Affective Correlates of Psychosis in Parkinson's Disease

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Abstract

**Objective**—To examine the nature of the association between affective disorders and psychosis in Parkinson’s disease (PD).

**Background**—In PD, psychosis and affective disorders are common and independently impact quality of life and mortality. Both depression and psychosis are correlated with the occurrence of cognitive dysfunction, suggesting that they may share neurobiological substrates. Anxiety has not been examined as a correlate of psychosis.

**Methods**—144 PD subjects were evaluated with the Schedule for Assessment of Positive Symptoms to assess psychotic features, while depression and anxiety were examined by the Structured Clinical Interview for DSM-IV-TR (SCID) and self-assessment scales Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI). Correlational analyses assessed associations between hallucinations and delusions with depression and anxiety.

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Conflict of interest
There are no conflicts of interest from all authors that relate to the research covered in the article submitted.

Author Contributions
S.A. Factor: Drafting and revising manuscript, Study concept or design, Analysis or interpretation of data, Acquisition of data, Study supervision or coordination, Obtaining funding
M. K. Scullin: Revising the manuscript for content, analysis or interpretation of data, Statistical analysis
A. Freeman: Revising the manuscript for content, Acquisition of data
D. L. Bliwise: Revising the manuscript for content, Analysis or interpretation of data, Other – consultant on the analysis
W. M. McDonald: Revising manuscript, interpretation of data
F. C. Goldstein: Drafting and revising manuscript, Analysis or interpretation of data, Statistical analysis

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Ethical Compliance Statement
We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.
**Results**—A diagnosis of anxiety (SCID) was significantly (p=.015) associated with hallucinations (OR=4.81, CI=1.36–16.99). Severity of anxiety (BAI) significantly predicted (p=.03) the presence of hallucinations (OR=1.08, CI=1.01–1.15) and delusions (OR=1.09, CI=1.01–1.17). Current depression (SCID) was significantly (p=.001) associated with the presence of hallucinations (OR=6.12, CI=2.04–18.39) and delusions (OR=7.14, CI=2.23–22.93). Multiple linear regressions revealed that severity of anxiety remained an independent predictor (p<.05) of both the number of types of hallucinations (t=3.06, p=.003) and delusions (t=2.87, p=.005). Severity of depression was a significant predictor of the total number of delusions (t=2.28, p=.024).

**Conclusions**—This study demonstrates an association between depression and psychosis and, for the first time, an association between anxiety and psychosis. These associations may have implications on pathophysiology and treatment of psychosis in PD.

**Keywords**
Parkinson’s disease; Anxiety; Depression; Hallucinations; Delusions

**Introduction**
Parkinson’s disease (PD) is a neurodegenerative disorder often encumbered with several non-motor, particularly behavioral, problems(1). Psychosis and affective disorders are particularly common and troublesome. Psychosis, characterized by hallucinations and delusions, impacts quality of life, tends to be chronic, may lead to nursing home placement and is a risk factor for increased mortality(2–5). Psychotic symptoms have been reported to occur in up to 60% of PD patients in longitudinal cohorts(6, 7). Depression and anxiety each impact ~35% of patients(8, 9). These may predate motor symptoms(10), and they also independently impact quality of life and mortality(11). Depression and psychosis are highly correlated with the occurrence of cognitive dysfunction(8). It would therefore make sense that these features are closely related and share a neurobiological substrate. There is some data in fact to support this premise(12, 13). Whether there is a direct association between psychosis and anxiety however has not been examined to our knowledge.

A 2011 multicenter study of 500 PD patients suggested that depression predicts the onset of psychotic symptoms(14). However, the measures included brief screening tools; psychosis was assessed by item 2 in the mental section (part 1) of the Unified Parkinson’s Disease Rating Scale (UPDRS) (15) and depression solely by the Beck Depression Inventory (BDI-II) (16). Anxiety was not examined.

The current study examines in greater detail the nature of the association between psychotic symptoms in PD with affective disorders. We used in depth measures of each symptom complex including the Schedule for Assessment of Positive Symptoms (SAPS)(17) for psychosis, and examination of depression and anxiety via validated questionnaires(16, 18) and the Structured Clinical Interview for DSM IV (SCID). (19) We hypothesized that mood disorders of depression and anxiety would both be associated with the presence of psychosis in PD patients suggesting common pathophysiological substrates and providing some clues to targeted therapeutic measures.
Methods

Subjects

This study was approved by the Emory University Institutional Review Board. All patients were recruited consecutively from the practices of two neurologists (SAF and AF) in the Emory University movement disorders clinic between February 9, 2009 and September 14, 2010. The subjects met standard clinical diagnostic criteria for PD (20). None of the patients met clinical diagnostic criteria for Lewy Body Dementia (21). Patients were enrolled regardless of age at disease onset, family history of PD, or treatment status (treated or not, with any combination of antiparkinsonian medications). Exclusion criteria were late stage dementia where subjects were unable to complete the visit assessments, history of primary psychotic disorder, history of cerebrovascular disease, findings suggestive of atypical parkinsonism (extraocular movement abnormalities, pyramidal tract signs, ataxia, early dementia, autonomic failure), past neuroleptic use, and past history of multiple head injuries.

Assessments

Patients were evaluated in a standardized fashion. Demographic and clinical information were collected including age, gender, education level, disease duration, motor severity measured in each patient with the UPDRS part 3 in the on state (completed by one investigator-SAF), Montreal Cognitive Assessment (MoCA) for cognition and PD medications taken at the time of the visit.

Psychotic Symptoms—Psychosis was diagnosed based on validated criteria(5). Measures of psychotic symptoms included the SAPS(17, 22) where symptoms are assessed via a patient and caregiver interview with a trained research coordinator. The hallucinations subscale assesses six subtypes (auditory, voices commenting, voices conversing, somatic or tactile, olfactory and visual). Minor hallucinations such as delusions and passage hallucinations are not measured in this scale. The delusions subscale evaluates 12 subtypes (persecutory, jealousy, sin or guilt, grandiose, religious, somatic, ideas of reference, being controlled, mind reading, thought broadcasting, thought insertion and thought withdrawal). Each subtype is rated on a scale ranging from 0 (absent) to 5 (severe). A Global Rating of Severity (ranging from 0–5) provides an overall score for the entire domain. We used two parts as measures of severity, the global rating for each hallucinations and delusions, and the number of types. We used both to assure consistency in our findings.

Depression and Anxiety—Depression and anxiety were evaluated in two ways. First, patients underwent a Structured Clinical Interview for DSM-IV-TR (SCID) (23) by a psychiatrist to assess past and present psychiatric diagnoses. The diagnosis followed DSM-IV established criteria for depression and anxiety. Second, they were also screened with two validated questionnaires. The Beck Depression Inventory (BDI-II) had patients rate their symptoms of depression in the past two weeks by completing 21 items, each scored on a scale ranging from 0 (no symptoms) to 3 (severe symptoms)(16). They also completed the Beck Anxiety Inventory (BAI) where patients rated their symptoms of anxiety over the prior week by answering 21 stress related questions, each scored on a scale ranging from 0 (not present) to 3 (severe) (18). Both were used as severity measures.
Analyses

Logistic regressions were conducted to examine predictors of the presence versus absence of psychosis on the SAPS with: 1) the presence versus absence of depression and anxiety on the SCID, and 2) severity of depression and anxiety on the BDI-II and BAI, respectively. The above analyses were repeated for hallucinations and delusions separately because we have found previously that these psychotic symptoms do not represent a continuum but instead are separate phenomena (22). Pearson Product Moment correlations and multiple linear regression analyses were conducted for continuous scales to evaluate predictors of the total number of types and global severity of hallucinations and delusions based on the severity of depression (BDI-II) and anxiety (BAI).

Covariates were included in all analyses reported below, and they consisted of age, gender, years of education, MoCA score, severity of motor symptoms (UPDRS part 3), disease duration, and the use of PD medications that could potentially produce psychiatric symptoms (Levodopa, Dopamine agonists, COMT inhibitors, Amantadine, MAO inhibitors). Each drug was assessed as prescribed or not. Dosage information was not compiled.

Results

One hundred and forty four PD subjects were included in the analyses. Ninety six (67%) patients had no psychotic symptoms whereas 48 (33%) had hallucinations and/or delusions. Hallucinations occurred in 26% (37 subjects) and delusions in 16% (22 subjects). There were non-significant trends for those with psychosis to have longer disease durations (p=.06) and to be on PD medications (p=.09) (Table 1). Of the individual drugs dopamine agonists were significantly associated with developing psychosis (p=0.02)(Table 1). Using the SCID to define anxiety and depression the following was the distribution of subjects taking individual medications. For depression 6 subjects were on levodopa and 11 were not, 11 were taking dopamine agonists, 8 were not, 3 were taking MAO inhibitors and 16 were not, 1 was taking COMT inhibitors and 18 were not, and 2 were on amantadine and 17 were not. For anxiety 8 were taking levodopa and 7 were not, 9 were taking dopamine agonists and 6 were not, 2 were taking MAO inhibitors 13 were not, 2 were taking COMT inhibitors and 13 were not, 1 was on amantadine and 14 were not. There were no associations between individual drugs and affective diagnosis. The groups did not significantly differ in age, education, gender, the MoCA total score, and the UPDRS motor score. SCID interviews were conducted on 139 patients. Of these, 12 (8%) patients met criteria for a diagnosis of major depression alone separate from psychosis, 8 (10%) met criteria for an anxiety disorder alone (most common were generalized anxiety disorder 32% and panic disorder 32%), and 7 (5%) had combined diagnoses. For depression, 32 (25%) of 128 patients had BDI-II scores of 14 and higher indicating the presence of depression(24). For anxiety, 26 (21%) of 125 patients had scores of 15 and higher on the BAI indicating the presence of anxiety(18).

Association of Psychosis with Depression and Anxiety

Logistic regression analyses revealed that a diagnosis of major depression (SCID) was a significant (p<.001) predictor of psychosis (OR=7.99, CI=2.50–25.55). A current diagnosis...
of anxiety (SCID) was associated with a trend (p=.07) as a predictor of psychosis (OR=2.97, CI=.93–9.48).

Logistic regression analyses were also performed to examine relationships between the severity of depression and anxiety, based on self-report measures, and the presence of psychosis. Results indicated that higher depression scores on the BDI-II were significantly (p=.012) associated with the presence of psychosis (OR=1.08, CI=1.02–1.14). Similarly, higher anxiety scores on the BAI were significantly (p=.012) predictive of psychosis (OR=1.08, CI=1.02–1.15).

Association of Hallucinations and Delusions with Depression and Anxiety

Logistic regression analyses were performed to examine predictors of hallucinations and delusions. Twenty five (17%) patients had hallucinations only, 11 had delusions only (8%), and 12 exhibited both symptoms. A diagnosis of current depression on the SCID was significantly (p=.001) associated with the presence of hallucinations (OR=6.12, CI=2.04–18.39) and delusions (OR=7.14, CI=2.23–22.93). A diagnosis of current anxiety (SCID) was significantly (p=.015) associated with hallucinations (OR=4.81, CI=1.36–16.99) but not delusions (OR=1.63, CI=.39–6.81, p=.50). Severity of anxiety (BAI) significantly predicted (p=.03) both the presence of hallucinations (OR=1.08, CI=1.01–1.15) and delusions (OR=1.09, CR=1.01–1.17). In contrast, the severity of depression (BDI II) was not a significant predictor of either one.

Association of Number of Types and Global Severity Ratings of Hallucinations and Delusions with Depression and Anxiety

Correlations were examined between the number and global severity ratings of hallucinations and delusions with self-ratings of severity of depression and anxiety. As shown in Table 2, increased severity of depression (BDI-II) and anxiety (BAI) were significantly associated with an increase in global severity ratings and number of types of hallucinations. Increased anxiety was also significantly correlated with an increase in the number of different types of delusions. Multiple linear regressions revealed that severity of anxiety remained an independent predictor (p<.05) of both the number of types of hallucinations (t=3.06, p=.003) and delusions (t=2.87, p=.005). Severity of depression was a significant predictor of the total number of delusions (t=2.28, p=.024) but not of hallucinations. Neither depression nor anxiety significantly predicted the global severity of hallucinations and delusions.

Discussion

Novel findings in the current study include the relationship between anxiety and psychosis. We found that anxiety correlated with hallucinations and delusions in 8 of 10 analyses that were completed. The presence of anxiety on the SCID was significantly associated with the presence of hallucinations. In addition, higher anxiety scores on the BAI were significantly associated with the presence of hallucinations and delusions as well as an increase in the number of types of hallucinations and delusions and global severity of hallucinations. We also demonstrated that depression correlated with hallucinations and delusions in 5 of 10
assessments. A diagnosis of depression on SCID is a predictor of the presence of hallucinations and delusions. In addition, the severity of depression measured by BDI-II was associated with global severity and the number of types of hallucinations. While it is true that the associations were not seen with all comparisons the number of significant correlations is very suggestive that relationships between anxiety/depression and hallucinations/delusions exist.

The prevalence of clinically significant depression in PD is estimated at 35% (8). Early studies examining a possible association between depression and psychosis demonstrated inconsistent results(13, 25–28). It has been suggested that a score of 2 or higher on item 2 of the UPDRS (thought disorder) increases the probability of major depression by a factor of 3.5 (29). One other study reported the prevalence of depression in psychotic PD patients to be 71% by SCID, and it often preceded the onset of psychotic symptoms(12). More recent studies using larger samples have indicated that depression is a correlate of psychosis in PD based on global scores such as the BDI-II and the observer rated Hamilton Depression Rating Scale (HDRS) even in early PD(14, 30). Our data would certainly support the findings that depression is associated with psychosis and are the first to examine hallucinations and delusions separately.

In contrast, little has been published on the role of anxiety. Anxiety occurs in approximately 20–35% of PD patients(8, 9, 12). One study found an association of psychosis with the combined anxiety/depression domain based on a semi-structured interview, but scores on the HDRS suggested depression, and not anxiety, was the primary symptom associated with psychosis (30). Others have cited the interplay between the symptoms of anxiety and delusions(1). We found an association between anxiety and psychosis as well as hallucinations and delusions independently. The comorbidity between mood and psychosis has several implications. Affective and psychotic symptoms may share pathophysiology. It had been shown that both correlate with pathology in the amygdala and hippocampus(31, 32) and both relate to alterations in brain dopamine, noradrenaline and serotonin(8, 33, 34). In addition, the finding that affective disorders may predate motor features in PD and may also predict later development of psychosis(35) supports the association of mood symptoms and psychosis. Longitudinal studies are needed to decipher this relationship. Furthermore, this could have implications for treatment as well. In a case series of ten patients, Voon et al. found that antidepressants, as monotherapy or as an adjunctive therapy, can improve psychotic symptoms in PD patients with comorbid depression or anxiety, even when the psychosis is previously refractory to antipsychotics(36). We believe the role of antidepressants should be examined further.

There are several limitations of this study. This is a cross-sectional study which limits our ability to address the temporal order of mood disorders and psychotic symptoms. The number of subjects in with hallucination, delusion and affective disorders are small, making the study exploratory in nature. We used the SAPS to measure psychosis in PD. This scale does not take into account minor hallucinations such as illusions and passage hallucinations. As these have recently been reported as early phenomenon (37) it is difficult to speculate how this omission might impact the predictive impact of affective disorders on hallucinations but affective disorders have also been reported in the early stages of disease as
well (38) so comorbidity even early on is possible. We did not include fluctuations or dyskinesia in the model. Data on these phenomena were not collected completely in our data set. We did examine the presence of dyskinesia via item 32 of the UPDRS and its relation to anxiety. There was no significant difference in the distribution of patients with or without dyskinesia as a function of whether they were diagnosed with current anxiety on the SCID, Chi-square (1) = .12, p=0.73. We did not collect data on fluctuations. Anxiety has been shown to relate to dyskinesia in previous literature(39).

Our findings highlight the association of psychosis in PD with mood disorders and the importance of assessing and treating these comorbidities. This association appears to be driven more by anxiety than depression. The association of anxiety with psychosis has not been previously reported. A large scale longitudinal study is needed to determine whether mood disorders are risk factors for the development of psychosis in PD patients, or whether mood disorders are by products of the presence of psychosis.

Acknowledgments

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References

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### Table 1

Demographic and clinical features of patients with vs. without psychosis

<table>
<thead>
<tr>
<th></th>
<th>No Psychosis (n=96)</th>
<th>Psychosis (n=48)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean +/- SD; Range</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age - Years</td>
<td>64.5 +/- 9.1; 46–86</td>
<td>65.2 +/- 8.7; 38–80</td>
<td>0.65</td>
</tr>
<tr>
<td>Duration of Disease - Years</td>
<td>7.3 +/- 4.3; 1–24</td>
<td>8.8 +/- 4.4; 1–21</td>
<td>0.06</td>
</tr>
<tr>
<td>Age of onset</td>
<td>58.1 +/- 9.7; 36–82</td>
<td>57.4 +/- 10.0; 32–76</td>
<td>0.67</td>
</tr>
<tr>
<td>Education – Years</td>
<td>16.0 +/- 2.3; 12–20</td>
<td>15.4 +/- 2.4; 11–20</td>
<td>0.20</td>
</tr>
<tr>
<td>MoCA Total Score</td>
<td>24.6 +/- 3.5; 15–30</td>
<td>23.9 +/- 3.6; 14–29</td>
<td>0.26</td>
</tr>
<tr>
<td>UPDRS motor score - points</td>
<td>17.0 +/- 8.2; 2–43</td>
<td>19.1 +/- 7.0; 8–38</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63 (66%)</td>
<td>30 (63%)</td>
<td>0.72</td>
</tr>
<tr>
<td>On PD meds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa</td>
<td>71 (74%)</td>
<td>42 (88%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Dopamine Agonists</td>
<td>43 (45%)</td>
<td>29 (60%)</td>
<td>0.08</td>
</tr>
<tr>
<td>COMT Inhibitors</td>
<td>38 (40%)</td>
<td>29 (60%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Amantadine</td>
<td>7 (7%)</td>
<td>6 (13%)</td>
<td>0.36</td>
</tr>
<tr>
<td>MAO Inhibitors</td>
<td>13 (14%)</td>
<td>8 (17%)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>20 (21%)</td>
<td>8 (17%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Psychosis assessed by Schedule for Assessment of Positive Symptoms (SAPS); UPDRS=Unified Parkinson’s Disease Rating Scale
Table 2
Correlations Between Mood Ratings and Psychotic Symptom ratings

<table>
<thead>
<tr>
<th></th>
<th>Hallucinations</th>
<th>Delusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Types</td>
<td>Global Severity Rating</td>
</tr>
<tr>
<td>Beck Depression Inventory-II</td>
<td>0.20 *</td>
<td>0.22 *</td>
</tr>
<tr>
<td>Beck Anxiety Inventory</td>
<td>0.35 **</td>
<td>0.24 **</td>
</tr>
</tbody>
</table>

* .05;
** .01