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Note

Striatal contributions to sensory timing: Voxel-based lesion mapping of electrophysiological markers

Michael Schwartze [a,b,*], Anika Stockert [b,c] and Sonja A. Kotz [a,b]

[a] School of Psychological Sciences, University of Manchester, Manchester, United Kingdom
[b] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[c] Language and Aphasia Laboratory, University of Leipzig, Leipzig, Germany

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ABSTRACT

To achieve precise timing, the brain needs to establish a representation of the temporal structure of sensory input and use this information to generate timely responses. These operations engage the basal ganglia. Current research in this direction is limited by reliance on animal models, motor and/or offline tasks, small sample sizes, the low temporal resolution of functional magnetic resonance imaging, and the study of progressive neurodegeneration. Here, we combine the excellent temporal resolution of electrophysiological potentials with the high spatial resolution of structural neuroimaging to investigate basal ganglia contributions to sensory timing. Chronic-stage lesion patients and healthy controls listened to pure-tone sequences differing exclusively in temporal regularity. Event-related potentials (ERPs) indicate a selective indifference against this manipulation in patients, attributable to the striatal part of the basal ganglia on the basis of a lesion-mapping approach. These findings provide evidence for a crucial contribution of the basal ganglia to basic sensory functioning.

1. Introduction

Adequate timing, defined as the ability to be in the right place at the right time, requires reactions to events in the environment and predictive adaptation of behavior in constant anticipation of the future (Bar, 2007; Schwartze & Kotz, 2013). The complex dynamics of some distinctive facets of human behavior provide ample evidence for the smooth interplay of these mechanisms. In speech and music, dance and sports, timing partly determines the quality of a message or a melody of interaction and competition.

The link between timing and efficient behavior is not always as evident as in the win-or-lose situations found in sports. Nevertheless, its existence provides a means to influence and optimize behavior via manipulations of temporal

* *Corresponding author*. School of Psychological Sciences, Room T7C, 3rd Floor, Zochonis Building, University of Manchester, Brunswick Street, Manchester, M13 9PL, United Kingdom.
E-mail address: michael.schwartze@manchester.ac.uk (M. Schwartze).
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structure, i.e., the duration, temporal relation, or temporal predictability of events. Optimized behavior at one end of a spectrum, however, suggests suboptimal behavior with inadequate timing towards the other, potentially compromising the ability for predictive adaptation of behavior. Notable timing dysfunctions have been observed in neuropathologic and psychiatric conditions with relatively high prevalence, including autism, attention deficit hyperactivity disorder, schizophrenia, Huntington's and Parkinson's disease (Allman & Meck, 2012; Cope, Grube, Singh, Burn, & Griffith, 2014; Hart, Radua, Mataix-Cols, & Rubia, 2012; Jones & Jahanshahi, 2014). In light of such findings, it stands to reason to what extent timing factors into seemingly non-related motor and non-motor neurocognitive functions and symptoms, if it is cause or consequence of such symptoms, and if manipulation of temporal structure may foster compensation.

Converging evidence supports the idea that classical motor areas form part of a dedicated sensorimotor system compatible with the distinction of motor and non-motor structures within particular areas (Akkal, Dum, & Strick, 2007; Ivry & Schlerf, 2008; Strick, Dum, & Fiez, 2009). More specifically, a core network, comprising prefrontal areas and supplementary motor area but also cerebellum and basal ganglia engages in temporal processing (Coull, Cheng, & Meck, 2011; Merchant, Harrington, & Meck, 2013; Wiener, Turkeltaub, & Coslett, 2010). Accordingly, neurodegenerative diseases affecting the basal ganglia can impair motor function, but also sensory timing (Cope et al., 2014; Grahn & Brett, 2009; O'Boyle, Freeman, & Cody, 1996). Neurodegeneration in these cases is, however, progressive and not restricted to a focal area, while the typical experimental tasks involve motor components, which inevitably entail exteroceptive or proprioceptive feedback, i.e., a sensory aspect. To address these potential confounds it is necessary to define the role of specific areas of the overarching network in purely sensory timing.

Here, we use the auditory P50, an event-related potential (ERP) of the electroencephalogram (EEG) peaking at about 45–75 ms post-stimulus onset (Korzyukov et al., 2007), as a time-sensitive marker of differences in sensory timing. The P50 amplitude displays an inverse relation with predictability of stimulus type and timing, i.e., high degrees of stimulus predictability are associated with smaller relative to larger amplitudes associated with low predictability (Schwartze, Farrugia, & Kotz, 2013). Pure-tone sequences were varied along these dimensions as participants counted infrequent high-pitch deviants presented among frequent low-pitch standards (type), with either regular or irregular inter-stimulus-intervals (timing). This task established an attentive listening context, which did not require any overt behavior. In this context, the P50 served as an index for an individual's capacity to extract regular temporal relations and temporal predictability from the dynamic stimulation. Basal ganglia pathology was expected to impact on this capacity, thus diminishing the contrast between the responses obtained with regular and irregular timing. P50 amplitudes were used to perform a formal voxel-based lesion-symptom mapping (VLSM) based on volume information derived from structural MR scans of each patient to obtain more detailed information about the contribution of different basal ganglia subregions to the observed continuous neurocognitive behavior (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007).

2. Materials and methods

2.1. Participants

30 right-handed chronic-stage (Mean: 8.8, SD: 3.9 years since incident) basal ganglia lesion patients (10 women) ranging in age from 31 to 78 years (Mean: 55.2, SD: 12.0) and a corresponding number of healthy controls were recruited via databases at the Max Planck Institute for Human Cognitive and Brain Sciences, Germany (Fig. 1, Table 1). Controls matched patients in terms of gender, age (±1 year, Mean: 55.4, SD: 12.2), handedness, and education (Mean: 10.1, SD: 1.1 years). Participants provided informed written consent and received a compensatory fee. The study was approved by the ethics committee of the University of Leipzig.

2.2. Structural magnetic resonance imaging

For patients, high-resolution T1-weighted MR scans were obtained either on a Siemens TrioTim (Siemens Healthcare, Erlangen, Germany) or a Bruker BioSpin (BioSpin GmbH, Rheinstetten, Germany) 3T MR system with a 32-channel phased-array head array coil using an MP-RAGE sequence (Mugler & Brookeman, 1990). Unified segmentation (Friston et al., 1995) as implemented in *SPM8* (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm) was used to segment and spatially normalize images to MNI space. *MRIcron* (Rorden & Brett, 2000) was used to manually delineate lesions on axial slices of the normalized images to create binary lesion maps, which were then plotted onto a scalp-stripped T1-weighted single subject template in MNI space (Colin27_T1_seg_MNI.nii, available via http://brainmap.org/ale/index.html).

2.3. Electroencephalographic recordings

Participants sat in a dimly-lit sound-proof booth fixating an asterisk on a computer screen and listened to two types of sequences presented via loudspeakers (Fig. 2). These sequences varied two stimulus types (formal structure) and differed in timing (temporal structure). Each consisted of 450 equidurational (300 ms, 10 ms rise and fall) standards (600 Hz, $N = 360$, high formal predictability) and pseudorandomly interspersed deviants (660 Hz, $N = 90$, low formal predictability, maximal two in a row). Inter-stimulus-intervals were regular in one sequence (600 ms, full temporal predictability) and irregular in the other (random 200–1000 ms, low temporal predictability). Four standards were presented at the beginning of each sequence. EEG was recorded via 25 Ag/AgCl scalp electrodes mounted into an elastic cap (500 Hz sampling rate, mastoid reference, ground on sternum). Electrodes above and below, and left and right of the eyes were used to record electrooculography. Participants were asked to silently count the deviants in each sequence and to report the total number. Order of presentation was counterbalanced across participants and identical for individual patient-control

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