Electrophysiological and Behavioral Measures of Visuo-Motor Learning For Application in Movement Disorders

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***Abstract*-- Dystonia is the third most common movement disorder worldwide and drastically reduces the quality of life of those who are affected. Despite its prevalence, very little is known about the underlying pathology of the disorder. Recent literature has suggested that abnormal processing in the superior colliculus (SC) may play a role in Dystonia. The SC is known to be an important hub in the neural network that is used when learning a novel movement and therefore we would postulate that a disorder of SC should result in abnormal movement learning. Here 9 participants completed learning and non-learning movement tasks while behavioural and electrophysiological data were acquired. The results of this study show that there is a significant relationship between the behavioural and electrophysiological data (R^2 = 0.19, F(1, 46) =10.88, p<0.002) during the learning task but not in the non-learning task (p>0.05). The developed paradigm is ideally suited for probing the underlying pathology of Dystonia via movement learning.**

I. Introduction

Dystonia is a neurological syndrome manifested clinically by focal or generalized sustained muscle contractions, postures and/or involuntary movements [1]. Current literature suggests that the disorder may be sub-cortical in nature, specifically that there is an imbalance in the Superior Colliculus (SC) [2]. The SC is associated with visuo-motor learning hence we designed a paradigm to monitor the process of learning an action [3, 4]. In a recent study Bednark and colleagues asked participants to learn the location of a hidden target by exploring an on screen space using a track ball. Each experimental block consisted of 30 trails, meaning that the participant was required to learn the target location over 30 repetitions. The trials were divided into two sets of 15 trials. The authors demonstrated that the amplitude of electrophysiological response, known as the P3, decreased in the second set of 15 trails when compared to the first set, and suggested a link between movement learning and P3 amplitude. The subdivision of 30 trials into two subsets did not enable the authors to look at the time course of the learning process. Here, we extend the previous work to show these relationships and hence validate a movement learning paradigm on controls which can then be deployed on patients with dystonia.

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II. Methods

A. Participants/Ethics

Nine typically developing adults participated in this study. One participant was later excluded from analysis due to poor EEG data, leaving a total of 8 participants (1 female; 25 ± .5 years, mean ± SD). All participants were right-handed as revealed by self-report. In accordance with the declaration of Helsinki, all participants gave their informed consent to the study, which was approved by the Faculty Ethics Committee of the Faculty of Health Sciences at Trinity College Dublin.

B. Experimental Conditions

Participants were seated in a comfortable chair 70cm from a computer monitor in a dark and quiet room and asked to complete two separate experimental conditions. Participants were instructed to move a computer cursor on a computer monitor within a search space (10.8°, visual degrees) using a Kensington Orbit Optical Trackball until they located a target location (3.2°). When the target location was discovered, a green circular stimulus (1.1°) was presented at the center of the search space for 500ms. The cursor then appeared at a new random starting position inside the search space and the participant was instructed to find the target location. To complete an experimental block the participant was required to find the target location 30 times. At the beginning of each block a new target location was selected at random. A white cross-hair was presented at the center of the search space to give participants a focal point during the trials.

The participants completed two conditions. In the movement learning (ML) condition the position of the target location was hidden and participants were expected to learn the new location over the course of each block. In the continuous cue condition (CC) there was no movement learning as the target location was highlighted by a grey annulus. Participants completed 10 experimental blocks for each condition in alternating order, starting with ML, in a single testing session (Figure 1).

C. Data Acquisition

Continuous EEG data, sampled at 512Hz, was collected from 64 scalp electrodes and 8 external electrodes using a BioSemi high impedance recording system. Stimuli were presented using Neurobehavioral Systems' Presentation

software. Movement trajectories were sampled via the Presentation software at a rate of 60Hz, allowing for offline behavioural analysis. These trajectories were synchronised to the EEG data.

D. Data Analysis

EEG data were analyzed using custom MATLAB R2013b scripts and EEGLAB [5]. EEG data were first de-trended by removing the line of best fit from each channel to correct for signal drift. The data were then filtered using a 4th order band-pass Butterworth filter with a pass band of 0.1 – 30 Hz. An external electrode on the supernasion was employed to reject trials that contained eye blinks; any channel that contained a voltage greater than 80µV was also rejected as artefact. Trials that consisted of more than 10% bad channels were excluded from further analysis. In trials where the number of bad channels was fewer than 10%, the bad channels were interpolated using four nearest 'good' neighbors, as described in [6].

Each block of 30 trials for the ML and CC conditions were subdivided into six sets of five trials, where the 1st set was made up of trials 1-5, the 2nd was comprised of trials 6-10 etc. (Figure 1). These sets were then employed when averaging both the EEG and behavioral results. This step was used in the EEG analysis to ensure a high signal to noise ratio and was also carried out in the behavior data to allow for statistical testing with the EEG data. To account for inter-participant variability, each participant's behavioral and electrophysiological data was normalized with respect to the first set of trials.

Average event related potentials (ERPs) were calculated for each participant using seven frontal-central electrodes (F1, Fz, F2, FC1, FCz, FC2 and Cz (Figure 2). Individual participant ERPs were calculated for each set across all 10 ML and CC blocks. Grand Average ERPs were then calculated across all participants for both the ML and CC condition.

The P3 is a commonly employed component of EEG data; it is a positive component with an onset of 300ms which is usually related to a novel stimulus [7] for different sensory systems [8] but it is also associated with learning and decision making [9]. A recent study has indicated that the amplitude of the P3 component may be linked to movement learning [10]. The normalized P3 amplitude was calculated for each set by taking the mean value of the ERP data in a short time interval centered on the peak of the P3 component (310 – 350ms).

Response time (RT) was defined as the length of time taken by a participant to maneuver the cursor into the target location. Average normalized RTs were calculated for all subjects and for all sets. Group average RTs were then calculated for comparison with the group average P3 amplitudes. These group averages and corresponding standard errors were plotted on a double-y plot.

E. Statistical Analysis

In order to develop a general understanding of the statistical differences present in the ERP data, statistical cluster plots (SCPs), which tested every possible sub-pair of the six sets for each experimental condition, were generated. This method has been employed effectively to more fully explore statistical significance in larger datasets [11]. To create the SCPs a point wise t-test was carried out for each time point and for all 64-electrode locations. This method was repeated for all 15 possible combinations of two from six sets and for each experimental condition. The results of this t-test were then displayed as an intensity plot where the x-, y- and z-axis respectfully correspond to time, channel location and t-score (represented on a color scale). Only t-values with a corresponding p-value < 0.05 and occurring in clusters greater than 30ms are considered significant which is known to increase the likelihood of type II errors through

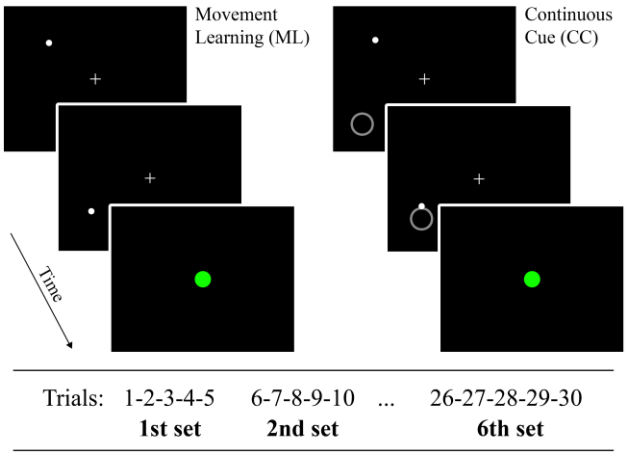

Figure 1 Top: Sample fames from the movement learning and continuous cue conditions progressing from the start of a single trial to the location of the target and finally the presentation of the 500ms stimulus. Bottom: The subdivision of the block in six sets of five trials.

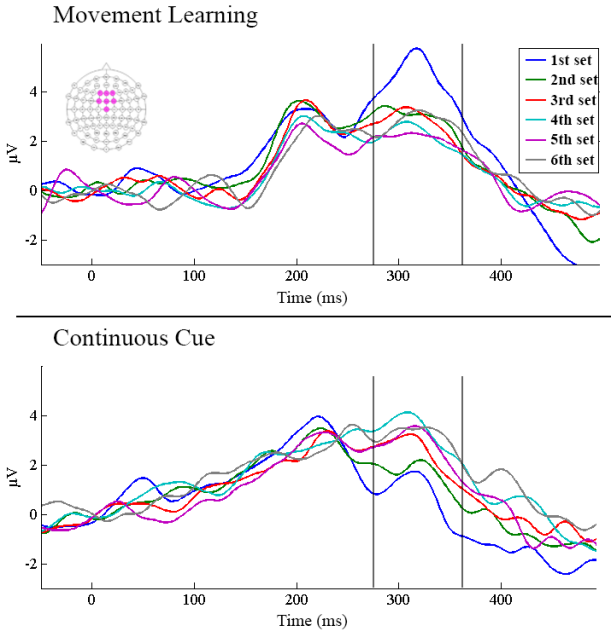

Figure 2 Grand average event related potentials (ERPs) calculated using frontal central electrodes as shown. The top plot shows 6 EEG traces corresponding to the 6 sets of the movement learning condition. The bottom plot shows traces from the continuous cue condition. Grey vertical lines

overcompensation for type I errors [12].

III. Results

A. Behavioral Results

The behavioral data from the six subsets were submitted to a one-way ANOVA for the ML condition and CC condition. The analysis revealed significant difference in the ML condition ($F(5, 42) = 40.7$, $p<0.0001$). Planned comparisons demonstrated that this was driven by the 1st set. The analysis revealed no significant difference in the CC condition ($F(5, 42) = 1.892$, $p=0.13$).

B. EEG Results

The grand-average ERPs from the ML experimental condition revealed that the amplitude of the P3 component in the first set is substantially larger than that observed in any of the later sets. It may also be seen that the offset of this component is far steeper in amplitude than that of the traces corresponding to the later sets (Figure 2). The normalized P3 data from the six subsets were submitted to a one-way ANOVA for both the ML condition and CC conditions. The analysis revealed a difference in the ML condition ($F(5, 42) = 7.61$, $p<0.001$). Planned t-test comparisons demonstrated that this difference was driven by the 1st set (Figure 3). The analysis revealed no significant difference in the CC condition ($F(5, 42) = 0.58$, $p=0.712$), suggesting that the normalized P3 amplitude across all six sets are consistent. This analysis was carried out on the ML data with the first trial being excluded from the set. Trending differences were observed in the modified ML data ($F(5, 42) = 2.23$, $p=0.0687$), demonstrating that the observed result is not driven by the first trial.

To further explore the spatiotemporal properties of the ML data, point-wise paired t tests between the different sets were computed for all 64 electrodes (y-axis) at each time point (x-axis) are presented in SCP. For each experimental condition there were 15 different SCPs outputted, each one corresponding to combinations of 2 from 6 sets. Two plots exemplary from each experimental condition were selected, the 1st set vs. 2nd set and the 4th set vs. 5th set (Figure 4).

The results from the ML condition show a large cluster of significant difference between the 1st set and 2nd set that onsets at 300ms and carries on until ~600ms. This time scale corresponds to the timing of the P3 component. This result was seen for all SCPs where 1st set was compared with any other set (2nd-6th) in the ML data. However, the SCPs for the 4th set vs. 5th set shows little significant difference.

The SCPs for the CC condition show little difference for the 1st set vs. 2nd and 4th vs. 5th. This result was observed across all the different combinations of sets.

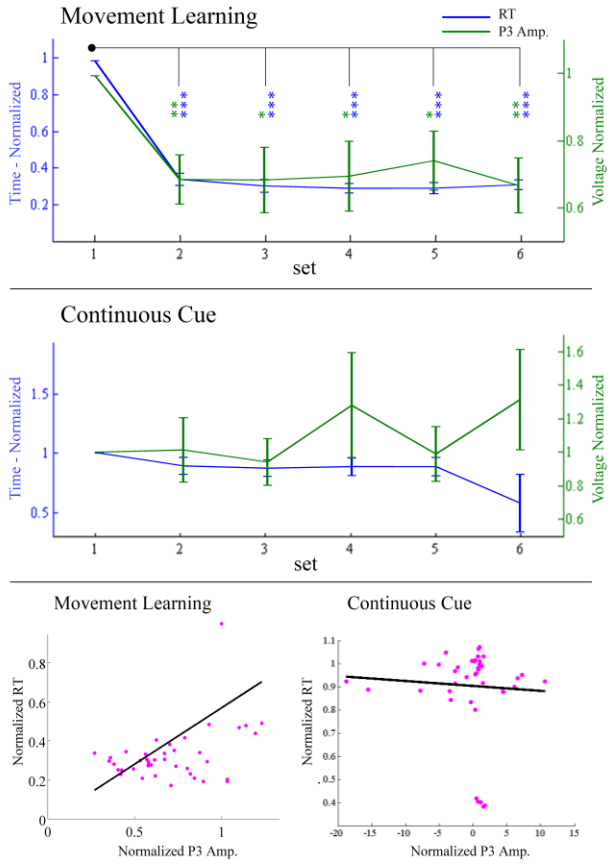

Figure 3 These plots show the normalized P3 amplitude and response times for the movement learning (top) and continuous cue (middle) conditions. The green curve in each plot represents the normalized grand average P3 amplitude. The Blue curve corresponds to the normalized grand average response times. The bottom plots show the distribution of participant P3 amplitude and RT values that was used for the linear regression in both experimental conditions as labeled. * p < 0.05, **p <0.01 ***p<0.001

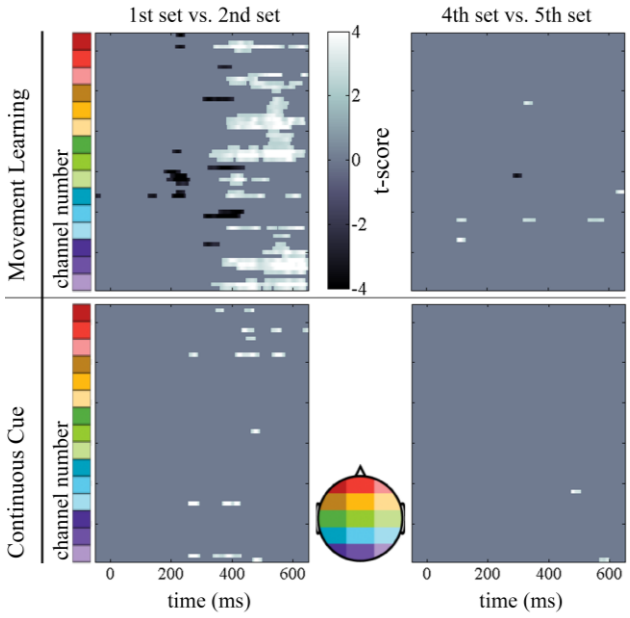

Figure 4 SCPs were created to assess the onset and distribution of differential ERP responses between the six different sets of data. Carrying out a point-wise t-test on two sets across all eight subjects at every electrode site created these plots. This process was repeated for every possible pair of sets. For the 600ms epoch window t-scores were then represented by color values. For clarity, only t values with a corresponding p values < 0.05 were shown, and only then when fifteen consecutive data points, or 30ms, exceeded this criterion.

C. Behavioural Electrophysiological link

To elucidate the link between the electrophysiological and behavioral data, the normalized amplitude of the P3 component and RT were plotted on a double y-axis plot to allow for comparison of line morphology (Figure 3). Visual inspection of the two curves indicated that a similar trend was present in both data sets.

To further investigate the relationship of behavioral and electrophysiological responses the individual participant normalized P3 and RT data for the six sets were submitted to a linear regression for the ML and CC conditions. The results for the ML condition showed a significant relationship, $R^2 = 0.19, F(1, 46) = 10.88, p<0.002$, thus confirming the link between the movement learning behavior and electrophysiological data on a sub trial basis. There was no significant relationship for the CC ($p>0.05$).

IV. Discussion

This study established a link between the behavioural and electrophysiological response for the time course of movement learning. The ERP plots clearly show a decrease in P3 amplitude over the time course of the ML block, which extends the results of Bednark et al. [10]. The amplitude of the P3 is largest for the first set trials and decreases to a near constant value over the subsequent sets. This observation was also evident in the behavioural data. While in the CC condition, where there was no learning, the grand average ERPs and the behavioural response exhibited no significant changes over the time course of the block.

The results of the regression analysis of single participant data between the electrophysiological response and behavioral data for the ML condition showed a significant relationship, reinforcing the link between the datasets. One possible confound to the experimental design is that the amplitude of the P3 may be driven by a response to a novel stimulus and the decrease is therefore related to decreasing novelty. For this reason the control CC condition was also included in the experimental protocol. The regression analysis results demonstrate that there was no significant relationship between the P3 and behavioural performance in the CC condition. These findings provide further support to the argument that the decrease in the amplitude of the P3 observed in the ML condition was related to movement learning and not novelty. Furthermore, analysis of the SCPs demonstrates the robust spatial temporal nature of the comparison between the first set and subsequent sets in the ML condition while no such differences were observed in the CC condition.

Currently, one of the main behavioral endophenotypes for dystonia is an abnormal discrimination of asynchronous tactile or visual stimulus which has been attributed to a disorder of the SC [13, 14]. In future studies, we intend to deploy the movement learning paradigm in dystonic patients, to further probe the link between dystonia and abnormal subcortical neural processing as well as providing a more ecologically relevant behavioural test.

V. Conclusion

Here, we validated a novel paradigm to investigate behavioural and electrophysiological responses for movement learning in a healthy control group. Furthermore, this novel paradigm would be ideal for deployment in clinical population, which are known to have abnormal movement learning such as dystonia.

VI. References

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