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Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease

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ABSTRACT

Apathy and depression are heterogeneous syndromes with symptoms that overlap clinically. This clinical overlap leads to problems with classification and diagnosis in clinical populations. No functional imaging study has attempted to separate brain regions altered in apathy from those altered in depression in a clinical population. Parkinson disease (PD) is a disorder in which apathy and depression co-exist in a single population. We evaluate the relationship between apathy, depression, and motor severity of disease in PD, focusing on the relationship between these factors and the amplitude of the low frequency fluctuation (ALFF) in the resting state. We first evaluated if the resting ALFF signal is a reliable measure for our clinical question. For this, we develop and introduce a cross validation approach we term the "Regional Mapping of Reliable Differences" (RMRD) method to evaluate reliability of regions of interest deemed "significant" by standard voxel-wise techniques. Using this approach, we show that the apathy score in this sample is best predicted by ALFF signal in the left supplementary motor cortex, the right orbitofrontal cortex, and the right middle frontal cortex, whereas depression score is best predicted by ALFF signal in the right subgenual cingulate. Disease severity was best predicted by ALFF signal in the right putamen. A number of additional regions are also statistically (but not reliably) correlated with our neuropsychological measures and disease severity. Our results support the use of resting fMRI as a means to evaluate neuropsychiatric states and motor disease progression in Parkinson disease, and the clinical and epidemiologic observation that apathy and depression are distinct pathological entities. Our finding that "significance" and "reliability" are dissociated properties of regions of interest identified as significant using standard voxel-wise techniques suggests that including reliability analyses may add useful scientific information in neurobehavioral research.

Introduction

Major depression is a heterogeneous disorder with distinct subgroups that may result from involvement of distinct and individual neurotransmitter systems (Mayberg et al., 1997; Videbech, 2000; Winokur, 1997). Apathy refers to a set of behavioral, cognitive, and affective features including reduced interest and participation in the main activities of daily life, a lack of initiative, a trend towards early withdrawal, indifference, and flattening of affect (Dujardin et al., 2008; Marin et al., 1991). Apathy is also a common behavioral syndrome that may bear a relationship to loss of interest commonly described in depression (DSM IV, 2000), but also clearly exists as a unique and distinct entity in a number of neurologic diseases (Levy et al., 1998). Apathy and depression may be clinically distinguished by the presence or absence of altered mood, however in practice the two syndromes may co-occur in the same individual and they are often confused by both patients and clinicians. There are a number of studies evaluating functional imaging features associated with apathy, or with depression. However there are no imaging studies that attempt to distinguish the specific characteristics of these distinct, sometimes overlapping syndromes.

Parkinson disease (PD) is a disorder that is characterized by de-novo development of a number of affective symptoms, including depression, apathy, compulsive behaviors, and anxiety (Chaudhuri et al., 2006). PD is pathologically characterized, at least initially, by relatively selective vulnerability of certain neuronal populations

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including brainstem serotoninergic, dopaminergic, and noradrenergic systems (Braak et al., 2004). With more severe disease, PD pathologically impacts limbic regions such as the amygdala, basal forebrain areas, and mesial regions of the temporal mesocortex (a region that additionally sends bidirectional projections into the entorhinal regions, the hippocampus, and the amygdala — Braak et al., 2003).

Apathy and depression may co-exist in PD and are often de-novo syndromes in individuals without previous affective symptoms. Recognition of an internal state of depressed mood can occur during rest (e.g. when not physically occupied), and in fact sense of well being and symptoms of depression may fade when individuals are in an active state (Fox, 1999; Stephens, 1988). Conversely, emerging into action requires exiting a resting state, a process that might be impaired in the syndrome of apathy. Therefore, an evaluation of the resting state may be useful in evaluating the underpinnings of apathy and depression. The relationship between motor symptoms and nonmotor symptoms such as apathy and depression in PD is not well established. Nonmotor symptoms may predate onset of motor symptoms in some patients. It is unclear, however, on whether increasing severity of motor symptoms might correlate with increasing apathy or depression (Huber et al., 1988; Schrag, 2004; Stella et al., 2007).

We sought to determine how apathy, depression, and motor progression would differentially affect the resting state in PD. In order to characterize the resting state, we use an analysis of the low frequency function (ALFF), a full brain measure that allows us to look at the resting state across the entire brain in our sample on a voxel-wise basis. We evaluated how apathy and depression were related to disease severity in our sample, and additionally evaluate how changes in the ALFF signal relate to disease severity within the sample.

While our primary objective in this manuscript is to better understand possible functional alterations in the brain associated with apathy and depression in PD, general concerns have been raised about the validity of functional imaging as a measurement tool in studies of emotion, personality, and social cognition (Vul et al., 2009). While a variety of authors have responded to these arguments (Leiberman et al., 2009; Poldrack and Mumford, 2009), debate has primarily focused on issues related to lack of appropriate multiple comparison analysis in some papers, and more general the possible issue of “non-independence” resulting in the development of high correlations that occur “by chance”. However, little attention has focused on some other standard causes of error in regression analyses, such as the effects of outliers on datasets and issues of reliability. Since resting state ALFF analysis has not commonly been used in evaluating behavioral traits, we considered it an open question whether a task-free or resting condition might provide reliable information with regard to a behavioral trait. We therefore sought not just to evaluate the significance of our correlations, but also reliability, by generating a reliability map and modifying a statistically standard cross validation analysis (prediction error sum of squares or PRESS analysis) to be applicable to a functional imaging dataset (Weisberg, 1985). Specifically, we first use a repeated analysis at a particular voxel-wise threshold to develop repeated regional significance maps. Secondly, these repeated regional significance maps are used as a basis for cross-validation to generate a prediction. We term the combined approach of generating a reliability map using repeated analysis and subsequently using this map to generate prediction estimates the “Regional Mapping of Reliable Differences” (RMRD) approach.

Material and methods

Participants

Participants include 22 subjects with Parkinson disease (PD). Subjects had a Mini-Mental Status score of $\geq$24. Subjects were diagnosed on the basis of a history and neurologic examination by a fellowship trained movement disorders specialist. Analysis for motion artifact occurred prior to any further image processing or analysis. Six subjects with PD were excluded from analysis due to excessive head motion. After processing but prior to statistical or reliability analysis, an additional subject with PD was excluded due to a subsequent diagnosis of multiple systems atrophy (MSA) based on clinical progression and a confirmatory fluorodopa PET image. All subjects came in off medication for imaging and neuropsychological testing. All subjects had a neurological examination and neuropsychological testing including a Unified Parkinson's Disease Rating Scale (UPDRS) examination (Fahn and Elton, 1987), the Mini-Mental Status (MMSE — Folstein et al., 1975), the Montreal Cognitive Assessment (MoCA — Nasreddine et al., 2005), the Trail Making Test (Reitan, 1958), the Stroop Color-Word Test (Stroop, 1958), a Judgment of Line Orientation (JLO) test (Benton et al., 1983), the Hamilton Rating Scale for Depression (HRSD — Hedlung and Vieweg, 1979), and both the subject and a spouse or caregiver completed the relevant version of the Lille Apathy Rating Scale (LARS — Dujardin et al., 2008). Table 1 shows the demographics of the sample.

Functional imaging and data preprocessing

Functional imaging was performed on a Philips Achieva 3.0 T scanner (Philips Medical Systems, Best, The Netherlands) with the parameters: TR = 2000 ms, TE = 30 ms, FOV = 240 mm, slice thickness = 3.8 mm, Gap = 0, Flip Angle = 80°, totally 36 slices, parallel to AC–PC line, acquisition matrix = 64 × 64. Three dimensional structural images are also obtained. Analysis is performed using the Analysis of Functional Neuroimaging (AFNI) software package (Cox, 1996), and included the following initial processing steps: (1) slice time correction for acquisition time difference between slices; (2) head motion correction for head movement during the scan — head motion covariates are later used as signals of no interest during analysis; (3) linear detrending of signal drift; (4) spatial normalization to a standard MNI axis with a sample resolution of 1 × 1 × 1 mm to match resolution of the underlying anatomic map; and (5) spatial smoothing with a 6-mm Gaussian kernel to minimize individual variance and enhance signal-to-noise ratio (SNR). An initial data quality step involves determining the overall coefficient of variance in all subjects across all voxels; individuals with a coefficient of variance of >1.5% are excluded from the dataset. Retrospective viewing of all data sets disclosed that in all cases, individuals with variance >1.5% had visible excess motion not well captured by AFNI's least squares method of motion correction, while individuals with a coefficient of variance of <1.5% had no visible excess motion after least squares correction. Overall calculated motion on the basis of motion correction covariance residuals was <5 mm. With respect to individuals with overall dataset coefficient of variance of >1.5% (those excluded from the sample), among the six subjects excluded, 4 had significant resting tremor and 2 had executive dysfunction and appeared to have difficulty following instructions in the scanner to remain still. The ALFF signal was calculated within a frequency band of 0.01–0.08 Hz using described methods (see description below). We analyzed ALFF within a defined anatomic region including the brain, cerebellum, and basal ganglia but excluding the ventricles and brainstem. A total of 1,919,208 voxels were within our regional mask (see Statistical analysis section below for details on analysis within the mask).

Determining the ALFF signal

For each scan and each participant, we performed an analyses to identify those voxels with significantly detectable the amplitude of low frequency fluctuations (ALFF). For a time series x(t), ALFF is calculated as the sum of amplitudes within a specific low frequency range (Zuo et al., 2010). In our case, based on the work of Yu-Feng