Supporting Information

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SI Text

Note A. The version of the task used was the same as the one used in the event-related potential study by Lenartowicz et al. (1) but with interstimulus intervals modified, in the case of the functional MRI (fMRI) experiments to account for the hemodynamic response, and in the case of the transcranial magnetic stimulation (TMS) experiment to allow sufficient time between delivery of pulses (details in *Materials and Methods*).

Note B. For experiment 1 (whole-brain fMRI), mean accuracy was high (95.2%, SD = 3.5%) and did not differ between context-dependent and context-independent trials [$t(11) = 0.58$; $P = 0.58$; two-sample t test]. Mean (±SD) reaction time for correct trials was 543 ± 56 ms and also did not differ across conditions [$t(11) = 1.01$; $P = 0.34$; two-sample t test].

For experiment 2 [single-pulse TMS (spTMS)], mean accuracy was also high (97.0%, SD = 2.1%) and did not differ across conditions (a three-factor repeated-measures ANOVA of stimulation site by trial type by pulse time yielded no significant main effects or interactions at $P < 0.05$). Mean reaction time was 518 ± 63 ms and differed significantly across conditions as reported in the text. Note that although accuracy was comparable to the fMRI experiments, mean reaction time was somewhat faster in the TMS session. There are at least two possible reasons for this. The first is the shorter cue-probe intervals that were used in the TMS relative to the fMRI sessions (*Materials and Methods*). It has previously been shown that shorter intervals can be associated with faster performance in context-dependent trials (2). Second, faster reaction times could also have been due to a practice effect, because the TMS session in experiment 2 always followed the fMRI session in experiment 1. It is also worth noting that, in the TMS experiment, if the shorter cue-probe intervals, practice effects, or both led to better performance, this should have diminished the likelihood that we would detect a disruptive effect. Nevertheless, we observed a statistically significant effect of TMS pulses during context-dependent trials.

For experiment 3 [brainstem and dorsolateral prefrontal cortex (DLPFC) fMRI], mean accuracy was again high (96.89%, SD = 2.3%) and did not differ across conditions [$t(23) = 0.74$; $P = 0.46$; two-sample t test]. Mean reaction time for correct trials was 552 ± 135 ms and also did not differ across conditions [$t(23) = 0.99$; $P = 0.33$; two-sample t test].

Note C. The aim of this analysis was to identify brain areas in each individual participant that were associated with context updating, as target sites for spTMS. Application of the same contrast used in our group analysis (context-dependent minus context-independent trials) to the analysis of the data for each individual participant revealed activity for some but not all participants. Note, however, that although this is the most specific test for context processing, it may not be the most sensitive. As noted in the Introduction, participants may have sometimes chosen to update context representations in context-independent trials (because doing so could help prepare the response mappings, even though it was not required). If participants did sometimes update context in context-independent trials, then subtracting these from context-dependent trials may have reduced sensitivity for detecting context updating. This, coupled with the reduction in statistical power intrinsic to single-subject analyses, may have limited our ability to identify areas associated with context updating in individual participants. To address this problem, we sought to gain the additional statistical power required for the single-subject analyses by combining context-dependent and context-independent trials and contrasting these with control trials (in which the identity of the cue had no bearing on any subsequent response or the processing of any subsequent stimuli, and therefore should not have been associated with context updating whatsoever).

Our findings validated this approach: using this contrast [(context-dependent + context-independent) – (control trials)], areas of activity were identified in every participant. These areas were contained entirely within the areas identified in the group analysis [that used the contrast (context-dependent – context-independent); Fig. 3*A*]; and, for those participants who displayed activity in both contrasts, the regions of activity were nearly identical. Thus, the more sensitive contrast seems to have identified areas associated with context updating, as judged by their similarity to the areas identified by the more specific contrast at the group level. Nevertheless, because this contrast may have compromised specificity, we do not stake any interpretative claims on these individual participant findings. Rather, their sole purpose was to identify candidate regions in each participant as targets for the spTMS experiment. The more stringent and important test of the specificity of these regions to context updating was the behavior resulting from the independent experimental manipulation of them in the TMS study. As reported in the main text, our spTMS results exhibited a highly specific pattern of effects: a disruption of behavior was observed only when spTMS was targeted at these regions in the context-dependent and not the context-independent condition (Fig. 4).

Finally, we should note that, other than the single-subject fMRI analyses, the analysis of all other data reported in this study—including, as just noted, the behavioral data from the spTMS experiment, as well as the fMRI data from the brainstem imaging experiment and its correlation with behavior—used the more stringent and specific contrast of context-dependent vs. context independent trials. The findings from those analyses, together with the overlap of the regions identified in the single-subject analyses with those identified using the more conservative contrast in the group analysis, provide strong convergent support for the specificity of these regions to context updating, and the prediction that although context updating sometimes occurred in context-independent trials, it occurred more frequently and reliably in context-dependent trials.

Note D. In addition to the disruptive effect of spTMS in right DLPFC when applied at 150 ms after context-dependent cues, there may have been some facilitation of reaction time when the pulse was applied earlier (at 10 or 100 ms), although this was not statistically significant. spTMS can have either a disruptive or facilitative effect, depending on the timing and/or duration of the pulse delivery relative to the process of interest (e.g., refs. 3 and 4). More specifically, a TMS pulse applied in an appropriate window of time before a process may facilitate that process by nonspecifically enhancing cortical excitability, whereas a TMS pulse applied at the beginning of or early during a process may disrupt functioning by exciting neurons not involved in that process, thereby decreasing the signal-to-noise ratio (3). In our study, if the gating signal did not begin until ∼150 ms after cue onset, then the TMS pulse at 10 ms or 100 ms could have enhanced updating, whereas a pulse occurring at 150 ms would have impaired it, with a possible (but weaker) effect at 200 ms, as was observed.

Note E. The higher-resolution cardiac-gated acquisition methods used in experiment 3 (brainstem fMRI) allowed us to localize blood oxygen level-dependent (BOLD) responses to a region containing the substantia nigra (SN) and ventral tegmental area (VTA). Although these nuclei are the source of all dopaminergic signaling in the brain, they also contain other populations of neurons, and it is important to keep in mind that the BOLD response is a composite signal that reflects contributions from all neuronal populations within a given voxel (5). Nevertheless, dopamine neurons make up the majority of neurons in these nuclei. Furthermore, previous work has shown that BOLD responses measured from this midbrain area reflect computations that are characteristic of the dopaminergic neurons within these nuclei (6). For example, consistent with direct recordings from dopaminergic neurons (e.g., refs. 7 and 8), we have shown previously (6) that SN and VTA BOLD responses track reward prediction errors (cf. 9) but not reward or anticipated reward signals alone (which are assumed to be afferent signals used by the SN and VTA to compute reward prediction errors). For these reasons, we believe that our brainstem findings reflect a dominant contribution of the dopamine system.

Note F. Although some computational models propose that the gating of PFC is carried out by the basal ganglia (e.g., ref. 10), our power to detect such an effect was limited by restricted coverage in the striatum (Fig. 5*A*) (11).

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Table S1. Sites of TMS stimulation

	Right DLPFC			Left DLPFC		
Participant	Volume (mm^3)	Peak activation (%)	BOLD *x y z*	Volume (mm^3)	Peak activation (%)	*BOLD x y z*
1	677	0.51	29 38 28	356	0.79	−38 37 40
2	463	0.49	28 38 22	998	1.02	−26 42 38
3	784	0.57	33 33 39	891	1.15	−35 30 43
4	1,889	0.7	37 27 39	2,709	1.34	−34 32 44
5	5,097	2.4	39 38 37	4,170	2.13	−50 40 27
6	713	0.45	36 32 41	1,533	1.01	−37 34 39
7	143	0.72	36 46 37	677	0.84	−40 52 27
8	1,639	1.46	35 33 43	1,247	1.46	−48 24 43
9	71	0.27	43 24 37	499	0.99	−45 29 41
10	143	0.87	39 15 54	71	0.48	−49 24 36
11	998	0.59	41 17 38	1,568	0.74	−48 17 48
12	214	0.43	26 36 21	606	0.91	−46 38 28
Centroid (mean)			35 31 36			−41 33 38
Centroid (SD)			5 9 9			7 9 7

fMRI contrast images were generated for each participant by comparing the BOLD response evoked by context-dependent and context-independent cues to the BOLD response evoked by control cues. Statistical maps were thresholded ($P < 10^{-6}$), and the most active voxels in the right and left DLPFC (Brodmann Area 9) were chosen as the sites of stimulation. All coordinates are in Talairach space.