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Striatal disorders dissociate mechanisms of enhanced and impaired response selection — Evidence from cognitive neurophysiology and computational modelling

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ABSTRACT

Paradoxically enhanced cognitive processes in neurological disorders provide vital clues to understanding neural function. However, what determines whether the neurological damage is impairing or enhancing is unclear. Here we use the performance of patients with two disorders of the striatum to dissociate mechanisms underlying cognitive enhancement and impairment resulting from damage to the same system. In a two-choice decision task, Huntington's disease patients were faster and less error prone than controls, yet a patient with the rare condition of benign hereditary chorea (BHC) was both slower and more error prone. EEG recordings confirmed significant differences in neural processing between the groups. Analysis of a computational model revealed that the common loss of connectivity between striatal neurons in BHC and Huntington's disease impairs response selection, but the increased sensitivity of NMDA receptors in Huntington's disease potentially enhances response selection. Crucially the model shows that there is a critical threshold for increased sensitivity: below that threshold, impaired response selection results. Our data and model thus predict that specific striatal malfunctions can contribute to either impaired or enhanced selection, and provide clues to solving the paradox of how Huntington's disease can lead to both impaired and enhanced cognitive processes.

1. Introduction

Paradoxically enhanced cognitive processes in neurological disorders both present stern challenges to our understanding of their underlying mechanisms and provide vital clues to furthering that understanding (Frank et al., 2004; Shiner et al., 2012; Kapur et al., 2013). A key challenge is to solve the underlying paradox of how damage to the same neural system can result in both enhanced and impaired cognitive processes. We took a novel approach to tackling this challenge by using the same cognitive task in two neurological disorders affecting the same system to dissociate their separate functional implications; we then used computational analyses to test the inferred hypothetical effects on the neural system.

We previously showed that Huntington's disease patients have a paradoxical enhancement in a simple auditory decision-making task (Beste et al., 2008; Saft et al., 2008): on trials with irrelevant sensory information, a significantly enhanced mismatch negativity (MMN) signal from EEG recordings corresponded to significantly reduced errors and response times compared to controls. The MMN is defined as a phasic negativity of the event-related potential (ERP) of the EEG evoked by rare deviant stimuli in a sequence of stimuli and may reflect the recognition of rare events deviating from frequent background events by the auditory system (Kujala et al., 2007; Näätänen et al., 2012).

As Huntington's disease primarily affects the striatum, we hypothesized that such paradoxical enhancement of response selection is the result of the interaction between two factors in Huntington's disease progression (Beste et al., 2008): (i) increased NMDA receptor sensitivity at corticostriatal synapses (Fan and Raymond, 2007) and (ii) the consequent degeneration of medium spiny neurons through excitotoxicity, potentially driven by the increased calcium influx through the NMDA receptors. Yet, how or even if this interaction leads to an enhancement of striatal processing is unknown; and even if it does,

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BHC, benign hereditary chorea; EEG, electroencephalography; ERP, event related potential; GABA, γ-aminobutyric acid; MMN, mismatch negativity; NMDA, N-methyl-D-aspartate; RON, reorientation of attention; MSN, medium spiny neuron; FSIs, fast spiking interneurons; MMSE, Mini Mental Status Examination.

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how this interaction then usually leads to impaired cognitive performance in Huntington's disease (Lawrence et al., 1998, 2000; Stout et al., 2001) is unknown.

A critical test for these hypotheses would require an examination of sensory decision-making processes in a neurological condition that is characterized by medium spiny neuron dysfunction but without the corresponding enhancement of NMDA receptor function. In this regard, benign hereditary chorea (BHC, MIM 118700) may serve as a model (for review see Kleiner-Fisman and Lang, 2007 and Inzelberg et al., 2011). BHC is a rare autosomal dominant disease (prevalence between 1 and 2 in 1,000,000 people), which is caused by mutations in the TITF1 gene on chromosome 14q13 encoding the thyroid transcription factor-1 (also known as TITF1, TEBP or NKX2-1) (Inzelberg et al., 2011). TTF1 mediates striatal interneuron migration from the medial ganglionic eminence (a precursor of the globus pallidus) to the lateral ganglionic eminence (a precursor of the striatum) (Sussel et al., 1999). This migration is reduced in TITF1 mutation and leads to dysgenesis of the formation of medium spiny neurons (Kleiner-Fisman et al., 2005; Yoshida et al., 2012). By contrast, TITF1 has no known role in NMDA receptor function (Sussel et al., 1999) and thus NMDA receptor function in BHC is likely unaltered.

Consequently, we tested a BHC patient and manifest Huntington's disease patients against age-matched controls to dissociate the contributions of striatal changes in NMDA sensitivity and network structure to enhanced response selection. Using a computational model of the striatum, we tested the hypothesis that either of these changes in the striatum could directly affect response selection, and then tested the hypothesis that increased NMDA sensitivity in the striatum of Huntington's disease patients could enhance selection despite the loss of neurons. Critically, we sought from the model the key explanation for the paradox of why both impaired (Jahanshahi et al., 1993; Lawrence et al., 1998) and enhanced response selection could arise in Huntington's disease.

2. Materials and methods

2.1. Patients and participants

A group of manifest Huntington's disease patients ($N = 10$; 6 females) between 20 and 40 years of age (mean age 33.45 ± 5.5) without any medication and a group of controls ($N = 10$; 6 females) matched to the manifest Huntington's disease group in age, sex and educational background were recruited. Along with these groups, a case of benign hereditary chorea (BHC) (female, 24 years of age) with strong motor symptoms was recruited and compared to the other groups using single-case *t*-statistics (Crawford and Garthwaite, 2012). BHC was genetically confirmed by detecting the mutation in the TTF1 gene and the BHC case did not take any medication at the time point of examination. The clinical and neuropsychological test data of these groups and the BHC case are shown in Table 1. The study was approved by the Ethics Committee of the Ruhr-University of Bochum. The study was conducted according to the Declaration of Helsinki. All participants and the BHC case gave written informed consent.

2.2. Task

Subjects performed a distraction paradigm (Beste et al., 2008; see also Schröger and Wolff, 1998) in which tones at three different frequencies (1000 Hz, 1100 Hz, 900 Hz) were presented for either 400 or 200 ms. One pitch (i.e., 1000 Hz) served as the standard tone, which was presented in 80% of trials. The other pitches were presented with a frequency of 10% each. The subjects were asked to respond with their thumb and indicated, whether the tone was short (right button press) or long (left button press). Variations in the pitch of the tone thus served as distraction.

2.3. EEG recording and analysis

The EEG was recorded from 32 scalp electrodes at standard positions according to the 10/20 system. Electrode signals were sampled at 1000 Hz with Cz as primary reference. The resulting time-series were downsampled to 256 Hz in offline post-processing and re-referenced to linked mastoids. After a first visual inspection of the time-series a bandpass filter from 0.5 to 20 Hz (48 dB/oct) was applied. Ocular artefacts (blinks and saccades) as well as pulse artefacts were corrected using independent component analysis (Infomax algorithm), applied to the un-epoched time-series. Besides the MMN, other processes related to the reorientation of attention (RON (Schröger et al., 2000)) have also been found to be increased in their efficacy in Huntington's disease, whilst attentional shifts (reflected by the P3a; Escera and Corral, 2007) are not affected (Beste et al., 2008). If exaggerated glutamatergic neural transmission is of similar importance for reorientation processes, the RON and P3a mechanisms should be similarly modulated to the MMN. To measure the MMN, P3a and the RON the EEG time-series were epoched in segments from −200 till 800 ms after the stimulus onset. Within these epochs an automated artefact rejection procedure was applied. Rejection criteria included a maximum voltage step of more than 60 μV/ms, a maximal value difference of 150 μV in a 250 ms interval or activity below 0.1 μV. After this, a baseline correction was −200 till 0 (i.e., time point of stimulus presentation was applied). To measure the MMN, P3a and RON, difference waves were calculated (distractor minus standard ERPs) (Kujala et al., 2007). In these difference waves the MMN was defined as the most negative peak between 100 and 250 ms. The P3a was defined as the most positive peak between 250 and 500 ms and the RON was defined as the most negative peak between 400 and 600 ms post-stimulus presentation. The ERPs and the behavioral data are shown in Fig. 1.

2.4. Statistical tests

Behavioural data of the BHC case in relation to the Huntington's disease group and controls were analysed using single-case *t*-statistics (Crawford and Garthwaite, 2012) applying Crawford and Howell's method. This method is widely used and offers the best possible way to compare single cases with groups of other subjects (for review see Crawford and Garthwaite, 2012). ANOVAs were used to examine effects between the Huntington's disease and control groups. Post-hoc tests in the Huntington's disease and control group were Bonferroni-corrected where necessary. All descriptive statistics are given as mean and standard error of the mean.

2.5. Population model of competing striatal populations

We used reduced models of the striatal microcircuit (Figs. 2 and 3) to understand the mechanisms by which Huntington's disease- and BHC-like changes in the striatum could potentially alter selection. In the baseline model, each medium spiny neuron population's firing rate a was modelled as a leaky integrator of inputs from the cortex and other medium spiny neuron population:

$$\tau \dot{a}_i = -a_i + w_{ji}\lfloor a_j \rfloor^+ + w_I I_i \quad (1)$$

$$\tau \dot{a}_j = -a_j + w_{ij}\lfloor a_i \rfloor^+ + w_I I_j \quad (2)$$

which decays with time constant τ, and is driven by the sum of weighted cortical input I_i,I_j and feedback inhibition (w_{ij},$w_{ji} \leq 0$) from the other medium spiny neuron population. The operation $\lfloor \cdot \rfloor^+$ indicates that negative medium spiny neuron population activity is rectified to zero.