Neural mechanisms of attention and control: losing our inhibitions?

Sander Nieuwenhuis & Nick Yeung

How are we able to focus our attention on the task at hand while ignoring myriad distractions? An elegant neuroimaging study in this issue finds that, contrary to a widely held view, the prefrontal cortex implements attentional control by amplifying task-relevant information, rather than by inhibiting distracting stimuli.

As you read this article, you focus your attention on the page in front of you and you try (we hope) to think about the meaning of these words. All around you are myriad distractions: the habitually loud conversation of your colleague across the hall, your email program indicating you have new mail and the beckoning sunshine outside your window. How are we able to focus our attention on the task at hand and ignore these distractions? What are the neural mechanisms involved? Egner and Hirsch[1] present important new evidence relevant to these questions, using brain imaging methods to look directly at cortical representations of attended and ignored information, and at neural activity correlated with this attentional focusing. Specifically, their research addresses a fundamental question about how attentional focusing is implemented in the brain. Does attention operate by amplifying relevant information, by inhibiting distracting information or both?

A widely held view is that a critical function in the brain is the suppression of cognitive processing that is irrelevant to the current task[2]. Another view proposes that regions within prefrontal cortex (PFC) may be specialized for supporting inhibition of irrelevant stimuli and inappropriate responses[3]. The concept of inhibition provides an attractively simple account of the complex and wide-ranging cognitive deficits observed following damage to the frontal lobes: failing to inhibit distracting information or inappropriate responses would impair all but the simplest cognitive processes and would be expected to have particularly strong impact on higher-level cognitive processes of flexible planning, task switching, problem solving and decision making—the kinds of tasks classically affected by frontal damage[4]. According to this view, PFC-guided attention may operate primarily (or even exclusively) by suppressing the processing of irrelevant information.

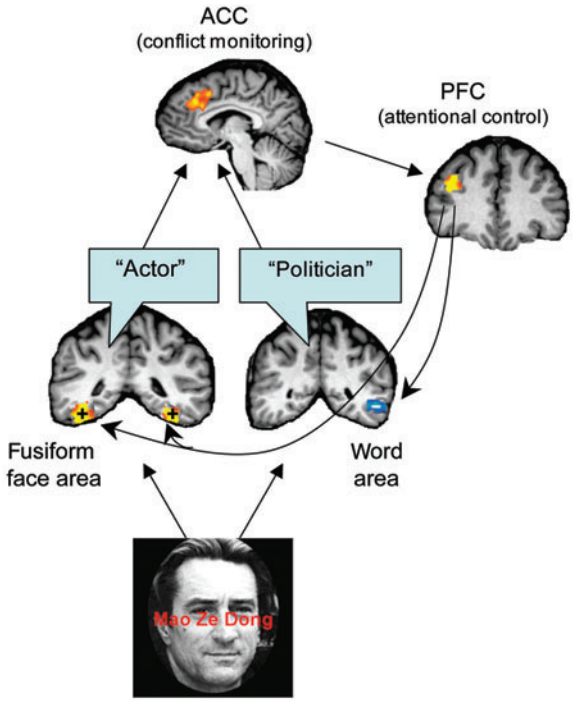

Figure 1 Possible attentional functions of prefrontal cortex (PFC) in the task used by Egner and Hirsch[1]. On this example trial, participants are required to classify the face as that of an actor or a politician and to ignore the superimposed written name. The fusiform face area (FFA) recognizes Robert de Niro, resulting in a tendency to respond "actor". However, the automatic processing of the name Mao Ze Dong by word-processing areas tends to activate the conflicting response "politician", thereby causing interference in the choice process. The PFC could resolve this stimulus-induced conflict either by inhibiting task-irrelevant representations in word processing areas or by amplifying task-relevant representations in the FFA. The results of Egner and Hirsch provide strong support for amplification as the primary means by which PFC exerts attentional control. Also shown is the putative link between a conflict monitoring system in anterior cingulate cortex (ACC) and the attentional control system in PFC. This conflict-control loop is thought[15] to mediate the conflict-adaptation effects exploited by Egner and Hirsch to vary participants' levels of attentional focus.

However, the idea that inhibition is a principal control function of the PFC has not gone unchallenged. First, computational modeling studies show that PFC-guided amplification of task-relevant information may be sufficient to account for behavioral effects of frontal damage that, at a phenomenological level, seem to require inhibition[5,6]. Second, and more generally, it has been questioned whether inhibition, as used in the present

Sander Nieuwenhuis is at the Department of Cognitive Psychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands. Nick Yeung is at the Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA.
e-mail: stn20@dds.nl or nyeung@cmu.edu.

context, is a useful explanatory concept. To update Richard Gregory's famous example[7], a short-circuit in your desktop computer might conceivably cause random blotches of color to appear on your monitor, but you would not infer that the damaged region usually functions as a "color inhibition" system. Instead, it would be more accurate to conclude that the damaged region—the video card—previously performed detailed, sophisticated computations that resulted in the delivery of meaningful, rather than random, patterns of color to your screen. By analogy, although PFC damage is often followed by a reduced ability to inhibit unwanted thoughts and behaviors, it does not logically follow that one function of the PFC is 'inhibition'; instead, it might be more appropriate to understand PFC function in terms of the complex computations that it usually performs to support effective, goal-directed thought and action.

Egner and Hirsch's new study complements these theoretical challenges by attempting to empirically distinguish between amplification and inhibition as the mechanism of attention. To address this issue, the authors used a modified version of the Stroop task. In the standard Stroop task, participants are required to name the ink color of a printed color word. Performance is typically worse if word and color are incongruent (for example, RED printed in green ink) than when the two attributes are congruent (RED printed in red ink). Critically, participants could, in principle, perform the Stroop task successfully by amplifying relevant information (ink color), inhibiting irrelevant information (word) or both. To determine which approach is actually implemented in the brain, Egner and Hirsch used a variant of the Stroop task in which subjects responded to superimposed faces and words (rather than to colors and words). They then used brain imaging to measure activity in the fusiform face area (FFA), an extrastriate visual area activated by face stimuli[8], to provide an index of the degree to which face stimuli are processed when they are relevant or irrelevant to the task at hand.

Participants in the study were presented with a series of stimuli, each composed of a face of a familiar actor or politician with the written name of another actor or politician superimposed (**Fig. 1**). For half of the experiment, participants were instructed to attend to the face and to ignore the written name; in the other half, they attended to the name and ignored the face. In both cases, their task was to indicate with a button press whether the relevant attribute (face or name) belonged to an actor or a politician. The face and name could be associated with the same (congruent) response or with a different (incongruent) response. Thus, on congruent trials (for example, an actor's face with another actor's name), unintended processing of the irrelevant attribute would tend to activate the same response as that required for the relevant attribute. In contrast, on incongruent trials (an actor's face with a politician's name, or vice versa), unintended processing of the irrelevant attribute would tend to activate the incorrect response, inducing processing conflict as in typical Stroop designs (**Fig. 1**). Of particular interest to Egner and Hirsch were the well-documented 'conflict adaptation' effects that are observed in the Stroop task: levels of attention are generally increased on trials immediately following incongruent (conflicting) trials, as demonstrated by improved performance on such trials[9,10]. Thus, by classifying trials according to whether the previous trial was congruent or incongruent, Egner and Hirsch were able to distinguish between physically identical trials depending on whether they were associated with low or high attention.

Using this new design, Egner and Hirsch were able to contrast the following critical predictions. If attention involves inhibition of task-irrelevant information, then one should observe decreased FFA activation under conditions of high attentional focus on the printed names (that is, when faces are irrelevant). Conversely, if attention involves amplification of task-relevant information, then one should observe increased FFA activation under conditions of high attentional control in the face-relevant task condition. The results were clear-cut: the neural response of the FFA to faces varied with the degree of attention paid to the faces, but only when faces served as target stimuli and not when they served as distracting stimuli. That is, when participants were responding to faces, heightened attention led to increased FFA activity. However, when participants were responding to words, heightened attention did not lead to a decrease in FFA activity. Thus, the results showed clear evidence for amplification of task-relevant information, but no evidence for inhibition of task-irrelevant information.

Extending this analysis, Egner and Hirsch found evidence that the observed amplification effects in the FFA were uniquely mediated by PFC. The correlation between the activity patterns in the FFA and right lateral PFC (but not in other control areas) increased reliably when participants had to classify the faces under conditions of heightened attention (previous trial incongruent), as opposed to when faces were distractors. These context-dependent increments in functional connectivity between the PFC and FFA are consistent with the proposed role for PFC in guiding attention in posterior brain areas[11,12]. Notably, the observed activation focus in PFC overlaps with regions previously implicated in inhibitory function[3]. Thus, taken together, the results present a strong challenge to the theory that PFC-guided attention operates primarily through the inhibition of irrelevant stimulus information.

A key question for future research is whether corresponding principles of attentional amplification operate in the selection of task-relevant responses, or whether inhibitory processes are more critical in action selection than perceptual selection. Computational considerations suggest that inhibition may be more feasible in systems responsible for the control of movement than in systems responsible for processing perceptual stimuli. Given the massive range of distracting stimuli that could, in principle, appear in any particular situation, it may simply be impractical to predict and inhibit all possible perceptual distractions. In contrast, the range of available responses is typically far more tightly constrained, and thus inhibition of incorrect actions may be a computationally feasible strategy. Existing evidence suggests a role for inhibitory processes in response selection[13], and future studies might profitably extend Egner and Hirsch's clever methodology to investigate this hypothesis further. Specifically, such studies might address the question of whether focused attention reduces activation of the cortical representations of irrelevant responses.

Looking beyond these questions of amplification versus inhibition in perceptual and response selection, the broader question remains of how PFC 'knows' or 'decides' which information is currently relevant. To return to Gregory's instructive example[7], we would learn little from a theory that merely states that the video card of a computer promotes correct displays or inhibit incorrect ones, with no explanation of the circuits and computations that support this function. Correspondingly, our theories of PFC functioning will remain incomplete to the extent that they focus solely on whether this region serves to amplify task-relevant information or inhibit distractions. Instead, the ultimate goal of research in this area must be to understand the nature of the computations within PFC that might support these attentional functions[14]. Answering this deeper question will require the development of detailed computational theories that are capable of explaining how PFC comes to represent task-relevant information, and the development of correspondingly sophisticated neuroimaging methods capable of evaluating the predictions of these theories.

1. Egner, T. & Hirsch, J. *Nat. Neurosci.* **8**, 1784–1790

(2005).
2. Dagenbach, D. & Carr, T.H. (eds.) *Inhibitory Processes in Attention, Memory, and Language.* (Academic, San Diego, 1994).
3. Aron, A.R., Robbins, T.W. & Poldrack, R.A. *Trends Cogn. Sci.* **8**, 170–177 (2004).
4. Stuss, D.T. & Benson, D.F. *Psychol. Bull.* **95**, 3–28 (1984).
5. Kimberg, D. & Farah, M. *J. Exp. Psychol. Gen.* **122**, 411–438 (1993).
6. Cohen, J.D. & Servan-Schreiber, D. *Psychol. Rev.* **99**, 45–77 (1992).
7. Gregory R.L. in *Current Problems in Animal Behaviour* (eds. Thorpe, W.H. & Zangwill, O.L.) 547–565 (Cambridge University Press, Cambridge, UK, 1961).
8. Kanwisher, N., McDermott, J. & Chun, M.M. *J. Neurosci.* **17**, 4302–4311 (1997).
9. Gratton, G., Coles, M.G. & Donchin, E. *J. Exp. Psychol. Gen.* **121**, 480–506 (1992).
10. Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S. & Cohen, J.D. *Psychol. Rev.* **108**, 624–652 (2001).
11. Duncan, J. *Nat. Rev. Neurosci.* **2**, 820–829 (2001).
12. Miller, E.K. & Cohen, J.D. *Annu. Rev. Neurosci.* **24**, 167–202 (2001).
13. Burle, B., Vidal, F., Tandonnet, C. & Hasbroucq, T. *Brain Cogn.* **56**, 153–164 (2004).
14. Rougier, N.P., Noelle, D.C., Braver, T.S., Cohen, J.D. & O'Reilly, R.C. *Proc. Natl. Acad. Sci. USA* **102**, 7338–7343 (2005).
15. Kerns, J.G. *et al. Science* **303**, 1023–1026 (2004).

Flipping the switch from electrical to chemical communication

Karl Kandler & Edda Thiels

Immature neurons in many brain regions are electrically coupled through gap junctions, which are lost as chemical synaptic transmission matures. This developmental uncoupling is now shown to require NMDA receptor activation.

Early in brain development, neurons communicate with one another, even before synapses have formed. At this stage, electrical coupling through gap junctions is widespread and may contribute to neuronal and circuit maturation[1]. A transition from electrical to chemical synapses has been documented for multiple brain areas, but the cues and mechanisms that mediate the switch have remained elusive. In this issue, Arumugam and colleagues[2] provide exciting new insight into the signaling pathways involved in this developmental regulation of gap-junction coupling in hypothalamic neurons.

Gap junctions are specialized cell-cell contacts composed of membrane channels that join the cytosol of neighboring cells, allowing electrical current to flow between them[3]. Because they are permeable to small molecules (≤1 kDa), such as the second messengers inositol 1,4,5-triphosphate (IP_3) and cyclic AMP (cAMP), gap junctions provide a means to coordinate not only electrical activity but also metabolic and signaling processes in coupled cells[4]. Although neuronal gap junction coupling is not exclusive to the immature brain, in mammals it is most extensive and widespread before and during the time of synapse formation and occurs in many areas, including the retina, cortex, thalamus, brainstem and spinal cord[3]. Neurons joined by gap junctions form functional assemblies with coordinated patterns of spontaneous activity and changes in intracellular calcium levels[5]. These early gap junction–mediated activity patterns are thought to be important for neurogenesis, neuronal maturation and synaptogenesis.

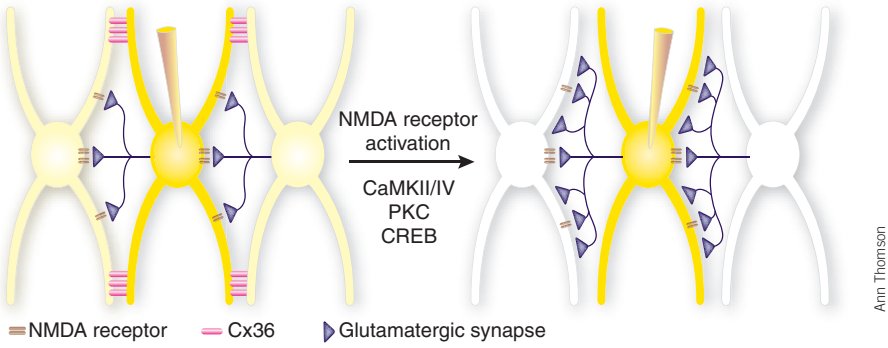

Figure 1 NMDA receptor–mediated uncoupling of developing hypothalamic neurons. During synaptic circuit development in the medial hypothalamus and many other brain regions, the primary mode of neuronal communication switches from one based on gap junctions (left) to one based on chemical synapses (right). Arumugam and colleagues[2] now show that downregulation of the neuronal gap-junction protein connexin36 (Cx36) and dye coupling (yellow) require activation of NMDA receptors, along with CaMKII/IV, PKC and CREB. In the intact brain, additional glutamatergic inputs are provided by other extrinsic sources.

Arumugam and colleagues examined developmental changes in gap junction coupling in magnocellular neurons of the rat hypothalamus. They measured expression levels of the neuronal connexin protein Cx36 and looked for functional gap junctions by assessing the ability of coupled neurons to pass small dyes or neuronal tracers between them (dye coupling). By both measures, they found that electrical coupling increases *in vivo* during the first two postnatal weeks and then decreases during the third and fourth weeks, a time of intense synapse formation (**Fig. 1**).

Blocking NMDA receptors attenuates the loss of gap junction coupling in developing spinal motoneurons[6], so the authors asked whether signaling through NMDA receptors might be important for the developmental decrease in coupling in the hypothalamus. They chronically blocked NMDA receptors *in vivo* by injecting newborn rats daily with the antagonist dizocilpine (MK-801), and they measured gap-junction coupling two and four weeks later. NMDA receptor blockade had no effect on the initial increase in cou-

Karl Kandler and Edda Thiels are in the Department of Neurobiology and Center for the Neuronal Basis of Cognition, University of Pittsburgh School of Medicine, 3500 Terrace Street, Pittsburgh, Pennsylvania 15261, USA.
email: kkarl@neurobio.pitt.edu or thiels@neurobio.pitt.edu