displaying pain and sadness at the loss of loved ones, children and adults suffering or dead from starvation, and many people injured or bleeding from serious wounds (117 s in length). These images were accompanied by the slow and sad classical piece "Adagio for Strings" by Samuel Barber. In previous research this film was found to effectively elicit high levels of subjective concern and distress in healthy young, middle-aged, and older adults (Sze et al., 2012).

Apparatus

Audiovisual. An unintrusive video camera focused on the participant's face and upper torso, enabling the coding of facial expressions. The output of the camera was sent through video time-code generators that added timing information before being recorded in DVD and digital formats.

Physiology. Continuous recordings of eleven physiological measurements of autonomic nervous system activity were measured using BIOPAC modules and a computer equipped for processing multiple channels of analog information. Using a program written by Robert W. Levenson, physiology was monitored and averaged on a second-by-second basis for each of the following measures: (a) heart rate (disposable pregelled ECG electrodes were placed on opposite sides of the participant's abdomen; the interbeat interval was calculated as the number of milliseconds between successive R waves), (b) finger pulse amplitude (on the nondominant hand, a UFI photoplethysmograph attached to the tip of the ring finger recorded the volume of

blood in the finger, and the trough-to-peak amplitude of the finger pulse), (c) finger pulse transmission time (the number of milliseconds between the R wave of the electrocardiogram (ECG) and the upstroke of the peripheral pulse was recorded by the photoplethysmograph on the finger), (d) ear pulse transmission time (a UFI photoplethysmograph attached to the left earlobe recorded the volume of blood in the ear and the number of milliseconds between the R wave of the ECG and the upstroke of peripheral pulse at the ear), (e) systolic blood pressure and (f) diastolic blood pressure (on the nondominant hand, a cuff was placed on the middle finger and blood pressure was measured on each heartbeat using an Ohmeda Finapres 2300), (g) skin conductance (on the ring and index fingers of the nondominant hand, a constant-voltage device passed a small voltage between two BIOPAC electrodes filled with an electrolyte of sodium chloride in Unibase), (h) finger temperature (on the nondominant hand, a thermistor was attached to the top of the pinky finger), (i) respiration intercycle interval (a cloth belt wrapped around the participant's chest compressed an inflated rubber bladder to provide a measure of chest wall movement; intercycle interval was calculated as the number of milliseconds between the peaks of each respiration cycle); (j) general activity (an electromechanical transducer attached to a platform under the participant's chair generated an electrical signal proportional to the amount of body movement in any direction); and (k) pre-ejection period (on the participant's body, four ECG electrodes were placed on the following regions of the participant's torso: region between clavicle bones, xiphoid process, base of neck, mid-back; pre-ejection period was calculated as the number of milliseconds between the Q wave of the ECG and the B point of the impedance cardiography wave). See table 2 for correlations between physiology measures.

Donation boxes. The donation box was approximately 15cm x 10cm x 8cm and had a slot located at the top that was large enough to insert dollar bills. The box was labeled "Darfur Donation" and was located on a cabinet at the far-end of the room across from the participant. Participants were not informed about the donation procedure until the end of the experiment; participants who have completed this protocol in past studies have never asked about or commented on the boxes prior to being given the option to donate money.

Structural imaging. Structural images were acquired at the UCSF Neuroscience Imaging Center on a 3T Trio Tim scanner (Siemens, Iselin, NJ) equipped with a 12-channel head coil. High-resolution, T1-weighted whole brain images were acquired using a magnetization prepared rapid gradient echo 3D MPRAGE sequence (repetition time [TR]/echo time [TE]/inversion time [TI] = 2300/2.98/900 ms, 9 degree flip angle). The field of view was 240 × 256mm in plane matrix, with a FOC of 0.94 and 1mm slice thickness.

Measures and Data Reduction

Autonomic and somatic activation. All participants had continuous recordings of eleven physiological measurements (see above). The second-by-second data obtained for each participant for each physiological measure were averaged across three time periods: pre-film baseline, task, and post-task periods. For each physiological measure, a reactivity score was computed by regressing the average during the film on the average of the 60-second pre-film baseline. These reactivity scores were normalized using means and standard deviations for the entire sample. To examine cardiac reactivity, a cardiovascular composite was computed to be consistent with previous research on empathy and prosocial behavior, which has largely focused on heart rate and cardiovascular measures. This composite measure was computed by standardizing and then averaging the reactivity scores for the following physiological channels: cardiac interbeat interval, finger pulse amplitude, finger pulse transmission time to the finger, pulse transmission time to the ear, systolic and diastolic blood pressure, and pre-ejection period.

The scores for cardiac interbeat interval, pulse transmission time to the finger, finger pulse amplitude, and pulse transmission time to the ear were multiplied by -1 so that higher numbers represented greater activation. In order to examine whether analyses of physiological reactivity would differ if the composite was determined by factor analysis, a maximum-likelihood factor analysis of the eleven physiology channels was also conducted, followed by varimax rotation. Using parallel analysis (Horn, 1965) four factors were extracted based on the factor loadings of the individual channels. For each of these rotated factors, the standardized physiology channels that were most highly correlated with each factor were summed and averaged (unweighted, see Table 3 for rotated physiology factors and factor loadings of the individual channels). Factor one is comprised of variables measuring sympathetic activity, factor two is comprised of variables measuring temperature, factor three is comprised of variables measuring blood pressure, and factor four is comprised of variables measuring heart rate activity. If any of the four physiology factors were revealed to be significant predictors of prosocial behavior, follow-up analyses at the level of individual physiological variables were conducted to examine the robustness and specificity of the findings.

Emotional facial expressions. Trained coders (blind to the film stimulus and to the hypotheses) used the Emotional Expressive Behavior coding system (Gross & Levenson, 1993) to code participants' behavioral responses while they watched the film stimulus. In this system, raters coded the occurrence of ten emotional behaviors: anger, concern/confusion, contempt, disgust, embarrassment, fear, happiness, interest, sadness, and surprise. For each second that an expression was observed, its intensity was rated using a 0 to 3 scale, with 3 indicating the highest intensity level. For each facial behavior code, means were computed for each participant by summing the intensity scores for each second in which the expression is seen and then dividing by the total number of seconds in the film. Thus, each participant ended up with ten scores (one for each emotional facial expression). The present study focused specifically on sadness and concern facial expressions. Typical reliabilities for facial emotional behaviors were high ($\alpha > .75$).

Dementia Severity. Patients' dementia severity was assessed using the Clinical Dementia Rating Scale Sum of Boxes (Morris, 1993), a clinician-rated scale designed to examine six domains: memory, orientation, judgment, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of impairment (0=no impairment, 0.5=questionable impairment, 1=mild impairment, 2=moderate impairment, 3-severe impairment). Each domain score is then summed to obtain a Sum of Boxes score. Scores can range from 0-18, with higher scores indicating greater functional impairment.

Prosocial Behavior. The total amount of money donated by the participant (from \$0 - \$10) was used as an index of prosocial behavior. This approach has been used effectively in other studies that have assessed helping behaviors (Sze et al., 2012).

Imaging. Structural images were visually inspected for artifacts and then corrected. Five patients' data were removed due to motion artifacts. Structural data was pre-processed and analyzed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). SPM12 default parameters and default tissue probability priors of the International Consortium for Brain Mapping was utilized. All images were warped to a Montreal Neurological Institute template, and segmented into gray matter, white matter, and cerebrospinal fluid. All segmented images were then summed and smoothed with an 8-mm full-width at half-maximum Gaussian kernel. Six regions of interest were then extracted using the AAL Wake Forest University Pick Atlas

Toolbox in SPM12. These regions include: the dorsolateral and ventromedial PFC (Brodmann areas 8, 9, 46 and 10-12, 35, respectively), subgenual cingulate (Brodmann area 25), anterior insula (Brodmann areas 13-14), anterior cingulate (Brodmann areas 24, 32, 33), and ventral striatum (Brodmann area 34). Additionally, regions for posterior cingulate and hippocampus (Brodmann areas 23 and 28, respectively) were also extracted for analyses on anatomical specificity. A measure of total intracranial volume (TIV) was also obtained so that ratios of gray matter volume to TIV could be computed to control for head size. Descriptive statistics of these variables can be viewed in Table 1. Regions of interest can be viewed in Figure 1.

Hypotheses

The present study had two primary aims: (1) to determine whether there are diagnostic differences in prosocial behaviors, and (2) to examine whether emotional responses and neural regions mediate the relationship between diagnosis and prosocial behavior. To examine the first aim, prosocial behavior (as indexed by money donated) was compared across patients with bvFTD, AD, and non-symptomatic caregivers. To examine the second aim, relationships between diagnosis, emotional responses (as indexed by facial expressions of sadness and concern, and autonomic and somatic responses), neural degeneration in specific neural regions (i.e., greater neural loss in the dorsolateral and ventromedial PFC, anterior insula, anterior cingulate, subgenual cingulate, and ventral striatum), and prosocial behavior were examined.

Aim 1: To determine whether patients with bvFTD engage in less prosocial behaviors than patients with AD and non-symptomatic caregivers.

Hypothesis 1. Patients with bvFTD will donate less money compared to both patients with AD and non-symptomatic caregivers.

Rationale: Deficits were hypothesized for patients with bvFTD because the ability to recognize and share the emotions of others—i.e., empathy, a capacity in which this patient group has shown deficits—are important precursors for engaging in helping behaviors. Such impairments have not been found in patients with AD or in non-symptomatic caregivers.

Aim 2: To examine whether emotional responses and neural regions mediate the relationship between diagnosis and prosocial behavior.

Hypothesis 2. Decreased emotional responses (as indexed by cardiac reactivity and target facial expressions of sadness and concern) will mediate the relationship between diagnosis (i.e., patients with bvFTD) and lower levels of prosocial behavior.

Rationale. Patients with bvFTD have established deficits in empathy, as they have difficulty sharing and responding appropriately to the emotions of others. These deficits are also important precursors to prosocial behavior, suggesting that these measures of emotional responses may be an important mechanism that mediate the relationship between diagnosis and prosocial behavior.

Hypothesis 3. Greater neural loss in the dorsolateral and ventromedial PFC, anterior insula, anterior cingulate, subgenual cingulate, and ventral striatum will mediate the relationship between diagnosis (i.e., patients with bvFTD) and lower levels of prosocial behavior.

Rationale: The stated regions are more vulnerable to degeneration in patients with bvFTD, who show a number of deficits in empathy, but are not vulnerable in patients with AD or

in non-symptomatic caregivers, who often do not show deficits in empathy. Extant research indicates that greater activation in the listed neural regions are also predictive of more prosocial behaviors, suggesting that these neural regions may be an important mechanism that mediates the relationship between diagnosis and prosocial behavior.

Data Analytic Strategy

Preliminary analyses were first conducted to examine group differences in sex, age, or income. For patients, differences in dementia severity were also examined. Any significant differences were then included as covariates in subsequent analyses. For the first hypothesis, a one-way ANOVA was utilized, in which diagnosis (i.e., bvFTD, AD healthy caregivers) was the independent variable and donation amount was the dependent variable. Post-hoc contrasts were conducted to examine whether patients with bvFTD donated less money when compared to patients with AD and non-symptomatic caregivers.

For hypothesis two, analyses were first conducted to examine whether participants' emotional responses were plausible statistical mediators. Specifically, the associations between (a) diagnosis and participants' emotional responses and (b) between participants' emotional responses and prosocial behavior were examined. The first association was examined using a MANOVA in which diagnosis (i.e., bvFTD, AD, non-symptomatic caregivers) was the independent variable and participants' emotional responses (i.e., physiological composite, target facial expressions of sadness and concern) were the dependent variable. The second association was tested with two linear regressions. The first regression was conducted with the cardiac reactivity composite and two target facial expressions as the independent variables, and prosocial behavior as the dependent variable. A second regression was also conducted with the four factor-analyzed physiological composites to examine whether differences in methodology revealed differences in results. Thus, the four factor-analyzed physiology composites and the two target facial expressions were entered as independent variables, and prosocial behavior was entered as the dependent variable. If both associations were significant, mediation analyses were conducted using the PROCESS macro, with bias-corrected bootstrapped confidence intervals produced from 5000 samples to test the indirect effects.

For hypothesis three, analyses were first conducted to examine whether neural degeneration in specific regions were plausible statistical mediators. Specifically, the associations between (a) diagnosis and neural degeneration and (b) between neural degeneration and prosocial behavior were examined. The first association was examined using a MANOVA in which diagnosis (i.e., bvFTD, AD) was the independent variable and all neural regions of interest were entered as dependent variables. The second association was examined using a linear regression. The neural regions of the dorsolateral and ventromedial PFC, anterior cingulate, subgenual cingulate, anterior insula, and ventral striatum were the independent variables, while prosocial behavior was the dependent variable. *A priori* significance for hypothesized regions was established at $p < .05$, uncorrected.

The examination of the second association was repeated with the inclusion of the hippocampus and posterior cingulate to illustrate that only hypothesized neural regions, and not all regions, were associated with prosocial behavior. The hippocampus plays an important role in processing and encoding emotion, but has not been associated with prosocial behavior (LeDoux, 1995; Phelps, 2004). The posterior cingulate has been found to be important for memory and spatial orientation (Vogt, Finch, & Olson, 1992) but has not been implicated in studies examining prosocial behavior.

RESULTS

Preliminary Analyses

Preliminary analyses were conducted to examine group differences among patients with bvFTD, AD, and non-symptomatic caregivers. These descriptive statistics can be viewed in Table 1.

Age and Sex. Group differences in age were analyzed using a one-way ANOVA, while sex differences were analyzed using a Chi-square test. Results indicated that groups did not differ in age $F(2, 86) = .720, p = .490$ or sex $\chi^2(2, N=89) = .114, p = .944$.

Income. Group differences in income were analyzed using a one-way ANOVA. Results indicated that groups did not differ in income $F(2, 73) = .890, p = .415$.

Dementia Severity. Excluding non-symptomatic caregivers, group differences in patients' dementia severity were analyzed using a one-way ANOVA. Results indicated patient groups did not differ in dementia severity $F(1, 26) = 2.033, p = .166$.

Given the lack of group differences in these variables, no covariates were entered in subsequent analyses.

Diagnostic Differences in Prosocial Behavior

Diagnostic differences in prosocial behavior were examined with a one-way ANOVA. Results revealed a significant main effect of diagnosis $F(2, 87) = 4.935, p = .009$, where patients with bvFTD ($M=4.82, SD=4.217$) donated significantly less money than non-symptomatic caregivers ($M=8.93, SD=5.192$), $p = .008$. No significant differences were found between patients with AD and non-symptomatic caregivers ($p = 1.0$), or between bvFTD and AD patients ($p = .110$). Findings support our hypothesis, as patients with bvFTD engaged in significantly less prosocial behavior than non-symptomatic caregivers, while differences between patients with bvFTD and AD were trending. Correlations between prosocial behavior and disease severity were trending ($r = -.385, p = .07$), indicating that greater disease severity was associated with less prosocial behavior. These results can be viewed in Figure 2.

Emotional Responses Mediating the Association between Diagnosis and Prosocial Behavior

In our analyses, we tested (1) whether diagnosis was associated with participants' emotion responses (as indexed by physiological responses and target facial expressions of sadness and concern) and (2) whether participants' emotional responses were associated with prosocial behavior. If these associations were significant, analyses were conducted with patients' emotion responses as a mediator.

Diagnosis and emotion responses. MANOVA results revealed no significant diagnostic differences in the physiology composite $F(2, 84) = .455, p = .636$, sadness $F(2, 84) = 0.099, p = .906$, or concern facial expressions $F(2, 84) = 2.309, p = .106$. Results can be viewed in Figure 3A and 3B.

Emotional responses and prosocial behavior. The regression analysis revealed no significant associations between prosocial behavior and the physiology composite ($B = -.030, SE(B) = .120, \beta = -.027, p = .806, CI = [-.268, .209]$), sadness ($B = .022, SE(B) = .018, \beta = .133, p = .235, CI = [-.014, .058]$), or concern facial expressions ($B = .014, SE(B) = .029, \beta = .055, p = .619, CI = [-.043, .071]$). Results can be viewed in Table 4.

Mediation. Links between diagnosis and participants' emotional responses, and between participants' emotional responses and prosocial behavior were not significant. Thus, participants' emotional responses were not tested as a viable mediator. These findings did not support our

hypothesis that participants' emotion responses would mediate the association between diagnosis and prosocial behavior.

Neural Degeneration Mediating the Association between Diagnosis and Prosocial Behavior

In our analyses, we tested (1) whether diagnosis (i.e., patients with AD and bvFTD only) was associated with neural degeneration in the ventral striatum, vmPFC, dlPFC, subgenual cingulate, anterior insula, and anterior cingulate and (2) whether neural degeneration in the regions listed above were associated with prosocial behavior. If these associations were significant, analyses were conducted with neural degeneration as a mediator.

Diagnosis and neural degeneration. Although patients with bvFTD had less neural volume in the hypothesized regions than patients with AD, MANOVA results revealed no significant diagnostic differences ($p > .263$). Differences for the anterior cingulate were trending $F(1, 21) = 2.879, p = .105$. Results can be viewed in Figure 4.

Neural degeneration and prosocial behavior. The regression analysis revealed a significant association between the ventral striatum and prosocial behavior ($B = 3187.64, SE(B) = 14464.54, \beta = 1.00, p = .036, CI = [2524.18, 63851.10]$). Associations with all other regions (i.e., dlPFC, vmPFC, subgenual cingulate, anterior insula, anterior cingulate) were not significant ($p > .153$). Additionally, no associations were found between our control neural regions (i.e., hippocampus, posterior cingulate) and prosocial behavior ($p > .367$). Results can be viewed in Table 5.

Mediation. Links between diagnosis and hypothesized regions of neural degeneration, and between the majority of our hypothesized regions of neural degeneration and prosocial behavior were not significant. Thus, hypothesized regions of neural degeneration were not tested as a viable mediator. These findings did not support our hypothesis that specific regions of neural degeneration would mediate the association between diagnosis and prosocial behavior.

Discussion

Prosocial behaviors can range from small acts of kindness, such as opening a door for someone, to grand heroic gestures, like firefighters entering a burning building to save lives. Regardless of magnitude, prosocial behaviors are an essential part of our interpersonal interactions. Responding appropriately to others in distress and engaging in prosocial behaviors has a significant impact on our social lives, relationships, and personal well-being. In the present study, prosocial behavior was examined using a sample of patients with neurodegenerative disease (i.e., patients with bvFTD and AD) and non-symptomatic caregivers as they viewed a film of others in distress. Participants were then given the option to donate their own money as a measure of prosocial behavior. By characterizing the physiological, behavioral, and neural correlates of prosocial behavior, the study was able to investigate two broad questions.

The first question was concerned with differences among diagnostic groups in prosocial behavior. More specifically, the study tested the hypothesis that patients with bvFTD would show deficits in prosocial behavior compared to patients with AD and non-symptomatic caregivers. As hypothesized, findings revealed that after viewing a film of others in distress, patients with bvFTD donated significantly less money to a charity than non-symptomatic caregivers, while patients with AD and non-symptomatic caregivers donated comparable amounts. The second question addressed in this study was whether differences in prosocial behavior among diagnostic groups were mediated by emotional responses (as indexed by peripheral physiological responses and target facial expression of sadness and concern to the film) or by neural degeneration in particular brain regions associated with prosocial behavior.

Hypotheses related to the second question were not supported. Each of these questions are discussed below.

Differences in Prosocial Behavior among Diagnostic Groups

Patients with bvFTD have core deficits in empathy. Patients' deficits in accurately recognizing the emotions of others is well established (Goodkind et al., 2015; Lavenex et al., 1999; Lough et al., 2006; Rosen, Perry, et al., 2002; Werner et al., 2007), as they often mislabel both positive and negative emotions. Fewer studies have examined patient deficits in their ability to generate and share appropriate emotions and behaviors with others, but results indicate that these capabilities are also diminished (Eckart et al., 2012; Lough et al., 2006; Rankin et al., 2005; Sturm, 2006; Sturm et al., 2008). Being able to share and respond to the emotion of others is an important precursor for engaging in prosocial behaviors (Batson, 1987; Decety & Jackson, 2004; Eisenberg & Miller, 1987). Because patients with bvFTD show deficits in these abilities, this study hypothesized that these patients would also show diminished prosocial behaviors. The present study examined this behavior by giving participants the opportunity to donate to a charity for people in need, and results revealed that patients with bvFTD donated significantly less money than non-symptomatic caregivers. This finding aligns with studies that have examined caregiver reports of bvFTD patient apathy, as most caregivers will state that their loved ones seem to care less about others, and show diminished motivation for goal-directed behavior (Merrilees et al., 2013).

This finding provides the first objective measure of prosocial behavior in patients with bvFTD. Unfortunately, the finding also further highlights the deficits that patients with bvFTD have in responding appropriately in social contexts, even when the need for aid is obvious or dire. However, this finding does not generalize across all patients with neurodegenerative disease. For patients with AD, prosocial behavior was largely intact, as the amount they donated was comparable to non-symptomatic caregivers. This supports research which has found that patients with AD have largely intact emotional functioning (Kipps et al., 2009; Rankin et al., 2006; Sturm et al., 2010; Zhou et al., 2010) and may even show higher levels of empathic responses than healthy controls (Sturm et al., 2013). This decrease in prosocial behavior displayed by patients with bvFTD is also in stark contrast with what is found in healthy aging adults, as a study by Sze and colleagues examining older adults between the ages of 60-80 revealed that older adults are more likely to engage in prosocial behaviors than middle-aged and young adults (Sze et al., 2012).

Our results reveal how prosocial behaviors can be an important indicator of neurological health, and have important clinical and social implications. Clinically, it provides greater clarity to diagnostic criteria. Loss of empathy has always been a central diagnostic symptom of bvFTD, yet research indicates that this descriptor has been problematic because it is vague and unclear (Rascovsky et al., 2007; Rascovsky et al., 2011). The present study allows for a straightforward measure of one type of empathy – prosocial behavior – that could be easily implemented as a bedside diagnostic measure. For example, patients could be shown a brief film of people in distress and then given money to donate as an index of their prosocial behavior. Greater diagnostic accuracy can in turn lead to improved and targeted care. Socially, deficits in prosocial behaviors can impact patients' relationships with their spouses and loved ones because it is an essential component of successful and meaningful social interactions. Recognizing when another person needs aid builds social bonds, and increases the likelihood that aid will be reciprocated (Batson & Powell, 2003). Although caregivers of patients with bvFTD recognize that their loved one has impairments in empathy, it is not uncommon for these impairments in empathy and

prosocial behavior to increase caregiver burden and stress (de Vugt et al., 2006; Merrilees et al., 2013; Schulz & Martire, 2004). Caregivers who have difficulty managing or accepting these deficits may feel less socially connected to their ill loved one, and these weakened social bonds can lead to worse mental and physical health, and decreases in marital satisfaction (Cacioppo et al., 2002; Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Robles & Kiecolt-Glaser, 2003). Elucidating these deficits can give caregivers and medical providers a greater understanding of patient behaviors. This, in turn, can create opportunities for developing interventions and strategies that would aid caregivers in managing these behaviors.

Emotional Responses Mediating the Link between Diagnosis and Prosocial Behavior

Extant literature has established that patients with bvFTD have deficits in the ability to generate appropriate emotional responses (Eckart et al., 2012; Sturm, 2006; Sturm et al., 2008) and feel concern for others (Lough et al., 2006; Rankin et al., 2005). Being able to generate and experience appropriate emotions to the distress of others are precursors to prosocial behavior. Thus, the present study examined whether emotional responses to the distress of others mediated the relationship between diagnosis and prosocial behavior. To examine emotional responses as a potential mediator, analyses were first conducted to examine whether diagnosis was associated with participants' emotional responses, and whether participants' emotional responses were associated with prosocial behavior. Due to non-significant results in both analyses, participants' emotional responses could not be considered as viable mediators of the deficits in prosocial behavior found in this sample of bvFTD patients. The non-significant link between diagnosis and participants' emotional responses was unexpected, but laboratory research in this area has been scarce. It is possible that patients with bvFTD may showed diminished responses in some emotions, like disgust and self-conscious emotions (e.g., embarrassment) (Eckart et al., 2012; Sturm, 2006) but not all emotions. In our sample, patients with bvFTD did show diminished (although not significantly diminished) emotional responses, so it is possible our sample size may have been too small to detect small effect sizes. Future studies examining emotional responses in bvFTD would benefit from including a wider range of emotions to examine potential patterns in patients' emotional responses. It may also be beneficial to examine prosocial behavior using another measure (e.g., social aid versus financial aid), because patients with bvFTD may be more motivated than patients with AD to attain monetary gains. The non-significant association between participants' emotional responses and prosocial behavior was less surprising in this sample, because research examining these associations has largely focused on children and young-adults (Barraza et al., 2015; Eisenberg et al., 1989; Eisenberg et al., 1988; Zahn-Waxler et al., 1995). These links may be weakened or changed in older adults, who can show different emotional responses to stimuli when compared to young and middle-aged adults (Haase, Seider, Shiota, & Levenson, 2012; Levenson, Carstensen, Friesen, & Ekman, 1991; Seider, Shiota, Whalen, & Levenson, 2011; Shiota & Levenson, 2009), or may just not apply to abnormal aging.

Neuroanatomy Mediating the Link between Diagnosis and Prosocial Behavior

Neural degeneration in patients with bvFTD begins in medial regions such as the anterior cingulate, frontoinsula cortex, medial PFC, and striatum (Rosen, Gorno-Tempini, et al., 2002; Schroeter et al., 2008; Seeley et al., 2012) and spreads into frontal regions such as the orbital and dorsolateral frontal regions (Seeley, 2008; Seeley et al., 2012). These regions are also important for engaging in prosocial behavior (Hein et al., 2010; Mathur et al., 2010; Morelli et al., 2014; Rameson et al., 2012), and thus provided the foundation for the hypothesis that neural

degeneration in these regions would mediate the relationship found between diagnosis and prosocial behavior. To examine these neural regions as potential mediators, analyses were first conducted to examine whether there were diagnostic differences across the hypothesized regions of neural degeneration, and whether neural degeneration in hypothesized regions was associated with prosocial behavior. Due to largely non-significant results in both analyses, neural regions were not examined as viable mediators. The lack of significant diagnostic difference across regions of neural degeneration was surprising, but may be related to the kinds of Alzheimer's disease patients often referred to the Memory and Aging Center (MAC). Alzheimer's patients at the MAC tend to be less typical, and may have degeneration in frontal regions while also meeting criteria for AD. Indeed, our sample had three frontal AD patients. Our sample also lacked scans from healthy aging adults, likely constraining the variance needed to detect differences. Future research examining prosocial behavior would benefit from including more typical AD patients and healthy aging adults in a larger sample size to detect potential differences.

When examining the link between neural degeneration and prosocial behavior, only ventral striatum volume was found to be significantly associated with more prosocial behavior. This finding supports research which has found the ventral striatum to be involved in tasks involving charitable donations in young adult samples (Genevsky et al., 2013; Hare et al., 2010; Moll et al., 2006). Research also suggests that the ventral striatum plays a central role in the reward network of the brain (Haber & Knutson, 2010), which aligns with current theories that state how evolutionarily, feeling reward when engaging in prosocial behaviors likely conferred benefits in the context of interpersonal relationships (De Waal, 2012).

Contrary to expectations, frontal and medial regions [i.e., orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), anterior insula, anterior cingulate, subgenual cingulate] and control regions (i.e., hippocampus, posterior cingulate) were not significantly associated with prosocial behaviors. Furthermore, only four of the hypothesized neural regions were positively, albeit non-significantly, associated with prosocial behavior (i.e., dlPFC, vmPFC, anterior cingulate, ventral striatum). This unexpected null finding may have resulted from the study focusing solely on prosocial behavior, whereas other studies examining this behavior measured both prosocial behavior and the period of decision-making participants underwent before engaging in prosocial behavior (Hare et al., 2010; Moll et al., 2006). Alternatively, other methodological differences might be important. For example, all prior studies examining the neural correlates of prosocial behavior utilized the fMRI approach, whereas the present study used patients with neurodegenerative diseases. Additional research studying the anatomy of prosocial behavior in patients with neurodegenerative disease would clearly be useful.

Strengths and Limitations

A major strength of this study was that it measured prosocial behavior using a direct and objective behavioral measure, which avoids many of the potential biases that can result from second-hand caregiver reports. Additionally, the study design allowed for an examination of potential mechanisms (i.e., emotional responses measured via facial expressions and physiological responses, neural degeneration) that underlie the association found between diagnosis and prosocial behavior, and used an ecologically valid film stimulus that has effectively elicited concern and distress in healthy older adults (see Sze et al., 2012). Finally, analyses included two different patient groups in comparison to non-symptomatic caregivers, which allowed for the investigation of whether deficits in prosocial behavior were specific in

patients with bvFTD, or generalized across patients with neurodegenerative disease. Weaknesses included the small sample size, which consequently may have also limited the ability to detect relationships with smaller effect sizes. Given the heterogeneity in the neural regions that may underlie prosocial behaviors and the abilities that serve as precursors to this behavior (e.g., recognizing the emotions of others), the neural mechanisms linked to prosocial behaviors may be particularly difficult to detect. It may also be erroneous to assume that the neural regions undergirding these behaviors are similar across all patients. Additionally, although we included non-symptomatic caregivers who reported minimal to no symptoms of depression or anxiety, caregivers may be undergoing a number of challenges that distinguish them from their healthy peers; future research should include healthy older adults as a comparison group. Finally, the study only assessed prosocial behavior and emotional reactivity in response to a single film stimulus.

Summary and Conclusion

The present study examined diagnostic differences in prosocial behavior using a sample of patients with neurodegenerative disease (i.e., bvFTD and AD) and non-symptomatic caregivers. Results revealed that patients with bvFTD donated significantly less money than non-symptomatic caregivers, while patients with AD and non-symptomatic caregivers donated comparable amounts. The study also examined emotional responses and neural degeneration as potential mediators of the relationship between diagnosis and prosocial behavior, but neither was found to mediate the findings. One finding that did emerge from the anatomical analyses was the association between lower ventral striatum volume and lower levels of prosocial behavior. The study extends our understanding of a neurodegenerative disease that profoundly impacts the lives of patients and their families and contributes important new information to the literature on prosocial behavior.

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Table 1

Sociodemographic characteristics of patients with behavior variant frontotemporal dementia, Alzheimer's disease, and non-symptomatic caregivers

	Patients with bvFTD	Patients with AD	Non-symptomatic caregivers
<i>n</i>	17	12	59
Age (<i>M</i> [<i>SD</i>])	63.35 (7.81)	65.17 (9.54)	62.61 (9.24)
Females (%)	47	50	53
Income	> \$20,000	> \$20,000	\$20 - \$35,000
Dementia Severity	1.06 (0.58)	0.86 (0.45)	-
Mental Health			
Depression (CES-D)	-	-	8.63 (6.01)
Anxiety (BAI)	-	-	4.48 (3.91)
Emotional Responses (<i>M</i> [<i>SD</i>])			
Physiology Composite	0.53 (2.24)	-0.92 (2.16)	-.57 (5.40)
Sadness Expressions	16.64 (30.43)	18.64 (32.13)	20.73 (31.49)
Concern Expressions	4.91 (19.36)	19.05 (31.61)	6.60 (16.05)
Neural Regions			
vmPFC	.003 (.001)	.003 (.000)	-
dlPFC	.007 (.002)	.007 (.001)	-
anterior insula	.003 (.001)	.003 (.001)	-
anterior cingulate	.005 (.001)	.005 (.001)	-
subgenual cingulate	.001 (.000)	.001 (.000)	-
ventral striatum	.001 (.000)	.001 (.000)	-
Prosocial Behavior	4.82 (4.22)	8.67 (3.14)	8.93 (5.19)

Note: Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD), ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC).

Table 2.

Correlations between physiology measures.

	IBI	ACT	SCL	EPT	FPT	FPA	TEM	ICI	SBP	DBP
IBI	1									
ACT	.019									
SCL	-.209	.041								
EPT	-.085	-.171	-.310**							
FPT	-.023	-.054	-.048	.192						
FPA	.123	.014	-.119	.114	-0.706***					
TEM	-.112	.138	-.076	-.054	.022	.093				
ICI	.162	-.085	-.195	.077	.149	-.177	.204			
SBP	-.245	.205	-.012	-.440*	.053	-.438*	-.325	.559*		
DBP	-.333	.287	.109	-.320	-.104	-.246	-.381	.298	.894***	
PEP	.060	-.247	.025	.182	.059	.162	-.044	-.186	-.126	-.002

Note: * $p < .05$, ** $p < .01$, *** $p < .001$. IBI = interbeat interval, ACT = activity, SCL = skin conductance level, EPT = ear pulse transmission time, FPT = finger pulse transmission time, FPA = finger pulse amplitude, TEM = temperature, ICI = intercycle interval, SBP = systolic blood pressure, DBP = diastolic blood pressure, PEP=pre-ejection period.

Table 3
Rotated Factor Loadings of Physiology Channels

	Factor			
	1	2	3	4
EPT	.948	-.017	.084	.305
ICI	.650	-.400	-.029	-.307
PEP	.637	.068	-.316	-.248
SCL	.056	.832	-.188	-.048
TEM	-.152	.875	-.067	-.009
ACT	-.214	.116	-.563	-.173
SBP	-.531	-.333	.728	-.021
DBP	-.243	-.046	.968	.025
IBI	-.063	-.373	.216	.591
FPA	.229	.223	-.186	.929
FPT	.213	.044	-.216	-.531

Note: On the basis of parallel analysis (Horn, 1965; O'Connor, 2000) four factors were extracted. For each of the three rotated factors, an unweighted average of the standardized physiology channels was computed. EPT = ear pulse transmission time, ICI = intercycle interval, PEP=pre-ejection period, SCL = skin conductance level, TEM = temperature, ACT = activity, SBP = systolic blood pressure, DBP = diastolic blood pressure, IBI = interbeat interval, FPA = finger pulse amplitude, FPT = finger pulse transmission time.

Table 4

Emotional Response Variables as Predictors of Prosocial Behavior

	Prosocial Behavior					
	Model 1			Model 2 with physiology factors		
	<i>B (SE[B])</i>	β	95% CI	<i>B (SE[B])</i>	β	95% CI
Emotional Responses						
Sadness Expression	.022 (.02)	.133	[-.014, .058]	.027 (.02)	.158	[-.013, .067]
Concern Expression	.014 (.03)	.055	[-.043, .071]	.013 (.03)	.052	[-.045, .071]
Physiology Composite	-.03 (.12)	-.027	[-.268, .209]	-	-	-
Physiology Factor 1	-	-	-	.012 (.01)	.172	[-.004, .029]
Physiology Factor 2	-	-	-	.449 (2.2)	.024	[-3.86, 4.76]
Physiology Factor 3	-	-	-	-.230 (.18)	-.155	[-.580, 0.12]
Physiology Factor 4	-	-	-	-.026 (.03)	-.099	[-.089, .036]

Note: Physiology factor 1 = ear pulse transmission time, intercycle interval, pre-ejection period, factor 2 = skin conductance level, temperature, factor 3 = activity, systolic blood pressure, diastolic blood pressure, and factor 4 = interbeat interval, finger pulse amplitude, finger pulse transmission time.

Table 5

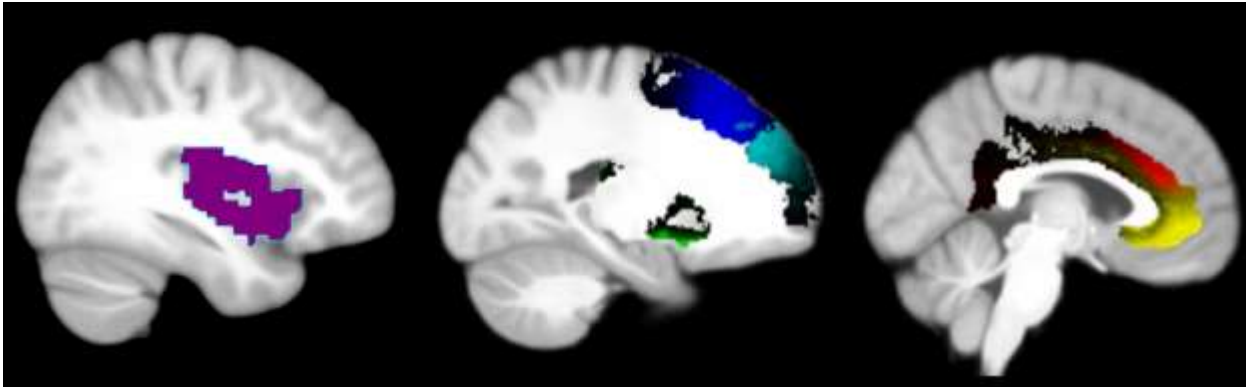
Regions of Neural Degeneration as Predictors of Prosocial Behavior

Prosocial Behavior			
	Model 1		
	<i>B (SE[B])</i>	β	95% CI
Neural Regions			
vmPFC	846.53 (901.06)	.198	[-1063.64, 2756.70]
dIPFC	610.79 (995.62)	.234	[-1499.83, 2721.40]
anterior insula	-7895.80 (5263.52)	-1.11	[-19053.95, 3262.35]
anterior cingulate	3969.95 (3283.76)	.758	[-2991.32, 10931.22]
subgenual cingulate	-16672.29 (22493.15)	-.692	[-64355.63, 31011.05]
ventral striatum	33187.64 (14464.54)	1.00*	[2524.18, 63851.10]

Note: * $p < .05$, ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC)

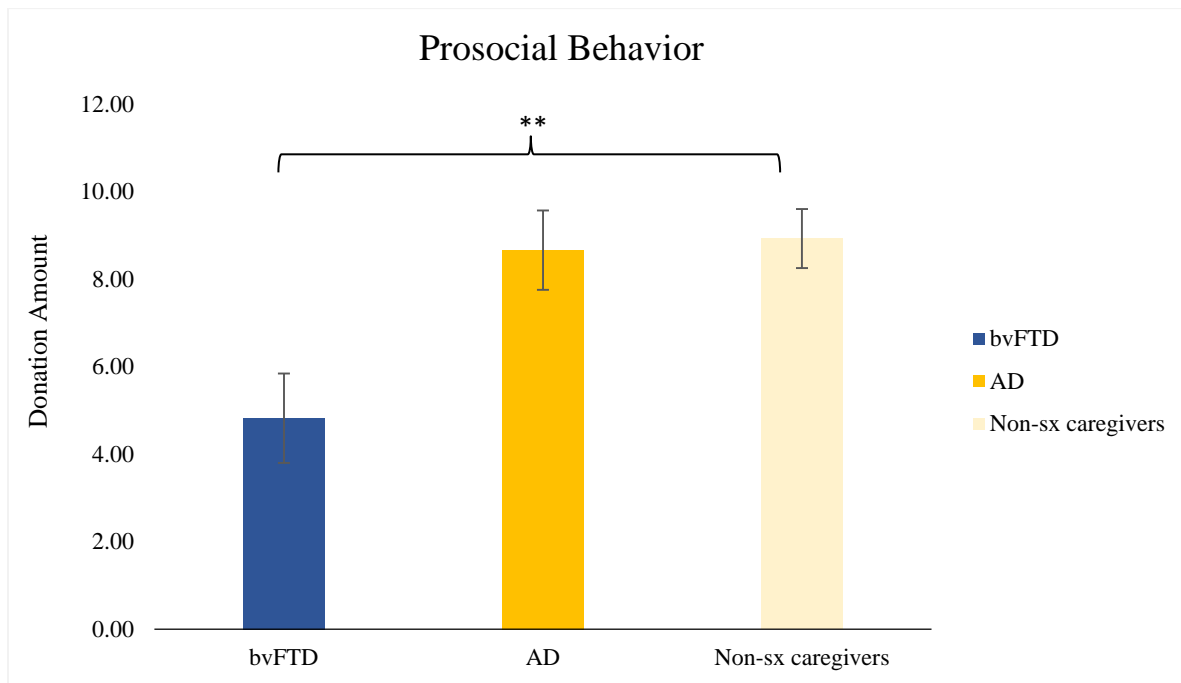
Figure 1

Neural Regions Examined in Association with Prosocial Behavior



Note: The AAL atlas was utilized to extract regions of interest, but masks from Brainnetome were utilized for their visual clarity in depicting the neural regions examined in association with prosocial behavior. Plum = insula, blue = dorsolateral PFC, teal = ventromedial PFC, green = ventral striatum, red = anterior cingulate, yellow = subgenual cingulate.

Figure 2
Diagnostic Differences in Prosocial Behavior and Emotional Responses



Note: ** $p < .01$. Correlations between disease severity and prosocial behavior were trending ($r = -.385$, $p = .07$).

Figure 3A and 3B
Diagnostic Differences in Emotional Responses

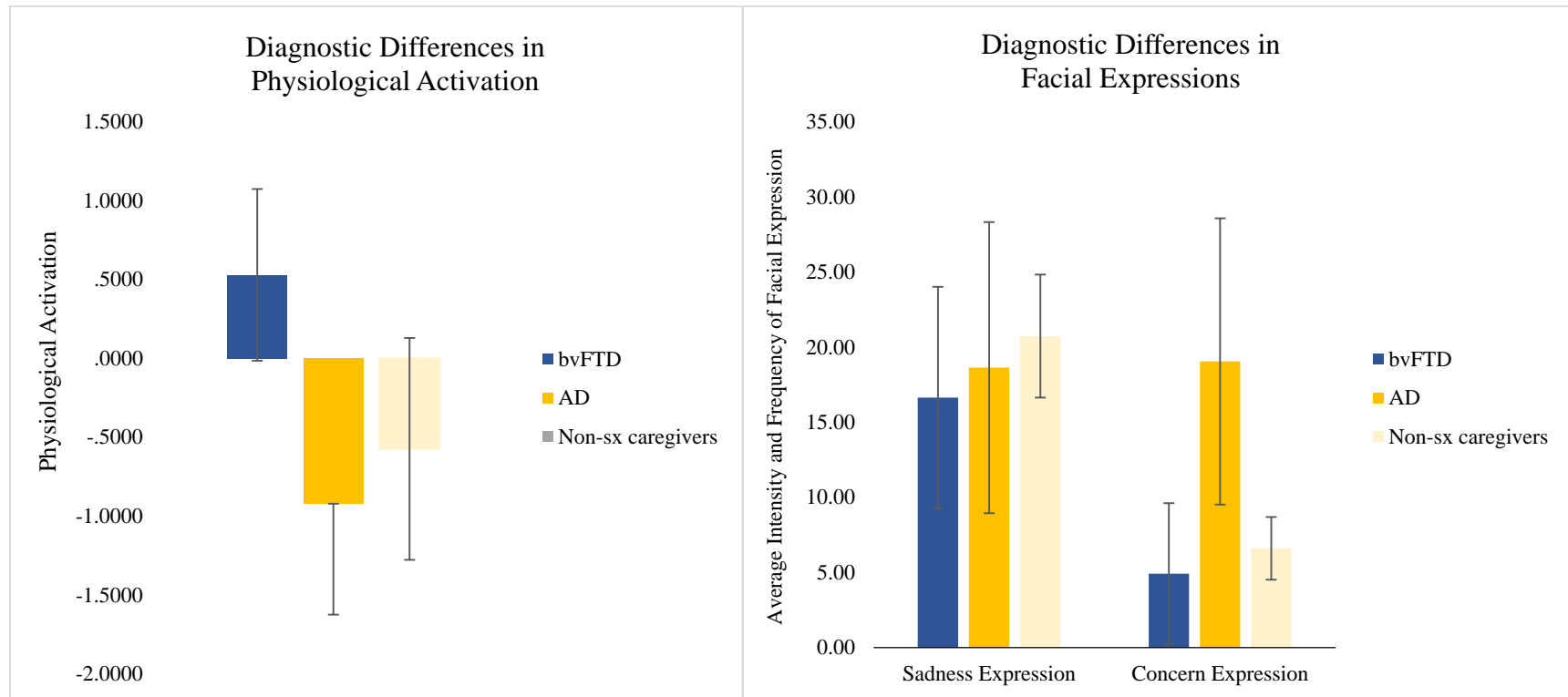
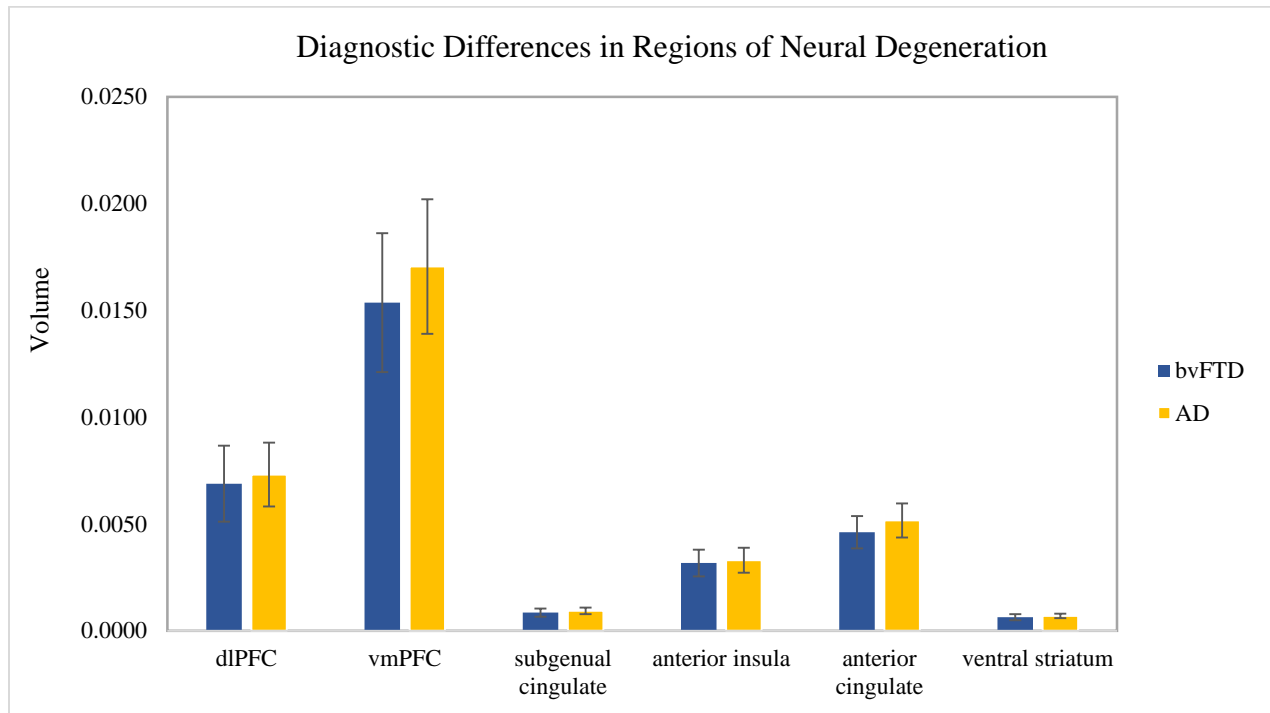


Figure 4
Diagnostic Differences in Regions of Neural Degeneration



Note: ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC)