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Domain-specific cognitive impairment in non-demented Parkinson's disease psychosis

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Abstract

Introduction—In Parkinson's disease (PD), psychosis is associated with cognitive impairment that may be more profound in particular cognitive domains. Our goal was to determine whether psychosis in non-demented PD participants is associated with domain-specific cognitive impairment on the Mini-Mental State Exam (MMSE).

Methods—The Morris K. Udall Parkinson's Disease Research Center of Excellence Longitudinal Study at Johns Hopkins is a prospective study that was initiated in 1998. Clinical assessments are conducted at two-year intervals at the Johns Hopkins Hospital. We analyzed data from 137 enrolled participants with idiopathic PD. Psychosis diagnoses were established by psychiatrist interview per DSM-IV criteria. An incident dementia diagnosis resulted in exclusion from analysis for that evaluation and any future evaluations in that participant. We used logistic regression with generalized estimated equations (GEE) to model the time-varying relationship between MMSE subscale scores and psychosis, adjusting for potential confounding variables identified through univariable analysis.

Results—Thirty-one unique psychosis cases were recorded among non-demented participants. Fifty total evaluations with psychosis present were analyzed. In multivariable regressions, psychosis was associated with lower scores on the orientation (relative odds ratio, rOR: 0.73; 95% CI: 0.58–0.93; $p = 0.011$), language (rOR: 0.64; 95% CI: 0.48–0.86; $p = 0.003$), and intersecting pentagon (rOR: 0.43; 95% CI: 0.20–0.92 $p = 0.030$) subscales of the MMSE.

Conclusions—In PD, executive dysfunction, disorientation, and impaired language comprehension may be associated with psychosis. Our findings suggest that the corresponding MMSE subscales may be useful in identifying participants with a higher likelihood of developing psychosis.

Keywords

Parkinson's disease; psychosis; cognitive impairment; MMSE; cognitive domains; hallucinations

Introduction

Parkinson's disease (PD) is complicated by an array of non-motor neuropsychiatric disorders (Chaudhuri, Healy and Schapira, 2006). As the disease progresses, patients often develop symptoms of psychosis, including visual hallucinations and delusions; the lifetime prevalence of visual hallucinations in PD is approximately 50% (Williams and Lees, 2005). Psychosis elevates the risk of nursing home placement more than motoric impairment or cognitive decline in the absence of dementia (Goetz and Stebbins, 1993; Aarsland *et al.*, 2000). Cognitive dysfunction, another important and common complication of PD, is significantly heterogeneous (Litvan *et al.*, 2012) and can involve a variety of cognitive domains, some of which may be relatively more impaired in PD patients with psychosis (Ramírez-Ruiz *et al.*, 2006, 2007; Factor *et al.*, 2014; Llebaria *et al.*, 2010). A recent critical review of this hypothesis (Lenka *et al.*, 2017) analyzed 16 relevant studies and suggested that executive function and visuoperceptive performance appear to be most consistently impaired in PD patients with psychosis, with memory, language, and attentional deficits being somewhat less consistently reported. However, there is significant variability among these studies, both in terms of how psychosis is defined and measured and also with respect to the assessment of dementia and the inclusion of participants with dementia. Nonetheless, the different results among prior studies highlight the current uncertainty about how PD psychosis may relate to domain-specific cognitive impairment and the need for continued investigation. Advances in this area could suggest the use of cognitive biomarkers for predicting PD psychosis, which would be non-invasive and cost-effective (Lenka *et al.*, 2017).

Imaging studies have linked visual hallucinations to changes in activity in various frontal-executive brain regions, suggesting that widespread cortical involvement may engender both cognitive dysfunction and psychotic symptomatology (Alzahrani and Venneri, 2015). However, essentially all studies connecting domain-specific cognitive deficits to psychotic symptoms in PD patients have done so with batteries of neurocognitive tests that are not routinely used in the clinical setting. In contrast, an understanding of how psychosis-related cognitive impairment manifests in the context of routine cognitive screening tests such as the Mini-Mental State Exam (MMSE) may afford more clinical utility for early identification of PD patients who are at elevated risk for psychosis. Additionally, identifying types of cognitive dysfunction that are specifically associated with psychosis, even in the absence of dementia, may direct clinicians to ask patients and their caregivers about the presence of minor psychotic symptoms that might otherwise go unrecognized. This is important because even "benign" visual hallucinations comprise a risk factor for conversion to severe psychosis and marked cognitive dysfunction (Goetz *et al.*, 2001, 2006).

The MMSE (Folstein, Folstein and McHugh, 1975) is a widely utilized cognitive screening test composed of six subscales: orientation, attention and calculation, registration, recall, language fluency, and intersecting pentagons. We modeled the association between psychosis and cognitive impairments in these subscales or domains in a sample of 137 non-demented participants using multivariable regression with GEE. These subjects were followed longitudinally and evaluated approximately every two years. Generalized estimated equations allow for correlation within subjects to be estimated, which allows for modeling of

longitudinal repeated-measures data (Locascio and Atri, 2011). At each assessment, the MMSE was administered and a psychiatrist provided DSM-IV guided diagnoses of psychiatric disorders. We hypothesized that domain-specific cognitive performance—quantified using the MMSE subscale scores—would be impaired by the presence of psychosis.

Methods

Participants and study design

The Morris K. Udall Parkinson's Disease Research Center of Excellence, located at the Johns Hopkins School of Medicine, recruits individuals with PD, patients with related movement disorders, and healthy controls for a number of research studies. All studies have received approval from the Johns Hopkins Institutional Review Board and include written informed consent from all participants or their power of attorney. Participants included in this analysis were drawn from the Center's longitudinal study, which was initiated in 1998 and has enrolled 269 individuals since inception. Of these 269 participants, 182 have a diagnosis of idiopathic PD by UK Brain Bank criteria (Hughes *et al.*, 1992), 19 have related non-PD movement disorders, and 68 are controls with no movement disorder. At the time of enrollment and approximately every two years subsequently, participants underwent a full psychiatric evaluation to assess the presence of neuropsychiatric abnormalities in accordance with standards of the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV) (American Psychiatric Association, 2000). Screening for psychiatric disorders was conducted using the Schedule for Clinical Interview and Diagnosis (SCID) (First *et al.*, 1997). The SCID symptom checklist for psychotic disorders assesses the presence of delusions or hallucinations. The diagnosis of psychosis requires endorsement of prominent hallucinations—visual, auditory, tactile, gustatory, or olfactory—or delusions. Additionally, symptoms were required to be primary (i.e. not caused by using drugs, taking medication, illness, or drinking habits) and occur in the absence of a concurrent mood episode for a psychosis diagnosis to be made. These visits also included an MMSE, Hoehn and Yahr stage determination (Hoehn and Yahr, 1967), and medication list/dosage updates.

We aimed to evaluate the longitudinal association between diagnosis of psychosis and scores on the six subscales of the MMSE, which are outlined in Table 1. These subscales were structured as originally described (Folstein, Folstein and McHugh, 1975), with the exception that we examined the intersecting pentagon construction item as a separate subscale testing visuospatial skills and executive function, as has been done previously (Nagaratnam, Nagaratnam and O'Mara, 2014; Cagnin *et al.*, 2015). Inclusion criteria for this analysis were a clinical diagnosis of idiopathic PD and complete information regarding the results of psychiatric assessment, MMSE scores, medications, and disease course. In the present study, 137 participants met these criteria. Participant age was defined as age at enrollment, and disease duration was defined as the time that elapsed between diagnosis and baseline evaluation. The levodopa equivalent daily dose (LEDD) was calculated for each subject based on their medication lists in accordance with convention (Tomlinson *et al.*, 2010). Where carbidopa/levodopa was prescribed to be used "as needed," we estimated its LEDD

contribution as the midpoint between the usual maximum (3 doses per day) and minimum (0 doses per day) daily values.

Statistical analysis

The dependent variable for the present study was diagnosis of psychosis in accordance with DSM-IV criteria. The independent variables of interest were scores on MMSE subscales (Table 1). Regression with generalized estimating equations (GEE) was used to model the association between a binary outcome (psychosis diagnosis) and predictor variables of interest. Generalized estimating equations allow for correlation of within-subjects to be estimated, facilitating the analysis of time-varying metrics in repeated-measures data (Locascio and Atri, 2011). Univariable models were first created to identify which variables were most strongly associated with psychosis and to determine which covariates were appropriate to include in subsequent multivariable models. To produce adjusted model estimates of the correlations between MMSE subscales and psychosis, several multivariable GEE models were created, one for each MMSE subscale that was significantly associated with psychosis in an unadjusted univariable model. Non-MMSE variables that were significantly associated with psychosis in univariable were selected for each multivariable model as covariates; however, antipsychotic medications were not included as a covariate because psychosis is an indication for their use, which reduces the signal from other variables. An exchangeable correlation structure was employed in all GEE analyses, and the scale parameter was fixed at the default value of 1 for binomial outcome modeling. We report odds ratios with corresponding 95% confidence intervals and *p*-values for each GEE model. Relative odds ratios were calculated as the exponentiated regression coefficients and confidence interval endpoints. Statistical significance was accepted at $p < 0.05$.

Results

Demographic and clinical characteristics at baseline for the 137 participants in our study are presented in Table 2. The mean age (± standard deviation) at enrollment in the longitudinal study was 66.2 ± 10.1 years, and the ratio of males to females was typical for PD, with 58.4% of the sample being male. Participants ranged from newly diagnosed to three decades beyond diagnosis, with the mean disease duration being 6.3 ± 5.1 years. The duration and frequency of follow-up psychiatric and MMSE evaluations are presented in Table 3. A total of 97 participants were evaluated longitudinally (at least twice) for up to 16 years. The median total follow-up time for participants who were evaluated longitudinally was 3.8 years (interquartile range = 2.0–6.9) and the number of serial evaluations per participant ranged from 2 to 8. A total of 358 evaluations were included in the GEE regression analyses. Nineteen participants (13.9%) were diagnosed with psychosis at their baseline evaluation upon enrollment, and 12 additional participants were diagnosed throughout study follow-up. Sixteen of these 31 unique psychosis cases (51.6%) used antipsychotic medications during the study, whereas only eight of the remaining 106 participants (7.5%) with no psychosis diagnoses used an antipsychotic. Among the 31 participants with psychosis, there were 50 evaluations where a psychosis diagnosis was made.

Logistic regressions with GEE were used to model associations between psychosis and several independent variables of interest, including MMSE total scores and subscale scores (Table 4). Lower total MMSE scores and lower scores on three MMSE subscales were significantly associated with psychosis in univariable analysis: orientation, language, and intersecting pentagons. Hoehn and Yahr stage, higher LEDD, and fewer years of education were significantly associated with psychosis, and these three variables were used as covariates in subsequent multivariable regression models to produce adjusted estimates of the associations between MMSE subscales or total score and psychosis. These models indicated that the presence of psychosis was associated with lower total MMSE scores (rOR: 0.88; 0.81–0.96; $p = 0.003$) and scores on the orientation (rOR: 0.73; 95% CI: 0.58–0.93; $p = 0.011$), language (rOR: 0.64; 95% CI: 0.48–0.86; $p = 0.003$), and intersecting pentagon (rOR: 0.43; 95% CI: 0.20–0.92 $p = 0.030$) subscales of the MMSE.

Discussion

In the present manuscript, multivariable analyses showed that lower total MMSE scores, as well as lower scores on the orientation, language, and intersecting pentagon components of the MMSE were associated with psychosis per DSM-IV criteria in non-demented PD participants. Registration, attention and calculation, and recall were not similarly associated. These findings are largely in agreement with a recent review of prior studies of cognitive impairment patterns in PD psychosis, which reported executive function and visuospatial skills—assessed by intersecting pentagon construction in our analysis—to be most consistently impaired in the literature (Lenka *et al.*, 2017). This review also reported that language skills are impaired more often than not in relevant studies. (Lenka *et al.*, 2017). Attentional deficits have also been reported in PD psychosis, but we did not detect an association using the corresponding MMSE subscale-item (serial sevens). By adjusting for potential confounding variables, including LEDD, years of education, and Hoehn and Yahr stage, we can conclude with reasonable certainty that the impairments we noted are not artifacts of the disease process or its management, but deficits specific to psychosis in the absence of co-morbid dementia.

Although cognitive dysfunction occurs on a clinical continuum and manifests heterogeneously in PD, it is generally recognized as a symptom that accompanies PD psychosis (Fénelon and Alves, 2009; Factor *et al.*, 2003; Litvan *et al.*, 2012; Monastero *et al.*, 2013). Most existing literature on cognitive dysfunction associated with PD psychosis has focused on its most common symptom: visual hallucinations, which have a lifetime prevalence of approximately 50% among PD patients (Williams and Lees, 2005). However, perceptual disturbances in PD psychosis vary; hallucinations can occur in olfactory, auditory, tactile, or gustatory sensory modalities. Delusions are less common in PD psychosis, with a prevalence of about 5–10%; nevertheless, they represent a clinically important problem (Fénelon and Alves, 2009). Additionally, not all studies on the nature of cognitive impairment in PD patients with psychosis exclude those with dementia or at least require some threshold of cognitive function. Our study used DSM-IV guided diagnosis of psychosis as the outcome of interest and visits where patients were diagnosed with dementia were excluded from analysis, increasing the specificity of our findings for psychosis-related cognitive impairment in PD patients. Although early cognitive dysfunction often transitions

to dementia in PD (Litvan *et al.*, 2012), our findings indicate that domain-specific cognitive impairment preceding dementia can be associated with psychosis. Recognizing these deficits may help clinicians identify psychotic symptoms earlier in the disease and initiate effective antipsychotic medication regimens before the onset of dementia contraindicates their chronic use.

We found the language subscale of the MMSE to be most strongly associated with psychosis in our study. Deficits in various aspects of language proficiency have been previously reported in PD patients with visual hallucinations. Multiple studies have shown reduced performance on the Boston Naming test in PD patients with visual hallucinations (Ramírez-Ruiz *et al.*, 2006; Factor *et al.*, 2014), a test for anomic aphasia which requires patients to recognize and name various line-drawn objects. One study noted slightly lower performance among such patients on the Token test (Ramírez-Ruiz *et al.*, 2006), which assesses language comprehension as well as object recognition, working memory, and the ability to act in response to verbal instructions. Similarly, the MMSE language subscale includes questions testing object recognition, instruction-following, and the ability to write a full sentence. Thus, this subscale might be better understood to test a small range of functions that all depend on verbal comprehension.

In our analysis, scores on the MMSE subscale that assesses orientation were significantly lower in participants with psychosis. Impaired orientation is a hallmark of dementias (Burrell and Piguet, 2015); however, as we excluded participants with dementia in our study, we conclude that psychosis is independently associated with decreased orientation. Relatively little work has been done on this aspect of cognitive function in PD, although the Parkinson Psychosis Questionnaire (PPQ), a screening test intended to detect drug-induced PD psychosis, tests orientation to place and time as the MMSE does (Brandstaedter *et al.*, 2005). While the authors noted that this component of the questionnaire is a weaker predictor of DSM-IV psychosis than hallucinations or delusions, they conclude that it may be useful as an additional marker of psychotic symptoms. In the absence of dementia, psychosis is a more important determinant of nursing home placement than either reduced motor control or cognitive impairment in PD (Goetz and Stebbins, 1993). Thus, PD psychosis may be associated with disorientation that reduces the ability for self-care in a manner similar to that which is common in dementia.

We also found that participants with psychosis were significantly less likely to be able to complete the intersecting pentagon item. This item comprises its own MMSE domain and serves as a simple test of executive function and visuospatial skills (Nagaratnam, Nagaratnam and O'Mara, 2014). Both of these functions are impaired in patients with visual hallucinations (Ramírez-Ruiz *et al.*, 2006; Factor *et al.*, 2014). Multiple imaging modalities (fMRI, voxel-based morphometry, PET, SPECT) have demonstrated dysfunction in various frontal-executive and visuoperceptual brain regions—including the cingulate, prefrontal, and visual cortices and the superior frontal and fusiform gyri—in PD patients with visual hallucinations (Alzahrani and Venneri, 2015). These patients also show reduced performance on many tests of executive function, including set shifting tasks (Trailmaking B test) timed alternation of numbers and symbols (Digit symbol test), top-down inhibition (Stroop color-word test), and hypothesis guided strategy (Wisconsin card sorting test) (Factor *et al.*, 2014).

The significant association between MMSE intersecting pentagon construction and psychosis in our study suggests that this simple assessment may be sufficient to demonstrate the executive and visuospatial impairment of PD psychosis. Furthermore, deficits in pentagon construction (and semantic verbal fluency) have been isolated as deficits associated with subsequent progression from mild cognitive impairment to PD dementia, suggesting that a process involving temporal, parietal, and occipital regions may underlie both cognitive impairment and psychosis (Williams-Gray *et al.*, 2007).

The range of MMSE scores at baseline in our study was 17–30, and the cutoff for PD-dementia is 24/25; however, this cutoff has a positive predictive value of approximately 83% when compared against DSM-IV based diagnosis for dementia, which includes a consideration of impact on functioning (Hoops *et al.*, 2009). Studies using MMSE scores alone to exclude demented patients may therefore misclassify patients whose dementia status is not accurately captured using the MMSE cutoff. Other cognitive screening tests, such as the Montreal Cognitive Assessment, are more robust for accurately diagnosing dementia in PD (Hoops *et al.*, 2009). Participants in our study remained non-demented per their DSM-IV interview data for each evaluation considered. Additionally, if a participant was diagnosed with dementia, we excluded data from that evaluation and censored all visits going forward.

A limitation of our study is some degree of variability in participant follow-up due to attrition and/or mortality. Excluding patients after a dementia diagnosis also reduced the effective length of follow-up among our participants as well as the total number of psychosis cases observed, which may have introduced sampling bias and perhaps reduces the generalizability of our findings for patients with very severe disease. We lack the data to comment conclusively on whether psychosis specifically may have been a factor that catalyzed attrition. However, the variability in our subject evaluation spacing was not dramatic; a median of 2.1 (IQR = 1.9–2.2) years separated serial evaluations, suggesting that no concerning deviation from the scheduled 2-year evaluation interval occurred. A strength of GEE models is that they remain robust even when repeated measures are not separated by equal time intervals (Locascio and Atri, 2011). Our relatively large sample size—made more effective through GEE modeling of repeated measurements—permitted us to observe more cases of psychosis than a cross-sectional study would have revealed, especially given that we excluded patients with dementia. Additionally, this study design permitted the temporal onset of psychosis to be related to cognitive impairments longitudinally. However, the use of this methodology does not produce information on how MMSE subscale scores might be used to predict later incident psychosis, which remains an area for future investigation. Use of additional cognitive tests as comparators to qualify our MMSE findings would be ideal, but unfortunately such tests were not included in the study. Additionally, day-to-day variation or fluctuations in cognition impairment, even in non-demented PD patients, may have impacted MMSE scores. Finally, DSM-IV psychotic disorder criteria require prominent hallucinations or delusions, potentially making our findings less generalizable to patients with illusions or minor hallucinations, which are not uncommon in PD. Importantly, these criteria also exclude patients with symptoms that are likely secondary to medication. This may partly explain the negative association we noted between DSM-IV psychosis and dopamine agonist use (Fénelon and Alves, 2009). Another key explanation could be

withdrawal of these medications by the neurologists following our participants outside the context of the study.

We conclude that PD psychosis is associated with lower scores on the orientation, language, and intersecting pentagon subscales of the MMSE. Importantly, whereas prior studies relating domain-specific cognitive deficits to PD psychosis have used specialized tests that are not relied upon in the clinical setting, our findings show how psychosis-related cognitive impairment manifests in the context of the MMSE, a widely used cognitive screening test that is easy to administer. Our findings also contribute to a growing understanding that PD patients with psychosis may be more likely to experience cognitive impairment in specific domains of function. These deficits are likely to represent an earlier and more specific association with psychosis than the severe global cognitive impairment observed in dementia.

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Key points

- Domain-specific cognitive impairment on the MMSE is associated with PD psychosis.
- Language, executive function, and orientation are impaired in PD psychosis.
- The MMSE may be useful for identifying increased psychosis likelihood in PD.

Table 1

MMSE subscales

MMSE subscale	MMSE item(s) #	MMSE item	Points
Orientation	1–5	Day of the week/date/ month/season/year	5
	6–10	Current city/state/ name location/floor of building/name one street surrounding hospital	5
Registration	11	Repeat three words	3
Attention and calculation	12	Serial sevens up to five iterations	5
Recall	13	Recall three words	3
Language	14	Identify wrist watch	1
	15	Identify pencil	1
	16	Repeat “no ifs, ands, or buts”	1
	17	Read and respond to written instruction	1
	18	Following instructions (folding paper, three- stage process)	3
	19	Write any complete sentence	1
Intersecting pentagons	20	Draw intersecting pentagons	1
Total			**30**

Table 2

Clinical and demographic characteristics of sample at baseline (n = 137)

Characteristic	Mean or *n* (%)	Standard deviation	Range
Age at enrollment, years	66.2	10.1	42.1 to 90.4
Age at PD diagnosis, years	59.9	10.8	36.0 to 86.4
Disease duration, years	6.3	5.1	0.0 to 31.0
Education, years	10.2	4.5	2 to 27
MMSE	27.7	2.7	17 to 30
Male sex	80 (58.4%)	—	—
Hoehn and Yahr, *n* (%)		—	—
(1)	11 (8.0%)		
(1.5)	6 (4.4%)		
(2)	51 (37.2%)		
(2.5)	32 (23.4%)		
(3)	25 (18.2%)		
(4)	11 (8.0%)		
(5)	1 (0.7%)		

Table 3

Overview of patient participation in longitudinal follow-up evaluations with psychosis frequency summary (*n* = 137)

Variable	Statistic
Length of follow-up, years, median (IQR) (range)	3.8 (2.0–6.9) (1.4–15.8)
Time between serial evaluations, years, median (IQR) (range)	2.1 (1.9–2.3) (0.9–4.7)
No. serial evaluations (1/2/3/4/5/6/7/8)	40/47/14/19/5/6/3/3
Total evaluations included in analysis	358
DSM-IV psychotic disorder	
Baseline prevalence	19 (13.9%)
Incidence during follow-up evaluations	12
Number of evaluations with diagnosis	50

IQR = interquartile range. Length of follow-up and average time between evaluations only calculated for participants with at least two serial observations (*n* = 97). For psychotic disorder, baseline prevalence indicates the number of participants with a psychosis diagnosis at the time of study enrollment; incidence indicates unique participants *not* diagnosed with psychosis at baseline who were diagnosed at a subsequent evaluation.

Table 4

Univariable and multivariable regression analyses with GEE evaluating factors associated with psychosis

	Univariable regression		*Multivariable regression*	
Independent variable	**rOR (95% CI)**	***p***	**rOR (95% CI)**	***p***
Antipsychotic medication usage	7.97 (3.5–17.9)	<0.001***	—	—
Anticholinesterase inhibitor usage	2.37 (0.43–13.2)	0.325	—	—
Dopamine agonist usage	0.36 (0.19–0.67)	0.001**	—	—
Anticholinergic medication usage	2.00 (0.83–4.82)	0.120	—	—
Age	1.02 (0.98–1.06)	0.276	—	—
Disease duration	1.06 (0.99–1.13)	0.110	—	—
Hoehn and Yahr stage	1.72 (1.00–2.94)	0.048*	—	—
LEDD (daily mg/300)	1.26 (1.05–1.52)	0.015*	—	—
Education	0.90 (0.83–0.98)	0.017*	—	—
Female sex	0.48 (0.20–1.18)	0.110	—	—
MMSE score (total)	0.85 (0.78–0.93)	<0.001***	0.88 (0.81–0.96)	0.003**
MMSE: Registration	0.54 (0.26–1.14)	0.100	—	—
MMSE: Attention and calculation	0.82 (0.62–1.07)	0.140	—	—
MMSE: Recall	0.83 (0.64–1.09)	0.180	—	—
MMSE: Orientation	0.68 (0.53–0.87)	0.002**	0.73 (0.58–0.93)	0.011*
MMSE: Language	0.62 (0.46–0.83)	0.001**	0.64 (0.48–0.86)	0.003**
MMSE: Intersecting pentagons	0.36 (0.18–0.72)	0.004**	0.43 (0.20–0.92)	0.030*

rOR, relative odds ratio (increase in outcome odds per unit increase in independent, holding any other covariates constant). LEDD, levodopa equivalent daily dosage.

* $p < 0.05$;

** $p < 0.01$.

A univariable logistic regression model with GEE was created for each of the independent variables listed, with the corresponding rOR, 95% confidence intervals, and *p*-values. LEDD values were divided by 300 to facilitate odds ratio interpretation. Four multivariable logistic regression models with GEE were created for the three MMSE subscales that were significantly associated with psychosis in univariable, as well as the total MMSE score. Each multivariable model included Hoehn and Yahr stage, LEDD, and years of education as covariates.