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Effects of Attention and Emotion on Repetition Priming and Their Modulation by Cholinergic Enhancement

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Bentley, Paul, Patrik Vuilleumier, Christiane M. Thiel, Jon Driver, and Raymond J. Dolan. Effects of attention and emotion on repetition priming and their modulation by cholinergic enhancement. *J Neurophysiol* 90: 1171–1181, 2003. First published March 20, 2003; 10.1152/jn.00776.2002. We examined whether behavioral and neural effects of repeating faces are modulated by independent factors of selective attention, emotion, and cholinergic enhancement, during functional MRI. Face repetition occurred either between task-relevant (spatially attended) or task-irrelevant (unattended) stimuli; faces could be fearful or neutral; subjects received either placebo or physostigmine. Under placebo, a reaction time advantage occurred with repetition (i.e., priming) that did not differ between levels of attention, but was attenuated with emotion. Inferior temporo-occipital cortex demonstrated repetition decreases to both attended and unattended faces, and showed either equivalent or greater repetition decreases with emotional compared with neutral faces. By contrast, repetition decreases were attenuated for emotional relative to neutral faces in lateral orbitofrontal cortex. These results distinguish automatic repetition effects in sensory cortical regions from repetition effects modulated by emotion in orbitofrontal cortex, which parallel behavioral effects. Under physostigmine, unlike placebo, behavioral repetition effects were seen selectively for attended faces only, whereas emotional faces no longer impaired priming. Physostigmine enhanced repetition decreases in inferior occipital cortex selectively for attended faces, and reversed the emotional interaction with repetition in lateral orbitofrontal cortex. Thus we show that cholinergic enhancement both augments a neural signature of priming and modulates the effects of attention and emotion on behavioral and neural consequences of repetition.

INTRODUCTION

Stimulus repetition is associated with decreases in cortical activity (Buckner et al. 1998), which may reflect more efficient stimulus processing and underlie perceptual priming (Schacter and Buckner 1998). In sensory-perceptual areas, where this effect occurs most robustly (Badgaiyan 2000), the degree to which the underlying neural mechanisms operate automatically (Desimone 1996; Wiggs and Martin 1998), versus being influenced by top-down factors (Henson et al. 2002), remains unclear. Similar repetition decreases for both target and foil faces have been observed in extrastriate visual cortex during a working memory task (Jiang et al. 2000), and in superior temporal gyrus to written words after both divided and full attention study phases using spoken words (Badgaiyan et al.

2001). Nevertheless, differences in face-repetition effects in early visual areas have been observed depending on task (Henson et al. 2002; Reber et al. 1998), in keeping with electrophysiological data (Dale et al. 2000; Puce et al. 1999), suggesting that sensory repetition effects may be influenced by reentrant signals from regions involved in higher levels of processing. If repetition effects in sensory cortex are entirely dependent on task-related processing (e.g., in prefrontal cortex), then it might be expected that stimuli that are completely irrelevant to the task (at both study and test) would not engender repetition effects. Our first aim in the current experiment was to determine whether repetition effects in extrastriate visual cortex, as measured by functional MRI (fMRI), would be observed for faces both when selectively attended and ignored as distractors.

A further factor that may influence priming, independently of attention, is the emotional value of a stimulus. Emotional stimuli can enhance activity within extrastriate visual areas separately from an effect of attention (Vuilleumier et al. 2001), which appears to be related to association learning in the context of fear conditioning (Morris et al. 2001). Because priming may represent a similar form of perceptually based implicit memory (Schacter and Buckner 1998), it might also be expected to be enhanced by emotion. Thus behavioral studies suggest a priming benefit for emotional stimuli in healthy adults (LaBar and Phelps 2002), as well as depressed and social phobic patients (Lundh and Ost 1997; Watkins et al. 2000). On the other hand, unpleasant (vs. neutral) faces have been found in one fMRI study to result in less of a repetition decrease in temporo-occipital cortex, which was interpreted in terms of reduced adaptation to negative valence stimuli (Rotshtein et al. 2001). An alternative explanation, however, was that the critical faces in this particular study were not just unpleasant but also bizarre (i.e., mouth and eyes were inverted), which could have influenced repetition effects through indirect attentional factors. In the present experiment we examined the effect of face-emotion on repetition effects, orthogonal to effects of attention, by using an event-related design that repeated faces only once so as to minimize habituation (Brown and Xiang 1998).

In the second part of this study, we examined whether cholinergic enhancement would modulate behavioral and fMRI

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repetition effects in a separate group of subjects given the anticholinesterase physostigmine. Behavioral and hemodynamic measures of priming have both previously been found to be impaired by cholinergic blockade with scopolamine (Thiel et al. 2001, 2002a), in line with known effects of acetylcholine on cortical plasticity and learning (e.g., Rasmussen 2000). By contrast, cholinergic enhancement may improve an fMRI measure of perceptual processing in extrastriate cortex, selectively for stimuli that must be remembered (Furey et al. 2000a), while increasing the behavioral effect of word-priming in Alzheimer's disease (Riekkinen and Riekkinen 1999). On this basis, plus the proposal that cholinergic modulation may favor processing selectively of attended stimuli (Sarter et al. 2001), we hypothesized that physostigmine would result in greater neural and behavioral repetition effects specifically for attended (task-relevant) stimuli. Furthermore, because acetylcholine enhances cortical plasticity specifically for emotional stimuli, as in fear-conditioning (Ji et al. 2001; Thiel et al. 2002b; Weinberger et al. 1998), we predicted that priming effects to fearful, relative to neutral, faces would be greater under physostigmine.

METHODS

Subjects

Thirty healthy right-handed volunteers with no history of medical or psychiatric disease gave written informed consent. They were divided into 2 groups of 15 (placebo: 7 female, 8 male; mean age = 26.8 ± 2.3 ; physostigmine: 8 female, 7 male; mean age = 23.5 ± 2.0). No subject was taking active medication. Although 2 subjects were mild smokers, they were in different groups, and refrained from smoking on the test day. A between-subjects design was chosen for the pharmacological manipulation, to exclude any between-session repetition effects (e.g., van Turrenout et al. 2000), and to minimize any long-term habituation to emotional stimuli (e.g., Thiel et al. 1999).

Cognitive task

Subjects performed a matching task (after Vuilleumier et al. 2001) for 2 black and white photographs situated in either the north–south or east–west coordinates of a cross-format display that consisted of 4 concurrent photographs ($3^\circ \times 5^\circ$ visual angle each), arranged into a cross around a central fixation point (Fig. 1). At the start of each block, subjects were cued (for 2 s) to attend selectively to either the 2 vertically arranged or 2 horizontally arranged positions, whereas the alternative 2 locations were to be ignored throughout the block. Thus attention was directed on the basis of spatial location, rather than on the basis of stimulus type per se (face vs. house). In total there were 4 blocks of 40 trials each. Each trial consisted of a central fixation cross (1 s) followed by the 4-picture display for 250 ms. Subjects were required to indicate, as accurately and rapidly as possible, whether the 2 stimuli at task-relevant locations were the same or different, by either of 2 possible key presses with the right hand. Reaction time (RT) and accuracy were recorded. The median intertrial interval was 2.5 s (range: 1.5–14.4 s).

Within each trial, either the 2 attended or the 2 unattended locations were occupied by 2 nonfamous faces (taken from The Karolinska Directed Emotional Faces set; Lundqvist et al. 1998), in an intermingled and unpredictable sequence. The remaining 2 locations were occupied by 2 house pictures; hence a trial could be classified as faces-attended (A) or faces-unattended (U), depending on the faces' position with respect to the currently attended locations (i.e., attention was spatially based, and we use the terminology of "faces-attended," for instance, only as a shorthand for "faces-appearing-at-the-attended-locations"). Furthermore, both faces had either a fearful emotion (E) or neutral (N) expression, independent of whether they were at task-relevant locations. This resulted in 4 conditions (AE, AN, UE, and UN faces); these conditions plus the pair identities (i.e., same/different, which was independent between the attended and unattended pair in each trial) were randomly counterbalanced throughout each block. The order of task-relevant locations (i.e., either vertical or horizontal) between blocks was randomly picked from one of 4 alternatives (HVHV, VHVH, HVVH, VHHV), and counterbalanced across subjects within each group.

Stimulus repetition occurred for only particular face stimuli. Every

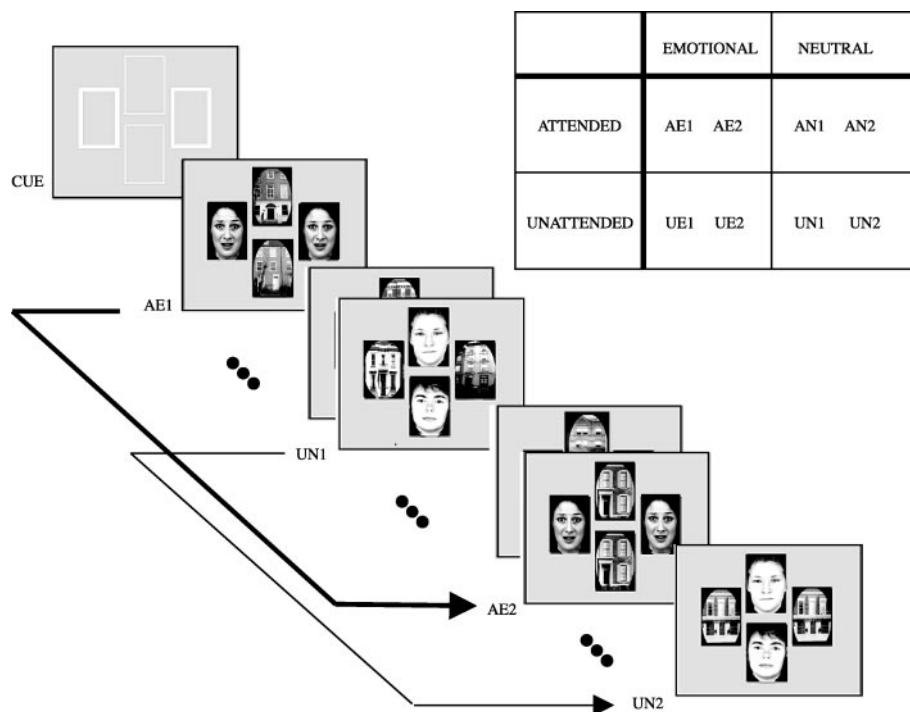


FIG. 1. Stimulus format. Each block started with cue stimulus that indicated whether subjects must attend to horizontal or vertical locations in cross-array for performance of subsequent matching task (in this example, this would be horizontal locations). Each trial consisted of a pair of faces that may be either in task-relevant (A) or task-irrelevant (U) locations; together with a pair of houses occupying alternate 2 locations. Face pairs were repeated with lag of 2 to 5 intervening trials; houses were never repeated. Face pairs could be either fearful and thus emotional (E) or neutral (N). Experiment thus had a $2 \times 2 \times 2$ factorial design, with factors of face-repetition, attention (toward or away from faces), and emotion.

first presentation of a pair of faces (suffixed 1 henceforth) was followed by only one other repetition of the same pair of faces (suffixed 2) that occurred after an interval of 2 to 5 intervening trials (with approximately equal distribution across each block). Thus 8 conditions existed: AE1, AE2, AN1, AN2, UE1, UE2, UN1, and UN2 (where AE1, for example, would represent the first presentation of a particular pair of fearful faces appearing at task-relevant locations, and AE2 would represent their subsequent repetition). There were 20 trials of each condition per subject. Because of the small number of intervening stimuli between first and second repetitions, the influence of any time confound is minimal (<5% trials fell outside of the time window in which stimulus order was fully counterbalanced with respect to time).

The cross-format spatial array and brief exposure time has previously been shown to be effective at engaging covert attention to the relevant pair of locations without saccades (Vuilleumier et al. 2001; Wojciulik et al. 1998), and without awareness of identity, gender, or expression of faces when these appear in task-irrelevant locations only (Vuilleumier et al. 2001). Nonetheless, to exclude possible between-group differences in saccade frequency or compliance with the requirement for central fixation, we monitored eye movements throughout the task using an infrared eye tracker (ASL Model 540, Applied Science Group, Bedford, MA; refresh rate = 60 Hz). For technical reasons, eye-position data were lost for 6 subjects (2 placebo, 4 from drug group).

Drug treatment

A double-blind placebo-controlled drug administration technique was used. Each subject received an intravenous cannula into the left cubital fossa and an infusion of either physostigmine or saline. Dosage and rate of physostigmine infused was identical to that used in a recent study (Furey et al. 2000b), providing stable levels of plasma drug concentration and butyrylcholinesterase inhibition, as well as significant and stable effects on cognitive performance for 40 min, after a 40-min loading period. Furthermore, the same protocol was also found to result in changes in both regional cerebral blood flow (rCBF) and blood oxygenation level-dependent (BOLD) activity, during visual working memory tasks (Furey et al. 1997, 2000a).

Subjects in the drug group first received 0.2 mg intravenous glycopyrrolate, a peripheral muscarinic receptor antagonist, to reduce peripheral side effects. The placebo group were injected with an equivalent volume of saline. Both groups then received an intravenous infusion. In the case of the drug group this consisted of physostigmine at a rate of 1.93 mg/h for 10 min, followed by a constant rate of 0.816 mg/h for 40 min, before scanning. The same rate was then continued until the end of study so that each subject received no more than 1.3 mg physostigmine in total. The placebo group received an equivalent volume of saline over the same time course. Both groups of subjects had their blood pressure checked before and at 40 min into infusion; pulse-oximetry was performed continuously throughout the experiment. Subjects were given a questionnaire at both time points that allowed a ranked measurement (0–6 scale) of 7 recognized adverse reactions to physostigmine and glycopyrrolate, as well as a list of visual analog scales for estimating subjective feelings (Bond and Lader 1974).

Imaging and image processing

MRI data were acquired from a 2T VISION system (Siemens, Erlangen, Germany) equipped with a head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD contrast. The acquired image consisted of 32 × 3-mm-thick axial slices that covered the entire brain. Volumes were acquired in a single continuous session with an effective repetition time of 3.26 s. The first 8 volumes were discarded, to allow for T1 equilibration effects. Images were realigned, time-corrected, normalized to a standard echo-

planar image template, and smoothed with a Gaussian kernel of 8-mm full-width half-maximum.

Statistical analysis of images

Data were analyzed with a general linear model for event-related designs (SPM99; Wellcome Dept. of Cognitive Neurology, London, UK; Friston et al. 1995) using a random-effects analysis. Data were globally scaled and high-pass filtered at 1/120 Hz. Eight event types were defined for each subject (see above). Individual events were modeled by a canonical synthetic hemodynamic response function and its temporal derivative (Friston et al. 1998). The 6 head movement parameters were included within the model as confounding covariates.

Linear contrasts of parameter estimates were made for each subject and used to generate statistical parametric maps (SPMs) of the *t*-statistic. To test for regions showing face-repetition effects common to different conditions (i.e., to both attended and unattended faces; or to both emotional and neutral faces), contrasts of first versus second presentation under each condition were performed for each subject and entered into a repeated-measures analysis of variance (ANOVA) corrected for nonsphericity (Glaser et al. 2002). A conjunction analysis was then performed over contrasts from both conditions (Price and Friston 1997). To test for regions showing a different magnitude of repetition decrease between conditions, contrasts representing the repetition × condition interaction for each subject were entered into a one-sample *t*-test; only regions showing a significant repetition decrease ($P < 0.001$, uncorrected) in at least one of the tested conditions are reported. Regions found to show repetition × condition interactions that also showed a significant 3-way interaction (repetition × attention × emotion; thresholded at $P < 0.001$, uncorrected) are noted.

Repetition × drug interactions were analyzed separately for attended and unattended faces by comparing between-subject repetition effects with *t*-tests. Repetition × condition × drug interactions were similarly assessed by comparing the repetition × condition interactions, for each subject, between groups, but only the volume of voxels showing a repetition main effect or repetition × condition interaction in the placebo group was searched (masks thresholded at $P < 0.001$, uncorrected). Any effects of physostigmine on attention and emotion, independent of repetition, are considered elsewhere (Bentley et al. 2003). We emphasize that the drug effects reported here are condition specific, as mean session effects are modeled separately. All regions that showed significant repetition × drug, or repetition × condition × drug, interactions were found to show insignificant between-group session effects ($P > 0.05$, uncorrected). Furthermore, the global session mean activity did not differ between groups ($P > 0.05$), suggesting that physostigmine did not engender significant general vascular effects.

We report areas that achieve significance either after correction for whole brain (or effective search volume in the case of repetition × condition × drug interactions; see above), or regions of interest (ROI) where indicated (Worsley et al. 1996). Two ROIs of approximately 20 cm³ each were defined (Rorden and Brett 2001) in right and left inferior temporo-occipital cortices so as to encompass coordinates previously found to show repetition decreases in event-related fMRI designs for repetition of unfamiliar faces (Henson et al. 2002; Jiang et al. 2001). Regions surviving a threshold of $P < 0.001$, uncorrected, are also reported descriptively. Any activations smaller than 5 contiguous voxels were discounted.

RESULTS

Behavioral

Behavioral effects of priming were determined by calculating median RT and mean accuracy differences between the first and second presentations for each face pair, separately for each

of the 4 conditions in each participant. In the placebo group, a significant speeding of responses when attended neutral (AN) faces were repeated [mean RT difference between first and second presentation = 30.3 ± 17.5 ms, $t(14) = 3.5$, $P < 0.005$], plus a trend for more accurate performance with repeated stimuli [mean accuracy difference = $5.3 \pm 5.8\%$; $t(14) = 1.8$, $P < 0.1$] was evident, consistent with previous studies of repetition priming (e.g., Henson et al. 2002).

To ascertain any effects of condition (attention and emotion) and group (cholinergic enhancement vs. placebo), we entered RT and accuracy differences (between first and second presentation) for each subject, for each condition, into a repeated-measures, mixed ANOVA. Although there was no main effect of group on the RT priming effect, there were significant group \times attention [$F(1,28) = 4.4$; $P < 0.05$] and group \times emotion interactions [$F(1,28) = 4.3$; $P < 0.05$; Fig. 2A]. These represented a significant reduction of the RT priming effect for emotional versus neutral trials under placebo [$F(1,14) = 11.7$; $P < 0.005$], but not under physostigmine [$F(1,14) = 0.7$; ns], whereas the RT priming effect was significantly greater for attended versus unattended faces under physostigmine [$F(1,14) = 12.8$; $P < 0.005$], but not under placebo [$F(1,14) = 0.3$; ns]. A separate ANOVA comparing absolute RTs between groups over condition (attention \times emotion \times stimulus order)

did not reveal any between-group differences, although there was a trend to faster overall RTs in the physostigmine group [$t(28) = 1.4$, $P < 0.1$, 1-tailed based on Furey et al. 1997].

There was no group \times condition interaction for priming in accuracy measures, but a trend for greater priming with attended repeated faces versus unattended repeated faces [$F(1,14) = 3.0$; $P < 0.1$; Fig. 2B]. Overall accuracy (mean score = $85 \pm 3.2\%$, and $83 \pm 3.2\%$, under drug and placebo, respectively) was comparable to that of a previous study using the same task in which limited awareness of task-irrelevant compared with task-relevant faces was demonstrated (Vuilleumier et al. 2001). There were no behavioral effects of the specific attended location (i.e., horizontal or vertical pair), nor any interactions of location \times group.

fMRI data: effect of selective attention on face-repetition effects

The main effect of faces presented in task-relevant, versus task-irrelevant, locations (i.e., independent of repetition) identified bilateral mid-fusiform regions (44, -50, -24 and -42, -44, -28; $Z \geq 4.29$; $P < 0.001$, uncorrected; Fig. 3A), whereas the opposite contrast (houses in task-relevant, vs. task-irrelevant, locations) identified bilateral parahippocampal cortex (16, -52, 6 and -24, -36, -14; $Z \geq 5.50$; $P < 0.01$, corrected for whole brain). This replicates previous results using a similar task (Vuilleumier et al. 2001; Wojciulik et al. 1998) and demonstrates that subjects selectively processed the pair of stimuli at cued locations.

We next identified areas that showed fMRI face-repetition effects common to when faces occurred in attended or unattended locations, by performing a conjunction analysis across contrasts comparing first and second presentations under both attentional conditions in the placebo group. Areas showing repetition *decreases* under both levels of attention were bilateral inferior temporo-occipital cortex, left inferior prefrontal gyrus, and premotor areas (Table 1A, Fig. 3B). By contrast, superior temporal sulcus, middle occipital gyrus, and striatum showed greater repetition decreases for faces presented in attended versus unattended locations (Table 1C). We note that the inferior temporo-occipital regions showing a repetition effect independent of attention did not show a main effect of attention (Fig. 3B), and, conversely, the mid-fusiform peaks showing a main effect of attention did not show any repetition effects (Fig. 3A). Areas that showed repetition *increases* across both levels of attention included biparietal cortex and posterior cingulate (Table 1B), an effect also reported by Henson et al. (2002).

Finally, as our behavioral data suggested a performance advantage on house judgments when faces were repeated at task-irrelevant locations, we examined the contrast of first versus second presentations of task-irrelevant faces (i.e., when house judgments were performed), and restricted the analysis to house-selective regions (by masking with the main effect of house-attention, thresholded at $P < 0.001$, uncorrected). This identified a left parahippocampal region (-22, -32, -10; $Z = 4.09$, $P < 0.05$, corrected) that showed *increased* activity with repetition of unattended face stimuli, presumably as the houses became more dominant when the same faces were ignored. This repetition enhancement was indeed specific to trials when house judgments were required (and faces ignored), as shown

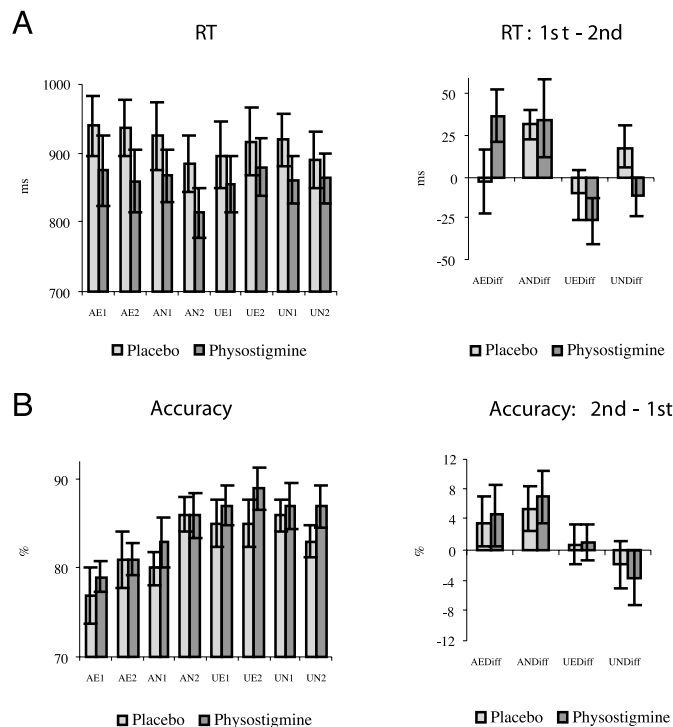


FIG. 2. A: median RT for each of 8 conditions (AE, Attended Emotional faces; AN, Attended Neutral; UE, Unattended Emotional; UN, Unattended Neutral; -1: 1st presentation; -2: 2nd presentation), separately for placebo and physostigmine groups. Second graph shows itemwise differences in RTs to novel minus primed stimuli for each of 4 main conditions (hence positive values represent repetition advantage). B: mean accuracy for same 8 conditions. Second graph shows itemwise differences of accuracy to primed minus novel stimuli for each of 4 main conditions (hence positive values represent repetition advantage). SE bars are shown. Note that statistical inferences concerning priming are based on subject-specific differences, and that inferences on behavioral effects are based on item-specific repetition (not conveyed by error bars on group means).

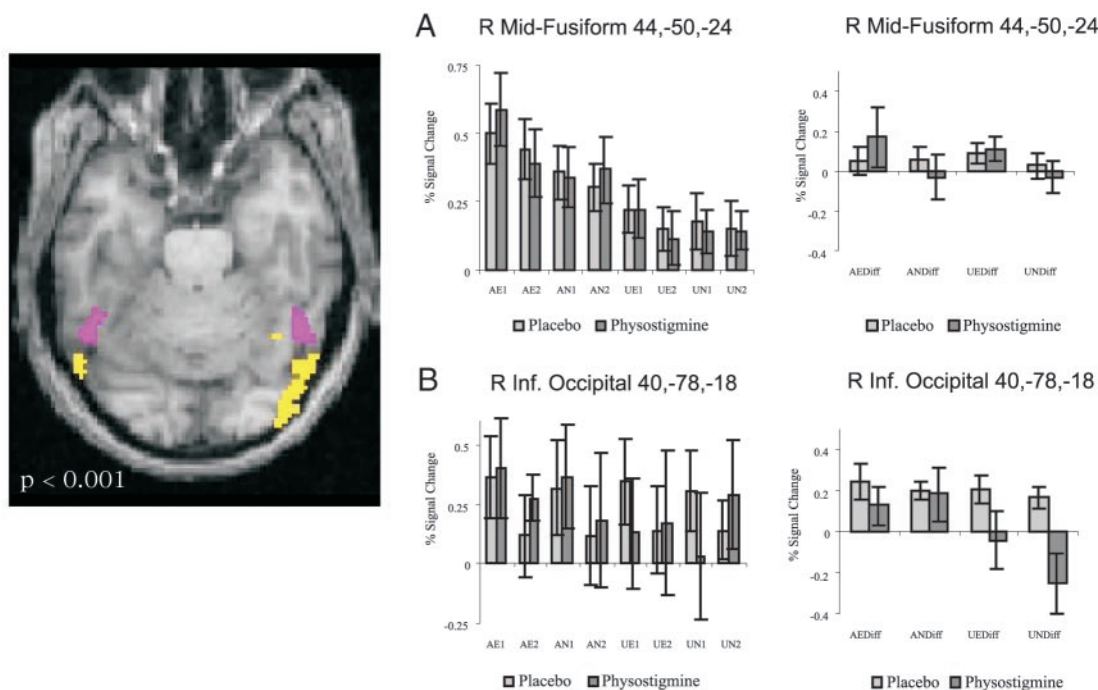


FIG. 3. Regions of inferior temporo-occipital cortex showing main effect of faces in attended vs. unattended locations, independent of repetition (mauve; *A*), and conjunction of repetition decreases to faces in both attended and unattended locations (yellow; *B*); both contrasts $P < 0.001$, uncorrected. Activation map is superimposed on single-subject T1-weighted MRI brain, pitched to visualize inferior cortical surface. Graphs show percentage signal change from baseline in right mid-fusiform (*A*) and inferior occipital cortex (*B*) during first and second presentations of faces from each of 4 conditions (AE, AN, UE, UN). On right are plots of mean subject-specific signal differences between first and second presentations for each of 4 conditions (positive values represent repetition decreases; negative values represent repetition enhancements). Regions showing main effect of face-attention ($P < 0.001$) did not show a significant effect of repetition ($P > 0.05$), whereas regions showing repetitions to both attended and ignored faces ($P < 0.001$) did not show a significant effect of face-attention ($P > 0.05$). Placebo and physostigmine groups are shown separately. Left-sided plots are corrected for mean over all conditions between groups (no significant main effect of drug).

by a significant repetition \times attention interaction [$F(1,14) = 5.0$; $P < 0.05$].

fMRI data: effect of emotion on face-repetition effects

Comparison of signal estimates between emotional and neutral face conditions at the peak of the conjunction of face-repetition effects across attended and unattended contrasts suggested a similar repetition decrease in occipital cortex for both emotional and neutral faces (Fig. 3*B*). This was confirmed formally by performing the conjunction of priming effects between fearful and neutral-face trials, independent of attention (Table 2; yellow area in Fig. 4, graph *A*). The same posterior visual (and premotor) areas that showed face-repetition decreases for both levels of attention thus also showed repetition decreases to both neutral and emotional faces.

We next examined for repetition effects modulated by emotion (i.e., repetition \times emotion interaction). This showed that left postero-inferior occipital cortex, as well as a region at posterior amygdala-hippocampal border, exhibited a greater repetition decrease for emotional, relative to neutral, stimuli (Table 2; blue area in Fig. 4, graph *B*). Conversely, the only area showing a greater repetition decrease to neutral, relative to emotional, faces was lateral orbitofrontal cortex (OFC; red area in Fig. 4). The pattern of repetition decreases in this region across conditions (Fig. 4*A*) parallels the RT priming effects observed behaviorally. Furthermore, a correlation analysis comparing the size of the emotional effect on RT priming with

the size of the emotional effect on BOLD repetition decreases at the OFC peak (38, 38, -14, $Z = 4.16$) showed a positive trend [$r(28) = 0.46$, $P = 0.08$], whereas this was significant [$r(28) = 0.54$, $P = 0.05$] for the neighboring secondary peak (40, 46, -16; $Z = 4.14$). Thus subjects showing the greatest attenuation of RT priming with emotional faces also tended to show the greatest diminution of repetition decreases in OFC toward emotional faces.

We note that none of the extrastriate areas exhibiting repetition effects showed a main effect of emotion, but such a main effect of emotion, independent of attention, was found in left fusiform (-40, -48, -24, $Z = 3.27$, $P < 0.001$, uncorrected), and medial amygdala-substantia innominata (10, -8, -16, $Z = 3.09$, $P = 0.001$, uncorrected), in keeping with Vuilleumier et al. (2001).

fMRI data: effects of cholinergic enhancement on repetition effects

Given the role of cholinergic inputs on selective attention, we had hypothesized that physostigmine might enhance repetition-suppression effects (see Thiel et al. 2001, 2002a) specifically for *attended* faces (see also Furey et al. 2000a). Therefore we examined group \times repetition interactions for attended and unattended trials separately. With faces at attended locations, this interaction identified left inferior occipital cortex as showing a greater repetition decrease under physostigmine relative to placebo (-32, -66, -22; $Z = 3.91$; $P < 0.05$,

TABLE 1. Common and differential effects of attention on priming in placebo group

Area	x	y	z	Z Value
<i>A. Repetition decreases to faces in both attended and unattended locations</i>				
Right Inferior Occipital	40	-78	-18	6.25**
	36	-86	-16	3.92*
	46	-62	-22	3.98*
Right Inferior Temporal	32	-40	-22	3.85
Left Inferior Occipital	-48	-62	-22	4.49*
Left Temporo-Parietal Junction	-54	-40	34	4.09
Right Lingual Gyrus	12	-56	6	3.94
Cuneus	6	-86	14	4.34
Left Inferior Frontal Gyrus	-52	38	8	4.21
Right Inferior Frontal Gyrus	60	24	10	3.29
Left Posterior Superior Frontal Gyrus	-6	14	50	3.67
Right Posterior Middle Frontal Gyrus	58	16	30	3.95
<i>B. Repetition increases to faces in both attended and unattended locations</i>				
Right Parietal	54	-38	56	4.52
	22	-68	32	4.16
Left Parietal	-32	-56	30	3.42
Posterior Cingulate	8	-34	18	3.67
Left Middle Temporal Gyrus	-54	0	-30	3.85
Right Premotor Cortex	14	-8	68	4.05
Left Central Sulcus	-24	-16	44	3.70
<i>C. Repetition decreases greater for faces in attended than unattended locations</i>				
Left Superior Temporal Sulcus	-62	-36	12	4.26
Left Middle Occipital Gyrus	-34	-80	16	3.91
Right Striatum	22	8	0	3.68
Medial Orbitofrontal Cortex†	-2	42	-22	4.20
<i>D. Repetition decreases greater for faces in unattended than attended locations</i>				
No regions approached significance				

* $P < 0.05$ corrected for ROI (based on Henson et al., 2002; Jiang et al., 2000). ** $P < 0.01$ corrected for whole brain. † Regions also showing a three-way interaction of repetition \times attention \times emotion, that is, (AN1-AN2)-(AE1-AE2)-[(UN1-UN2)-(UE1-UE2)].

corrected for ROI; Fig. 5). This occipital area also showed a repetition \times attention \times drug interaction [$F(1,28) = 4.0$; $P < 0.05$] that reflected physostigmine, but not placebo, engendering a greater repetition decrease for attended, versus ignored, faces [physostigmine: $F(1,28) = 7.0$; $P < 0.05$; placebo: $F(1,28) = 0.6$; ns]. Furthermore, in the same region, we note that physostigmine, versus placebo, resulted in reduced activity to the repeated face [$t(28) = 2.4$; $P < 0.05$], but did not change activity to the first face [$t(28) = 1.1$; ns]. These results complement previous findings of modulation of repetition effects within left inferior occipital cortex by cholinergic blockade, when scopolamine resulted in a reduced repetition decrease, attributed specifically to an elevation in activity to the repeated stimulus (Thiel et al. 2001).

No regions showed attenuation of repetition decreases to faces at attended locations under physostigmine, relative to placebo, and no regions showed a significant drug \times repetition interaction for faces at unattended locations.

We also tested for 3-way interactions of drug \times repetition \times condition (for conditions of attention and emotion, separately), given that these interactions showed significant effects in the RT data. We restricted our search volumes to those voxels showing a main effect of repetition decrease (regardless of

attention and emotion condition) or a repetition \times condition interaction in the placebo group (thresholded at $P < 0.001$, uncorrected). Importantly, no areas showed a repetition \times drug interaction over all conditions (i.e., there was no main effect of physostigmine on repetition independent of conditions).

In the repetition \times drug \times attention interaction, we found that the right inferior occipital region showing a maximum repetition decrease common to faces in both attended and unattended locations (as well as to both emotional and neutral faces) under placebo was found under physostigmine to show a repetition decrease selectively for attended faces only [i.e., repetition \times attention \times drug interaction: $F(1,28) = 5.5$; $P < 0.05$; a similar interaction was found in the left inferior occipital region showing a repetition \times drug interaction for attended faces; see above]. As shown in Fig. 3B, under physostigmine, the right inferior occipital region manifested a similar degree of repetition decrease for faces in attended locations as under placebo, but showed a trend for repetition increases for faces at unattended locations [$t(14) = 1.7$; $P = 0.1$], in contrast to the placebo group. There were no regions in which this interaction survived correction for search volume.

Finally, the repetition \times drug \times emotion interaction revealed that the lateral orbitofrontal region (38, 38, -12), previously found in the placebo group to display less repetition effects with emotional, relative to neutral, faces, was not associated with this pattern under physostigmine ($Z = 4.51$; $P < 0.05$, corrected; Fig. 4B). In fact, physostigmine produced the opposite effect at this point, that is, greater repetition decreases with emotional than neutral faces [$F(1,28) = 10.3$; $P < 0.01$].

TABLE 2. Common and differential effects of emotion on priming in placebo group

Area	x	y	z	Z Value
<i>A. Repetition decreases to both emotional and neutral faces</i>				
Right Inferior Occipital	40	-78	-16	5.17**
	46	-62	-24	4.17*
Right Inferior Temporal	32	-52	-22	3.42
Left Inferior Occipital	-46	-62	-22	4.57*
Left Middle Occipital Gyrus	-34	-84	16	3.36
Left Temporo-Parietal Junction	-52	-42	34	3.68
Cuneus	-2	-86	6	4.02
Left Amygdala	-26	0	-26	3.34
Right Posterior Middle Frontal Gyrus	58	12	30	3.67
Left Posterior Superior Frontal Gyrus	-8	12	48	3.63
<i>B. Repetition increases to both emotional and neutral faces</i>				
Right Parietal	22	-68	32	3.56
Posterior Cingulate	6	-24	32	3.52
Left Hippocampus	-22	-34	-10	4.13
Left Central Sulcus	-24	-16	42	4.01
Left Superior Frontal Sulcus	-18	38	30	3.70
Right Middle Frontal Gyrus	38	56	-10	3.77
<i>C. Repetition decreases greater for emotional than neutral faces</i>				
Left Posterior Inferior Occipital	-36	-90	-14	3.45
Right Posterior Amygdala-Hippocampus	18	-10	-12	3.47
<i>D. Repetition decreases greater for neutral than emotional faces</i>				
Right Lateral Orbitofrontal Cortex	38	38	-14	4.16
	40	46	-16	4.14

* $P < 0.05$ corrected for ROI (based on Henson et al., 2002; Jiang et al., 2000). ** $P < 0.05$ corrected for whole brain.

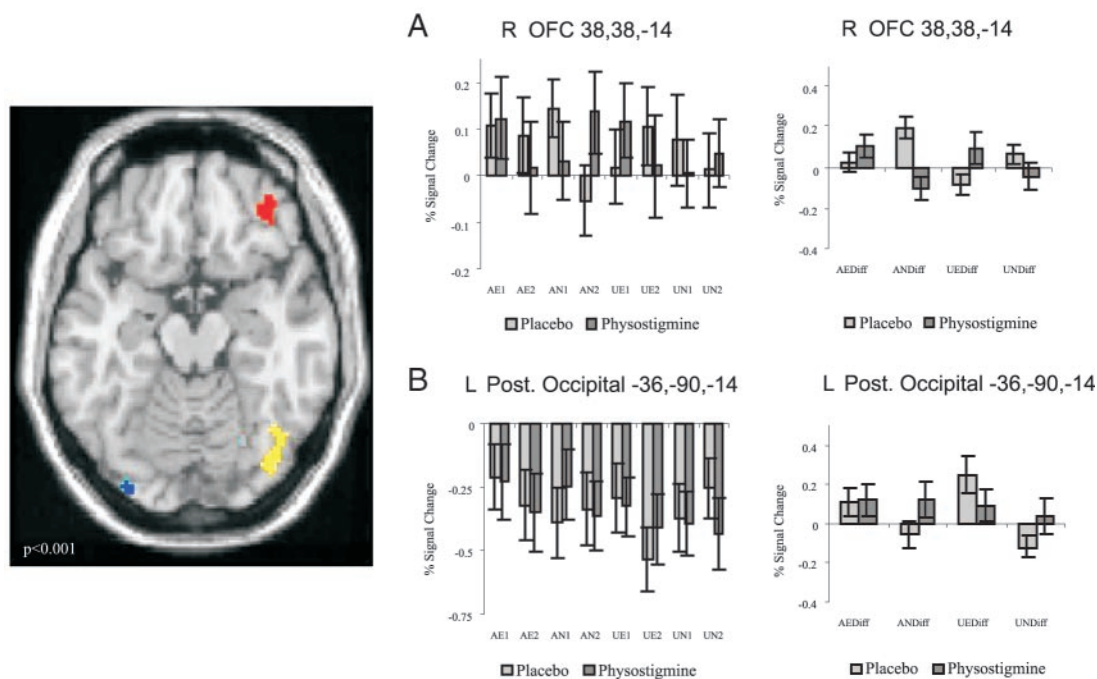


FIG. 4. Regions of inferior temporo-occipital and orbitofrontal cortex showing conjunction of repetition decreases for both emotional and neutral faces (yellow; activity plot similar to that shown in Fig. 3B; a left inferior occipital cluster occurred on lower slice); or greater repetition decreases to neutral, relative to emotional, faces (red; A); or greater repetition decreases to emotional, relative to neutral, faces (blue; B); all contrasts thresholded at $P < 0.001$, uncorrected. Activation maps are superimposed on single-subject T1-weighted MRI brain ($z = -14$). Graphs show percentage signal change from baseline in right lateral orbitofrontal cortex (OFC: A), and left posterior occipital (B) regions during first and second presentations of faces from each of 4 conditions (AE, AN, UE, UN). Scales differ between regions. On right are plots of mean subject-specific signal differences between first and second presentations for each of 4 conditions (positive values represent repetition decreases; negative values represent repetition enhancements). Placebo and physostigmine groups are shown separately for each contrast. Left-sided plots are corrected for mean over all conditions between groups (no significant main effect of drug).

Furthermore, the right OFC under physostigmine did not show any correlation between RT and BOLD measures of an emotion \times repetition interaction [$r(28) = -0.12$ and $r(28) = -0.06$ for the 2 peaks within OFC showing an emotion \times repetition interaction under placebo], unlike the case under placebo (normalized differences from placebo correlation coefficients given by $z = 1.6$ and 1.7 , respectively, $P \leq 0.10$ for both).

Eye tracking and adverse drug effects

The frequency of saccades and median angular deviation of the eye were measured during 250-ms epochs before and after the onset of each stimulus. The mean percentage of trials with saccades over both epochs was only 3.2 and 3.0, under placebo and physostigmine, respectively, with no reliable group differences during the 2 peristimulus epochs [$F(1,22) = 1.44$ and 1.78 , respectively; $P \geq 0.2$]. There were no significant effects interactions within a 4-way ANOVA with factors of group, repetition, attention, and emotion, during either of the 2 peristimulus periods, for either saccade number, or median ocular position (all values of $F < 1.8$; $P \geq 0.2$).

Questionnaires detailing possible side effects and subjective feelings, as well as measures of blood pressure and pulse, were recorded before infusion and just before scanner entrance, when a steady state of physostigmine would be expected (Furey et al. 2000b). Although subjects given physostigmine with glycopyrrolate were more likely to experience a dry

mouth ($U = 62$, $P < 0.05$) and dizziness ($U = 68$, $P < 0.01$), the mean intensity of these symptoms was very small (1.3 ± 0.95 and 0.5 ± 0.40 , respectively, on a scale of 0 to 6). Two subjects given physostigmine who vomited were excluded and replaced with alternative subjects. A pooled measure of subjective alertness (Bond and Lader 1974) suggested that the physostigmine group felt more drowsy at test relative to preinfusion [mean percentage difference between preinfusion and prescan = $-1.3 \pm 2.2\%$ for placebo, and $+8.8 \pm 3.7\%$ for physostigmine; $F(1,28) = 6.4$; $P < 0.05$], although the simple effects of group for absolute subjective alertness at each time point were insignificant. There were no significant cardiovascular main effects or interactions.

DISCUSSION

Effect of selective attention on repetition effects

Previous functional imaging studies have shown decreased repetition, predominantly in extrastriate cortical areas, with repetition of attended visual stimuli (e.g., Badgaiyan 2000; Buckner et al. 2000; Henson et al. 2002; Vuilleumier et al. 2002a). The present study demonstrates that repetition decreases in inferior temporo-occipital cortex can be independent of whether stimuli occur in attended (task-relevant) or ignored (task-irrelevant) locations. These results provide a neural counterpart to behavioral studies showing that perceptual priming can occur without the need for attention or awareness of stimuli at study phase (Parkin et al. 1990; Stone et al. 1998; Szymanski

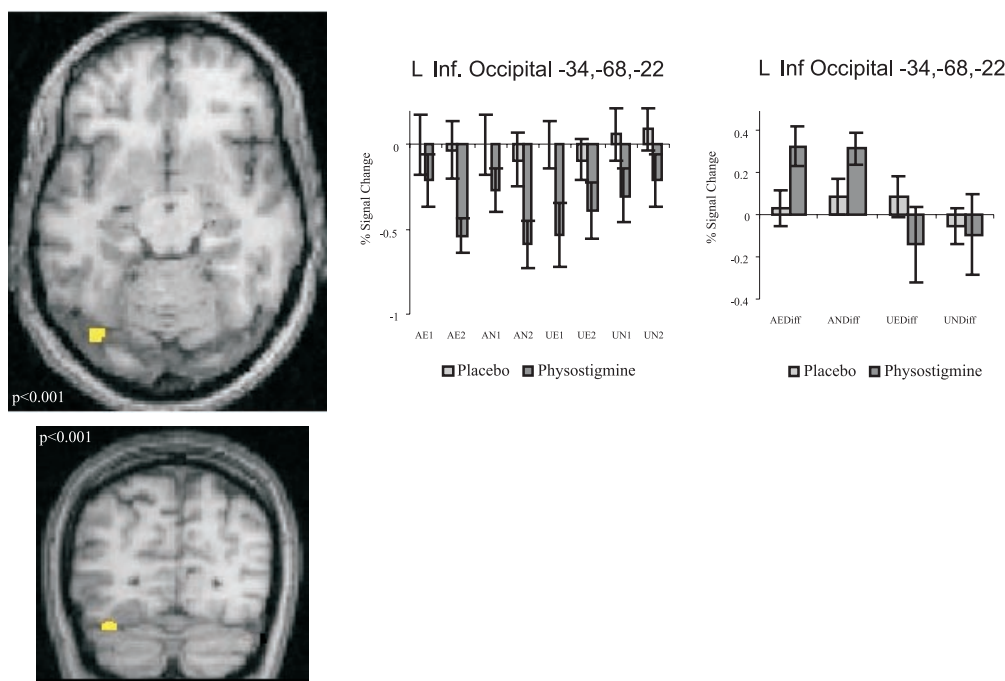


FIG. 5. Regions of inferior temporo-occipital cortex showing greater repetition decreases for physostigmine than placebo, specifically for faces in attended locations ($P < 0.001$, uncorrected). Area showing this significant interaction was close to region previously showing repetition decreases in face priming study (Henson et al. 2002), and to region previously showing diminution of repetition decrease under cholinergic blockade (Thiel et al. 2001). Activation map is superimposed on single-subject T1-weighted MRI brain. Transverse slice taken at $z = -22$; coronal slice taken at $y = -68$. Graph shows percentage signal change from baseline in left inferior occipital cortex during first and second presentations of faces from each of 4 conditions (AE, AN, UE, UN). On right are plots of mean subject-specific signal differences between first and second presentations for each of 4 conditions, at the same point. Placebo and physostigmine groups are shown separately for each contrast, and are not mean-corrected.

and MacLeod 1996; Vuilleumier et al. 2002b). Furthermore, our data support proposals that the neural mechanisms underlying repetition suppression reflect intrinsic properties of cell populations within temporo-occipital cortex that are expressed without top-down attentional facilitation (Desimone 1996; Wiggs and Martin 1998).

An earlier fMRI study using a working memory task similarly found that repetition decreases occurred in inferior temporal regions to both target and nontarget faces (Jiang et al. 2000). However, because both types of face were task-relevant, it is likely that attention to both types of stimuli would have initially been equal, and (may have) changed only *after* stimulus discrimination had been made. In the present task, attention was systematically manipulated by cueing subjects toward selective locations *before* presentation of brief multistimuli arrays. That this can be successfully achieved is suggested by a study with a similar procedure and stimuli (Vuilleumier et al. 2001) in which subjects were unaware of the identity and features of task-irrelevant, but not task-relevant, faces. Moreover, our own fMRI results show that attention-independent repetition effects and attention-dependent main effects in inferior temporo-occipital cortex may co-occur within the same task. The fact that these effects occurred, respectively, in posterior versus more anterior extrastriate regions (Fig. 3) is in line with the idea that “top-down” modulation of visual regions becomes increasingly influential at progressively later stages of stimulus processing (see Martinez et al. 2001).

Although these findings imply a degree of autonomy for repetition effects in sensory cortex, this need not imply that repetition effects in other areas cannot be modulated by atten-

tional processes. Indeed, middle occipital and superior temporal cortex showed greater repetition decreases for faces when in task-relevant locations than in irrelevant locations. Similarly, the nature of the task can influence repetition effects in extrastriate cortex (Henson et al. 2002; Reber et al. 1998). Furthermore, electrophysiological studies have suggested that some repetition effects within inferior temporal regions do not occur within an “initial wave” of perceptual discrimination (i.e., <200 ms poststimulus; Nagy and Rugg 1989; Puce et al. 1999), but there remains uncertainty as to whether later repetition effects occur subsequent to (and possibly as a result of) activity within task-related frontal regions (Dale et al. 2001; Dhond et al. 2001). Although our study cannot resolve these issues of temporal order, we do show that repetition decreases may occur both independently and dependently upon “top-down” attentional factors in different brain areas, at least under conditions where repetition is incidental to task.

We note that repetition decreases were prominent in inferior occipital cortices but did not extend into the fusiform gyrus, in which there was a main effect of attention. This is consistent with a previous priming study that also used unfamiliar faces (Henson et al. 2002) and may reflect a functional separation of perception (which is repeated) versus recognition (which can occur only on the second presentation of a previously unfamiliar face) between occipital and fusiform regions, respectively (see Henson et al. 2000). Our results additionally show that attention-independent repetition effects may also occur in inferior frontal and premotor cortex, suggesting that automatic repetition effects can be expressed in higher processing centers, as well as in early visual regions. Note that repetition

effects have previously been found to extend into frontoparietal regions even for unconscious, masked primes (Dehaene et al. 1998) again reflecting attention-independent processes (see Naccache and Dehaene 2001).

Our finding of similar fMRI repetition effects for faces presented in both task-relevant and task-irrelevant locations in inferior temporo-occipital cortex was mirrored behaviorally, in that the RT advantage observed for primed faces was not significantly different between the 2 attentional conditions. In the case of task-irrelevant face repetition, such speeding of responses occurred while subjects were judging (nonrepeated) house stimuli, and repetition effects could therefore reflect a habituation to specific distractors (e.g., Lorch et al. 1984). Thus repetition decreases may serve not only to facilitate processing of task-relevant stimuli (Wiggs and Martin 1998), but also to reduce interference from competing task-irrelevant stimuli (Desimone 1996; Kastner and Ungerleider 2001). The latter possibility is supported by our finding that the response in parahippocampal cortex to task-relevant houses was enhanced when particular faces were repeated at task-irrelevant locations.

Effect of emotion on repetition effects

We found that the RT advantage normally observed with repetition of neutral faces was significantly diminished for repetition of fearful faces, without a main effect of emotion on RT. A possible explanation is that the emotional properties of stimuli interfered with mechanisms involved in behavioral priming or habituation. Our imaging data enabled us to identify brain regions that exhibited an equivalent repetition \times emotion interaction. Thus lateral orbitofrontal cortex (OFC) showed less repetition decrease specifically with fearful faces, mirroring the behavioral effect (Fig. 4A), as further evidenced by correlation analyses. Several findings accord with a role of this region in such emotion-sensitive reduction of priming. First, the OFC receives amygdala efferents (Amaral and Price 1984) and may relay the results of emotional evaluations within the amygdala to ongoing decision-making and motor-response centers within the prefrontal cortex (Bechara et al. 2000). Second, the pattern of activity in lateral OFC appears consistent with data implicating this region in response inhibition on the basis of emotional information (Elliot et al. 2000; Iversen and Mishkin 1970). Third, physostigmine was found to negate the effect of emotion on behavioral priming, while reversing the dependency of repetition decreases on emotion found within the same part of OFC (as discussed later).

In contrast to orbitofrontal cortex, extrastriate visual areas showed similar, or even greater, repetition decreases for emotional versus neutral faces (Fig. 4B). These regions were more posterior than the lateral fusiform sites showing increased responses to faces with attention or with fearful expression (see also Vuilleumier et al. 2001), again suggesting that repetition effects in occipital cortex occur largely independently of "top-down" attentional or emotional processing. However, the posterior occipital region showing greater repetition decreases for emotional faces might receive feedback influences from the amygdala, which activated as a main effect of emotion (see also Vuilleumier et al. 2001) and showed differential responses to first, versus repeated, presentation of fearful faces. In keeping with the latter finding, the amygdala also showed greater

habituation to unpleasant than neutral faces in a recent fMRI experiment that controlled for physical differences of stimuli (Rotshtein et al. 2001).

Effect of cholinergic enhancement on repetition effects

Because cholinergic blockade with scopolamine has previously been found to inhibit both behavioral and neuronal correlates of repetition priming to attended stimuli (Thiel et al. 2001, 2002a), we expected to find an increase of both measures with the cholinergic enhancer physostigmine. Consistent with this prediction, physostigmine produced a greater repetition decrease in left inferior occipital cortex (selectively for faces in attended locations), although this did not significantly benefit RT or accuracy. This occipital area was close to those previously showing repetition decreases to faces (Henson et al. 2002; Jiang et al. 2000), or showing an elimination of repetition effects after cholinergic blockade (Thiel et al. 2001). The fact that no behavioral priming advantage was observed with physostigmine suggests that an additional rate-limiting step of the task may lie downstream from perceptual processes in occipital cortex (e.g., response-related).

The nature of the physostigmine interaction with repetition was closely complementary to that previously found with scopolamine (Thiel et al. 2001) in another respect: both cholinergic manipulations affected only response to the repeated occurrence of an item, not to the initial presentation. This contrasts with other drugs (e.g., GABAergic modulators) that disrupt cortical repetition effects and priming through effects on novel stimulus processing (Thiel et al. 2001; Vidailhet et al. 1999). Our results may also be relevant in the context of Alzheimer's disease (AD), in which perceptual priming is impaired (Schwartz et al. 1996; Shimamura et al. 1987). Because AD patients have shown paradoxical repetition enhancements in inferior occipital cortex, in contrast to healthy age-matched subjects who show repetition decreases (Backman et al. 2000), we speculate that the beneficial effect of anticholinesterases on priming observed in AD (Riekkinen and Riekkinen 1999) may arise from an enhancement of repetition effects in inferior occipital cortex, as observed here in healthy subjects.

In contrast to the placebo group, who showed similar repetition decreases in inferior occipital regions for faces shown at either attended or ignored locations, we found in the physostigmine group that repetition decreases occurred preferentially to attended stimuli (Figs. 3B, 5B). These results complement our RT data in showing that physostigmine, but not placebo, induced a repetition benefit selectively with attended stimuli. Such an effect would be consistent with studies showing the importance of cortical cholinergic modulation on selective attention (Sarter et al. 2001), noise filtering (Sato et al. 1987), and selective perceptual processing of stimuli that need to be remembered (Furey et al. 2000).

Cholinergic modulation has also been shown to enhance processing of emotional stimuli (Holland and Gallagher 1999) and to facilitate experience-dependent cortical plasticity specifically to fear-conditioned stimuli (Ji et al. 2001; Thiel et al. 2002b; Weinberger et al. 1998). Our results extend the role of acetylcholine in emotional learning by showing that physostigmine favored repetition decreases to emotional, relative to neutral, faces in orbitofrontal cortex (thus reversing the normal

pattern); negated the detrimental effect of emotion on primed RTs seen under placebo; and tended to eliminate any behavioral-BOLD correlation within OFC found under placebo. The OFC has especially strong interconnections with cholinergic neurons of the nucleus basalis (Cavada et al. 2000) and is modulated by acetylcholine during reinforcement learning in animals (Aou et al. 1983).

In conclusion, our experiment has shown that repetition priming, and its associated hemodynamic marker of extrastriate cortex repetition decrease, can occur by a similar amount for stimuli appearing at task-relevant or -irrelevant locations. In contrast, emotional stimuli reduced behavioral priming, associated with an attenuation of repetition decreases in lateral orbitofrontal cortex. Additionally, we demonstrated that cholinergic enhancement can augment the size of repetition effects in inferior occipital cortex, and favor behavioral and neural priming effects for both attended and emotional stimuli (the latter being attributed to a reversal of the emotion-selective impairment of priming in untreated subjects). These results suggest that cortical mechanisms underlying priming may occur automatically (in extrastriate areas) and yet be influenced by intrinsic stimulus value (in orbitofrontal cortex) and cholinergic modulation (in both regions).

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DISCLOSURES

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