

# Analysis of Neural Interactions Explains the Activation of Occipital Cortex by an Auditory Stimulus

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**McIntosh, A. R., R. E. Cabeza, and N. J. Lobaugh.** Analysis of neural interactions explains the activation of occipital cortex by an auditory stimulus. *J. Neurophysiol.* 80: 2790–2796, 1998. Large-scale neural interactions were characterized in human subjects as they learned that an auditory stimulus signaled a visual event. Once learned, activation of left dorsal occipital cortex (increased regional cerebral blood flow) was observed when the auditory stimulus was presented alone. Partial least-squares analysis of the interregional correlations (functional connectivity) between the occipital area and the rest of the brain identified a pattern of covariation with four dominant brain areas that could have mediated this activation: prefrontal cortex (near Brodmann area 10, A10), premotor cortex (A6), superior temporal cortex (A41/42), and contralateral occipital cortex (A18). Interactions among these regions and the occipital area were quantified with structural equation modeling to identify the strongest sources of the effect on left occipital activity (effective connectivity). Learning-related changes in feedback effects from A10 and A41/42 appeared to account for this change in occipital activity. Influences from these areas on the occipital area were initially suppressive, or negative, becoming facilitatory, or positive, as the association between the auditory and visual stimuli was acquired. Evaluating the total effects within the functional models showed positive influences throughout the network, suggesting enhanced interactions may have primed the system for the now-expected visual discrimination. By characterizing both changes in activity and the interactions underlying sensory associative learning, we demonstrated how parts of the nervous system operate as a cohesive network in learning about and responding to the environment.

## INTRODUCTION

Events in our world have a number of features such as form, sound, taste, and texture. Although specialized neural systems process specific modalities, the nervous system integrates activity across sensory systems, providing a unified percept of the event (Stein and Meredith 1993), and permits learning about relations among sensory stimuli. For example, the sound of an automobile horn raises an expectancy of an automobile.

We tested two hypotheses related to this integrative capacity with an associative learning task where an auditory stimulus predicted a visual stimulus. First, we hypothesized that, once the association between the events was learned, presentation of the auditory stimulus alone would be sufficient to elicit activity in brain regions usually thought of as visual. Because the activation of visual areas would occur without

overt visual stimulation, the second hypothesis was that this activation would be mediated through effects from higher order cortical areas, likely posterior association or prefrontal cortices. What follows is a description of how we addressed these two hypotheses.

## METHODS

Subjects ( $n = 10$ , mean age 25, 6 females) pressed a button on a keyboard when one of two visual stimuli appeared on a computer screen. Two highly discriminable visual stimuli ( $13^\circ$  visual angle) were displayed on a black background: a circle made of thick white concentric lines (target) and one of thin white lines (distractor). A fixation cross ( $2^\circ$  visual angle) was displayed between stimulus presentations. Subjects were informed a tone would be presented through headphones (1 kHz FM tone, 65 dB) but were not instructed further about its significance.

The relation between the tone and visual stimuli was manipulated in two phases (unpaired and paired). During the unpaired phase (1st 22 trials), 12% of tones predicted a visual event and was increased to 80% in the paired phase (4 blocks of 50 trials). All stimuli were presented for 500 ms, and on paired auditory–visual trials the auditory stimulus preceded the visual stimulus by 250 ms. The tone was equally paired with the target and distractor so that subjects expected a visual event, not a particular visual stimulus. The average intertrial interval (ITI) was 7 s (range 4–12 s).

Six positron emission tomography (PET) scans were conducted after bolus injections of 40 mCi  $^{15}\text{O}$ -H $_2$ O for each scan (protocol information can be found in Nyberg et al. 1996). Radioactive counts were used as an indirect indication of regional cerebral blood flow (rCBF) (Herscovitch et al. 1983). Written informed consent was obtained; subjects were paid for participation. The Human Subjects Use Committee of Baycrest Center approved the protocol.

The first two PET scans, one of the visual distractor and one of the tone, were taken during the unpaired phase. The four remaining scans, three tone scans followed by one visual distractor scan, were done during the paired phase. Each scan consisted of 10 presentations of the single stimulus and occurred in the middle of the training block. The visual distractor scans at the start and finish of the study were used to identify effects not specific to learning. Motor responses were not required during any scans.

Subject's images were corrected for movement across the experiment with Automated Image Registration program (AIR 3.0) (Woods et al. 1992), transformed to a PET rCBF template conforming to a standard brain atlas (Talairach and Tournoux 1988), and smoothed with a 10-mm isotropic Gaussian filter with SPM95 (Friston et al. 1996).

The first hypothesis concerning activation of visual cortex was addressed with a univariate repeated-measures multiple regression analysis (Grafton et al. 1991; Pedhazur 1982). Activated areas in occipital cortex having a probability  $\leq 0.01$ , one tailed, were

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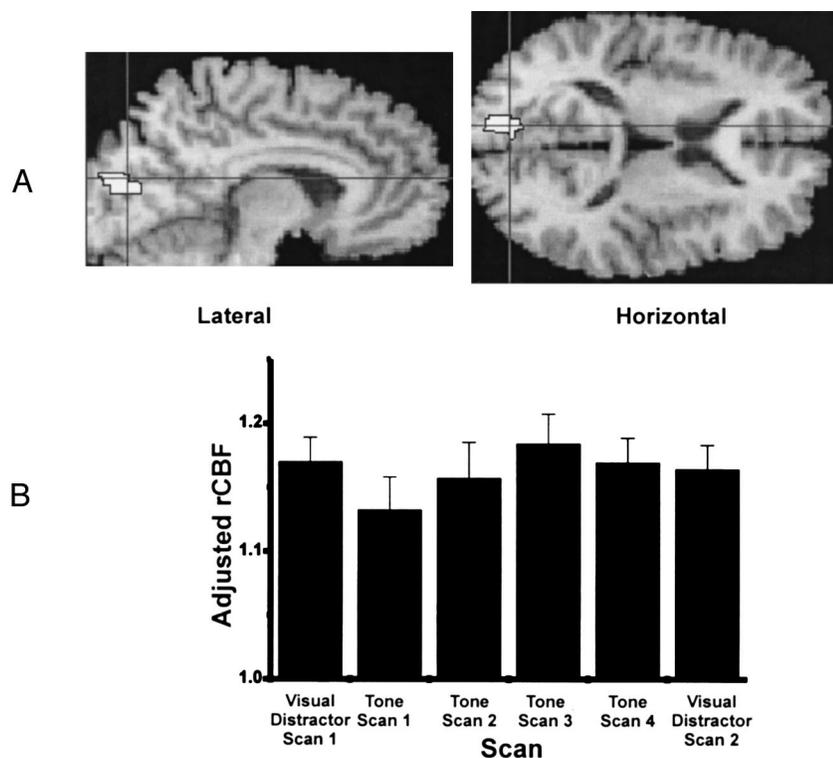


FIG. 1. Area of left dorsal occipital cortex that changed activity as a function of learning. *A*: overlay of statistically significant voxels on a structural magnetic resonance image (MRI). *B*: mean ratio adjusted rCBF ( $\pm$ SE) for the peak voxel across scans.

considered significant because of the smaller statistical search space (Friston et al. 1994; Worsley et al. 1992). Three orthogonal contrasts were included; one coded a linear effect of scan order (general effects of time) and the second compared visual scans with tone scans (stimulus modality effects). The third contrast, which was residualized on the first two, tested the first hypothesis by comparing the unpaired tone scan with paired tone scans.

### Network analysis

The second hypothesis concerning the network interactions mediating the activity changes required multivariate analyses because it emphasized relations among brain regions. We were interested in interactions elicited by the tone, so the covariance patterns from the two visual distractor scans were not included. A left occipital voxel identified from the regression analysis was used as the “seed” to construct the network. Correlation maps of the seed voxel with the remaining voxels from each of the four tone scans were put into a single large matrix and analyzed at the level of the entire image with partial least-squares (PLS) analysis (McIntosh et al. 1996a, 1997). This “seed-voxel PLS” analysis, conceptually similar to the PLS analysis of brain-behavior relations, was used to determine if there was a covariation pattern (latent variable, LV) that distinguished the unpaired from the paired tone scans. This required identification of a covariation pattern with the occipital region that changed in a systematic way across the four tone scans. This covariation is visualized by within-scan scatterplots of the LV scores and rCBF in the occipital voxel. The scores are the dot-product of the LV and each subject’s PET scan within each scan and can be regarded as the degree to which a subject’s scan reflects the LV pattern.

The inferential significance of a LV is assessed through permutation tests, and the reliability of a voxel’s contribution to the LV was assessed by bootstrap estimation of SEs for the voxel weights (salience) within the LV (Braun et al. 1998; Efron and Tibshirani 1986; McIntosh et al. 1996). Voxels with salience to SE ratios

$>2.3$  were considered reliable. Because the LVs are derived in a single analytic step, it is not necessary to correct for multiple comparisons as is done for univariate image analyses (Friston et al. 1995; Worsley et al. 1992).

Interactions between occipital areas and the salient regions identified by PLS were quantified with covariance structural equation modeling (CSEM) (McIntosh et al. 1994), which assessed whether feedback effects onto occipital areas accounted for the activity change. An anatomic network, derived from the primate literature (Felleman and Van Essen 1991; Forbes and Moskowitz 1974; Gattas et al. 1997; Markowitsch et al. 1987; Pandya and Yeterian 1985; Petrides and Pandya 1994; Seltzer and Pandya 1994; Ungerlieder et al. 1989), was combined with the covariances between regions within each scan. This provided a functional network indicating how areas affected one another in that scan. Functional networks among scans were compared statistically to assess differences in afferent and efferent influences (McIntosh et al. 1994). Residual influences were fixed at 0.4 for all areas in the network.

To summarize, a univariate analysis identified the visual cortex region showing the greatest learning-related change. Candidate regions that as a group could have affected the activity change were identified with the seed PLS analysis, and the direct effect of salient regions from the PLS on the occipital area was evaluated using anatomically based structural equation modeling. These final two steps are an analysis of functional connectivity (Friston 1994) with the occipital area of interest and then of effective connectivity (Friston et al. 1993) to determine whether feedback effects onto the occipital area could account for the activity change.

## RESULTS

### Performance

By the end of training, reaction times were faster on paired trials than when the target was presented alone [repeated measures analysis of variance,  $F(4,36) = 3.49$ ;  $P < 0.025$ ].

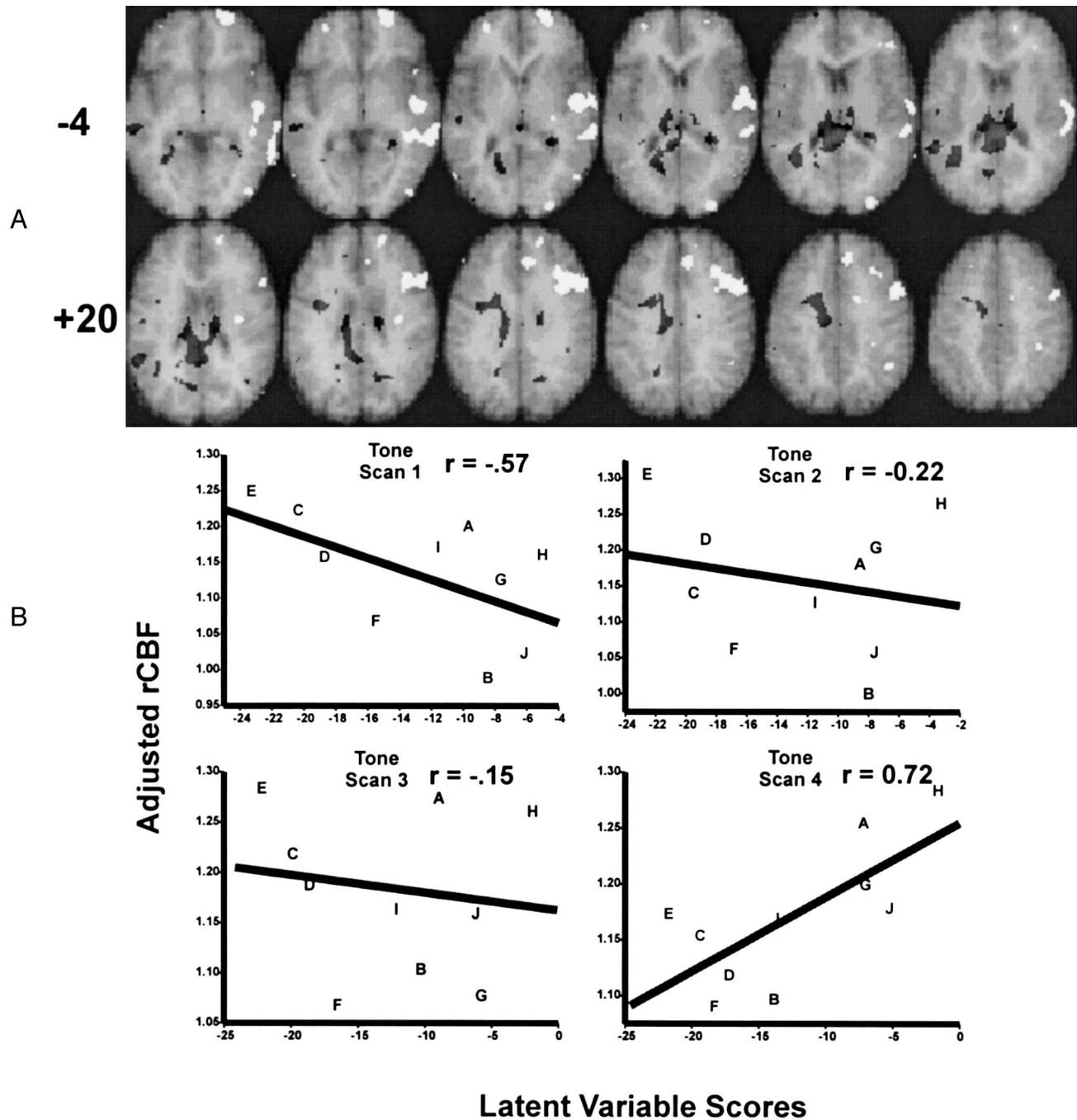


FIG. 2. Results of seed partial least-squares analysis. A: singular image showing regions whose covariation changes during learning with the dorsal occipital seed voxel (Fig. 1). White and black regions indicate positive and negative covariation (saliences), respectively. The image is displayed on a structural MRI conforming to stereotaxic atlas space. Horizontal slices start at  $-4$  mm from the AC-PC line (top left slice) and move in increments of 4 mm to  $+40$  mm (bottom right). Left is left and the top is anterior. B: scatterplot of adjusted regional cerebral blood flow in the dorsal occipital region with latent variable (LV) scores for each of the 10 subjects, where a subject is identified by a unique letter. The  $r$  value in each plot is the correlation of voxel activity with LV scores.

This facilitation developed across experiment, indicative of a learned behavior.

#### Regional activation

An area in left dorsal occipital cortex showed progressively more activity in tone scans as training proceeded until,

by the last tone scan, activity was equivalent to that elicited by the visual distractor [ $t(47) = 2.41$ ,  $P < 0.01$ , atlas coordinates  $x = 12$ ,  $y = 90$ ,  $z = 12$ , Brodmann area 18, A18L]. According to functional maps of human visual cortex created with fMRI (De Yoe et al. 1996; Sereno et al. 1995), the area of activation lied roughly in V2 (Fig. 1A). A plot of

TABLE 1. *Interregional correlations of ratio-adjusted counts from voxels used for structural models*

	A18L (-12, -92, 12)	A18R (28, -94, 8)	A41/42 (44, -12, 0)	A10 (16, 60, -4)	A6 (44, 8, 36)
<i>Tone scan 1</i>					
A18L	1				
A18R	-0.45	1			
A41/42	-0.61	0.54	1		
A10	-0.53	0.48	0.61	1	
A6	-0.47	0.36	0.71	0.53	1
Diff RT	0.42	0.22	-0.45	0.10	-0.04
<i>Tone scan 2</i>					
A18L	1				
A18R	0.04	1			
A41/42	-0.55	0.22	1		
A10	-0.31	-0.32	0.10	1	
A6	-0.46	0.32	0.75	0.26	1
Diff RT	0.51	0.23	-0.48	-0.45	-0.23
<i>Tone scan 3</i>					
A18L	1				
A18R	-0.09	1			
A41/42	-0.30	0.32	1		
A10	-0.49	0.52	0.05	1	
A6	-0.23	0.19	0.66	0.34	1
Diff RT	0.60	0.34	0.44	-0.24	0.35
<i>Tone scan 4</i>					
A18L	1				
A18R	0.49	1			
A41/42	0.66	0.82	1		
A10	0.62	0.42	0.31	1	
A6	0.58	0.51	0.72	0.42	1
Diff RT	0.13	0.28	0.35	0.41	0.58

Region labels are in the first row, with stereotaxic coordinates below. The row labeled Diff-RT is the correlation of voxel rCBF with the reaction time difference between unpaired and paired trials.

activity is shown in Fig. 1*b*. Other areas within left and right occipital cortex showed a similar pattern of rCBF changes across scans but were not statistically significant by the univariate test.

#### Network analysis

The second LV identified by the seed PLS depicted a pattern of covariation with A18L that changed from negative to positive across the tone scans (permutation  $P = 0.04$ ). The first LV was also significant and depicted covariances patterns common to all scans. All stable regions on the second LV, based on bootstrapping, are shown in Fig. 2*A*. As a group, the covariation of these areas with A18L became more positive across tone scans (Fig. 2*B*). Four regions showing strong positive saliences (white areas in Fig. 2*A*) were selected to assess whether their impact on A18L accounted for the activity changes across tone scans. Areas negatively salient were posterior and middle cingulate, and left supramarginal cortices (not used for CSEM).

Voxel-wise correlations for the four tone scans are presented in Table 1. The largest correlation differences across tone scans were with A18L (negative to positive). The correlations of this area were negative or zero in both visual

distractor scans (data not shown). This suggests that the change in interregional interactions across tone scans was specific to the learned significance of the tone.

Also shown in Table 1 are the correlations of each voxel with the difference in reaction time of paired and unpaired trials preceding the particular scan (diff RT). Both occipital regions showed a moderate positive correlation with diff RT (indicating more activity with faster RT to paired trials), whereas the remaining regions were initially negatively correlated, becoming more positive across successive scans. The systematic change in the brain-behavior relations of these latter areas suggests some involvement in mediating the behavioral change (McIntosh et al. 1998).

The functional networks for the four tone scans are depicted in Fig. 3. When interpreting these results, is important to keep in mind the covariance patterns are in response to the tone alone. The only significant differences reflected influences on A18L [ $\chi^2(6) = 26.07, P < 0.01$ ]. No other pathways showed significant changes across the four tone scans. This is perhaps not surprising when the correlations among these areas are considered (Table 1). Changes in two pathways dominated, the effects on A18L from prefrontal cortex A10 and temporal cortex A41/42. In the first tone scan (unpaired phase), effects from both regions were

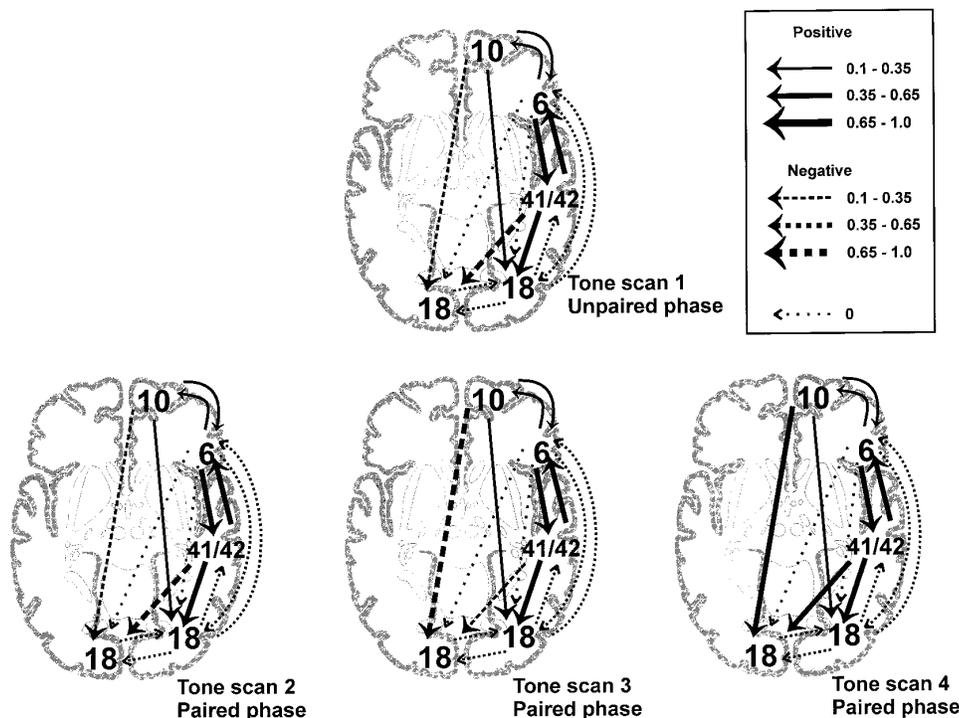


FIG. 3. Functional network models from the 4-tone scans. Models are displayed graphically on a horizontal brain section, and numbers on the section refer to Brodmann area designations. Arrow thickness indicates the functional influence conferred through the anatomic connections (legend in upper right corner).

negative. The prefrontal effect became positive in the final tone scan, and the effect from temporal cortex became less negative and then positive by the final tone scan. The switch from negative to positive effects suggests a switch from inhibitory to excitatory influences at the level of neural populations (Nyberg et al. 1996).

A separate model adding reciprocal connections between A18L and A41/42 and A18L and A10 tested the specificity of our contention that changes in A18L were mediated through higher order cortical influences. Although this model was less mathematically stable because of numerous loops, the networks showed stronger afferent influences onto A18L than efferent effects from A18L. Moreover, the model presented in Fig. 3 provided a better overall fit to the correlation matrices [ $\chi^2(43) = 31.96, P = 0.86$ ] than a model containing only afferents from A18L to A10 and A41/42 [ $\chi^2(43) = 62.29, P = 0.029$ ]. These two outcomes add tentative confirmation of our second hypothesis.

The switch from inhibitory to excitatory influences impacted on the total effects transmitted through the functional networks. Total effects are effects transmitted through direct and indirect routes. Despite weak direct effects from frontal A6 on A18L, total effects from A6 went from negative to positive (Table 2), which implies that the facilitatory effects from A10 and A41/42 were carried through the entire network. This may have allowed the associative effects of the tone to be more easily transmitted, thus priming occipital cortex for the impending visual discrimination.

The initial inhibitory prefrontal effect is consistent with findings from ERP studies suggesting prefrontal feedback suppresses posterior cortices during normal sensory processing (e.g., Knight et al. 1989). The change from inhibitory to excitatory influences during the paired phase would allow activity between auditory and visual systems to be

integrated, resulting in the formation of the association between the tone and the visual events—a result congruous with theories that purport a special role for prefrontal regions in linking events in the world (Cohen et al. 1996; Knight et al. 1995; Petrides 1997). Concurrent changes in the influence of temporal cortex and the correlations of the more anterior areas with behavior indicates a broader recruitment of cortical regions as the associative link between stimulus events was formed. Our results thus emphasize that learning the relations among events in the world is mediated through the interactions among specialized brain regions.

It is possible that the changes in occipital cortex reflect focused attention to the visual domain. However, because activity and effective connectivity of occipital cortex changed across tone scans, and paralleled the change in behavior, attention could not be the only modulating effect. Instead, it is likely that the change of activity in the occipital areas resulted from a learned expectancy concerning the tone and visual stimuli. Learning and attentional processes are not independent but work together to identify salient features in the environment to facilitate responses. Such a position was echoed by some learning theorists (Mackintosh 1975).

This paper demonstrated two specific points. First, we showed how neurobehavioral hypotheses can be framed and tested from the perspective of interacting neural systems. Our analysis was optimized to address a hypothesis about a specific region, and this approach could be extended to address issues concerning putative functional systems (e.g., Mesulam 1990). Second, and perhaps more importantly, our results underscore the importance of characterizing nervous system function not only by regional activity but also in terms of how an area's activity relates to other areas in the

TABLE 2. Total effects from each functional model

	A18L	A18R	A41/42	A10	A6
<i>Tone scan 1</i>					
A18L	0	0	-0.69	-0.28	-0.28
A18R	0.06	0.03	0.55	0.20	0.31
A41/42	0	0.07	0.25	0.10	0.55
A10	0	0	0.41	0.05	0.34
A6	0	0	0.51	0.21	0.27
<i>Tone scan 2</i>					
A18L	0	0.01	-0.75	-0.26	-0.30
A18R	0.06	0.03	0.55	0.21	0.31
A41/42	0	0.07	0.25	0.10	0.55
A10	0	0	0.14	0.05	0.34
A6	0	0	0.51	0.21	0.27
<i>Tone scan 3</i>					
A18L	0	0.03	-0.47	-0.50	-0.25
A18R	0.06	0.03	0.57	0.19	0.32
A41/42	0	0.07	0.25	0.10	0.55
A10	0	0	0.14	0.05	0.34
A6	0	0	0.51	0.21	0.27
<i>Tone scan 4</i>					
A18L	0	0.08	0.64	0.43	0.46
A18R	0.07	0.04	0.61	0.24	0.35
A41/42	0	0.07	0.26	0.10	0.55
A10	0	0.00	0.14	0.05	0.34
A6	0	0	0.51	0.21	0.27

Rows list structures being affected and columns list origin of effects. Total effects are the sum of direct and indirect effects.

context of functional networks (Friston et al. 1997; McIntosh et al. 1996b, 1997; Paus et al. 1996; Tononi et al. 1992; Vaadia et al. 1989).

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