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Neural Mechanisms of Visual Attention: How Top-Down Feedback Highlights Relevant Locations

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Attention helps us process potentially important objects by selectively increasing the activity of sensory neurons that represent the relevant locations and features of our environment. This selection process requires top-down feedback about what is important in our environment. We investigated how parietal cortical output influences neural activity in early sensory areas. Neural recordings were made simultaneously from the posterior parietal cortex and an earlier area in the visual pathway, the medial temporal area (MT; Fig. 1A). We recorded 29 pairs of neurons from MT and LIP, each pair having overlapping receptive fields. When the monkey selectively attended to a location, the timing of activities in the two regions became synchronized, with the parietal cortex leading the medial temporal area. Parietal neurons may thus selectively increase activity in earlier sensory areas to enable focused spatial attention.

Attention allows us to engage with our environment by selecting information relevant for behavior (1–3). This enables preferential processing of particular locations in the visual field or specific features of objects. Attention maintained on a location is usually referred to as spatial attention and that on a feature as feature-based attention (4, 5). Both types of attention manifest in visual cortical areas as increased activity of neurons representing the attended location or feature and reduced activity of other neurons (6–14). This may require top-down feedback about what is relevant in the environment; however, such feedback has not been empirically demonstrated. There is evidence (6, 11, 15–17) that the posterior parietal cortex (PPC) is critical for spatial attention. The PPC is a higher-order structure along the dorsal stream of visual areas (Fig. 1A), which are particularly concerned with spatial aspects of a scene. It has been suggested that the spatial information about a scene extracted by the PPC forms the basis for feedback signals to earlier levels of the visual pathway, highlighting spatial locations of potential interest (18, 19) and gating responses depending upon the state of attention.

We simultaneously measured the activity in a part of the macaque PPC called the lateral intraparietal area (LIP), and the immediately earlier stage of the dorsal pathway, the medial temporal area (MT; Fig. 1A). We tested whether LIP feedback increases MT responses to attended visual stimuli. The monkeys performed a delayed match-to-sample (DMS) task, which manipulated both where they were attending and what stimulus feature they were attending to (Fig. 1B) (20). We recorded 29 pairs of neurons from MT and LIP, each pair having overlapping receptive fields (RFs) and the same preferred orientation. Local field potentials (LFPs) from the two sites were also recorded.

We first tested whether our paradigm resulted in increased responses of MT neurons to attended stimuli. Figure 2A shows the effect of spatial attention on a single MT neuron and Fig. 2B, the average population response. For both data sets, the MT response to the second stimulus was significantly increased in the “spatial and feature-based attention” and “spatial attention” conditions, compared to the “neutral” control. When “attention was elsewhere,” the MT response to the second stimulus was significantly reduced (Holm’s controlled Wilcoxon test, P < 0.05). These attentional effects on MT neurons are consistent with those reported in other types of cognitive

References and Notes
21. Materials and methods are available as supporting material on Science Online.
22. Positive and negative departures from the good phase relation toward the bad phase relation were pooled because our previous analyses had demonstrated symmetrical effects in both directions.
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Materials and Methods SOM Text Figs. 51 to 56 References 5 January 2007; accepted 1 May 2007 10.1126/science.1139597
tasks and other cortical areas (2, 6–14) and are not due to simple stimulus repetition (fig. S1).

If LIP neurons code attention priorities, then their activity should differentiate between attention conditions. Figure 2, C and D, show the activity of a single LIP neuron and the population, respectively. Both show a significantly increased response to the second stimulus with “spatial and feature-based attention” compared to the “neutral” first stimulus, but a significantly reduced response when “attention was elsewhere” (Holm’s controlled Wilcoxon test, \( P < 0.05 \)). For the “spatial attention” condition, the increased response to the second stimulus was significantly different from the “attention elsewhere” control, though not the “neutral” control. The activity of LIP neurons increased through the delay period after the first stimulus, with the overall delay period activity significantly greater in those cases where attention included the RF location (Holm’s controlled Wilcoxon test, \( P < 0.05 \)). Because LIP activity increased before the MT response to an attended stimulus, LIP is in a position to provide feedback to MT.

If LIP causes the effect of attention on MT, then the activity in the two areas should be correlated and spikes from LIP neurons should be closely followed by spikes from MT neurons. We calculated the coherence of MT and LIP activities [using multi-taper spectral methods (20–22)], which measures the degree of association between two oscillatory processes (here the spike trains or LFPs in MT and LIP), as a function of oscillation frequency. We generally observed increased coherence between MT and LIP LFPs in the “spatial and feature-based attention” and “spatial attention” conditions (Fig. 3, A and B). The coherence in the 10- to 35-Hz range increased when the first stimulus appeared in the RF. It was also significantly elevated during the delay period (Student’s \( t \) test, \( P < 0.05 \)), increasing just before the second stimulus. The coherence peaked around the second stimulus and remained elevated for up to 400 ms around the stimulus. Figure 3C shows the coherence when the first stimulus was flashed outside the RF and thus spatial attention was not drawn to the receptive-field location. The coherence is much weaker in this case, particularly around the second stimulus. Figure 3D shows the average coherence of the population of 29 paired recordings for the two attention conditions and two control states. The coherence was significantly greater (Holm’s controlled Wilcoxon test, \( P < 0.05 \)) when attention was focused on the receptive-field location compared to the “neutral” and “attention elsewhere” controls.

The significant coherence of LFPs in MT and LIP during spatial attention means that there was correlated activity between ensembles of MT and LIP neurons. To determine the relative timing of action potentials between the two areas, we calculated the coherence between simultaneously recorded spike trains from single neurons in MT and LIP (0 to 300 ms after stimulus onset). The coherence between the spikes elicited by MT and LIP neurons was generally low but nonetheless significantly above zero (Student’s \( t \) test, \( P < 0.1 \)) in the gamma-frequency range for 34% of neuron pairs. The lower coherence between spike trains than between LFPs is expected, because any particular sampled pair of neurons has a low probability of being strongly connected. Nevertheless, the “spatial and feature-based attention” and “spatial attention” conditions produced significant coherence (Fig. 4A). In contrast, there were no cases of significant coherence in the “neutral” and “attention elsewhere” controls.

If LIP has a top-down influence on MT responses during focal attention, then the phase of the coherence should show LIP leading MT. Figure 4B shows the phase when the coherence was significantly above zero, which occurred only during the two attention conditions. The phase of the peak coherence showed the LIP preceding MT by 4.55 \( \pm \) 1.04 ms for the “spatial attention” condition.
and feature-based attention” condition and by 7.43 ± 2.02 ms for the “spatial attention” condition (mean ± SE of the 34% of neuron pairs showing significant coherence). This phase relationship is physiologically plausible for feedback from the LIP to MT, assuming a conduction velocity of 1 m/s (23) for intracortical connections. To ensure that the coherence we saw was due to within-trial physiological interactions, we shifted, across time, the LIP spike train relative to the MT train by integer multiples of trials for each recording session and recalculated the coherence (Fig. 4C). This control abolished the attention-enhanced coherence.

We next tested whether LIP spikes preceded enough MT spikes to cause the increased MT activity during spatial attention. We observed a significant increase in the percentage of MT spikes preceded by LIP spikes in the spatial attention conditions compared with the “neutral” and “attention elsewhere” controls (Holm’s controlled Wilcoxon test, \( P < 0.05 \); Fig. 4D). The magnitude of this effect (percentage of MT spikes preceded by LIP spikes within 10 ms: spatial and featural attention, 11.5%; spatial attention, 8.3%) could potentially account for a substantial amount of the increase in MT activity (spatial and featural attention, +14.0%; spatial attention, +9.6%). However, a greater increase in LIP activity, relative to MT activity, could lead to the results in Fig. 4D without LIP feedback to MT. This possibility is discounted by the finding of a significant increase in the percentage of LIP spikes followed by MT spikes with attention (Holm’s controlled Wilcoxon test, \( P < 0.05 \); Fig. 4E). Both increased coherence of oscillatory LFPs and LIP spikes preceding MT spikes in the attention conditions are evident in the raw data from single trials (Fig. S2).

Synchronization between LIP neurons may be a fundamental mechanism ensuring that the output from LIP neurons has an increased impact on sensory areas such as MT. We calculated the spike-field coherence in LIP, which indicates the degree of synchronization between spike times and the LFP. The mean spike-field coherence between 25 and 45 Hz was significantly increased in the two spatial attention conditions (Fig. 4F) compared to the “attention elsewhere” control (Holm’s controlled Wilcoxon test, \( P < 0.05 \)). This suggests that spike timing, in addition to spike rate, may be important for increased efficacy of attentional feedback.

Our results show that LIP feedback can account for attention-enhanced MT responses. This feedback manifests in the coherent activities of MT and LIP neurons within the gamma-frequency range (25 to 45 Hz), supporting the role of gamma synchronizaton in information processing (24–26). The phase of the observed coherence is such that LIP feedback can potentially arrive at MT during a depolarizing phase of membrane-potential oscillations, increasing the probability of spike generation. Synchronization of feedback may also increase sensory activity during attention.

The response of LIP neurons to the second stimulus of preferred orientation depended upon whether the first stimulus, though at the same location, was of the preferred or orthogonal orientation. In MT neurons, however, there was no significant difference in response to the second

![Fig. 3. Coherent neural activity between MT and LIP. The coherence (color-coded) of the MT LFP and LIP LFP from a pair of recording sites during the DMS task. The coherence was calculated in successive 300-ms windows with a step size of 50 ms. S2 is the preferred stimulus in the RF and is the same in each panel. (A) S1 and S2 match for location and orientation; (B) S1 and S2 match for location only; and (C) S1 and S2 differ in location. (D) Population average of the transformed coherence (20) between the MT LFP and LIP LFP, 0 to 300 ms after stimulus onset (solid lines), and the control, where the LIP LFP was shifted relative to the MT LFP (dotted lines).](image-url)

![Fig. 4. Synchronized LFP feedback to MT during attention. (A) Coherence of spikes from a pair of LIP and MT neurons, 0 to 300 ms after stimulus onset. Color coding as in Fig. 3D. (B) Phase of significant coherence between the pair of neurons in (A). Only two traces are shown, because neither control showed significant coherence in the gamma range. (C) Relative shifts between spike trains by integer multiples of trials abolished attention-enhanced coherence; compare with (A). (D) Population median of the percentage of MT spikes preceded by LIP spikes, in the 300 ms after stimulus onset. (E) Population median of the percentage of LIP spikes followed by MT spikes, in the 300 ms after stimulus onset. (F) Population average of the transformed spike-field coherence in LIP (solid lines). Increased coherence is seen for the two attention conditions in the gamma range. Shifting spike trains relative to the LFP in LIP abolished attention-enhanced coherence (dotted lines).](image-url)
stimulus between these two attention conditions. This is consistent with the idea that the parietal cortex uses both spatial and feature-based information to determine purely spatial priorities for its feedback (18). Such a scheme provides a neural framework for “guided search” models of attention (3, 18) and is consistent with feedback to auditory and somatosensory systems (27, 28) being spatial.

The dorsal and ventral cortical pathways are said to represent the spatial and feature-based aspects of a visual scene, respectively, and LIP is part of the dorsal pathway. However, the feature selectivity shown by LIP neurons in our and other studies (29, 30) means that LIP could be involved in processing object features through its direct connections with the ventral pathway (19, 27, 28) or by gating neuronal activity at the level of V1 via MT (18, 19). The attentional modulation of activity in ventral cortical areas (2, 7) and even in V1 (8, 10, 12, 13) may have its origin in LIP as the gain controller.

References and Notes

20. Materials and methods are available as supporting material on Science Online.

α-Klotho as a Regulator of Calcium Homeostasis

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α-klotho was identified as a gene associated with premature aging-like phenotypes characterized by short lifespan. In mice, we found the molecular association of α-Klotho (α-Kl) and Na+,K+-ATPase (Na+,K+-ATPase) at the plasma membrane. The increased Na+ gradient created by Na+,K+-ATPase activity might drive the Na+,K+-ATPase at the plasma membrane. Low concentrations of extracellular free calcium ([Ca2+]e) have also been identified and named klotho (klotho). A homolog has been previously detected in mouse kidney and in human parathyroid complex (Fig. 1B). These molecules also associated in mouse kidney and in human parathyroid glands (Fig. 1, C and D).

To avoid confusion, we refer to the original gene as α-Klotho (α-Kl). The α-Klotho (α-Kl) gene encodes a type I membrane protein with considerable similarity to β-glycosidase that is predominantly expressed in tissues that are involved with calcium homeostasis; that is the parathyroid glands, kidney, and choroid plexus (4, 5) (supporting description 1). Although α-Kl has been predicted to be present on the cell surface, large amounts of α-Kl are detectable in the cytoplasm and the cleaved extracellular domain is secreted into the blood and cerebrospinal fluid (CSF) (6). In this paper, we show a pivotal role of α-Kl in calcium homeostasis (mouse breeding conditions are described in supporting description 2 and fig. S1).

We identified the α1 subunit of Na+,K+-ATPase (α1-Na+,K+-ATPase) as an α-Kl binding protein (7) (supporting description 3) and further confirmed the binding by Western blot analysis and with reciprocal immunoprecipitation (Fig. 1, A and B). α-Kl precipitated by monoclonal antibody to α1-Na+,K+-ATPase contained proteins that migrated as two bands of 120 and 135 kD, indicating that Na+,K+-ATPase binds to α-Kl regardless of its sugar moieties (Fig. 1B) (6). The β subunit of Na+,K+-ATPase, which has a major role in the regulation of membrane recruitment of Na+,K+-ATPase (8), was included in the α1-Kl-α1-Na+,K+-ATPase complex (Fig. 1B). These molecules also associated in mouse kidney and in human parathyroid glands (Fig. 1, C and D).

In these tissues, the majority of α-Kl immunoreactivity was detectable in the cytoplasm, whereas α1-Na+,K+-ATPase immunoreactivity was observed at or near the cell surface and diffusely in the cytoplasm (fig. S2). We verified the above histological observations by the surface biotinylation and subcellular fractionation using the choroid plexus and the HeLa cells introduced with both α-Kl and α1-Na+,K+-ATPase fused with enhanced green fluorescence protein (α1-Na+,K+-ATPase-EGFP), respectively. α-Kl was primarily detected in the nonbiotinylated cyto-