1. Introduction

Clinical observations in PD suggest that patients have difficulty co-ordinating control of their upper limbs in tasks which require sequential [1] or simultaneous movements [2]. A common interpretation of this phenomenon is that PD subjects have difficulty in simultaneously executing separate motor programs, although the underlying pathological mechanisms of such difficulty are unclear. A potential mechanism is abnormal synchronisation of activity between regions normally responsible for planning and sequencing of movements [3].

Electrophysiological studies have demonstrated that PD is characterised by pathological oscillations within both basal ganglia- and cortical loops and cortico-cortical loops, in which synchronised basal ganglia activity is linearly related to activity of the cortex [4–10]. Resting-state EEG recordings have shown that PD subjects demonstrate an increase in theta (5–8 Hz) and low alpha (8–10 Hz) power and a decrease in beta and gamma frequency power compared to controls [11]. These resting-state changes are only slightly modulated by L-dopa [11]. Changes in synchronisation between cortical regions are also seen at rest, with prominent increases in the alpha range connectivity apparent in early, untreated PD, and increases in theta and beta bands appearing later in the disease [12].

During movement, the basal ganglia may release task-related cortical areas from normal resting-state z activity [13], which is manifest as a pre-movement desynchronisation of cortical EEG activity in the z band over the recruited regions. In PD, this desynchronisation is delayed [14]. Wang and colleagues demonstrated that L-dopa treatment improved the pre-movement desynchronisation of cortical activity in PD patients, and the extent of this improvement correlated with a reduction in bradykinesia (slowness of movement) during performance of simple unimanual movement [14]. The location of this
correlation shifted when both movements were performed simultaneously, indicating that simultaneous movements may require synchronisation between alternative or additional regions.

Because abnormalities in PD have been more apparent during performance of a dynamic motor task, typical approaches that assume stationarity of the EEG (such as coherence) may be problematic. Therefore we utilised a recently developed technique that segments the EEG into quasi-stationary, task-related segments based upon the temporal dynamics of the cross-spectrogram of the Independent components (ICs) [15]. To determine the connectivity between EEG channels, we applied mutual information to calculate both linear and non-linear statistical dependencies. Using this approach, we have previously demonstrated that PD subjects are unable to independently recruit different areas of the brain while performing simultaneous movements, and instead recruited disparate clusters of synchronous activity [15].

Here, we investigate synchronisation between distributed regions during simultaneous movements by measuring mutual information between pairs of EEG channels. We investigated the same PD subjects off and on L-dopa to determine whether connectivity changes during simultaneous movements are modulated by dopamine, since prior studies suggest that task-dependent changes in EEG coupling in PD are dopamine-dependant [5].

2. Materials and methods

2.1. Subjects

This study was approved by the University of British Columbia Ethics Board and all subjects gave written, informed consent prior to participating. We recruited seven volunteers with clinically diagnosed, mild to moderate PD (5 men, 2 women, mean age 63.7 ± 7.1 years, 6 right-handed, 1 left-handed, mean symptom duration 7.1 ± 2.8 years, Hoehn and Yahr stage 1–3) [16] and six healthy, age-matched control subjects (1 man, 5 women, mean age 60.5 ± 11.3 years, 6 right-handed, 1 left-handed). Exclusion criteria included atypical parkinsonism, presence of other neurological or psychiatric conditions, and use of antidepresants, hypnotics, or dopamine blocking agents. All PD subjects were taking L-dopa, and some subjects also took other medications such as dopamine agonists. Detailed information regarding medications can be found in Table 1.

All PD subjects withdrew from L-dopa for at least 12 h before the study, and stopped other anti-parkinsons medications for at least 18 h (e.g. dopamine agonists, anticholinergics). The mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score during the off-medication state was 28 ± 7. Subjects completed the experiment once off-medication, then received their usual morning dose of L-dopa (mean 168 ± 80 mg Sinemet IR), followed by a 1 h interval to allow L-dopa to reach peak dose, before repeating the task on-medication.

2.2. Experimental design

Subjects sat facing a computer screen and in their right hand they held a custom in-house-built rubber "squeeze-bulb" using an isometric handgrip. Each subject had their maximum voluntary contraction (MVC) measured at the study onset and subsequent movements were scaled accordingly.

Using the squeeze-bulb, subjects were asked to control the width of a black horizontal bar on the screen so that the ends of the bar remained within two thick white lines which formed a vertically scrolling, undulating pathway (Fig. 1). Applying increased pressure to the bulb increased the width of the bar, whilst releasing pressure reduced the width. The target pressures varied between 5 and 15% of MVC, and at any one time a deviation of more than 2% from the target pressure resulted in touching the "sides" of the pathway, resulting in visual "sparks" where the bar was touching. To appear smooth, but not easily predictable, the pathway was a linear combination of two equal-amplitude sinusoids with periods of 10 and 18 s. At regular intervals the bar changed colour from black to red. In the simultaneous movement trial subjects were asked to respond to the colour change by pressing a button using their left index finger, while continuing the squeeze task. During the unimanual trial, subjects used only the squeeze-bulb with their right hand and the bar would return to black automatically without any response from the subject. Both trials lasted 5 min and the order was pseudo-randomised across subjects.

2.3. Data acquisition

The EEG was recorded using a standard electrocap (Electro-cap International, Inc.). The International 10-20 System of electrode placement was used, with 19 scalp and 2 auricular tin electrodes. A reference electrode was placed at the tip of the nose. Two additional electrodes were used to record eye movements, with one positioned at the upper outer canthus of the right eye, the other at the lower outer canthus of the left eye. The EEG was recorded, amplified, digitized (Ceegraph 6.71, Gamma II Netlink, Biologic System Corps), and sampled online at 512 Hz. Offline, the data was re-referenced to the average reference, desampled at 128 Hz, and bandpass filtered at 0.55–55 Hz using a 4th order Butterworth filter prior to data analysis, as suggested in [17].

2.4. Data analysis

Behavioural data from the squeeze-bulb was used to calculate the error rates during tracking tasks in both simultaneous and unimanual conditions. Mean error rates across both task conditions were compared between each subject group using one-way ANOVA.

Artifactual components, for example eye blinks, cardiac signals, and muscle contamination, were removed using Independent Component Analysis, described in detail elsewhere [18]. We segmented the EEG into task-related segments in order to minimize task-unrelated activity and additionally address the non-stationarity of the EEG data [19]. Segmentation based upon behavioural data alone may be misleading since final motor output depends not only on cortical activity (as measured by the EEG) but also on subcortical and brainstem circuits.

After artefact removal using this method, task-related EEG segments were determined by examining autocorrelations of the cross-spectrogram of the ICs over three physiologically relevant frequency bands: 5–8 Hz (theta), 8–12 Hz (alpha) and 12–30 Hz (beta). The cross-spectrogram of every pair of ICs was examined using a short-term time shifting window (3 s shifted by 0.5 s). Task-related sections were obtained by selecting segments with a peak at 10 or 18–20 s (the periods used for the simultaneous task). After appropriate segmentation, the task-related sections were concatenated and used to derive a mutual information network. The reader is referred to [20] for a full description of the segmentation and mutual information methods.

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Table 1: PD subject demographics and medication information.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>L-Dopa/Carbidopa</th>
<th>Morning dose</th>
<th>Other medications and daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>P001</td>
<td>60</td>
<td>M</td>
<td>800/200</td>
<td>200/50</td>
<td>Pergolide 1 mg, Dopaminidone 40 mg</td>
</tr>
<tr>
<td>P002</td>
<td>74</td>
<td>M</td>
<td>800/200</td>
<td>200/50</td>
<td>None</td>
</tr>
<tr>
<td>P003</td>
<td>60</td>
<td>M</td>
<td>800/200</td>
<td>200/50</td>
<td>None</td>
</tr>
<tr>
<td>P004</td>
<td>53</td>
<td>M</td>
<td>400/100</td>
<td>100/25</td>
<td>None</td>
</tr>
<tr>
<td>P005</td>
<td>67</td>
<td>M</td>
<td>1100/275</td>
<td>400/100</td>
<td>Bromocriptine 10 mg</td>
</tr>
<tr>
<td>P006</td>
<td>70</td>
<td>F</td>
<td>500/125</td>
<td>100/25</td>
<td>Amantadine 200 mg, Pramipexole 1.5 mg</td>
</tr>
<tr>
<td>P007</td>
<td>62</td>
<td>F</td>
<td>600/150</td>
<td>200/50</td>
<td>Bromocriptine 7.5 mg</td>
</tr>
</tbody>
</table>

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Fig. 1. Experimental tracking task. Pressure-responsive squeeze-bulb was used to control width of black horizontal bar to keep ends along vertically scrolling white pathway. In the simultaneous task, left hand button-press was required whenever black bar turned to red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
The pair-wise information (MI) of two random variables \(X\) and \(Y\) is defined as

\[
I(X;Y) = \sum_{x,y} P_{XY}(x,y) \log \frac{P_{XY}(x,y)}{P_X(x)P_Y(y)}
\]

where \(P_{XY}(x,y)\) denotes the joint probability distribution function (pdf) of \(X\) and \(Y\), and \(P_X(x)\) and \(P_Y(y)\) are the marginal pdfs of \(X\) and \(Y\) respectively. MI measures the mutual dependence or information gained about one signal from another, or in other words, the amount of information about \(X\) that \(Y\) contains [21]. The higher the MI between two signals, the more information they contain about each other and hence the more likely that the two signals are biologically related. For this study, segmented EEG data was separated into 4 s epochs for MI computation to increase sample size and to make the distribution more Gaussian.

To compare mutual information measures when multiple factors of variability are present, for each frequency band, a two-way ANOVA with factors ‘task’ (unimanual, simultaneous; repeated measures) and ‘group’ (controls, PD off-medication, PD on-medication; independent measures) was first conducted to yield a preliminary set of interested connections. Further, based on the preliminary assessment from the two-way ANOVA, to investigate the effects of task, MI networks for the unimanual and simultaneous tasks were compared using one-way ANOVA, and connections where the MI significantly differed between tasks were displayed graphically. To investigate the effects of medication, the MI networks for PD subjects off and on medication were compared using one-way ANOVA and connections where MI significantly differed between medication conditions were displayed graphically.

3. Results

3.1. Behavioural data

There was no significant difference in the tracking error across the normal, PD subjects off-medication, and PD subjects on-medication groups: ANOVA \(F(17,3) = 0.567, p = 0.58\).

3.2. EEG data: comparison between simultaneous and individual movements

Fig. 2 demonstrates connections in which MI significantly differed between the unimanual and simultaneous tasks in each of the three frequency bands (theta: \(5–8\) Hz; alpha: \(8–12\) Hz; beta: \(12–30\) Hz). Healthy control subjects (Fig. 2, upper row) demonstrated few changes in MI when a simultaneous task was performed compared to an unimanual task. Decreased connectivity within parietal and occipital regions was seen in the left hemisphere in the alpha band, and bilaterally in the beta band during simultaneous tasks.

In contrast, PD subjects off-medication (Fig. 2, middle row) showed several changes in connectivity when performing simultaneous versus unimanual movement, with widespread increases in theta-band connectivity during simultaneous performance, and beta band increases in connectivity between right hemisphere occipital and temporal areas but decreases in the left hemisphere in midline frontal and central areas. Few changes were observed in the alpha band.

Following l-dopa medication (Fig. 2, lower row), similar to the normal case, connectivity was similar between simultaneous and unimanual tasks in theta and alpha bands, although some differences remained in the beta band that were not seen in control subjects.

3.3. Comparison between PD subjects and controls

3.3.1. PD subjects off-medication vs controls

Fig. 3 shows changes in PD subjects compared to healthy controls. During unimanual tracking, PD subjects demonstrated increased theta- and alpha-band connectivity between frontal and central EEG channels, and a decrease in connectivity between parietal and occipital channels compared to controls (Fig. 3, upper left). In the beta band, PD subjects showed frontal and occipital decreases in MI and central and parietal increases (Fig. 3, upper right). Increases in theta and alpha activity were more pronounced in PD subjects performing a simultaneous task (Fig. 3, upper left).

3.3.2. PD subjects on-medication vs controls

After l-dopa medication, PD subjects performing unimanual tracking showed fewer increases in frontal connectivity in the theta range, suggesting some normalisation of activity within this frequency range (Fig. 3, lower left). Normalisation in theta connectivity was more pronounced when performing the simultaneous task, during which there were only two frontal connections showing increased MI compared to controls. In the alpha band, normalisation occurred predominantly over the right hemisphere in connections between central and frontal areas (Fig. 3, lower center).

In the beta band, levodopa medication partially normalised connectivity in both unimanual and simultaneous tasks. Remaining differences between controls and PD subjects on-medication were seen mostly in the left hemisphere over temporal and central/parietal motor areas (Fig. 3, lower right).

In contrast, there were minimal changes seen in the alpha band after l-dopa medications with contrasts between PD subjects off-medication vs controls being similar to PD subjects on-medication vs controls (Fig. 3, lower center).

4. Discussion

Extensive prior research has demonstrated changes in resting-state synchronisation of the EEG in PD, with PD subjects showing a global increase in theta, alpha, and beta band activity across much of the cortex [11,12]. These changes have been shown to occur across different stages of disease progression, with alpha changes occurring early, followed by theta and beta changes at a later stage [12].

Resting-state studies have shown conflicting evidence of the effect of l-dopa treatment. Silverstein and colleagues [7] demonstrated that levodopa resulted in decreased coherence between 10 and 35 Hz, in correlation with improved motor function. In contrast, Stoффers and
4.1. Changes during simultaneous movement

Both PD subjects and normal controls demonstrated altered patterns of synchronisation in the beta band during simultaneous task performance. Concurrent up- and down-regulation of beta activity has been suggested to play a role in suppressing and facilitating competing responses [23], which would be particularly important in a bimanual task. In contrast to control subjects, bimanual task performance in PD subjects off-medication was characterised by increased right hemisphere connectivity and decreased left hemisphere connectivity. We suggest that in control subjects, a simultaneous task can be performed by execution of two motor plans in parallel without competition for additional resources. However, in PD subjects each motor plan requires additional, compensatory resources which then compete during simultaneous movement.

4.2. Effects of L-dopa

The task-related changes in activity seen in this study were modulated by L-dopa, suggesting dopamine is able to at least partially normalise connectivity changes related to simultaneous movement. PD subjects on-medication showed little change in connectivity patterns between the simultaneous and unimanual tasks, similar to what was seen in control subjects. Between-group comparisons showed that L-dopa was able to partially normalise task-related changes in theta and beta bands, although little effect was seen on the alpha range connectivity, in contrast to a prior motor study in which L-dopa had a similar effect across all frequency bands [5]. Due to the EEG segmentation methodology applied, the alpha-band changes seen in the PD subjects in this study were still apparent during movement, thus task-related changes are also apparent during the resting state, other symptoms such as bradykinesia become apparent during movement, thus task-related changes are also important for distinguishing between control subjects and PD.

Although the PD symptom of tremor is apparent during the resting state, other symptoms such as bradykinesia become apparent during movement, thus task-related changes are also important for distinguishing between control subjects and PD. However, due to the non-stationary nature of the EEG, prior studies that have examined synchronisation over a prolonged movement period may have included data points which were contaminated by resting-state connectivity. By using a recently developed segmentation method, we were able to ensure that such potentially contaminated segments of the EEG were discarded from analysis. Accordingly, we demonstrated task-related and L-dopa dependent altered patterns of connectivity in PD subjects that involved frequency-specific, regional changes. Unlike prior studies which have identified global increases in synchronisation, we found both increases and decreases in connectivity with specific topographic distributions.

4.3. Frequency-specific effects of L-dopa

Our finding of dopamine-sensitive changes in the theta and beta bands fits with prior studies of subcortical-cortical coherence, which have found changes in theta and beta synchrony between the thalamus and motor cortex in PD [24]. The pathophysiological nature of these changes in relation to the symptoms of PD has been debated, particularly in the beta band. One model suggests that theta and beta synchronisation changes are responsible for the generation of negative (akinetic) and positive (tremor) symptoms respectively [24]. An alternative suggestion is that excessive basal ganglia-cortical synchrony in the beta band is antikinetik, and in PD this acts to prevent the normal pre-movement desynchronisation in the beta band required to initiate a voluntary movement, thus contributing to bradykinesia [28].

In this study, the finding that connectivity changes between cortical areas are not completely normalised following treatment with L-dopa may suggest that dopamine is not responsible for all of the changes in cortical synchronisation seen in PD, particularly those changes seen in the alpha range. Interestingly, our finding that theta and beta changes appear to be subserved by a different mechanism than alpha-band changes in connectivity is supported by a prior study in which where theta and beta changes, but not alpha changes, correlated with the severity of motor symptoms as measured by the UPDRS [12]. However, increased alpha-range connectivity at rest was seen at an earlier stage than theta and beta changes, and alpha-band changes correlated with disease duration, suggesting that dopamine-sensitive changes in connectivity may not be the first to appear.

A recently proposed staging system for PD neuropathology by Braak and colleagues [25] suggests that one of the earliest
pathological stages in PD is degeneration of brainstem nuclei that give rise to thalamocortical projections, including noradrenergic projections from the locus coeruleus and serotonergic neurons in the dorsal raphe nuclei, as well as dopaminergic neurons. Degeneration in these projections may thus contribute to non-dopaminergic changes in cortical oscillatory activity. In addition, it has been shown that oscillations in the alpha band recorded from motor areas may arise partly from somatosensory cortex [26], while those in the beta band arise from primary motor cortex [27], suggesting that motor task-related changes in PD may arise both dopamine and non-dopamine dependent sources. Although we cannot directly conclude from surface EEG whether the synchronisation arises from cortico-cortical coupling or from common subcortical influences, we suggest that early changes in PD arise from the effects of subcortical degeneration, while later changes may include downstream alterations in cortico-cortical connections.

5. Conclusion

Understanding the changes in cortical synchronisation in PD is important given that basal ganglia dysfunction exerts its damaging effects on movement via motor projections that pass through the cortex [7]. Task-related dopaminergic-sensitive theta and beta changes may represent a marker for the greater recruitment required to accomplish individual tasks. It is this greater recruitment for individual tasks that leads to an inability to perform simultaneous tasks without interference, resulting in performance breakdown when simultaneous tasks are required. The alterations in theta and beta connectivity may be a quantitative marker of the conjecture that PD subjects have difficulty in simultaneously executing separate motor programs. Therapy that successfully reverses the changes in theta and beta band activity may therefore be particularly appropriate in assisting to prevent accidental injuries that occur when individuals with PD attempt to perform two movements simultaneously, for example taking a step back while opening a cupboard.

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References