

# How visual salience wins the battle for awareness

Steven Yantis

**Voluntarily paying attention to one object in a crowded scene enhances perception of that object and increases the activity of neurons representing it. Attention can also be drawn involuntarily by salient objects—for example, by the sudden onset of a bright stimulus. A study now shows how this involuntary type of attention may mediate competition between representations in human visual cortex.**

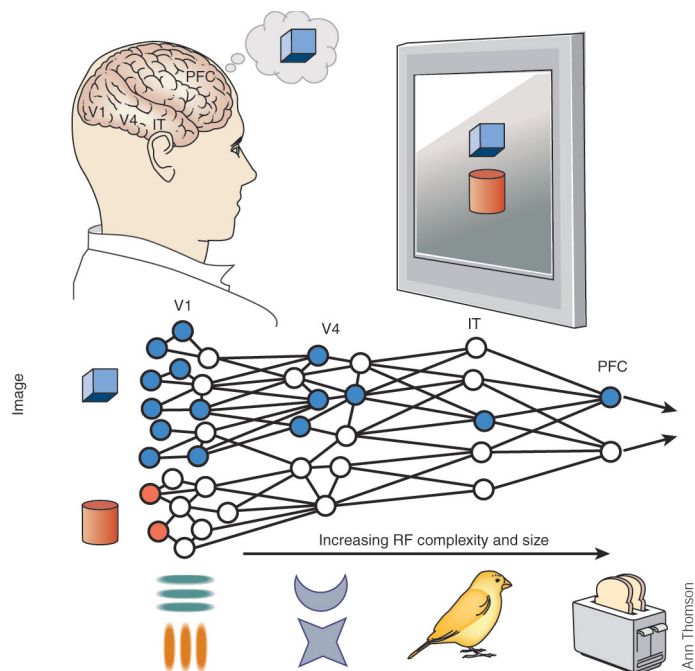
The intuition that we open our eyes and see all that is before us has long been known to be an illusion. In fact, vision is highly selective. Even without moving our eyes, we can choose voluntarily to attend to one or another object in a scene, and this leads to improved sensitivity and more rapid detection<sup>1</sup> as well as a more vivid appearance<sup>2</sup>. In other words, conscious experience of a scene depends both on the contents of the retinal image and on the attentive state of the brain. When multiple stimuli are present in a scene, they compete for cortical representation<sup>3</sup>. Voluntary deployments of attention can resolve the competition: ‘top-down’ signals that originate in executive control regions of prefrontal cortex promote increased spiking in neurons that represent the attended object. However, not all attention is voluntary: when a door slams in the library, every head looks up to the source. In this issue, Beck and Kastner report important new evidence about how this type of control—attentional capture by salient stimuli—may arise from a purely ‘bottom-up’ form of cortical competition in visual parts of the brain<sup>4</sup>.

Competition for cortical representation is a consequence of the hierarchical architecture of the visual system: neural receptive fields are small (0.5–1.5°) in primary visual cortex (V1) and represent simple, local visual properties such as edge orientation and contrast (Fig. 1). Neurons in later visual areas such as V2, V4 and inferotemporal (IT) cortex have receptive fields that increase in size and in complexity of visual properties to which they are tuned<sup>5</sup>. Neurons in area

V4 have receptive field diameters that are roughly equal to the distance of their centers from the fovea, and respond to moderately complex contours<sup>6</sup>. In IT, neurons can have large receptive fields that encompass much of a hemifield, and they can respond to complex shapes and faces<sup>7</sup>.

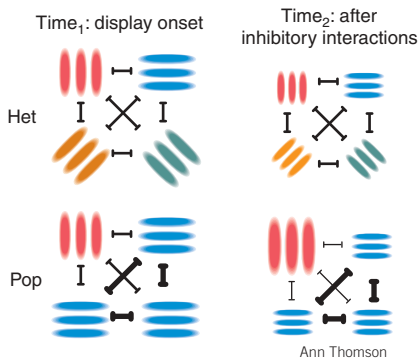
This hierarchical structure efficiently codes complex visual object properties, but the efficiency comes at a cost. When

both an effective sensory stimulus and an otherwise ineffective sensory stimulus are present within the receptive field of, say, a V4 or IT neuron, competition for representation arises: should the neuron’s response be robust, reflecting the effective stimulus, or weak, reflecting the ineffective stimulus? Without attention, the response is a compromise: roughly the mean of the strong and weak responses. When voluntary attention is



**Figure 1** The visual system is organized hierarchically; receptive field size and complexity increase from V1 to V4 to inferotemporal (IT) cortex. Cartoons below V1, V4 and IT represent oriented edges, simple contours and complex object shape, respectively. This presents a problem: when two objects appear with the same large receptive field (say, of the highlighted neuron in IT), which of the stimuli should drive the neuron’s response? In this example, the competition for representation has been biased in favor of the cube, either by a top-down signal that reflects current behavioral goals, or by differences in local feature contrast (salience). Every level of the visual hierarchy now cooperates to represent the attended object, which enters awareness. RF, receptive field.

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**Figure 2** Cartoon of the context effects described by Beck and Kastner<sup>4</sup>. Each panel shows an array of four colored, oriented Gabor patches; the size of each patch represents the magnitude of the neural response to that stimulus, and the thickness of the black lines between them (representing inhibitory connections) represents the strength of the inhibitory interaction. Left column represents initial appearance of stimuli, and right column represents relative neural response to the stimuli after some time has passed to allow inhibitory interactions to occur. Stimuli with different feature values (colors and orientations) show moderate-strength mutual inhibition, whereas stimuli with the same color and orientation produce strong isofeature inhibition. When stimuli first appear (left), their physical contrasts initially produce approximately equal neural responses. Following inhibitory interactions, (right), mutual inhibition in the heterogeneous displays (top) produces an approximately equal degree of sensory suppression for all stimuli. However, the unbalanced inhibitory pattern in the pop-out displays (bottom) produces more sensory suppression in the stimuli that share features (blue horizontal Gabor patches), which in turn reduces the degree to which they inhibit the feature singleton (red vertical Gabor patch), producing a relatively enhanced response to that object. Het, heterogeneous display; Pop, pop-out display.

directed to one of the stimuli, the competition is biased so that the attended stimulus in the receptive field drives the cell<sup>8</sup>, and that stimulus ultimately enters awareness and becomes available for report or encoding into memory. The effects of attention are propagated throughout the visual hierarchy so that a stable, coherent ensemble of neurons distributed across cortical areas represents the attended object via synchronized activity and reentrant feedback signals.

Kastner and colleagues previously documented how attention can bias competition in human cortex<sup>9</sup>. They compared brain activity evoked by a display containing multiple stimuli presented one at a time (so that inhibitory interactions could not occur), which produced a strong response, or presented simultaneously (allowing inhibitory interactions), which produced a weaker response. When attention was directed to one of the stimuli, it reduced the suppression caused by the competing stimuli, causing an increased response, particularly in area V4. Such voluntary deployments of attention allow observers to actively seek information needed to achieve current behavioral goals and can modulate activity in the representation of different spatial locations, sensory dimensions or objects<sup>10</sup>. Activity in a network of cortical regions that include the posterior parietal cortex and the frontal eye fields is critical for voluntary deployments of attention<sup>11</sup>.

On the other hand, it is sensible that certain sensory events should capture attention involuntarily, providing an 'early warning system' for rapid assessment and response to salient and potentially harmful events, obviating deliberation and saving precious time<sup>12</sup>. Many behavioral studies have documented the efficiency with which salient visual objects can be detected in visual search<sup>1</sup>.

In the new paper<sup>4</sup>, Beck and Kastner have investigated human brain activity to salient and non-salient visual stimuli using fMRI.

To ensure that the effects they measured were purely stimulus-driven (and not a consequence of voluntary attention), they required observers to carry out an attentionally demanding visual task at the fovea, and they measured response times in the foveal task to ensure that attention was not diverted to the peripheral stimuli that were the focus of their brain measurements.

Beck and Kastner found that the sensory suppression that usually results from simultaneous presentation of multiple competing stimuli is reduced if one of the objects is a feature singleton (that is, an object that differs in both color and orientation from the remaining items in the display). In a heterogeneous display (Fig. 2, top), multiple stimuli with different features interact in a mutually inhibitory, competitive fashion, producing a moderate degree of sensory suppression. Stimuli with identical features show stronger mutual inhibition, a phenomenon sometimes termed 'isofeature suppression'<sup>13</sup>. Thus, when the contextual elements all have the same color and orientation (Fig. 2, bottom), they strongly inhibit one another, and this reduces their combined inhibitory effects on the unique item, which in turn increases the neural response to that item. In the Beck and Kastner study, this was manifested in less sensory suppression for pop-out displays than for heterogeneous displays. In other words, the suppression caused by context items was greater for the heterogeneous displays, where mutual suppression was balanced among the items, than for the pop-out displays, where the strong isofeature suppression of the homogenous background reduced its inhibitory effect on the singleton.

This finding can be viewed as an instance of the very general principle that perceptual systems encode contrast, rather than the absolute level of some attribute. This kind of contrast effect has been documented through measurements of single-cell responses in macaque

area V1 (ref. 14). An oriented bar was placed in the receptive field of the cell, and a field of identically oriented bars, all outside the classical receptive field, was introduced. The presence of any context suppressed the cell's response compared with a blank surround, reflecting competitive intracortical interactions. When the bars in the contextual field had the same orientation as the center bar, the cell's response was more strongly suppressed than when they had a contrasting orientation. The authors interpreted this as a neural correlate of the perceptual salience of feature singletons.

Once the neural response to the salient item dominates the responses to the uniform contextual items, this signal can propagate to other levels of the visual hierarchy and increase the likelihood that this stimulus enters visual awareness. These stimulus-driven effects are combined with and modulated by top-down effects to determine the overall attentive state of the brain. For example, when two stimuli are presented within a V4 receptive field, increasing the contrast of one of them biases the competition in its favor<sup>15</sup>. This stimulus-driven effect is magnified if the animal is also induced to voluntarily attend to that stimulus.

These findings contribute to a growing understanding of the role of attention in perception. Cooperative interactions across levels of the visual hierarchy give rise to robust perceptual representations of attended objects; competitive interactions within visual areas lead to the suppression of competing representations. As the visual scene changes, local feature contrast will bias competition in favor of newly salient events. As behavioral goals change, modulatory signals from prefrontal and parietal cortex bias competition in favor of task-relevant information. The dynamic interplay of stimulus-driven and goal-directed factors determines the content of perceptual experience as it evolves over time.

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# The synaptic A $\beta$ hypothesis of Alzheimer disease

Rudolph E Tanzi

**A $\beta$  peptide is linked to Alzheimer pathology, but its toxic mechanism remains unclear. New work shows that A $\beta$  leads to internalization of NMDA receptors, reducing their availability at synapses. The authors also suggest a molecular mechanism for this endocytosis.**

The amyloid hypothesis of Alzheimer disease states that the accumulation and deposition of fibrillar  $\beta$ -amyloid is the primary driver of neurodegeneration and cognitive decline leading to dementia<sup>1,2</sup>. Recent studies, however, are prompting a shift to the synaptic A $\beta$  hypothesis, which places a greater emphasis on the pathogenic role of non-fibrillar A $\beta$  oligomers specifically at the synapse. Now, in this issue, Snyder and colleagues<sup>3</sup> report a signaling pathway through which A $\beta$  may act to impair glutamatergic transmission, compromise synaptic function and reduce long-term potentiation (LTP), a form of synaptic plasticity associated with learning and memory<sup>4</sup>.

Over the past twenty years, the amyloid hypothesis has been strongly supported by a wealth of evidence, including data from genetic studies of Alzheimer disease<sup>5</sup>. All four of the established Alzheimer disease genes, the  $\beta$ -amyloid precursor protein (APP), presenilin 1 and 2 (PSEN1, PSEN2) and apolipoprotein E (APOE) harbor mutations or variants that influence the accumulation of the A $\beta$  peptide. A $\beta$  is generated by cleavage from APP and is the central building block of  $\beta$ -amyloid. In the case of the early-onset Alzheimer disease genes (APP, PSEN1 and PSEN2), over 160 autosomal dominant mutations have been discovered that cause Alzheimer disease with virtual certainty<sup>5</sup>, usually before the age of 60. All but a handful of these mutations increase the relative rate of production of A $\beta$ 42, the longer form of the peptide that is much more prone to oligo-

merization and fibrillization than its more abundant counterpart in the brain, A $\beta$ 40.

The traditional amyloid hypothesis remains controversial, mainly because spatial and temporal patterns of amyloid deposition (mostly in the form of senile plaques consisting of fibrillar A $\beta$ ) do not correlate very well with the clinical degree of dementia in Alzheimer disease. In contrast, cognitive decline correlates very well with synapse loss<sup>6</sup>. This is particularly interesting in light of studies that strongly implicate non-fibrillar A $\beta$  oligomers in disrupting synaptic function. For example, synaptic perturbations, including impaired LTP, are observed in APP-V717 (PD-APP) mutant transgenic mice before the development of A $\beta$  deposits<sup>7</sup>. In addition, non-fibrillar, low molecular weight A $\beta$  oligomers block LTP in brain slices<sup>8</sup> and, *in vivo*, in PD-APP mice<sup>9</sup>. Soluble A $\beta$  oligomers, including dimers and trimers, are both necessary and sufficient to transiently disrupt learned behavior in APP-Swedish ('APP<sub>Swe</sub>' or TG2576) transgenic mice<sup>10</sup>. Collectively, these data implicate soluble A $\beta$  oligomers (as opposed to fibrillar  $\beta$ -amyloid deposits, such as senile plaques) in promoting 'synaptotoxicity' and ensuing neurodegeneration in Alzheimer disease. These findings, together with the strong correlation of synapse loss with degree of clinical dementia in Alzheimer disease, suggest that the original amyloid hypothesis may be in need of revision to a synaptic A $\beta$  hypothesis, underscoring the role of pre-fibrillar A $\beta$  oligomers in Alzheimer disease pathogenesis, particularly at synapses. The role of A $\beta$  oligomers in Alzheimer disease pathology has been further bolstered by the finding that auto-antibodies to small oligomeric cross-linked A $\beta$  peptides are selectively depleted in Alzheimer disease plasma<sup>11</sup>.

Researchers have only recently begun to address the mechanism by which A $\beta$  oligomers impair synaptic function. These studies have included attempts to identify the cell surface receptors and signaling pathways mediating A $\beta$ -induced synaptotoxicity. For example, A $\beta$ 42 can inhibit presynaptic nicotinic acetylcholine receptors (nAChR) and evoke changes in presynaptic Ca<sup>2+</sup> levels in rat hippocampus and neocortex<sup>12</sup>. Given that only picomolar concentrations of A $\beta$ 42 were effective in those experiments, the inhibitory action of A $\beta$ 42 was postulated to be the result of competing with nicotine to prevent it from stimulating the receptors. The effects were sensitive to  $\alpha$ -bungarotoxin and other agents, specifically implicating  $\alpha$ 7-nAChRs in the pathway by which A $\beta$ 42 disrupts synaptic plasticity.

Now, in a major leap forward, Snyder *et al.*<sup>3</sup> report a very elegant set of experiments elucidating a potential pathway by which A $\beta$  reduces glutamatergic transmission and NMDA receptor-dependent LTP. In their study, the application of A $\beta$ 42 to cultured cortical neurons promoted endocytosis of NMDA receptors, effectively reducing the density of NMDA receptors at synapses. In agreement with this result, reduced levels of surface NMDA receptors were observed on neurons in APP<sub>Swe</sub> (TG2576) transgenic mice that overproduce A $\beta$ 42. A $\beta$ 42 also engendered a rapid and persistent depression of NMDA-evoked currents. Delving further into the mechanism by which A $\beta$ 42 induces endocytosis of NMDA receptors, Snyder *et al.*<sup>3</sup> found that  $\alpha$ 7 nicotinic receptors, protein phosphatase 2B (PP2B; calcineurin) and the cytosolic form of the tyrosine phosphatase 'striatal enriched phosphatase' (STEP<sub>46</sub>) were required in the synaptotoxic pathway (Fig. 1). A $\beta$ 42, derived from processing of APP, enters into the synaptic cleft and binds the  $\alpha$ 7-nicotinic receptor, leading to

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