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Research Report

Features and timing of the response of single neurons to novelty in the substantia nigra

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ABSTRACT

Substantia nigra neurons are known to play a key role in normal cognitive processes and disease states. While animal models and neuroimaging studies link dopamine neurons to novelty detection, this has not been demonstrated electrophysiologically in humans. We used single neuron extracellular recordings in awake human subjects undergoing surgery for Parkinson disease to characterize the features and timing of this response in the substantia nigra. We recorded 49 neurons in the substantia nigra. Using an auditory oddball task, we showed that they fired more rapidly following novel sounds than repetitive tones. The response was biphasic with peaks at approximately 250 ms, comparable to that described in primate studies, and a second peak at 500 ms. This response was primarily driven by slower firing neurons as firing rate was inversely correlated to novelty response. Our data provide human validation of the purported role of dopamine neurons in novelty detection and suggest modifications to proposed models of novelty detection circuitry.

1. Introduction

It is well-established in animal models and neuroimaging studies that substantia nigra (SN) neurons, especially dopamine (DA) neurons, avidly respond to reward (Hollerman and Schultz, 1998) as well as novelty (Bunzeck and Düzel, 2006; Legault and Wise, 2001; Li et al., 2003; Ljungberg et al., 1992). A consensus has formed that both increases and decreases in DA neuron firing rate serve as learning signals (Schultz, 2007); a large phasic increase in DA from the SN/ventral tegmental area (VTA) to the nucleus accumbens likely strengthens hippocampal inputs when reward is located, leading to memory reinforcement of rewarded behaviors (Goto and Grace, 2005). These observations have led to the hypothesis

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that DA signaling is required for late long-term potentiation (LTP). Some predictions of this model have been confirmed by neuroimaging studies; notably, reward representations in the striatum appear to be enhanced by preceding novel scenes (Guitart-Masip et al., 2010), and memory for visual scenes at 24 h after an fMRI experiment correlated to activation within the hippocampus, ventral striatum, and SN/VTA (Bunzeck et al., 2012). However, human electrophysiology studies have not been performed to test key parts of this hypothesis.

Specifically, the timing of the substantia nigra response to novelty is unknown; a popular model predicts an early response to novelty, which serves to strengthen hippocampal synapses formed during behaviorally salient novel events (Lisman et al., 2011). Primate studies have also supported a very short latency (~100 ms) for phasic DA responses to novel stimuli (Ljungberg et al., 1992), but some longer-latency responses have been observed, on the order of 200 ms (Mirenowicz and Schultz, 1994). However, with some authors positing a "systems-wide computation…[to determine] that there is a high level of novelty or motivational salience" as a requirement for DA release (Lisman et al., 2011), it is critical to know when precisely this release occurs. Using event-related potentials in patients implanted with externalized DBS electrodes, novel stimuli were associated with both an early hippocampal peak (~180 ms) and a late nucleus accumbens peak (~480 ms) that was correlated to increased retention in memory (Axmacher et al., 2010). However, this study did not directly address the midbrain. The authors posit that the link between the hippocampal activation and the nucleus accumbens activation is the dopamine system; we used a novelty-oddball task to detect the posited early substantia nigra response that would conform to this hypothesis, as well as to characterize its features and timing, to a degree not possible with fMRI. This task is also used in electroencephalography (EEG) experiments to evoke the novelty P300, a hippocampally-dependent event related EEG potential (Knight, 1996) (Fig. 1).

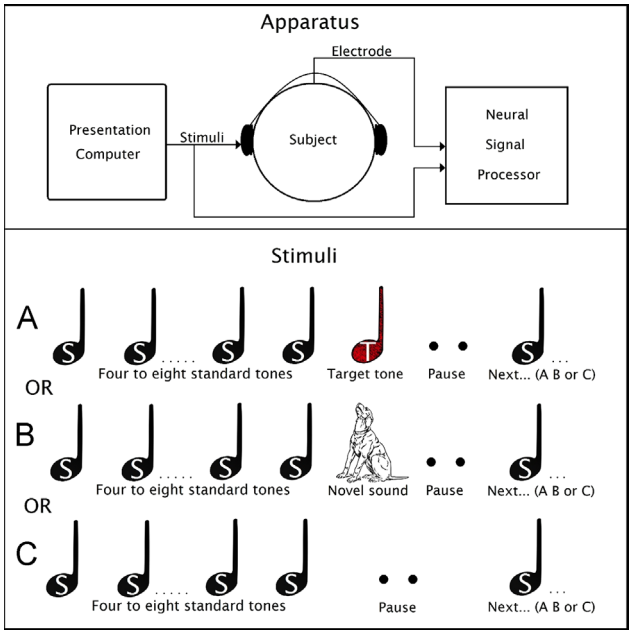

Fig. 1 – Apparatus and Task. The apparatus consisted of a presentation computer, headphones, a microelectrode, and a neural signal processor. We used a variation on the novelty P300 task as described by Fabiani and Friedman (1995) and Knight (1996) to study midbrain responses to stimuli. Novel sounds included environmental sounds (animal noises), mechanical sounds, or non-standard, non-target musical tones.

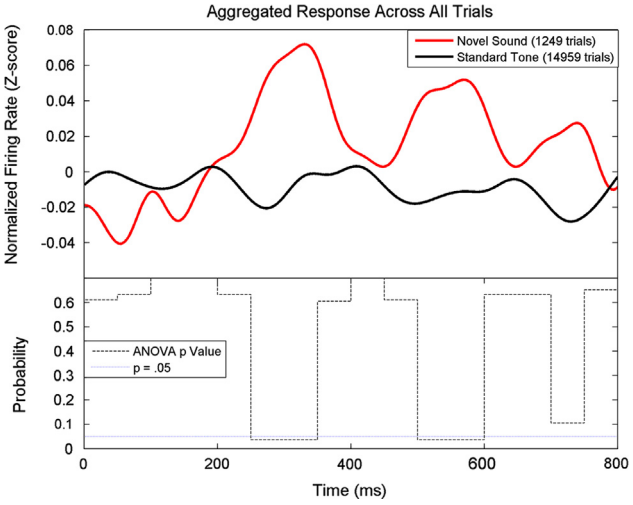

Fig. 2 – Aggregated Neuron Responses. The smoothed normalized firing rate was calculated at each millisecond for each trial as described in the text. The curves here depict the average firing rate across all novel trials (red) and all standard trials (black).

2. Results

Forty-nine putative neurons were identified. A total of 14959 standard trials, 912 target trials, and 1249 novel sound trials were performed. Novel sounds evoked a greater response compared to standard tones over the 250–350 ms interval ($F_{stimulus}=6.9$, $p=0.010$ (250–300 ms) and $F_{stimulus}=7.1$, $p=0.009$ (300–350 ms), $p=0.037$ (both intervals) after correction for multiple comparisons by FDR, Fig. 2). A second peak of significantly increased firing was seen from 500 to 600 ms ($F_{stimulus}=7.1$, $p=0.009$ (500–550 ms) and $F_{stimulus}=7.8$, $p=0.006$ (550–600 ms), $p=0.037$ (both intervals) after correction for multiple comparisons by FDR). Responses to target tones and standard tones did not significantly differ over any interval. The aggregated normalized firing rate following all standard tone and novel sound trials is displayed in Fig. 2, which shows a peak beginning approximately 250 ms following novel sounds, and reaching its zenith at 300 ms. A second peak was seen beginning at 500 ms.

To confirm that substantia nigra neurons differentiated standard and novel tones, we performed principal component analysis (PCA) on the 800 ms following the stimulus for responses to standard and novel tones. The population of neurons recorded was heterogenous, and not all neurons were expected to discriminate novels and standards. Furthermore, stimulus novelty seems likely to be only