

Depression, Anxiety, and Apathy in those with Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease that is caused by a decrease in dopaminergic neurons, which are typically involved in the transmission of motor signals within the central nervous system (Remy, Doder, Lees, Turjanski, & Brooks, 2005). PD has mixed correlations to increased rates of depression, anxiety, and apathy (Dissanayaka et al., 2010; Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011; Martínez-Horta, Pagonabarraga, Fernández de Bobadilla, García-Sánchez, & Kulisevsky, 2013; Prediger, Matheus, Schwarzbald, Lima, & Vital, 2012). Therefore, the current study tested whether each condition—depression, anxiety, and apathy—had a significantly increased incidence in patients with PD compared to those with musculoskeletal disorders (MSDs) and neither disorder. This study utilized the National Health Interview Survey (NHIS) database in the analysis. It showed that PD is not associated with an increased incidence in depression, anxiety, and apathy. However, it showed that females overall were significantly more apathetic and depressed than males. It did not show that females were more anxious than males. Lastly, measures of depression, anxiety, and apathy were correlated. In summary, the current study supports gender-reported differences in reported levels of depression and apathy, but it does not offer support that males and females with a MSD or PD reported feeling depressed differently than those with neither condition.

Key Words:

Parkinson's disease, depression, apathy, anxiety, neuropsychology

Parkinson's disease (PD) is a neurodegenerative malady (Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011) that has been shown to affect the dopaminergic system in the nigrostriatal axis (Bohnen & Albin, 2011; Prediger, Matheus, Schwarzbald, Lima, & Vital, 2012). Nigrostriatal neurons synapse from the substantia nigra to the dorsal striatum to produce body movements (Matsuda et al., 2009). Other areas of the brain have also been identified as affected (Bohnen & Albin, 2011). Motor changes that often occur in patients with PD include "tremor[s], muscular rigidity, postural instability, and bradykinesia (i.e. slowness of movement)" (Kirsch-Darrow et al., 2011).

In addition to motor changes, PD is also associated with cognitive abnormalities that occur due to changes in the cholinergic system in places other than the aforementioned nigrostriatal axis (Bohnen & Albin, 2011). The

cognitive dysfunction produced in patients with PD has also been termed executive dysfunction (Martínez-Horta, Pagonabarraga, Fernández de Bobadilla, García-Sánchez, & Kulisevsky, 2013).

Apathy refers to a person experiencing reduced interests, emotions, or motivation (Martínez-Horta et al., 2013). While this characterization of apathy is not a part of the Diagnostic and Statistical Manual-IV-Revision (DSM-IV-TR), it is used to define a certain state in the patient clinically and in research. Apathy can exist simultaneously with depression (Martínez-Horta et al., 2013).

Apathy can also occur without depression. When apathy exists without depression in patients with PD, it is correlated with the development of executive dysfunction (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009). Others have found that executive dysfunction predates the development of apathy

in PD (Martínez-Horta et al., 2013). The development of apathy is involved with changes in the dopaminergic system (Kirsch-Darrow et al., 2011).

Unlike apathy, depression, as listed in the DSM-IV-TR, is characterized by: one or more of the two core criteria (depressed mood, loss of interest or pleasure)... [and others such as]... psychomotor retardation or agitation... expression of worthlessness or guilt... (Gallagher & Schrag, 2012, p. 583)

Still, some doctors treat apathy as a symptom of depression, which, in turn, has led to misdiagnosis. Multiple case studies have shown that brain tumors can also produce PD-like motor symptoms and associated apathy. For example, brain scan indications of unexpected tumors have led to a reassessment of continuing depression treatments (Pawelczyk et al., 2011; Rocha, Murad, Stumpf, Hara, & Fuzikawa, 2013). Through an analysis of National Health Interview Survey (NHIS) data, the current study attempts to provide more evidence that apathy and depression are different constructs in patients with PD.

Newer methods such as the Lille Apathy Rating Scale have been developed to measure apathy. This scale, in particular, has been shown to measure apathy with high validity (Gallagher & Schrag, 2012) and could therefore be useful for testing patients with PD. However, this method has not been used very much because of its length (Kirsch-Darrow et al., 2011). It measures nine main criteria, including motivation, goal-orientedness, and the severity of the symptom causing the impairment (Gallagher & Schrag, 2012). The motivation portion of the Lille Apathy Rating Scale includes a portion that asks, "When you decide you want to do something, are you easily able to make an effort, or is it difficult?" Thus, the motivation section begins by asking about effortful feelings (Lille, 2013).

In summary, there is some evidence to support the notion that apathy and depression are different conditions. For instance, one study of those with PD found that 13% of patients had apathy but not depression (Gallagher & Schrag, 2012). Another study as found similar figures of about 10% (Martínez-Horta et al., 2013). Still,

those differences in the findings may be within the margin of error (Gallagher & Schrag, 2012; Martínez-Horta et al., 2013). To suggest that depression and apathy are different constructs, research has shown that dopamine activation reduces apathy in PD. More evidence includes the fact that modulation of dopamine receptors and transporters are not typical target actions for antidepressants (Thobois et al., 2013). In light of this research, the current study addresses whether those with PD are significantly more apathetic than those without it.

Theoretical Basis for Depression and Anxiety in Those With Parkinson's Disease

Often, depression is comorbid with PD (Remy, Doder, Lees, Turjanski, & Brooks, 2005). A meta-analysis showed that when asking Diagnostic and Statistical Manual-IV (DSM-IV) depression-related questions, depression was comorbid with PD approximately 35% of the time (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2007). Depression occurs most commonly in relation to PD in patients who are predisposed to developing depression. One such mechanism for the development of depression in patients with PD is a reduction in innervation via alternations of norepinephrine transporters (NET) and dopamine active transporters (DAT) and receptors. Norepinephrine (NE) and dopamine (DP) make up two of the three components of the catecholaminergic system, with serotonin (SR) being the third component (Remy et al., 2005).

Remy et al. (2005) found that, in patients with PD, there was significantly less dopamine binding in depressed brains than in nondepressed ones. Additionally, they found that the differences in the intensity of the binding were inversely proportional to the intensity of the depressive symptoms in patients with PD. Remy et al. (2005) identified that specific regions of the brain were most likely affected by PD, such as the limbic system. The limbic systems of PD patients with depression were found to have significantly less dopamine innervation than those of nondepressed patients. The role of the limbic system in PD depression was strengthened by the fact that no significant

differences were found for dopamine innervation between those two groups in the substantia nigra axis (Remy et al., 2005). Because Remy et al. (2005) did not state which particular dopamine receptor subtype was involved, this does not necessarily conflict with the findings by Thobois et al. (2013). In other words, the reduced dopamine found by Remy et al. (2005) may be specific to depression and not apathy. Different receptor subtypes or intensities may produce symptoms of either apathy or depression in patients with PD. Therefore, a main goal of the current study is to assess support for previous conflicting evidence on whether depression rates are higher in individuals with PD than in individuals without PD.

Changes in brain SR levels, DAT, and NE are associated with anxiety. This is consistent for people without PD (Blier & El Mansari, 2013) and those with it (Prediger et al., 2012). For instance, 14% of participants who had PD and depression also had an anxiety disorder (Dissanayaka et al., 2010). Changes in the levels of certain neurotransmitters, such as NE, have also been known to predate the development of motor dysfunction (Prediger et al., 2012). Nevertheless, the loss of catecholaminergic neurons contributes to the development of increased anxiety in patients with PD. While dopaminergic neurons are most heavily affected by PD, they are less involved in anxiety than other neurons (Shimizu & Ohno, 2013). Therefore, this study will test whether participants with PD have higher levels of anxiety than those without it.

While PD is characterized by catecholaminergic neural loss, it is important to recognize potential risk factors that might be associated with the condition (Shimizu & Ohno, 2013). While this study does not directly test the risk factors, studies have shown some overlapping risk factors between affective disorder(s) and PD. Therefore, potential co-associated risk factors help warrant testing whether there are higher levels of affective disorders in patients with PD (Johannessen, Strudsholm, Foldager, & Munk-Jørgensen, 2006). Many risk factors are correlated with an

increased incidence of PD, such as having a family member with PD, well-water drinking exposure, and pesticides. These factors do not determine the outcome of PD, nor are they associated with its severity. The aforementioned factor analysis ignored dosage effects (Noyce et al., 2012). Nevertheless, the existence of some overlapping risk factors (such as hypertension and pesticides) is evidence that PD should be examined in terms of its association with affective disorders (Johannessen et al., 2006; Noyce et al., 2012).

Current research has supported the notion that the largest differences between patients with PD in terms of gender are differences in the severity of motor symptom abnormality (Solla et al., 2012). Nevertheless, men's and women's levels of anxiety, depression, and apathy have been less researched (Miller & Cronin-Golomb, 2010). Some evidence has shown that women who have PD are more depressed and anxious than men with PD (Scott, Borgman, Engler, Johnels, & Aquilonius, 2000). The major problem with the supporting research by Scott et al. (2000) has been that the method used may have better allowed social effects to dictate how the participants answered questions. The present study gathers data using methods that are less invasive of privacy than those used in Scott et al.'s (2000) study to assess whether women with PD are more depressed and anxious than those without PD.

Musculoskeletal or connective tissue problems (MSDs) encompass a wide variety of disorders, including pain in the joints and carpal tunnel syndrome. MSDs are sometimes disabling, as they are often associated with pain. Research has shown that pain affects the intensity of a person's anxiety or depression (Gerrits et al., 2011). This study includes MSDs to assess the overall differences in apathy, anxiety, and depression of people with disabilities compared to nondisabled people. In addition, this group was chosen because those with MSD have mobility-related dysfunctions, but these dysfunctions do not typically originate from brain neural loss (Marras, Cutlip, Burt, & Waters, 2009). Overall, people with MSDs are assessed as

a comparison group to PD and healthy individuals.

Method

Participants

The data used for the study were derived from the National Health Interview Survey (NHIS) and were collected in 2002. Data from the year 2002 were obtained by the University of North Carolina at Charlotte for student use. The data file analyzed was the adult sample, which consisted of 31,044 people at or above the age of 18. The final response rate for the adult sample of this particular study was about 74%. The questionnaire was administered on the computer. The participants were questioned about the conditions they had and were subsequently asked a series of questions concerning how a condition affected their life if they indicated that it did (NHIS, 2002).

The adult sample answered questions about the aspects of mental health that are assessed in the current study. Items addressed feelings such as sadness and hopelessness. The adult sample also answered demographic questions. The initial number of participants who answered questions pertaining to either MSDs or PD was much larger ($N = 9,749$), than when the sample size was randomly reduced to approximately the same number for each group ($N \approx 280$).

Measures

Apathy was assessed using one question from the database. The original question followed the same format of the depression and anxiety scale questions. The question for apathy asked whether participants felt “that everything was an effort.” The responses to the question were as follows: “1-ALL of the time, 2-MOST of the time, 3-SOME of the time, 4-A LITTLE of the time, 5-NONE of the time, 7-Refused, 9-Don’t know.” For apathy, only respondent values between 1 and 5 were included for further analysis. Participants who refused to answer or said they did not know were excluded from further data analysis. This question served to

address apathy in terms of the diagnostic groups. This was the only question within the database that related to apathy, whereas other measurements of apathy in survey research have tended to be too lengthy and are not always used. Further, apathy measurements have been highly variable and have undergone validity testing (Clarke et al., 2010). While single-item measures have been shown to lack some validity, they are sometimes used to measure apathy in research. Therefore, this study used a simple, one-item measure that was similar to an item (effort) from the Lille Apathy Rating Scale to measure apathy (Kirsch-Darrow et al., 2011).

Three questions formed the depression scale, and all of the questions followed the same format. The first question was, “During the PAST 30 DAYS, how often did you feel . . . so sad that nothing cheers you up?” The two remaining questions asked how much hopelessness and worthlessness the person felt. The responses for each were one of the following: “1-ALL of the time, 2-MOST of the time, 3-SOME of the time, 4-A LITTLE of the time, 5-NONE of the time, 7-Refused, 9-Don’t know.” For the depression scale, based only on the included participants, individual participant values could be whole numbers between 3 and 15. Those who refused to answer or who responded that they did not know for any of the depression questions were excluded from the analysis.

The NHIS database contained two variables related solely to anxiety. The anxiety scale asked participants to evaluate their feelings of being “restless or fidgety” and “nervous.” The responses for each were one of the following: “1-ALL of the time, 2-MOST of the time, 3-SOME of the time, 4-A LITTLE of the time, 5-NONE of the time, 7-Refused, 9-Don’t know.” For the anxiety scale, based only on the included participants, individual participant values could be anywhere between 2 and 10. Those who refused to answer or responded that they did not know for any of the anxiety questions were excluded from the analysis. The data were assessed in terms of PD and MSDs. The participants’ PD data were obtained from the conditions sections of NHIS. One condition question was a primary focus of the current study: Have you ever been told by a

doctor or other health professional that you had PD? The responses were “1-yes” and “2-no.”

The MSD data were transformed from a variety of questions asking if the participants had any of a number of disorders, and if not, what was their unlisted condition. For example, some MSD conditions included back pain, arthritis, and carpal tunnel syndrome (NHIS, 2002).

One factor was named Diagnostic Groups. The included data were collected from three unique groups: those who had PD and did not have an MSD, those who had an MSD but did not have PD, and those who had neither condition. The three groups did not have the same number of participants (however, it was approximated and subjects were randomly selected from the large number of original respondents); the numbers for each group can be found in the results analysis. This removal of some respondents was an attempt to obtain normal data and have more equal group sizes. The diagnostic groups were tested for significance in terms of the anxiety scale, the depression scale, and the apathy scale. This variable was also tested for how it varied with gender.

The diagnostic groups contained 91 males and 180 females. They contained 55 people with PD, 107 with an MSD, and 109 with neither an MSD nor PD. Overall, the mean and median age of these participants was approximately 59 years old. Even when the actual age of a participant was over 85, only the age of 85 was entered into the database for subsequent analysis. Thus, the actual age range of the population was 19–85, but it may have included participants over 85.

A correlational analysis tested the anxiety and depression scales. Apathy was also tested for

correlation with anxiety and depression. Correlation was tested regardless of disorder status. Thus, it tested for correlation among all of the randomly reduced data ($N \approx 280$).

Results

High scores on the apathy measure indicated lower apathy severity. A two-way analysis of variance produced a main effect of gender on apathy, $F(1,267) = 6.95$, $p = .009$, partial $\eta^2 = .03$, showing that the mean apathy for males ($M = 8.45$, $SD = 1.74$) was statistically significantly lower than the mean apathy for females ($M = 8.00$, $SD = 2.03$). The main effect of diagnostic groups, including those who had Parkinson’s disease, those who had a musculoskeletal disorder, and those who had neither disorder, was not significant, $F(2,267) = .06$, $p > .05$, partial $\eta^2 = .00$. The interaction effect between gender and diagnostic group was not significant, $F(2,267) = 1.35$, $p > .05$, partial $\eta^2 = .01$.

High scores in the depression measure indicated lower depression severity. A two-way analysis of variance produced a main effect of gender on depression, $F(1,265) = 4.80$, $p = .029$, partial $\eta^2 = .02$, showing that the mean depression for males ($M = 13.69$, $SD = 2.19$) was statistically significantly lower than the mean depression for females ($M = 13.08$, $SD = 2.66$). The main effect of diagnostic groups on depression, including those who had Parkinson’s disease, those who had a musculoskeletal disorder, and those who had neither disorder, was not significant, $F(2,265) = .99$, $p > .05$, partial $\eta^2 = .01$. The interaction effect between gender and Diagnostic Group was not significant, $F(2,265) = .86$, $p > .05$, partial $\eta^2 = .01$.

Table 1.

Significance for the Two-way ANOVA Assessing the Gender and Diagnostic Group in Terms of Apathy, Depression, and Anxiety

Factor Assessment	<i>df</i>	<i>F</i>	η^2	<i>P</i>
Gender	1	^a 6.95*, ^b 4.80*, ^c 3.09	^a .03, ^b .02, ^c .02	^a .01, ^b .029, ^c .08
Diagnostic Group	2	^a .06, ^b .86, ^c .00	^a .00, ^b .01, ^c .00	^a .94, ^b .42, ^c .997
Interaction	2	^a 1.35, ^b .99, ^c .02	^a .01, ^b .01, ^c .00	^a .26, ^b .99, ^c .98

Note: F^* is significant if $p < 0.05$. Apathy = ^a, Depression = ^b, Anxiety = ^c. Diagnostic groups = those with Parkinson’s disease, those with a musculoskeletal disorder, and those with neither.

High scores in the anxiety measure indicated lower anxiety severity. The reported anxiety scale ratings and the severity of anxiety are inversely related. A two-way analysis of variance did not show a main effect of Gender on anxiety, $F(1,267) = 3.09, p = .08, \text{partial } \eta^2 = .02$. Therefore, the mean anxiety of males ($M = 8.45, SD = 1.74$) was not significantly different than that of females ($M = 8.00, SD = 2.03$). The main effect of diagnostic group on anxiety, including those who had Parkinson's disease, those who had a musculoskeletal disorder, and those who had neither disorder, was not significant, $F(2,267) = .00, p > .05, \text{partial } \eta^2 = .00$. The interaction effect between gender and diagnostic group was not significant, $F(2,267) = .02, p > .05, \text{partial } \eta^2 = .00$.

Apathy ($M = 4.16, SD = 1.18$) was highly positively correlated with anxiety, $M = 8.15, SD = 1.95, r(271) = .60, p < .05$. Apathy ($M = 4.16, SD = 1.18$) was highly positively correlated with depression, $M = 13.28, SD = 2.52, r(271) = .64, p < .05$. Depression ($M = 13.28, SD = 2.52$) was highly positively correlated with anxiety, $M = 8.15, SD = 1.95, r(271) = .71, p < .05$.

Discussion

Previous research has supported the notion that those with PD have greatly increased apathy (Dujardin, 2009; Gallagher & Schrag, 2012; Kirsch-Darrow et al., 2011). This is a function of altered dopamine active transporter and brain activity in the nigrostriatal axis (Remy et al., 2005). Although it has been supported that those with PD have significantly higher apathy than those without PD, this study did not confirm this finding. Instead, this study found that males and females had significantly different apathy scores (see Table 1). However, the overall results appear to be more complicated in terms of the original research question. By visually inspecting graphs for apathy (not shown), it can be seen that the most noticeable difference between genders is the differential effect of gender on apathy for the two disorders. In other words, males with PD appeared slightly less apathetic than males with either an MSD or neither disorder compared to females, who were most

apathetic with PD, less apathetic with an MSD, and even less apathetic with neither disorder (graph not shown). This means that reported apathy levels appears to converge (but not converging) for genders through the conditions: PD, compared to a MSD, and then further having neither disorder. Therefore, this study supports the notion that males are significantly less apathetic (particularly when they have either disorder) than females. The study does not support, however, that participants with PD are more apathetic than those without it.

As measured here, the current study provides mixed evidence that apathy is separate from depression. There was a strong correlation between depression and apathy; this relationship has also been supported by other research (Martínez-Horta et al., 2013). The strength of the depression-anxiety correlation has also been found by other researchers. In other words, apathy occurs more commonly with depression than with anxiety (Dissanayaka et al., 2010).

Still, the strength of the correlational differences between depression and apathy, as well as between anxiety and apathy, was not drastic. This shows that, for apathy, it would have been better to include more questions related to the full Lille Apathy Rating Scale. The NHIS database did not contain any other questions that could have been placed in the apathy scale. This may have also played a role in the mixed findings of apathy in patients with PD. Therefore, based on how apathy is defined in this study, the findings provide limited evidence that apathy and depression are two separate, measurable constructs. Additionally, a future NHIS should include more questions pertaining to apathy to retest apathy or that researchers conducting NHIS provide them to universities.

While Reijnders et al. (2007) showed that depression is often comorbid with PD, the current study does not support the notion that PD participants are more likely to be depressed than those who do not have PD. It did, however, find differences in how men and women report depression overall, with females more likely to be depressed than males.

In terms of the overall gender effects for depression, one potential explanation for the way in which males and females report differences in apathy or depression in PD, compared to those without PD, is the social influences involved in the reporting of difficulties. The roles of masculinity and femininity have been termed as confounders, as they may thwart proper assessment and treatment (Brown, 2014; Maxwell et al., 2013; Soffer, 2010).

Even when the survey is anonymously self-reported, men might report feeling better than they actually feel and may do so more commonly than women. Therefore, potentially, the differences observed between the genders may merely be a result of differences in truthfulness or awareness while answering questions pertaining to emotions. Future studies could ask whether participants have ever been diagnosed with a mood disorder, which disorder they have been diagnosed with, and whether they are currently seeking any treatment for it. However, this study made participants anonymous.

Previous studies have shown a weak relationship or no relationship between PD and anxiety (Dissanayaka et al., 2010). Concordantly, the current study shows no significant relationship. Still, the research on this has been largely conflicting (Dissanayaka et al., 2010; Noyce et al., 2012). One possible explanation for the findings in the current study is that the anxiety questions used might not have been inclusive enough. It may also be that anxiety is not significantly associated with PD.

It is possible that medication use, illegal drug use, or therapy can have an effect on an individual's tendency to be depressed, anxious, or apathetic. The way those extraneous variables may play into apathy, anxiety, or depression may be disproportionate among the groups tested. These factors were not controlled for in this study but might be involved in the findings. Either the NHIS database that the university obtained did not include these variables or NHIS did not include these variables in the survey. The only possible data which might have been included in the analyses in this paper, were if

they sought alternative therapies, needle drug use, or taking homeopathic "drugs" (NHIS, 2002). Future studies should restructure the experiment to control for these variables and other possibilities. Nevertheless, an attempt was made to separate anxiety, depression, and apathy as separate scales while also including another disabled group to try to control for the social effects of being disabled.

The study originally sought to find differences in depression between males and females in terms of having either of the measured disorders, but no observed interaction effect provided evidence against it. Still, suspected heteroscedasticity and non-normality can wreak havoc on power and errors (Lantz, 2013; Xu, Yang, & Qin, 2013). If such deviations are suspected and logarithm transformation is not sufficient, further analyses using a year of the NHIS database of parameters such as depression or anxiety might be also analyzed by bootstrapping or the box cox transformation. However, future data analyses and designs must be accommodated to include what is best completed via bootstrapping in either parametric or nonparametric approaches (Gaudard & Karson, 2000; Moder, 2010; Xu et al., 2013).

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