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DOPAMINERGIC ACTIVITY COINCIDES WITH STIMULUS DETECTION BY THE FRONTAL LOBE

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Abstract—For midbrain dopamine (DA) neurons to respond to sensory events, the presence of a stimulus must first be detected. Where is the signal that activates DA neurons coming from? Here we show that DA responses to a vibrotactile stimulus lag significantly behind those of the primary somatosensory cortex, but they arise with a latency that closely matches the onset of premotor neurons known to encode perceptual decisions. In agreement with previous findings, these data suggest that sensory evoked DA activity does not signal a stimulus physical presence but arises from the output of a perceptual decision.

Key words: dopamine, perception, reward, detection, somatosensory, decisions.

INTRODUCTION

Midbrain dopamine (DA) neurons can be activated by the onset of unpredictable or behaviorally relevant sensory events (Romo and Schultz, 1990; Schultz and Romo, 1990; Schultz, 1998; Redgrave and Gurney, 2006). This DA activity signals the likely availability of future reward, and it modulates learning processes in the basal ganglia and cortex (Montague et al., 1996; Wise, 2004; Bromberg-Martin et al., 2010; Surmeier et al., 2011). However, for DA neurons to participate in sensory processing and learning, the presence of a stimulus must first be detected. This opens an important question in relation to the source of DA activation. Are DA responses triggered by pre-attentive sensory information (Dommett et al., 2005), or do they arise after perceptual processing has occurred?In the context of vibrotactile stimulation, it is known that activation of primary somatosensory cortex (S1) does not guarantee stimulus detection (de Lafuente and Romo, 2005). It seems that primary sensory cortices are necessary but not sufficient to generate a sensory percept. On the other hand, it was recently demonstrated that premotor neurons on frontal lobe cortices closely covary with perceptual reports on stimulus presence or absence (de Lafuente and Romo, 2006). By recording from several cortical areas while monkeys performed a vibrotactile detection task, those experiments revealed that frontal lobe areas, in particular the medial premotor cortex (MPC), had the longer response latency and the closest association with perceptual reports. Microstimulation and control experiments demonstrated that MPC neurons reflect not only the onset of a motor plan or the outcome of a decision process, but they also reflect the subjective perception of stimulus presence (de Lafuente and Romo, 2005).

Here we analyze whether DA responses to vibrotactile stimuli arise from early sensory responses, or whether they are more closely related to the output of perceptual processing occurring in frontal cortices. To approach this question, we compared onset latencies of sensory activity in midbrain DA, S1 and MPC neurons, evoked by a vibrotactile stimulus.

EXPERIMENTAL PROCEDURES

Detection task

Monkeys were trained to communicate the presence or absence of a vibrotactile stimulus by pressing one of two push buttons located in front of their left arm at shoulder level (Fig. 1). They received a liquid reward for correctly reporting stimulus presence (hit trials) or absence (correct rejection trials), and received no reward when they failed to report stimulus presence (miss trials) or incorrectly reported stimulus presence when vibration amplitude was zero (false alarm trials). The vibrotactile stimulus consisted of a sinusoidal 20 Hz vibration that lasted for 0.5 s, and was superimposed on a 0.5 mm skin indentation. This stimulus was delivered through a 2 mm round tip plastic probe of a mechanical stimulator (BME Systems) placed on a fingertip. Recording sessions were initiated after monkeys achieved asymptotical detection performance, after at least 6 months of training.

Recordings

Extracellular spike potentials were recorded with quartz-coated platinum-tungsten microelectrodes (2–3 MΩ, Thomas Recording GmbH) inserted through a recording chamber. To record from

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Abbreviations: DA, midbrain dopamine; MPC, medial premotor cortex; S1, primary somatosensory cortex; SNc, substantia nigra pars compacta.

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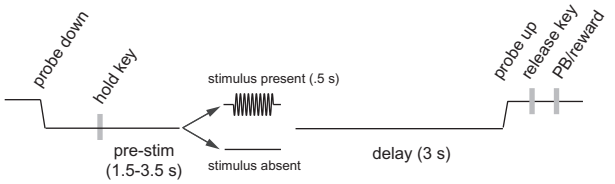

Fig. 1. Vibrotactile detection task. The position of the mechanical stimulator is plotted as a function of time (not drawn to scale). Trials started by indenting the fingertip of the right hand (probe down). Monkeys then placed their left non-stimulated hand on an immoveable key at waist level (hold key). After a 1.5–3.5 s pre-stimulus delay (uniform distribution), a 20 Hz sinusoidal vibration was delivered for 500 ms. Stimulus amplitude was zero on half of randomly selected trials, and it had amplitudes bracketing detection threshold on the other half. After a 3 s post-stimulus delay, the mechanical stimulator moved up (probe up) signaling the monkeys to release the immoveable key (release key) and press one of two push-buttons (PB) to communicate whether stimulus was present or absent. Reward was delivered immediately upon button press. No sensory cue other than reward itself was used to distinguish rewarded and unrewarded trials.

midbrain DA neurons, a cylindrical recording chamber (9 mm inside diameter) was placed 4 mm lateral from the midline, and 10 mm anterior of interaural line. Chambers were confirmed functionally to be over the representation of the lower extremities in the motor cortex. In their downward trajectory electrodes passed through the head representation in the ventral posteromedial nucleus (VPM) thalamic nucleus, then through a region with large extracellular action potentials (typical of the red nucleus), and finally into the dopaminergic midbrain (Schultz and Romo, 1987, 1990; Romo and Schultz, 1990). Midbrain DA neurons were identified on the basis of their characteristic regular and low tonic firing rates (1–10 spikes per second), and also by their long extracellular spike potential. We have no direct way to address whether electrodes arrived at ventral tegmental area (VTA) and/or substantia nigra pars compacta (SNc). However, the location of our recording sites suggests that neurons were sampled mostly from the SNc. Recent evidence has shown that DA neurons are not a homogenous population, and that some neurons located dorsolaterally in the SNc are actually excited by aversive stimuli (Matsumoto and Hikosaka, 2009). It is likely that our sample of neurons contains both aversive-excited and aversive-inhibited neurons. Two rhesus monkeys (*Macaca mulatta*) participated in this study and were handled in accordance with the US National Institutes of Health guide for the care and use of laboratory animals, and with the Society for Neuroscience guidelines. The number of recorded neurons was 59 in S1 (areas 1/3b, rapidly adapting neurons (de Lafuente and Romo, 2005)), 69 in the midbrain (de Lafuente and Romo, 2011), and 50 in the MPC (neurons with positive responses to the stimulus and delay activity (de Lafuente and Romo, 2005)).

Analysis of neuronal activity

For display purposes (Fig. 2) spike trains of each neuron were convolved with a causal exponential decay function (30 ms time constant), and standardized by subtracting the mean and dividing by the standard deviation of firing rates recorded within a 500 ms window before stimulus onset. To estimate response latency, spike trains were first convolved with a causal exponential decay function (10 ms time constant) displaced in 1 ms increments. Then, activity of each neuron was standardized as described above, and the trials of neurons for each area were pooled. In this manner, a distribution of standardized activity was obtained for each 1 ms bin. We defined response latency as the first of 10 consecutive bins in which mean standardized activity significantly departed from zero ($P < .01$, one sided z-test). We utilized a bootstrap procedure in which 1000 latency estimates were calculated by re-sampling, with replacement, from the pool of trials of

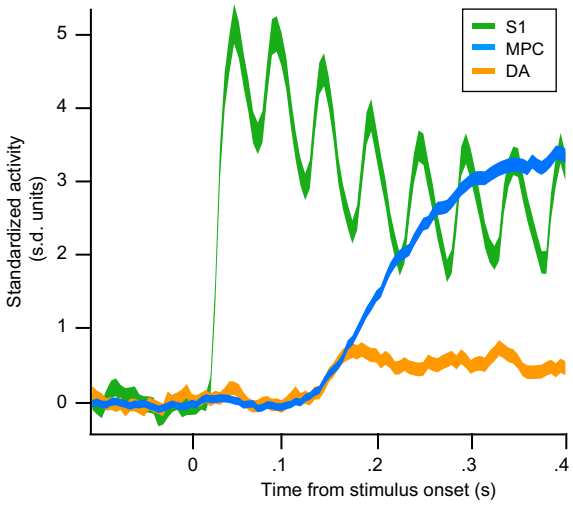

Fig. 2. Responses of midbrain dopamine (DA), primary somatosensory (S1) and medial premotor (MPC) neurons to a 20-Hz vibrotactile stimulus. Colored traces depict mean standardized activity (±1 s.e.m.) of hit trials for each cortical area. Note the short-latency and stimulus locked responses of S1 activity, and the similar onset latency of MPC and DA activity.

each recorded area. Given that our latency estimate makes use of a z-test, the comparison of latencies across areas is not valid unless the underlying activity distributions have the same standard error. Standard error of MPC and S1 activity was made equal to that of DA activity by adjusting the number of trials according to the formula: $n_a = n_b(\sigma_a/\sigma_b)^2$, where subindices a and b indicate the number of trials and standard deviation of two given areas.

RESULTS

Two monkeys were trained to indicate the presence or absence of a vibrotactile stimulus (Fig. 1). A sinusoidal vibration, whose amplitude was zero on half the trials, was presented after a variable pre-stimulus interval (1.5–3.5 s). Monkeys were required to indicate their decision by pressing one of two push buttons at the end of a post-stimulus delay period (3 s). By separating stimulus presentation from movement initiation we were able to study sensory responses without possible motor confounds. Recordings of DA and cortical neurons were performed on separate sessions while monkeys performed the discrimination task (no significant differences were found between detection thresholds of midbrain and cortical recording sessions; $P = 0.22$, Kruskal–Wallis test).

To compare the onset latency of sensory evoked activity across recorded areas, we selected hit trials, aligned extracellular spike potentials to the time of stimulus onset, and standardized firing rates with respect to a pre-stimulus activity window (Fig. 2). The mean activity of S1 neurons shows that responses of this primary sensory area initiate 27 ms (±2 ms, SD) after stimulus onset. As can be observed in Fig. 2, the activity of S1 neurons was phase-locked to the sinusoidal vibrations of the mechanical stimulator, a finding that is consistent with their role in encoding the physical parameters of tactile stimuli (Hernández et al., 2000; Andermann and Moore, 2006; Arabzadeh et al., 2006; Sripati et al., 2006; Reed et al., 2008).

Responses of MPC and DA neurons became significantly different from baseline activity at 146 ms (±8, SD) and 147 ms (±6, SD), respectively. The bootstrap analysis of response latencies did not show a significant difference in the latency of these areas ($P = 0.56$, two sided *t*-test). The slower rate of rise of mean MPC activity, as compared to S1, is explained by the higher variability of onset latencies that is observed across MPC neurons, and across trial repetitions of the same neuron (de Lafuente and Romo, 2006). Although midbrain DA neurons displayed considerably weaker sensory evoked activity, these results show that DA activity initiates with latency closely matching that of frontal lobe neurons.

In addition to being activated by the vibratory stimulus, DA neurons were modulated during the period of reward delivery (de Lafuente and Romo, 2011). A significant increase in DA firing rate was observed on rewarded trials, and a significant decrease was observed on unrewarded trials ($P < .01$, paired *t*-test). Given that reward plays a fundamental role in behavior and learning, we wondered to what extent the activity of cortical neurons were modulated during the period of reward delivery. To explore this, the activity of a wide range of cortical areas, recorded during the detection task (de Lafuente and Romo, 2005, 2006), was aligned to the period of reward delivery (Fig. 3). We found no differences in activity between rewarded and unrewarded trials in any of the recorded cortical areas. These results show that reward delivery, or the lack of it, exerts no direct influence on cortical areas that process somatosensory information.

DISCUSSION

The close temporal association of DA activity with frontal lobe neurons, together with the known role of MPC neurons in signaling subjective sensory perception (de Lafuente and Romo, 2006; Hernández et al., 2010), suggests that DA neurons could play a role in perception and perceptual decisions. Consistent with this idea, it was recently demonstrated that midbrain DA neurons respond only in those trials in which monkeys successfully detect the stimulus presence (de Lafuente and Romo, 2011). Unlike S1 neurons that activate regardless of the monkey's perceptual reports, DA neurons strongly covary with subjective reports.

Our recordings from cortical and subcortical neurons were performed in separate sessions. This might have blurred small latency differences only detectable by analysis of simultaneously recorded activity. It is thus plausible that sensory evoked activity in the midbrain arises after the successful detection of somatosensory stimuli by the frontal lobe. Under this hypothesis, DA activity would follow MPC activity with a short latency. However, an alternative possibility is that sensory detection occurs in a structure, or by a process, capable of modulating MPC and DA activity simultaneously. A possible cortical influence over DA neurons could be exerted directly by projections of prefrontal neurons to the midbrain, or indirectly through the basal ganglia (Haber and Knutson, 2010). There is evidence that subcortical projections to the midbrain might be responsible for short latency

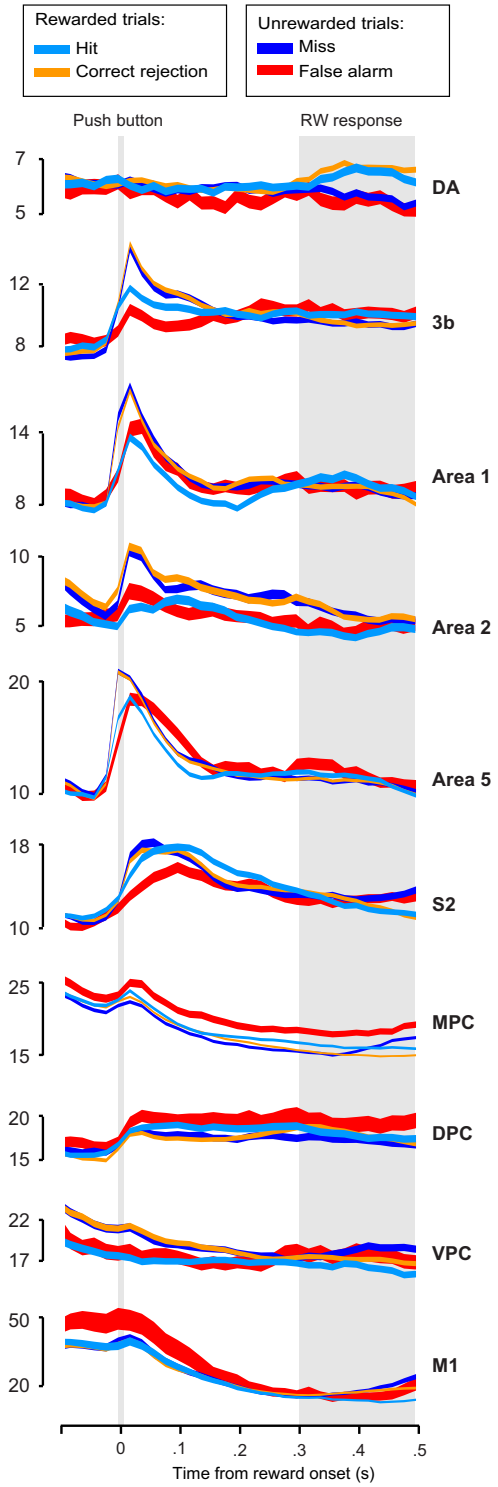

Fig. 3. Comparison spiking activity during rewarded and unrewarded trials in the midbrain (DA) and cross cortical areas. The mean firing rates are aligned to the time of reward delivery. A drop of liquid was delivered through a mouth piece on correct trials (hits and correct rejections). A significant difference between rewarded and unrewarded trials was found only on DA neurons ($P < .01$, two sided *t*-test). The gray shadow indicates the window used to test reward modulation. No sensory cue other than reward itself differentiated rewarded from unrewarded trials. Firing rate scales were adjusted so that the standard error of mean activity was comparable across areas (MPC, DPC and VPC; medial, dorsal and ventral premotor cortex, respectively).

nociceptive (May et al., 2009) and visual responses of DA neurons (Dommett et al., 2005). Our results indicate that those direct pathways are not available for relying vibrotactile information or, if present, are not used in the context of a detection task.

At the frontal lobes sensory stimuli are evaluated according to their behavioral context, and the possible actions required by those events are assessed. The sensory evoked responses of midbrain DA neurons could indicate the availability of future rewards, and additionally encode the confidence associated with a perceptual decision. Although the functional meaning of this activity is still not completely understood, the latency comparisons suggest that DA neurons do not reflect the physical presence of the stimulus, as S1 neurons do, but they might reflect the outcome of perceptual processing.

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