

Differential cingulate and caudate activation following unexpected nonrewarding stimuli

M.C. Davidson,^{a,*} J.C. Horvitz,^b N. Tottenham,^a J.A. Fossella,^a R. Watts,^c
A.M. Ulug,^c and B.J. Casey^a

^aSackler Institute for Developmental Psychobiology, Weill Medical College of Cornell University, New York, NY 10021, United States

^bBoston College, Chestnut Hill, MA 02467, United States

^cDepartment of Radiology, Weill Medical College of Cornell University, New York, NY 10021, United States

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This study examined the effects of varying the predictability of nonrewarding events on behavior and neural activation using a rapid mixed-trial functional magnetic resonance imagery (fMRI) design. Twelve adult subjects were scanned with echo planar imaging during performance of a visual detection task where the probability of events (target and nontarget) varied. This task included expected and unexpected nonrewarding events (expected target, unexpected nontarget, and omission of target) in a design that closely parallels studies of dopamine function and reward processing in the alert monkey. We predicted that activation in dopamine-rich areas of the forebrain would behave like the animal literature shows that dopamine neurons in the midbrain behave. Specifically, we predicted increased activity in these regions when an unexpected event occurred and decreased activity when an expected event was omitted. Two main regions, the anterior cingulate and dorsal striatum, showed this pattern. The response in these regions was distinguished by enhanced anterior cingulate activity following the occurrence of an unexpected event and greater suppression of caudate activity following the omission of an expected event. These results suggest that neural activity within specific dopamine-rich brain regions can be modulated by violations in the expectation of nonrewarding events and that the direction of the modulation depends on the nature of the violations.

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A great deal of our knowledge about the neural mechanisms of motivated or goal-directed behavior has been acquired through research with nonhuman animals. Much of this research has focused on the midbrain dopamine (DA) nuclei and forebrain regions that receive heavy dopaminergic innervation (e.g., Berridge and Robinson, 1998; Horvitz et al., 1997; Robbins and Everitt,

1996; Schultz, 1992). Through an extensive series of studies Schultz and colleagues (1992, 1993a,b, 1997, 1998, 2000) have shown DA cells in the midbrain nuclei of alert monkeys to have fairly consistent electrophysiological responses to rewards and stimuli that predict rewards. Rather than indicating the presence or absence of rewards per se, these neurons are argued to encode a prediction error, signaling the difference between actual and expected rewards (Montague et al., 1996; Schultz et al., 1997). In particular, these cells respond to the presentation of unexpected rewards, or rewards presented at unexpected times, but generally do not respond to well-predicted rewards. However, if an expected reward does not occur, there is often a depression in the cell's activity (below baseline levels) at the time the reward should have occurred, suggesting a bidirectional sensitivity to prediction and violation of expected rewards.

In an effort to understand motivated behavior in humans, several groups of researchers are using functional imaging techniques, including positron emission tomography (PET) and functional magnetic resonance imagery (fMRI) with reward-based paradigms. These studies have used a variety of motivating stimuli, including: pleasant, unpleasant, and neutral liquids (Berns et al., 2001; O'Doherty et al., 2001a,b, 2002; Rolls et al., 1999), monetary rewards (Breiter et al., 2001; Elliott et al., 2000, 2003; Knutson et al., 2000, 2001a,b, 2003; Pappata et al., 2002), video game performance (Koepp et al., 1998), and gambling outcomes (Critchley et al., 2001; Delgado et al., 2000, 2003) to identify brain regions involved in goal-directed behavior. The influence of prediction and expectation of reward has been explored in imaging studies with humans as well (Berns et al., 2001; Knutson et al., 2001a; McClure et al., 2003; Pagnoni et al., 2002; Pappata et al., 2002). In concordance with animal research, these studies found several brain regions (including the ventral striatum, cingulate, and ventromedial frontal cortex) that are sensitive to prediction and violation of expected rewards. These results suggest that dopamine-rich areas of the forebrain are sensitive to prediction errors for both the time and amount of reward delivery.

* Corresponding author. Sackler Institute for Developmental Psychobiology, Weill Medical College of Cornell University, 1300 York Avenue, Box 140, New York, NY 10021. Fax: +1 212 746 5755.

E-mail address: mcd2002@med.cornell.edu (M.C. Davidson).

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In this experiment, we used a rapid mixed-trial fMRI design to test the hypothesis that activity in dopamine-rich brain regions, as measured by changes in the BOLD signal, would be sensitive to prediction errors for non-rewarding events. We manipulated stimulus presentations to allow comparisons between expected events, unexpected events, and omissions of expected events (stimulus and temporal omissions). Based on the research discussed above, we predicted an increase in activation for unexpected events and a decrease in activation for omissions of the expected events in dopamine-rich areas of the forebrain.

Methods

Participants

Twelve healthy right-handed adults participated in this study (mean age = 27.5 years, five females). All subjects were screened for neurological disorders and contraindications for MRI before participating. Written consent was obtained before scanning and subjects were paid for their participation.

Paradigm

Subjects were asked to perform a visual detection task (using the stimuli shown in Fig. 1) by pressing a single response button with their right index finger whenever a ‘cheese’ stimulus was presented (expected events occurring for 76% of the trials) but not for other events. Subjects were not told explicitly about the three rare trial types (unexpected stimulus, stimulus omission, and temporal omission) that were presented with 8% probability for each, intermixed pseudorandomly with a single rare event occurring after two, three, or four consecutive cheese trials. The task involved eight blocks of 72 trials, with each stimulus presented for 500 ms followed by a 3500-ms interstimulus interval (ISI). During the ISI, a closed door remained on the screen, briefly opening to reveal one of the experimental stimuli in a continuous stream of trials. In four of the eight blocks, a partial opening of the door served as a temporal cue for the start of a trial and occurred 1000 ms before the complete opening (see Fig. 1). This cue did not indicate upcoming trial type (as it was presented for all trials in the cued blocks), and was designed to increase subject’s readiness to respond by providing temporal information. Cued and uncued blocks alternated for all subjects, with random selection of the initial block type at the start of each session. In the cued blocks, the

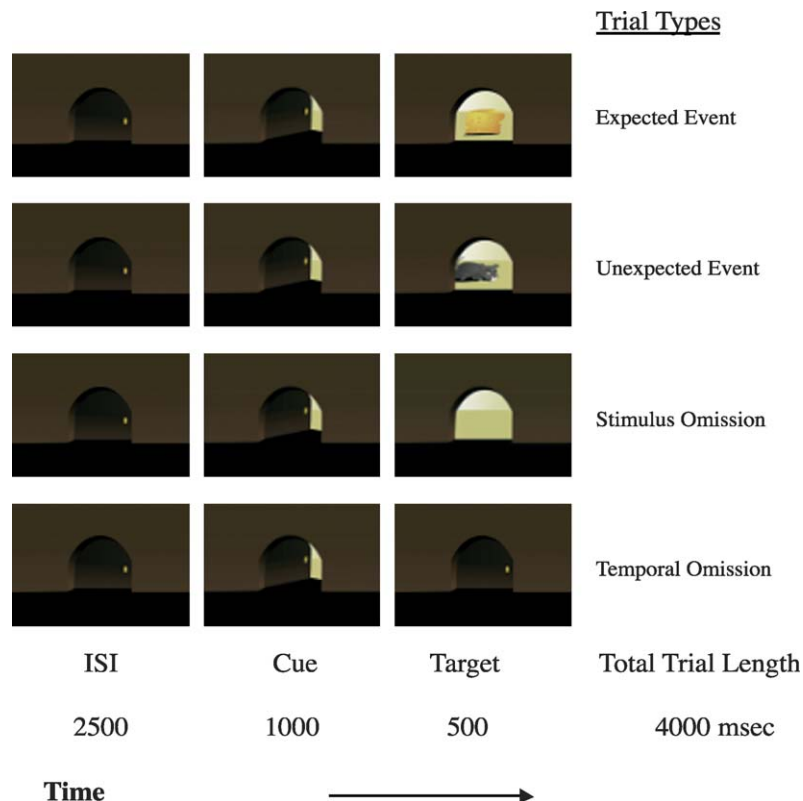


Fig. 1. Representation of the four trial types used in this experiment. The expected event (cheese stimulus) occurred on 76% of the trials with each of the other three trial types presented pseudorandomly on 8% of the trials. The three variations included an unexpected event (cat stimulus), a stimulus omission event (blank stimulus), and a temporal omission event (closed door stimulus), and were designed to mimic several of the manipulations used in single unit recordings in alert monkeys (e.g., Schultz, 2002). The interstimulus interval (ISI) was 3500 ms, with each target presented for 500 ms. There were a total of eight blocks, with four blocks containing a temporal cue (the cracking of the door, as shown) and four blocks without this cue. In the cued blocks the door opened slightly for 1000 ms before opening completely for the target presentation (or closing again in the temporal omission trials). This cue was presented for all trial types and provided temporal information only. In the uncued blocks, the door remained closed for the 3500 ms ISI (or the full 4000 ms in the temporal omission trials). Cued and uncued blocks alternated for all subjects, with random selection of the initial block at the start of each scanning session.

Table 1
Percent correct responses (and standard error) for each trial type and cueing condition

Trial type	Average	Cued	Uncued
Expected event	99.1 (0.5)	99.4 (0.4)	98.9 (0.6)
Unexpected event	86.6 (3.4)	87.5 (3.5)	85.7 (3.4)
Stimulus omission	95.8 (2.0)	98.9 (0.5)	92.7 (2.6)
Temporal omission	100	100	100

Subjects made significantly more errors for the unexpected event trial type relative to all other trial types, which did not differ from each other (Tukey's test with $\alpha = 0.01$).

cue was presented before all trial types (providing temporal information only) and subjects were not forewarned about the presence or relevance of the cue. Reaction times (RTs, for the cheese target trials) and accuracy measures (for all trials) were collected throughout the eight runs.

Scan parameters

EPI BOLD images were acquired in a 1.5-T GE scanner with a protocol of TR = 2000, TE = 40 ms, and flip angle = 90° . Twenty-four coronal slices of 4 mm slice thickness and zero gap (3.125×3.125 mm in-plane resolution) were collected for 152 repetitions (including four discarded acquisitions). Anatomical images (TR = 500, TE = minimum, 4 mm slice thickness) were collected in the same locations as the functional images as well as a set of high-resolution SPGR images (TR = 25, TE = 5, 1.5 mm slice thickness, 124 slices) that were used for 3D localization.

Image analysis

EPI images were reconstructed offline and then motion corrected with Automated Image Registration (AIR) version 3.08 (e.g., Woods et al., 1993). All subjects were then co-registered with a representative brain from the sample (female subject with mean brain size and good orientation). Following this spatial alignment, each subject's functional data were normalized and spatially smoothed with a FWHM distribution of 8 mm. Finally, the representative brain and functional data sets were brought into Talairach coordinate space by conventional landmarks using AFNI version 2.50 (e.g., Cox, 1996).

For each trial of interest, two image repetitions were selected, collected between 4–6 and 6–8 s following stimulus presentation. These time points were based on previous research showing the hemodynamic response to peak at approximately 5–6 s following stimulation and were selected to avoid overlap with previous or subsequent target stimuli presented in the rapid-mixed trial design (Boynton et al., 1996; Dale and Buckner, 1997; Durston et al., 2002, 2003a). Given the need for temporal consistency between trials (to establish temporal expectation), it was not possible to use a jittered design in this study. However, previous research has shown that it is possible to distinguish the BOLD responses for specific stimuli by using at least a 4-s interval between stimuli and by presenting the same stimulus type (in the current study, at least two expected trials) just before the trials of interest, thereby equating the level of baseline noise for all comparisons (Durston et al., 2002, 2003a). Finally, as there were more expected stimulus trials than the other trial types, a subset of images (the third trial in a sequence of expected trial types) was selected for this trial type to equate cell sizes and to avoid overlap in hemodynamic responses

(trials of interest were separated by at least 8 s). This selection resulted in a maximum of 12 data points per trial type in each of eight runs ($12 \times 4 \times 8 = 384$ data points per subject). Only correct trials were included in the analyses.

A repeated-measures omnibus ANOVA was performed, with subjects (12) as the random factor and trial type (4) as a within-subjects factor. A statistical threshold of $P < 0.005$ across 10 contiguous voxels was used to detect regions of significant difference between all four conditions (Forman et al., 1995). These analyses were conducted with the NeuroImaging Software package version 3.5 (Laboratories for Clinical Cognitive Neuroscience and Neuroscience of Cognitive Control, University of Pittsburgh and Princeton University) using a random-subject design (see Carter et al., 1998; Cohen et al., 1997; Delgado et al., 2000). Time-series analyses were then conducted on the main regions of activation to determine the directionality of signal changes as a function of trial type. The main regions were selected based on the size, intensity, and consistency across subjects of activation from the omnibus ANOVA. For each time-series comparison, a percent change in signal, relative to the expected stimulus trials, was calculated for each of the other trial types (SAS, version 8.2). These percent change values were used in subsequent correlation analyses with accuracy performance.

Results

Behavior

Accuracy scores were calculated as correct responses for the expected target trials and correct withholding of responses for the unexpected nontarget trial types. As shown in Table 1, there was a main effect of trial type [$F(3,33) = 14.45, P < 0.001$], with a post hoc Tukey's test showing accuracy for unexpected events to be significantly worse than the other trial types (see Table 1, Average). No significant differences in accuracy were found for cueing conditions or the cueing by trial type interaction. Reaction times (RTs) for the target trials did vary as a function of cueing condition, with significantly faster RTs for the cued than noncued trials ($F(1,22) = 4.39, P < 0.04$; means = 357 and 387, respectively).

Imaging

A whole-brain voxel-wise ANOVA revealed several regions with significant activation ($P < 0.005$ with at least 10 contiguous voxels], as presented in Table 2. Based on the size and intensity of

Table 2
Regions activated in the omnibus ANOVA beyond the thresholds $P < 0.005$ for 10 contiguous voxels

Region	Brodmann area	Talairach			Maximum F	Cluster size
		x	y	z		
Cingulate	9	-4	41	18	12.94	55
Superior frontal gyrus	6	5	35	55	10.09	59
Dorsal striatum		-6	8	10	9.02	95
Medial temporal lobe	34	-31	-4	-19	8.33	20
Thalamus		1	-17	5	6.98	14

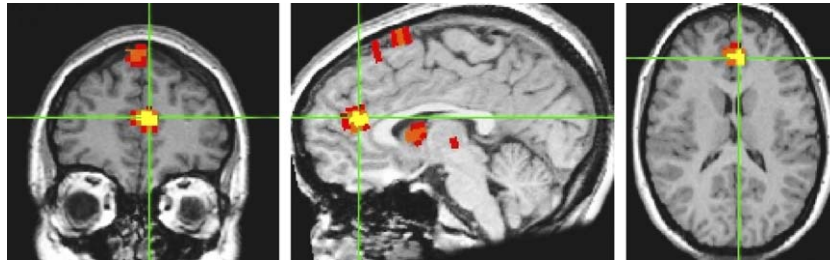


Fig. 2. Anterior cingulate activation for the omnibus whole-brain analysis.

these activations, we focused on two regions of interest, the cingulate cortex and the dorsal striatum (see Figs. 2 and 3). Both regions of activity were close to the midline, with the maximum F values located in the left hemisphere. A separate ANOVA testing the effect of cueing condition revealed no significant differences for these regions so the two cue conditions were collapsed in subsequent analyses.

In post hoc analyses for these two regions, we investigated the differences between the four trial types by calculating percent change scores for the three rare nontarget trial types relative to the expected target trials. As shown in Fig. 4, although the pattern of activity across these regions was similar, a significant increase in activation in the anterior cingulate was shown for the unexpected stimulus trials, relative to the expected target trials [paired $t(11) = 2.99$, $P < 0.05$], but no significant changes in MR signal for the two omission trial types in this region. The dorsal striatum, on the other hand, showed no significant increase for the unexpected event trials, but showed a significant decrease in activation for both the stimulus omission and temporal omission trials (paired $t(11) = -2.44$, $P < 0.05$; $t(11) = -3.72$, $P < 0.01$, respectively), relative to the expected trials (see Fig. 4). A correlation analysis for the unexpected trials showed a trend for a positive correlation ($r = 0.61$, $P < 0.06$) between the percent change in MR signal in the anterior cingulate and percent of false alarms.

Discussion

This study used a rapid mixed-trial fMRI design to measure brain activity following the presentation and omission of expected and unexpected nonrewarding stimuli. The results show that dopamine-rich brain regions are sensitive to prediction errors for nonrewarding events. These regions include the anterior cingulate cortex and dorsal striatum/caudate nucleus in the present study. In addition, the patterns of relative activation and deactivation observed for these regions correspond well with the patterns of activity observed for DA neurons in many of the reward and

expectation tasks used with behaving monkeys (e.g., Schultz et al., 1997). As shown in Fig. 4, the cingulate and caudate regions showed similar patterns of activation and deactivation for these manipulations but with different amplitudes. In particular, relative to the frequent target trials, the unexpected nontarget trials were found to enhance cingulate activity while the omission trials (stimulus and temporal omissions) were found to suppress caudate activity. These results provide insight into the mechanisms of prediction and expectation for simple events, in the absence of explicit rewards, by demonstrating that brain regions with DA innervation can be activated by the occurrence of unexpected events and suppressed by the omission of expected events, relative to the occurrence of expected events.

It is important to note that although the current study used the BOLD response to explore neural activity, the regions of activation are similar to those found in PET studies of reward and addiction using [^{11}C]-labeled raclopride to index DA binding activity (e.g., Koeppe et al., 1998; Pappata et al., 2002). However, in this study, the observed changes in BOLD signal may reflect differential processing via the activity of inputs to these regions or through the modulatory actions of DA within these regions. The differential activation between cingulate and caudate areas may also reflect differences in the point of origin or amount of DA innervation (e.g., Fuxe, 1965; Gaspar et al., 1989) or the rate of reuptake within these regions. For example, labeling studies have shown differences in the density and distribution of dopamine transporters (DAT) between these two regions, with greater density of DAT in the caudate (Ciliax et al., 1999). Each of these factors may have contributed to the differential changes in BOLD signal observed in this study.

In the current study, the anterior cingulate showed a significant increase in activation for the unexpected event trials. This increase may reflect the amount of conflict or difficulty subjects had withholding responses to these particular trial types (Botvinick et al., 1999; Carter et al., 1999). If subjects are expecting a particular stimulus and a different stimulus occurs they may experience greater stimulus-response conflict than if a stimulus does not occur. In support of this interpretation, the behavioral results show

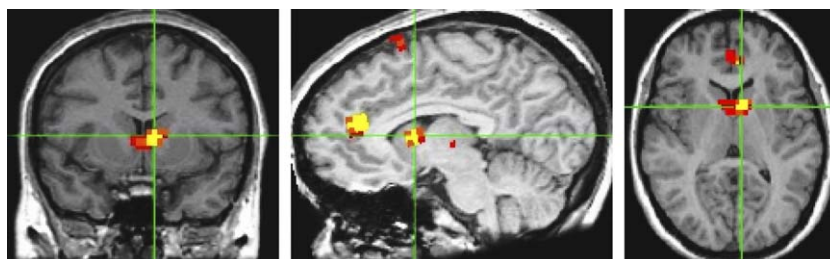


Fig. 3. Activation in the dorsal striatum for the omnibus whole-brain analysis.

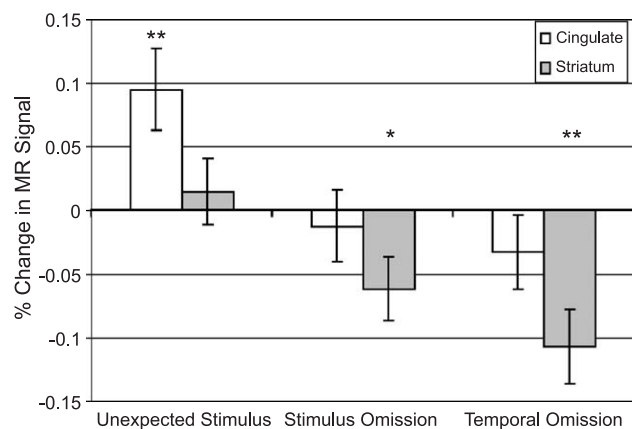


Fig. 4. Percent change in MR signal for the three rare trial types relative to the frequent trials (Expected) for the two main regions of activation (* $P < 0.05$; ** $P < 0.005$).

subjects made significantly more false alarms for the unexpected relative to the expected and omitted trial types (see Table 1). Similarly, the correlation results suggest a positive association between the number of false alarms and the percent change in MR signal, even with incorrect trials excluded from the fMRI analysis. In contrast, we found significant decreases in caudate activation for both types of omitted trial types (stimulus and temporal), relative to the expected trials. These decreases may reflect fluctuations in DA activity within the caudate, as predicted from the single-unit recording studies showing suppression of activity in the absence of expected rewards. However, in this study, these changes occurred in the absence of explicit rewards. Rather than selectively detecting rewards, or stimuli predicting rewards, these dopamine-rich regions appear to be responsive to any unexpected or behaviorally relevant stimuli that produce a change in attention or behavior (Braver and Cohen, 2000; Hayes et al., 1998; Redgrave et al., 1999). The importance of dopamine and dopamine-rich regions in attentional control and response inhibition is further supported by studies of ADHD (Bush et al., 1999; Durston et al., 2003b; Vaidya et al., 1998) and substance abuse (Volkow et al., 2004) that show abnormal patterns of activity in these regions.

A number of theories suggest different roles for basal ganglia and frontal cortex-related circuits, including movement, cognition, and reward-related behavior (Alexander et al., 1986; Braver and Cohen, 2000; Braver et al., 1999; Berridge and Robinson, 1998; Casey et al., 2000; Cohen and Servan-Schreiber, 1992; Cohen et al., 1996; Corbetta et al., 1991; Dayan and Balleine, 2002; Haber, 2003; Hayes et al., 1998; Holroyd and Coles, 2002; Kimberg and D'Esposito, 2003; Montague and Berns, 2002; Robbins and Everitt, 1999; Saint-Cyr, 2003; Servan-Schreiber et al., 1990). Interestingly, the projection zones within prefrontal and basal ganglia regions suggest these circuits may be differentiated by the type of information involved (Casey et al., 2001, 2002). Neuro-anatomical evidence suggests projections to ventral striatum are from limbic/reward-related regions including the amygdala and orbitofrontal cortex, and projections to the dorsal striatum, specifically the caudate nucleus, are from cognitive-related regions of the dorsolateral and ventrolateral prefrontal cortex (Alexander et al., 1986; Haber, 2003; Saint-Cyr, 2003). Our results show that the caudate was sensitive to violations in stimulus information that may parallel how the ventral striatum is sensitive to violations in predicted reward.

In conclusion, we were able to show changes in neural activation as a function of the expectancy of stimuli in the absence of explicit rewards (Horvitz, 2000; Zink et al., 2003, 2004). Relative to expected events, we found an increase in activation for events that were unexpected as well as decreases in activation for omissions of expected events. Activity in the anterior cingulate seemed particularly sensitive to the presence of an unexpected stimulus while caudate activity appeared more sensitive to the omission of an unexpected stimulus. These changes may reflect fluctuations in DA activity within these regions and may be important for updating context information that is relevant for current task performance, particularly when the information is unexpected. These findings suggest that dopamine-rich regions can be activated by a variety of stimuli, which include but extend beyond explicitly rewarding events, and have important implications for disorders such as ADHD and addiction.

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