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Intact action segmentation in Parkinson's disease: Hypothesis testing using a novel computational approach

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ABSTRACT

Action observation is known to trigger predictions of the ongoing course of action and thus considered a hallmark example for predictive perception. A related task, which explicitly taps into the ability to predict actions based on their internal representations, is action segmentation; the task requires participants to demarcate where one action step is completed and another one begins. It thus benefits from a temporally precise prediction of the current action. Formation and exploitation of these temporal predictions of external events is now closely associated with a network including the basal ganglia and prefrontal cortex.

Because decline of dopaminergic innervation leads to impaired function of the basal ganglia and prefrontal cortex in Parkinson's disease (PD), we hypothesised that PD patients would show increased temporal variability in the action segmentation task, especially under medication withdrawal (hypothesis 1).

Another crucial aspect of action segmentation is its reliance on a semantic representation of actions. There is no evidence to suggest that action representations are substantially altered, or cannot be accessed, in non-demented PD patients. We therefore expected action segmentation judgments to follow the same overall patterns in PD patients and healthy controls (hypothesis 2), resulting in comparable segmentation profiles. Both hypotheses were tested with a novel classification approach.

We present evidence for both hypotheses in the present study: classifier performance was slightly decreased when it was tested for its ability to predict the identity of movies segmented by PD patients, and a measure of normativity of response behaviour was decreased when patients segmented movies under medication-withdrawal without access to an episodic memory of the sequence. This pattern of results is consistent with hypothesis 1. However, the classifier analysis also revealed that responses given by patients and controls create very similar action-specific patterns, thus delivering evidence in favour hypothesis 2.

In terms of methodology, the use of classifiers in the present study allowed us to establish similarity of behaviour across groups (hypothesis 2). The approach opens up a new avenue that standard statistical methods often fail to provide and is discussed in terms of its merits to measure hypothesised similarities across study populations.

1. Introduction

Parkinson's disease (PD) is a condition with well-defined neurological changes. It results from a loss of dopaminergic cells in the substantia nigra (Bernheimer et al., 1973; Birkmayer and Wuketich, 1976), which leads to decreased levels of this neurotransmitter in the basal ganglia and the prefrontal cortex (PFC). PD is signified by prominent motor impairments such as tremor, bradykinesia, and rigor. These motor symptoms are often accompanied by cognitive changes, including compromised ability to learn from feedback and limited use of the predictability of external events (Flowers, 1978; Cameron et al., 2010; Cools et al.,

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2003, 2001, 2006; Crawford et al., 1989; Frank, 2006; Zalla et al., 1998; Shohamy et al., 2008). A related impairment in PD which has recently been linked to the basal ganglia and the prefrontal cortex is the internally driven prediction of external events (Schönberger, et al., 2013).

1.1. (Temporal) prediction in a basal ganglia network

The proposal that the basal ganglia are involved in prediction of the content and temporal onset of external events (referred to as sensory states in the original literature Bischoff-Grethe et al., 2003) is grounded in a combination of findings from patient data with data from animal, imaging, and modelling research (Alm, 2004; Balleine et al., 2009; Berns and Sejnowski, 1998; Bischoff-Grethe et al., 2003; Schönberger, et al., 2013). The research suggests that the basal ganglia and prefrontal cortex, and particularly the supplementary motor area (SMA), work in concert in learning, selecting, and timing predictions of external events (Lewis et al., 2003; Stocco et al., 2010; Schiffer et al., 2015; Schönberger, et al., 2013; see Coull and Nobre, 2008 for a dissenting view). Because decline of dopaminergic innervation of the basal ganglia and prefrontal cortex is a hallmark feature of PD, this research suggests that PD patients should be compromised in the fast prediction of event sequences, particularly under medication withdrawal. The present study tested this hypothesis explicitly, implementing an action segmentation task.

1.2. Action segmentation requires exploitation of semantic knowledge and benefits from prediction of forthcoming events

In the segmentation task participants observe an actor performing familiar activities and are required to indicate their subjective judgment whether an action boundary has occurred, i.e., whether an action step has been completed and a new action step has been initiated. These segmentation judgments, also referred to as boundary detection reports, are usually given in the form of a button press (Zacks et al., 2001; Schubotz et al., 2012; Baldwin et al., 2008; Newtson and Engquist, 1976). Because actions are highly structured and action observation is known to trigger online predictions of forthcoming action steps (Csibra, 2007; Colder, 2011; Botvinick and Plaut, 2004; Kilner et al., 2007, 2004; Schiffer et al., 2013; Stadler et al., 2011), reliable and fast performance in action-segmentation tasks requires two core abilities:

First, action segmentation benefits from the ability to generate a temporally precise prediction of the course of the current action, including the end of one action step and the beginning of the next action step thereafter. Detection of stimuli is not only aided by predictability of occurrence, but also additionally facilitated by predictability of stimulus onset (Rohenkohl et al., 2012). Thus, predicting which action step is to follow, and at what time this action step would naturally commence, aids boundary detection in the action segmentation task.

Importantly, if the basal ganglia are involved in real-time prediction of sequential events (Schiffer and Schubotz, 2011), we would expect increased variability in the timing of the response around action boundaries (Baldwin et al., 2008; Newtson and Engquist, 1976) in PD patients. The action-segmentation paradigm thus provides a sensitive test for the hypothesis that compromised dopaminergic innervation of the basal ganglia and prefrontal cortex leads to increased temporal variability in response behaviour, particularly under medication withdrawal (hypothesis 1), indicating impaired (temporal) prediction and delayed assessment of forthcoming sensory states.

A second, profound aspect of action segmentation is that observers have to rely on an internal representation of the single steps that together form specific actions (action semantics) to detect the end of one action step and the beginning of another. Some authors have argued that PD patients should be impaired in action segmentation (Zacks and Sargent, 2010). However, while learning and retrieval of action semantics has repeatedly been shown to involve a fronto-parietal network extending to the temporal lobes (Decety et al., 1997; Spunt et al., 2010; Watson and Chatterjee, 2011; Hoffman et al., 2012; Schubotz et al., 2012; Schiffer et al., 2013), evidence for an involvement of the basal ganglia is missing. We therefore propose that the ability to segment actions should be largely intact in non-demented PD (hypothesis 2), resulting in comparable segmentation profiles.

1.3. Assessing action segmentation components in a patient study

We tested these hypotheses in a cohort of patients with idiopathic Parkinson's disease and a group of age-matched controls. To assess whether changes in dopamine availability exert an effect on the ability to segment actions per se and increase the temporal variability of segmentation behaviour, PD patients underwent two experimental sessions, one with their usual dopamine replacement therapy unchanged (ON) and one under withdrawal of their dopamine replacement therapy (OFF). Healthy controls took part in two separate sessions without medication. Their virtual medication status (pseudo ON and OFF status) was yoked to the random order of ON and OFF tests in the matched PD patients. During each session, participants segmented a different set of 6 multi-step action movies twice, allowing comparison of segmentation reliability under different medication status.

1.4. Classification approach to assess similarity

Predictions of similarity, central to our second hypothesis, are statistically challenging, because inference statistic measures aim at establishing differences between groups. Even if these measures fail to establish a difference between groups or conditions, such null effects cannot be taken as a proof of similarity (Cohen, 1994). Moreover, our hypotheses demand an estimate of the exact *degree* of similarity between response patterns. We resolved this paradox by developing a novel methodology, which implements a computational classifier. To show that PD patients and healthy controls can rely on the same action models, we transformed their response behaviour in the action-segmentation task into a temporal profile of response probability, expressed as the function that represents the probability to make a response for each moment in time. Bringing the data into this format allowed us to use these temporal response profiles in a computational classifier (Fig. 1; please refer to Methods Section 2.2 and 2.4.1 for further explanation).

We trained a classifier to predict movie identity using the data from a subset of participants as a training set and another subset of participants as a test set. The hypothesised above-chance classification of movie-specific response profiles when testing data and training data are taken from different groups strongly indicates behavioural similarity. This behavioural similarity is evidence in favour of intact semantic representation of action structure in PD. At the same time, the predicted differences in classification performance between different (above-chance) cross-group classifications would show the predicted differences in the temporal precision of segmentation behaviour in PD.

2. Materials and methods

2.1. Participants

A total of 32 male participants took part in the experiments: 16