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Research Report

Longitudinal EEG Changes Correlate with Cognitive Measure Deterioration in Parkinson's Disease

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Abstract.
Background: QEEG could provide physiological biomarkers for changes over time in Parkinson's disease (PD) cognitive decline if they track with longitudinal neuropsychological performance.
Objective: Our aim was to correlate longitudinal changes in frequency domain quantitative electroencephalography (QEEG) measures with change in neuropsychological performance testing in PD.
Methods: 71 PD subjects, not demented at baseline, were studied from the Arizona Study of Aging and Neurodegenerative Disorders cohort. Baseline and follow-up digital EEG from PD subjects were analyzed for QEEG measures of background rhythm frequency and global relative power in delta (2.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz) bands. Baseline and subsequent evaluation included Mini Mental Status Examination and five other neuropsychological tests that load on cognitive domains known to decline in PD. Pearson coefficient was used to assess correlations. Multiple linear regression modeling was used to assess the effect of variable combinations of QEEG and other measures, including age and PD duration.
Results: Changes in delta bandpower showed the highest and most consistent pattern of correlations with longitudinal changes in neuropsychological testing. The highest correlation was between delta bandpower increase and decline in the Rey Auditory-Verbal Learning Test (-0.59:$p < 0.001$). Delta bandpower was also increased in the incident dementia group compared to non-dementia at followup.
Conclusions: 1) Longitudinal change in the QEEG frequency domain measure of delta bandpower correlated best with longitudinal neuropsychological performance change in PD; 2) These results constitute preliminary evidence that delta bandpower may be a suitable biomarker for evaluating PD cognitive deterioration longitudinally.

Keywords: Parkinson's disease, dementia, electroencephalography, biological markers

INTRODUCTION

Biomarkers, by definition, are objective indicators of a disorder beyond that obtained through routine clinical history and physical examination [1]. Such measures often assess a particular aspect of the disorder and may be used for diagnosis, prediction, or as a surrogate for severity. Successful clinical trials for Parkinson's disease (PD) cognition require that biomarker candidates be reliable, sensitive, non-invasive, and inexpensive. While multiple biomarkers have been proposed for motor and non-motor aspects of PD, the search for optimal biomarkers for each of the multiple aspects of PD continues [2, 3].

Quantitative encephalography (QEEG) measures may be ideal biomarkers to complement neuropsychological testing for studying cognitive decline among PD patients, as spectral measures have shown promise

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as surrogate biomarkers for cognitive state (i.e. non-dementia versus dementia) [4–10]. Similar QEEG spectral changes have been observed in Alzheimer's disease (AD), and therefore should not be considered specific for PD [11, 12]. Nevertheless, such changes could be successfully employed as a biomarker within PD groups. The resting EEG is simple to acquire, requires minimal patient cooperation, and is not dependent on verbal or motor responses which may be affected by motor dysfunction in PD. Moreover, EEG has good test-retest reliability and is not subject to learning effects like some cognitive testing. In addition, EEG peak background rhythm frequency was found to be a possible predictive biomarker for subsequent development of dementia in PD [13].

Multiple cross-sectional studies using EEG and magnetoencephalography (MEG) have shown slower spectral frequencies with advancing cognitive decline, suggesting a progression in cortical oscillatory activity with advancing PD stage and cognitive decline [9, 10, 14]. Recently, Olde Dubbelink et al. showed with MEG that such progression does occur longitudinally in resting-state brain activity [14]. Moreover, even though only 3 subjects in that study developed dementia on followup, there was a significant association between cognitive performance deterioration and with widespread increased slower and decreased faster MEG frequencies.

QEEG can provide useful physiological biomarkers for PD cognitive decline in clinical therapeutic trials if longitudinal changes in QEEG measures track sensitively and predictably with neuropsychological performance. Since digital EEG is readily available at most medical centers, there is a need to investigate its usefulness as a physiological biomarker of PD cognition. In this study, we evaluated the correlation of longitudinal frequency domain QEEG changes with changes in neuropsychological assessments with correlation coefficients. In addition, we examined which QEEG frequency changes were most specifically associated with PD dementia development.

METHODS

Standard protocol approvals, registrations, and patient consents

The Banner Health-Sun Health Research Institute (BH-SHRI) and Mayo Clinic institutional review boards approved all procedures and written informed consent was obtained from study participants.

Subjects

The PD cohort was studied as part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), a program under Banner Health-Sun Health Research Institute (BH-SHRI). AZSAND is a brain donation program that performs prospective, standardized, regular longitudinal pre-mortem assessments until death [15]. The PD cohort of subjects in AZSAND undergoes annual pre-mortem movement (including United Parkinson's Disease Rating Scale (UPDRS) part III (motor) and Hoehn and Yahr (H&Y) staging with PD medication held night before) and neuropsychological evaluation. Medications and health status are assessed every year. PD medications were converted to levodopa equivalents as in previous publications [9, 13]. Subjects also undergo biennial digital EEG recording [9, 13]. We queried our database for baseline diagnosis of PD in September 2014 that had baseline and followup EEG. PD was diagnosed as previously described along the lines of the UK Parkinson's Disease Society brain bank clinical diagnostic criteria (bradykinesia plus at least one other cardinal feature of PD, no atypical features or secondary cause, and response to dopaminergic medication) [16]. We excluded subjects with dementia at baseline, and we excluded EEG examinations with deep brain stimulation, and barbiturate, benzodiazepine or anti-seizure medication on day of EEG to avoid influencing the EEG. This procedure yielded 71 PD subjects with baseline and followup visits. Movement Disorder Society criteria for dementia were employed both at baseline and followup [17].

Neuropsychological testing

Baseline and followup test analyses included: 1) Mini Mental Status Examination as a global test of cognitive function, and 2) Five neuropsychological tests which load on cognitive domains known to decline in PD [3]. The five non-global neuropsychological tests were: long-term memory score on the Rey Auditory-Verbal Learning Test (AVLT-LTM), Controlled Oral Word Association Test (COWAT), Stroop Word-Color (W/C) Interference, Trails B, and Clock Drawing Test (scored on a 10 point scale as per Rouleau et al. [18]). The individual performing the QEEG analysis (JNC) was blinded to the neuropsychological evaluation. Likewise, the consensus conference to determine the cognitive status of the PD subjects was not aware of the EEG results.

EEG recording

Recordings during relaxed wakefulness were obtained from PD subjects in the "on" state, seated in a recliner with eyes closed as previously described [9, 13]. Briefly, Ag/AgCl EEG electrodes were placed on the scalp using twenty standard 10–20 EEG electrode positions. Recordings were referenced to the Fz electrode, with a right mastoid electrode serving as ground. Electrode impedances were closely monitored and kept below 5 kohms. Data were acquired using the Neuroscan Synamps2 system (Compumedics, Charlotte, NC, USA) at a sampling rate of 1000 Hz and a bandpass of 1 – 200 Hz. An EEG technician and neurophysiologist (JNC) were present during the entire recording session to observe the behavioral state of the patient and to monitor on-line for signal quality. Patients were asked every minute if they were awake, and drowsiness was further excluded by monitoring for background changes and slow eye movements of drowsiness during the course of the recording. When muscle, eye movement/blink, or other artifacts were identified, the subject was coached until an artifact-free signal was obtained. The final recorded sample consisted of an awake and artifact-free period of approximately 100–120 seconds.

EEG data processing

Baseline and followup EEG from PD subjects was analyzed for frequency domain QEEG measures of background rhythm frequency (BRF) and global relative power in delta, theta, alpha, and beta bands. The data from EEG were processed off-line using Neuroscan EDIT software (Compumedics, Charlotte, NC, USA). Consecutive, non-overlapping, 4096-point epochs were created from the continuous data, allowing for a frequency resolution of 0.244 Hz. Each epoch was visually inspected for artifacts, though rejection of artifacts was uncommon due to the monitoring of the online acquisition. The number of epochs accepted for further processing ranged from 25–30. The epochs were passed through a 10% cosine window, processed with a fast Fourier transform (FFT), and averaged to produce an averaged FFT power spectrum for each electrode. The background rhythm frequency (BRF) was defined as dominant peak in the power spectra of the posterior electrodes (P3, P4, Oz) determined by visual inspection of the FFT average.

Frequency bands were designated as follows: delta = 2.5–3.9 Hz; theta = 4–7.9 Hz; alpha = 8–12.9 Hz; beta = 13–30 Hz. The global (over multiple electrodes) relative (%) EEG bandpower for each of the four frequency bands was calculated (using all electrodes except Fp1, Fp2, A1, and A2) as a percentage of total EEG power between 2.5 and 30 Hz from the FFT average.

Statistics

The association between the change in EEG levels and the change in neuropsychology scores was assessed by using the Pearson correlation coefficient. Multiple linear regression modeling was also used to assess the association between neuropsychology score change, and combinations of multiple QEEG measures, age, PD duration, motor scores, levodopa equivalents, and follow-up time. Change from baseline among subjects with incident dementia was compared to that of subjects without incident dementia by using the two-sample *t* test.

RESULTS

Cohort characteristics

EEG examinations were performed between August 2000 and September 2014. After exclusions, including 19 subjects that had dementia at baseline, 71 PD subjects with a mean (SD) followup interval of 3.9 (2.2) years remained. Table 1 data shows baseline and followup characteristics for the cohort. The baseline data are consistent with our other EEG studies [9, 13]. At followup, the UPDRS in the off state was not significantly different, but the Hoehn and Yahr staging and levodopa equivalents had increased. Every neuropsychological test showed a significant group difference at followup, consistent with progressive deterioration of neuropsychological performance.

Correlation of QEEG measure change with neuropsychological testing

Table 2 shows the correlation *r* values and their significance for between the changes in neuropsychological and the change in QEEG spectral measure. Longitudinal delta bandpower change had the highest and most significant correlations with changes among the neuropsychological tests. There was much less of a consistent pattern of significant correlations seen with the other QEEG spectral measures. However,

Table 1
Baseline mean and standard deviation (SD) for demographic, motor scales, levodopa equivalents and neuropsychology test results

	Baseline (SD)	Followup (SD)	Change (SD)	*P* value
Age (y)	73.7 (8.0)	–	–	–
Male (%)	60	–	–	–
Parkinson's disease duration (y)	8.5 (4.9)	–	–	–
UPDRS III (off state)[1]	22 (12)	28 (16)	5 (17)	0.06
Hoehn and Yahr Stage[1]	2.27 (0.71)	2.66 (0.93)	0.39 (0.86)	0.001
Levodopa equivalents[2] (milligrams)	640 (360)	820 (420)	180 (310)	<0.001
Mini mental status exam	27.8 (2.0)	26.7 (3.3)	−1.1 (3.3)	0.007
AVLT-LTM	8.1 (3.7)	6.4 (4.0)	−1.7 (3.5)	<0.001
Controlled oral word association	36 (12)	31 (13)	−4.8 (9.5)	<0.001
Stroop Word-Color interference	29.2 (9.0)	23.4 (10.8)	−5.8 (9.4)	<0.001
Trails B (seconds)	121 (73)	179 (89)	58 (69)	<0.001
Clock drawing	9.2 (1.0)	8.6 (1.7)	−0.6 (1.4)	0.001

[1]UPDRS and Hoehn and Yahr Stage was assessed on a different day from the EEG. [2]Levodopa equivalents and other medication was assessed on day of EEG AVLT-LTM = Auditory verbal learning test-Long term memory.

Table 2
Correlation of neuropsychological test score changes with QEEG measure changes

Neuropsychological test change	Background rhythm frequency change	Delta bandpower change	Theta bandpower change	Alpha bandpower change	Beta bandpower change
Mini mental status exam	0.04	−0.27	−0.08	0.11	0.12
	$P=0.76$	$P=0.03$	$P=0.50$	$P=0.35$	$P=0.35$
AVLT-LTM	0.46	−0.59	−0.16	0.15	0.38
	$P<0.001$	$P<0.001$	$P=0.19$	$P=0.22$	$P=0.001$
Stroop Word-Color interference	0.43	−0.53	−0.37	0.43	0.21
	$P<0.001$	$P<0.001$	$P=0.002$	$P<0.001$	$P=0.09$
Controlled oral word association	0.14	−0.51	−0.14	0.27	0.11
	$P=0.26$	$P<0.001$	$P=0.25$	$P=0.03$	$P=0.38$
Trails B (seconds)	−0.22	0.39	0.19	−0.26	−0.11
	$P=0.08$	$P=0.002$	$P=0.13$	$P=0.04$	$P=0.39$
Clock drawing	0.16	−0.36	−0.11	0.18	0.11
	$P=0.18$	$P=0.002$	$P=0.39$	$P=0.14$	$P=0.39$

AVLT-LTM = Auditory verbal learning test-Long term memory.

longitudinal BRF change had smaller but still strong significant correlation with changes in AVLT-LTM and Stroop W/C interference. Overall, these correlations are in the expected direction, i.e. worst performance changes with increase in the slower bands (delta, theta) and with decreases in BRF and the faster frequency bands (theta, beta).

Multiple linear regression modeling

When combining the most significant correlation, which was with delta bandpower, with the other frequency domain variables, as well as age and PD duration, no or only relatively modest increases in correlation occurred with some neuropsychological tests. Specifically, combining change in delta bandpower with age improved the correlation with change in MMSE from −0.27 to −0.37. Controlling for change in BRF and change in alpha bandpower improved the correlation between delta bandpower change and change in AVLT-LTM from −0.59 to −0.69. Controlling for change in theta improved the correlation between change in delta bandpower and change in Stroop W/C interference from −0.53 to −0.60. Controlling for followup time improved the correlation between change in delta bandpower and change in Clock Drawing Test from −0.36 to −0.48. Change in the other neuropsychological assessments was not improved by combining the change in delta bandpower with any other QEEG, age, PD duration, motor scores, levodopa equivalents, or follow-up time variables.

Analysis of QEEG spectral measure differences between incident dementia and non-dementia groups at followup

Table 3 shows the QEEG differences between the incident dementia and non-dementia groups at followup. Thirteen subjects had incident dementia while

Table 3
QEEG differences between the incident dementia ($N = 13$) and non-dementia ($N = 58$) groups at followup

QEEG spectral measure	Incident dementia group mean (SD)	Not demented group mean (SD)	Difference between groups	*P* Value
Background rhythm frequency (Hz)	−0.86 (.79)	−0.82 (1.03)	−0.03	0.92
Delta bandpower	6.9 (8.3)	1.4 (4.6)	5.5	0.002
Theta bandpower	8.4 (9.3)	10.2 (13)	−1.9	0.63
Alpha bandpower	−11.6 (7.6)	−9.5 (14)	−2.2	0.60
Beta Bandpower	−3.6 (9.3)	−2.2 (8.4)	−1.5	0.58

58 subjects remained not demented. The time from baseline to dementia ranged from 0.9 to 5.3 years with a mean of 3.0 years. Only delta bandpower showed a meaningful change, with the incident dementia group having more delta bandpower when compared to the non-dementia group.

CONCLUSIONS

Our results demonstrate that the QEEG frequency domain measure of delta bandpower change showed the most significant longitudinal correlation with changes that occurred in neuropsychological assessments over time. Other spectral QEEG measures studied demonstrated significant but less correlation when compared to delta bandpower. Although cross-sectional studies have shown that QEEG frequency domain measures differ between demented and non-demented PD subjects, the current results show that longitudinal QEEG delta bandpower *change* is significantly correlated with neuropsychological testing change. Our results are in general agreement with the MEG physiological results of Olde Dubbelink et al. [14]. Our study provides preliminary evidence that delta bandpower may be suited as the best spectral QEEG objective biomarker for clinical trials that evaluate treatments for PD cognitive deterioration. For example, QEEG measure changes (e.g. delta bandpower change) could provide objective corroboration for the physiological therapeutic effect (or lack thereof) of the candidate treatment over the period of the clinical trial.

In this study, all QEEG spectral measures worsened in the expected direction during the followup period. Indeed, during this period, there was a decline in fast (alpha and beta) frequency band activity with an increased prominence of slow (delta and theta) frequency band activity (Table 3). However, delta band activity was the only QEEG spectral measure that significantly changed more in the incident dementia group versus the group that did not become demented at followup. Delta band activity has normal functions, but there is clinical and laboratory evidence that new delta band EEG activity correlates with the disconnection of cortical areas [19]. Studies have shown network disruption and inefficiency in PD by using fMRI and MEG [20–23]. The network measures in these studies have shown decreased connectivity and efficiency in PD cortical networks. Recently, Olde Dubbelink et al. studied longitudinal network changes in PD with MEG [23]. In early stage PD, they found evidence of local inefficiency and network decentralization. These changes worsened over time and were associated with motor and cognitive progression. The increased delta bandpower found in our study, which may reflect disconnection of cortical areas over time, could be viewed as consistent with the aforementioned PD cortical network studies.

There are limitations of this study that should be realized. The subjects in this study were part of an ongoing brain bank cohort [15]. Although a well-studied cohort, there may have been a bias introduced. We studied subjects without dementia, and most of these subjects had mild to moderate motor severity at baseline. If we had analyzed more advanced PD subjects, the results may have been different. Finally, the PD subjects were not demented at baseline and not treated with acetylcholinesterase inhibitors. However, three of the thirteen demented subjects at followup were being treated with acetylcholinesterase inhibitors. Such treatment has been reported to potentially partially normalize the slower frequencies in PD QEEG spectra [24]. This could have lessened the differences in the incident dementia group, but we believe that the small percentage of subjects potentially affected would not have changed our overall results.

Our accumulative work and of others reveal that spectral QEEG measures show differential abnormalities as PD cognitive decline progresses [9, 10, 13, 25]. Incidental Lewy body disease (ILBD) constitutes healthy individuals without dementia or parkinsonism that have Lewy body pathology at autopsy. Some have suggested that ILBD may represent a preclin-

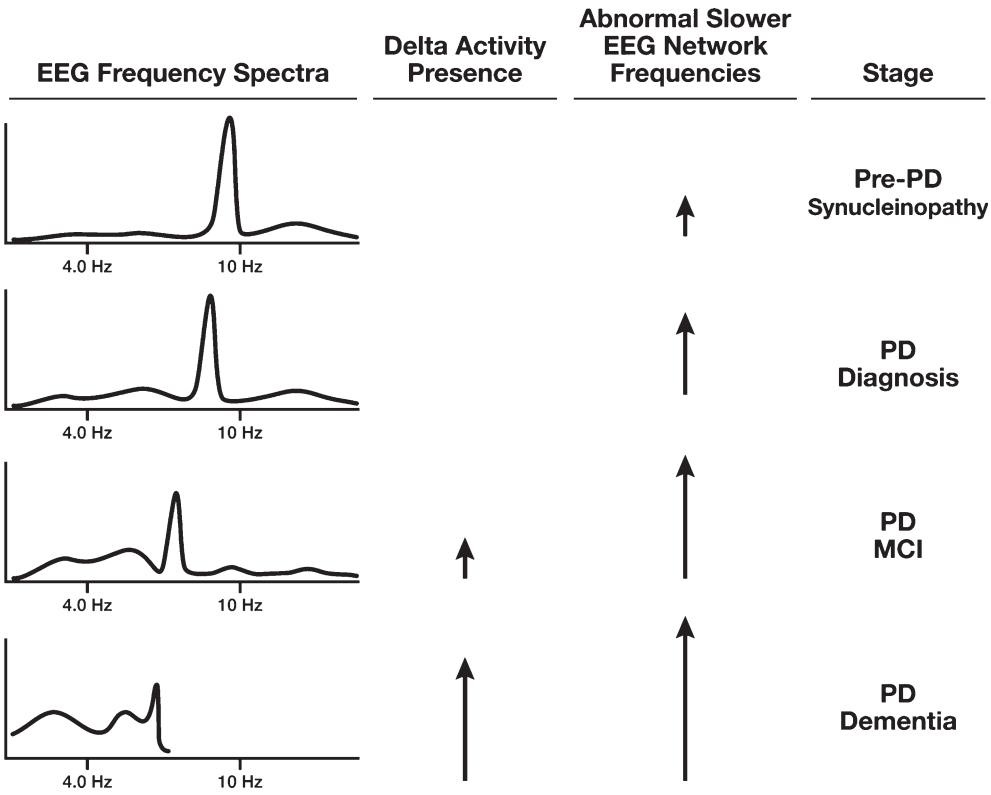

Fig. 1. The depiction is shown of hypothesized correlates between EEG frequency spectra, network disconnection, network slowing and stress, and clinical stage.

ical PD stage [25]. In ILBD, the BRF is already decreased mildly when compared to healthy autopsied controls without ILBD [25]. For diagnosed PD, studies have shown increased slower frequencies and less fast frequencies in the EEG spectra [4–10]. Previously, we showed that slower baseline BRF and increased theta bandpower predicts increased dementia risk for a cohort of non-demented PD that was followed for the transition to dementia [13]. The current study found delta bandpower to have the highest correlations with decreased cognitive performance in neuropsychological testing across multiple tests. Moreover, we found that increased delta bandpower at followup was associated with incident dementia. This later finding may suggest that delta bandpower is an important physiological marker for the transition to dementia in PD.

These combined findings of the current and the above mentioned studies in the literature may suggest a progressive sequence of different QEEG spectral measure changes at different stages of PD cognitive decline. The non-delta bands show progressively increased slower activity over the initial course of PD cognitive decline. Delta band activity increases as the cognitive progression becomes dementia. From a physiology view, cortical networks in PD are first associated with slower frequency activity early in the PD disease course in the non-delta bands. Progression of cortical dysfunction produces cognitive domain deficits with increased delta bandpower that may reflect cortical network disconnection. The evolution of this possible hypothesized scenario is depicted in Fig. 1.

In summary, longitudinal change in the QEEG frequency domain measure of delta bandpower in particular correlates with neuropsychological testing changes in PD. If confirmed, QEEG measures may be suitable for evaluating PD cognitive deterioration longitudinally. EEG biomarker measures may map differentially to the different cognitive PD stages.

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CONFLICTS OF INTEREST

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