

convey reward-related signals<sup>11</sup>, and their activity can strongly modulate cortico-striatal connections<sup>12</sup>. It has been hypothesized that monkeys might change their threshold to optimize reward rate in the motion discrimination task<sup>3</sup>. Reward-dependent plasticity in these connections could be responsible for altering the decision threshold to perform this optimization. It remains to be seen whether the mechanism hypothesized by Lo and Wang is actually responsible for flexible and optimal decision thresholds.

Although it is clear that a decision threshold is pivotal in a reaction-time setting, this basic mechanism need not be limited to situations where an explicit time pressure exists. Even when the environment establishes a definite epoch for decision making, people often reach decisions based on a limited amount of information. This is why the first five minutes of a job interview are so important. If you do not make a good first impression, you may not be deemed worthy of further consideration. It might seem like a poor strategy not to use all the available evidence for making a decision in these types of situations. However, there are costs associated with further deliberation, including the inability to consider other decisions during that time. Therefore, applying a decision threshold could be important even when there is no explicit time pressure.

This raises the intriguing possibility that the use of a decision threshold is ubiquitous in higher brain function. Threshold mechanisms

are involved in target selection and saccade initiation<sup>13</sup>. A less obvious role for these mechanisms might be for use in memory retrieval. The idea of using bounded accumulation to understand memory retrieval receives support from psychological measurements of memory retrieval time<sup>14</sup>, suggesting that similar mechanisms may operate in memory and perceptual decisions<sup>15</sup>. A decision threshold might also be useful for the perception of temporal intervals, which are essential for learning relationships between observations, inferring causes and consequences, and anticipating events. Indeed a 'done now' signal may be useful for flexible sequencing of behavior. This signal is what the brain needs to operate on a time frame that transcends reflexivity. It requires neurons that can detect the threshold crossing without being strongly tied to a motor response, such as the caudate neurons in the model.

Is there enough realism in Lo and Wang's model to lend credibility to their insights? Therein lies the art of computational neuroscience. In our view, the computational modeling of Lo and Wang should be viewed as an important step in the march from principle to circuits and cells. It is a critical part of the translational pathway from principles of systems neuroscience to a biological level of understanding that will produce treatments for disorders of higher function. The path in this case travels from mathematical formulations of the decision process to its neural correlates in

the brain and the uncovering of computational mechanisms like integration and threshold crossings. The next step is to understand how these operations are achieved by real neural circuits. This is an exciting area that will require experiments motivated in part by the type of quasi-realistic modeling of simplified neural circuits exemplified by the new paper. This balance between simplification and mechanistic insight may be of the very same nature as the balance between speed and accuracy in simple decisions. As Lo and Wang conclude, there is wisdom in preserving flexibility in this balance.

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## The ebb and flow of attention in the human brain

Trey Hedden & John D E Gabrieli

**Lapses in attention can impair performance independent of the task. A new imaging study reports that reduced activity in prefrontal attentional control regions at the beginning of a trial predicts longer reaction times.**

In 1988, world champion speed skater Dan Jansen entered the Winter Olympics as a heavy favorite, but—perhaps preoccupied by the recent death of his sister—he slipped and fell in both the 500- and 1,000-meter events. In the next Winter Olympics, a small stumble left Jansen in fourth place, a third of a second behind the gold medal winner. Making a final

attempt for an Olympic medal in 1994, Jansen lost his balance and managed only eighth place in the 500 meters, an event in which he was the world record holder. Yet in the 1,000 meters, Jansen not only won the gold medal, but also broke the world record in the process.

Although the stakes are rarely so high, performance in everyday tasks can vary tremendously within the same individual. One moment we are efficient; the next moment we have a lapse of attention and make an error. One source of variability is the occasional lapses of attention that can be caused by multitasking, daydreaming or an inability to block out distracting thoughts or environmental stimuli. Using functional magnetic reso-

nance imaging (fMRI), in this issue, Weissman and colleagues have begun to illuminate the neural correlates of such lapses in attention on a moment-to-moment time scale<sup>1</sup>.

The authors used a straightforward, yet sophisticated, technique. They measured localized blood flow with event-related fMRI during individual trials, and then correlated it with how long participants took to respond to each trial ('reaction time'). Participants identified the letters H or S in the global/local task<sup>2</sup>, in which a large (global) letter is made up of smaller (local) letters, and pressed one button for S and another button for H. Sometimes they had to identify the global letter, and other times the local letters. The global

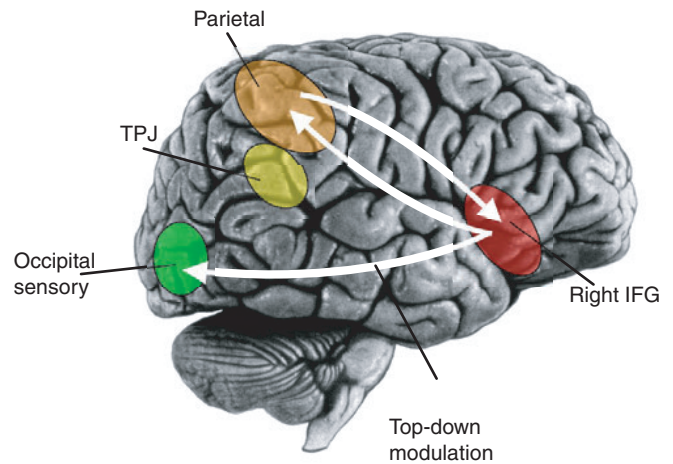
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and local letters sometimes matched (a large H made out of small Hs) and therefore indicated the same response (congruent stimuli), and other times mismatched (a large H made out of small Ss), in which case the global and local information indicated conflicting responses (incongruent stimuli). Thus, participants had to focus attention on either the large or the small letters, and sometimes had to inhibit conflicting responses to incongruent stimuli. Although error rates were small, there was enough variability in the distribution of reaction times to compare differential brain activation for trials with relatively fast reaction times (focused attention trials) versus trials with relatively slow reaction times (lapsed attention trials). The assumption made by the authors is that when participants were slower to respond correctly, this slowing was due to irrelevant thoughts or momentary inattention that was eventually corrected by an attentional control system.

Attentional control processes, sometimes referred to as executive functions, are associated with a network within the prefrontal and parietal lobes<sup>3–6</sup>. This network is thought to send top-down modulatory signals to posterior sensory regions to bias sensory processing in favor of task-relevant information<sup>7,8</sup>. The current study demonstrates that lapses of attention can be revealing about the operation of attentional control processes (Fig. 1). First, slower reaction times (ascribed to lapses of attention) were associated with reduced activation in prefrontal regions, including the right inferior frontal gyrus (IFG) and the anterior cingulate cortex (ACC). Critically, this reduced activation occurred before the stimuli were presented. Hence, when activation within attentional control regions in the prefrontal cortex decreased before stimulus presentation, the associated lapse in attention led to slower responses. These prefrontal regions seem to modulate how well focused people are in the moment just before they have to perform.

Brain activation during stimulus presentation and response execution could also be linked to attention via response speed. Lapses of attention were associated with decreases in sensory-related processing in the inferior occipital cortex, so that on trials with slower reaction times, both prefrontal and occipital regions showed reduced activation. The authors interpret this result as evidence that lapses of attention prevent prefrontal control regions from efficiently modulating sensory processing of behaviorally relevant stimuli. The association between slower response times and reduced activation in the occipital cortex only held true for congruent stimuli. For incongruent stimuli (in which global and local letters lead to opposing responses), activation did not vary with response time. This indicates

**Figure 1** Lateral view of the right hemisphere, highlighting some of the cortical regions associated with focused and lapsed attention. Arrows indicate reciprocal functional connections between prefrontal and parietal regions, and top-down modulation of occipital sensory regions by the prefrontal cortex. IFG, right inferior frontal gyrus; TPJ, temporal-parietal junction.



that the attentional modulation of sensory processing is relatively general and moves the focus of attention to the location of the stimulus as a whole. It would be interesting to investigate whether the global precedence effect (in which participants are faster to respond when directed to the global letter than to the local letters, as observed in this study) interacts with congruence. That is, when directed toward the local letter, can attentional control reduce activation related to the sensory precedence of an incongruent, and therefore distracting, global letter?

Although the time course analyses seem to indicate that the ACC reduction associated with slower reaction times begins slightly before that in the occipital cortex, the relative sluggishness of the hemodynamic response and the assumptions about the delay associated with task-related processing make the determination of order of onset difficult in fMRI. Future studies could examine correlations between activations in prefrontal and occipital regions to further strengthen the conclusion that reduced prefrontal activation leads to reduced sensory activation. Other methods with superior temporal resolution, such as magnetoencephalography, may also help pinpoint the temporal relationships among brain processes lapsing in attention. These findings suggest that lack of prefrontally mediated attentional focus diminishes the quality of sensory processing of a target stimulus.

This study next revealed two brain mechanisms that may help people recover from a lapse in attention. First, during stimulus presentation, the prefrontal and parietal regions known to mediate the control of attention showed greater activation during slower trials. This could be interpreted as reflecting extra attention that had to be paid to compensate for reduced prestimulus focus in prefrontal cortex and reduced sensory

processing of the stimulus in occipital cortex. The compensatory attention was effective in avoiding errors, but could not prevent slower performance. The same prefrontal areas implicated in focusing attention before stimulus presentation had greater activation during stimulation following a lapse, showing that ‘a stitch in time saves nine’ is a good proverb to describe brain activation too. Parietal cortex showed extensive activation for slower trials, but was not implicated in attentional control before the stimulus. The second mechanism is even more intriguing, as it seems to allow a lesson learned about a lapse of attention on the present trial to be applied to the focus of attention on the following trial. Increased activation for the current trial in the right IFG and the right temporal-parietal junction (another region often implicated in the prefrontal-parietal attentional control network<sup>9</sup>) was associated with faster responding in the following trial. The authors interpret this latter result as an indication that the right IFG and temporal-parietal junction are involved in compensatory reorientation of attention after a lapse has occurred, a reorientation that translates the lapse of attention from a current trial to enhanced focus of attention on the next trial.

Finally, this study investigated the relationship of lapses of attention to activation within two anticorrelated brain networks: the prefrontal-parietal network that showed greater activation during slow trials, and a ‘default’ network of the brain, including the posterior cingulate cortex, ventromedial prefrontal cortex, precuneus and temporal cortex, which is most activated during task-irrelevant resting baselines<sup>10</sup>. This default network is thought to reflect a focus on internal thoughts and feelings, rather than on external percepts and responses<sup>10,11</sup>. In the

present study<sup>1</sup>, deactivation within the default network decreased with slower response times, and presumably reflected a switch from internally to externally focused attention. The association of slower responses with greater default deactivation suggests that slower responses are associated with task-irrelevant processing during lapses of attention, rather than merely inefficient activation of the attentional control network. Lapses of attention may therefore involve the failure to switch from a focus on internal feelings and thoughts to the external task at hand. Functional connectivity analyses could be used to bolster this finding, as a lapse of attention should lead to both decreased activation in the prefrontal-parietal control network and increased deactivation in the default network<sup>12,13</sup>. The current results, however,

point to the necessity of understanding how multiple neural networks may compete for the internal versus external focus of attention.

Patients with right-hemisphere lesions are impaired on tasks of vigilance, with slowed response times on even simple tasks. Consistent with these data, activations associated with pre-stimulus focus and reorientation after a lapse of attention in the present study<sup>1</sup> were all right lateralized. This work moves forward our understanding of the specific neural mechanisms that modulate the waxing and waning of human attention to the external world. In addition to helping understand how people vary from focus to distraction, these findings may be useful in understanding the brain basis of disorders of attention, including attention-deficit hyperactivity disorder (ADHD) and deficits of attention after stroke or during aging.

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## Nitro-PDI incites toxic waste accumulation

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**In Parkinson disease and related disorders, nitric oxide may disable PDI, an enzyme critical for proper protein folding in the endoplasmic reticulum, resulting in the accumulation of damaged proteins and eventually neuronal death.**

Imagine your local garbage company going on strike. Pretty soon, the city would be clogged with trash, which would disrupt daily life. The situation is similar inside cells; misfolded proteins are degraded by specific machinery in the cell and the components recycled. When this 'garbage' removal and recycling process goes awry, the consequences can be deadly. Neurons that succumb in Parkinson disease and Alzheimer disease contain abnormal accumulations of misfolded and aggregated proteins:  $\alpha$ -synuclein and synphilin-1 in Parkinson disease, and amyloid- $\beta$  peptide and tau in Alzheimer disease<sup>1</sup>. The proteins are synthesized and folded in the endoplasmic reticulum (ER), and, when misfolded or oxidatively damaged, are normally tagged for degradation in the proteasome by the addition of a ubiquitin group.

A common dogma is that in Parkinson disease and Alzheimer disease, cellular stress (metabolic, oxidative or ionic) can interfere with the proper folding of proteins and increase their susceptibility to damage, and can also impair proteasome function<sup>2,3</sup>. Although perturbed cellular  $\text{Ca}^{2+}$  homeostasis and oxi-

native stress may contribute to ER and proteasome dysfunction, the underlying molecular mechanism is unknown. Now Uehara and colleagues<sup>4</sup>, in a recent paper in *Nature*, show that a nitric oxide (NO)-mediated modification of protein disulfide isomerase (PDI, a specific ER protein) is critical for proper protein folding and that this modification is pivotal to the pathogenesis of Parkinson disease.

NO is a highly diffusible gas that acts as an intra- and intercellular messenger. It is implicated in a wide range of adaptive structural and functional changes in the nervous system, including synaptic plasticity<sup>5</sup>. NO is produced in response to  $\text{Ca}^{2+}$  influx or release from intracellular stores;  $\text{Ca}^{2+}$  binds to calmodulin, which then activates NO synthase (NOS; **Fig. 1**). Transient moderate levels of NO production regulate a variety of physiological processes in neurons by directly or indirectly inducing post-translational modifications of proteins. NO can interact with sulphydryl groups in a reaction called nitrosylation; such a modification of NMDA glutamate receptors provides a feedback mechanism to reduce  $\text{Ca}^{2+}$  influx through the NMDA receptor channel<sup>6</sup>. Alternatively, NO activates soluble guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), which then activates a kinase (cGMP-dependent protein kinase) that phosphorylates various

protein substrates, including those involved in synaptic plasticity and cell survival. However, prolonged production of large amounts of NO can wreak havoc on cellular macromolecules, a process believed to contribute to the death of neurons in various disorders, including stroke and Parkinson disease<sup>7</sup>. NO damages cells by interacting with a superoxide anion radical to produce the nitrogen radical peroxynitrite. Peroxynitrite promotes membrane lipid peroxidation and can also damage proteins by nitrating tyrosine residues. Increasing evidence also points to a role for NO in protein garbage accumulation and in the degeneration of dopaminergic neurons in Parkinson disease; for example, parkin, an E3 ubiquitin ligase, which is associated with early-onset Parkinson disease, is S-nitrosylated in animal models of the disease, which then causes the accumulation of parkin substrates such as  $\alpha$ -synuclein<sup>8</sup>.

To determine the consequences of S-nitrosylation of PDI in neurons, Uehara *et al.* exposed cultured cerebrocortical neurons to a cytotoxic concentration of NMDA to induce  $\text{Ca}^{2+}$  influx and NO production. Under these conditions, PDI was S-nitrosylated in a NO-dependent manner, and there was a large increase in the amount of polyubiquitinated proteins in the neurons, consistent with increased accumulation of misfolded proteins. PDI is normally upregulated in response

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