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Contrasting network and modular perspectives on inhibitory control

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A prominent theory proposes that the right inferior frontal cortex of the human brain houses a dedicated region for motor response inhibition. However, there is growing evidence to support the view that this inhibitory control hypothesis is incorrect. Here, we discuss evidence in favour of our alternative hypothesis, which states that response inhibition is one example of a broader class of control processes that are supported by the same set of frontoparietal networks. These domain-general networks exert control by modulating local lateral inhibition processes, which occur ubiquitously throughout the cortex. We propose that to fully understand the neural basis of behavioural control requires a more holistic approach that considers how common network mechanisms support diverse cognitive processes.

Modular versus network approaches to understanding cognition

A major focus of contemporary neuroscience has been to map the functional architecture of the human brain by localising distinct cognitive processes to dedicated brain regions and their connection pathways. In the case of cognitive control, this modular approach has generated valuable markers for clinical research and assessment; however, *en masse* the resultant theoretical models are problematic because they often assign putatively distinct cognitive processes to the same brain regions. Furthermore, they distract from the role of more widespread functional networks in cognition. This problem is particularly notable for domain-general brain regions, which activate in a coordinated manner during the performance of a variety of cognitive tasks. The ongoing debate regarding the neural mechanisms that underpin motor response inhibition is a prominent example of this issue.

The inhibitory control hypothesis

Response inhibition refers to the process by which routine, initiated, or otherwise prepotent motor actions are effortfully withheld or cancelled. Classic paradigms such as the Stop-Signal Task (SST; see Glossary) [1] and Go/No-Go Task (GNG) are used to investigate the neural mechanisms of response inhibition in healthy individuals and to assess disinhibition in disease states. Quantitatively, the performance of response inhibition tasks can be modelled as a horserace, in which Go and Stop processes compete to determine behaviour [2–4]. Traditional approaches to functional–anatomical mapping have provided evidence that the right inferior frontal gyrus (rIFG) and anterior insula (aIns) are critically involved in response inhibition tasks. For example, neuroimaging has shown increased activation in the rIFG/aIns when routine responses are cancelled during the SST [5,6]. Activation in these regions is abnormal in disease states that are characterised by disinhibition [7–10]. Similarly, acquired damage within the rIFG/aIns is associated with poor SST performance [11] (Box 1). On the basis of these results the inhibitory control hypothesis has been proposed (Figure 1A), which states that 'a specific executive function, response inhibition, can be localized to a discrete region of the PFC [prefrontal cortex]' [11,12] and that 'inhibition is localized to the rIFG alone' [12]. When infrequent, salient, or surprising stimuli are detected the inhibition module is proposed to rapidly activate the subthalamic nucleus (STN) via a hyperdirect pathway. The STN then inhibits ongoing motor processes [13–16]. A recently revised version of this hypothesis emphasises that these brain regions form a network; however, it continues to assert that the rIFG area is specialised for the implementation of inhibitory control [17]. This is a modular view because it proposes that a specific brain region and its connection pathways support a discrete cognitive function.

Glossary

Default mode network (DMN): is a set of brain regions that tend to activate together when an individual is either at rest or performing a routine task.
Go/No-Go Task (GNG): is a paradigm that is used to measure motor response inhibition. It involves omitting a routine response.
Independent component analysis (ICA): is a data-driven method for blind source localisation, that is, it may be used to estimate source signals from mixtures of those signals without ever being exposed to the sources individually. When applied to neuroimaging data, ICA generates spatial maps that may be interpreted as networks because they capture statistical dependencies of regional brain activations across time. It also outputs a time course for each component, which may be interpreted as the level to which each network is activated at each point in time.
Multiple demand cortex (MDC): is a set of brain regions that are activated across a particularly broad range of task contexts. It should not be considered a network as such, because the method that was used to define it did not include any analysis of connectivity across brain regions; therefore, it may consist of multiple distinct networks.
Stop-Signal Task (SST): is a cognitive paradigm that is commonly used to measure motor inhibition. It involves the cancellation of an initiated response.

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Box 1. Inhibitory control in disease

Understanding the neural basis of inhibitory control is an important clinical challenge because patients with a wide range of pathologies show disinhibited behaviour. Motor inhibition has been extensively studied clinically using paradigms such as the Stop-Signal Task and Go/No-Go Task, which have proven to be valuable tools for identifying the pathophysiological correlates of abnormal behaviour. Impairments in inhibition have often been associated with rIFG/aIns abnormalities. For example, patients with frontotemporal dementia show impairments associated with abnormalities in the structure and function of this region [8,9], and the activation of this region is sometimes attenuated in patients with behavioural disinhibition, the most prominent examples being attention deficit hyperactivity disorder (ADHD) and addictions [9]. Drugs that are used to treat ADHD also modulate rIFG/aIns activation levels [7], and focal lesions that involve the rIFG and surrounding structures are associated with impairments in SST performance [11], which can be part of a disabling dysexecutive syndrome [28]. In addition, the presence of traumatic axonal injury to the white matter connections of rIFG/aIns is a key cause to behavioural problems [73]. Following traumatic brain injury (TBI), impairments of response inhibition are correlated with damage to the connections of the cingulo-opercular network (salience network), and this damage predicts a failure to control linked activity that usually accompanies increased cognitive control [10]. These results suggest a causal influence of the cingulo-opercular network on other networks such as the DMN when increased cognitive control is required, and also illustrate the value of quantifying network interactions when defining the neural basis of cognitive control.

Response inhibition paradigms provide important markers for clinical research and assessment. However, the inhibitory control hypothesis is controversial. Several researchers have argued that the attempt to map a discrete inhibitory ability onto a dedicated brain region is misguided [18–26]. Here, we review evidence in support of our alternative hypothesis, which states that common neural mechanisms of domain-general frontoparietal networks underlie a variety of cognitive control processes, with response inhibition being one important example.

Is motor response inhibition a valid behavioural construct?

It remains unclear whether inhibition is a discrete aspect of human cognition. For example, models of frontal lobe function based on neuropsychological evidence often do not include inhibition as an explanatory phenomenon [27,28]. Furthermore, there is limited psychometric evidence to support the assumption that response inhibition is a discrete cognitive construct [29], although see [30,31]. Performances of tasks that require inhibition tend not to correlate strongly with each other [32] unless the tasks are very similar [33], indicating that that they depend on different abilities [34]. Relatedly, a wide range of

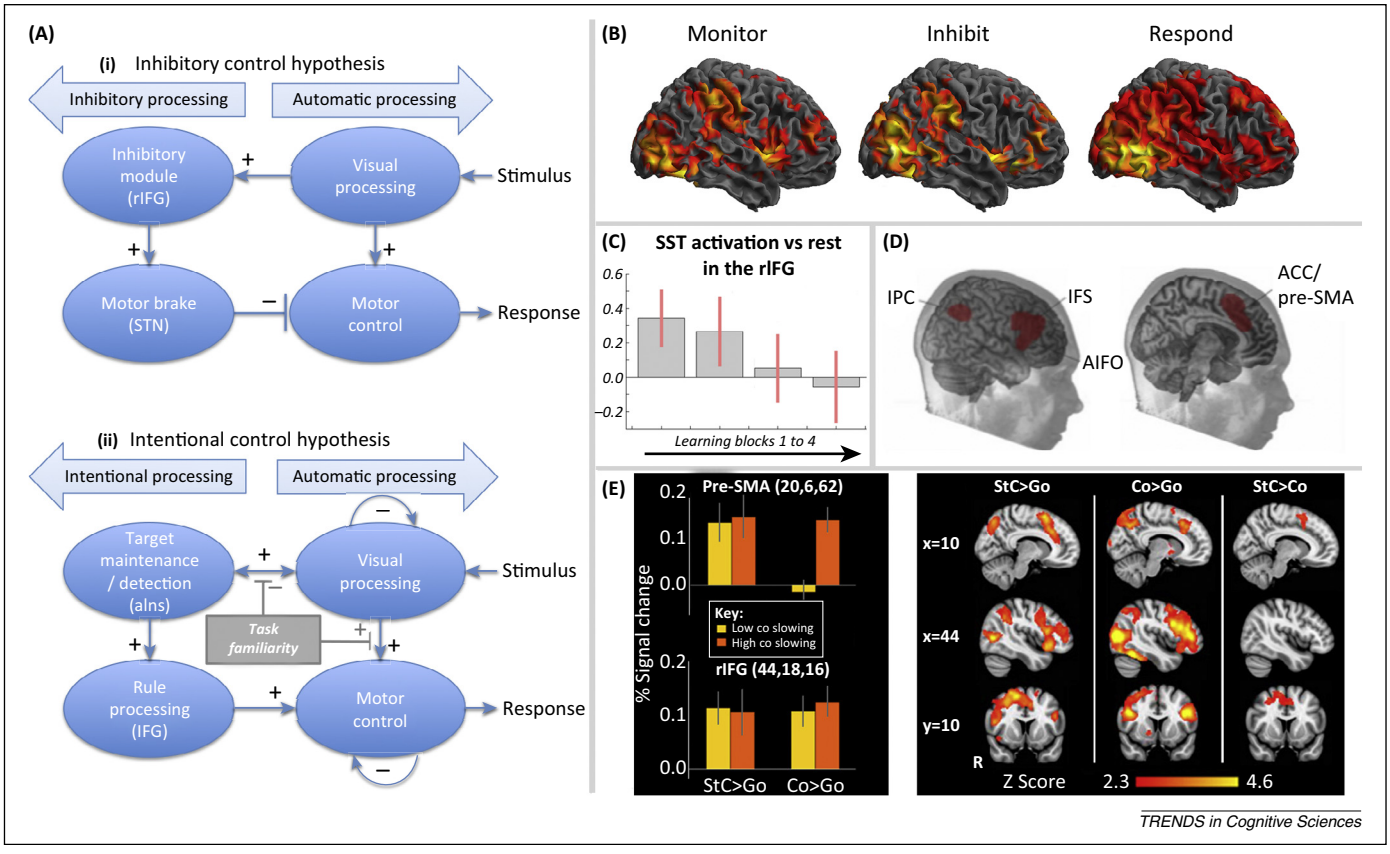

Figure 1. Theoretical models and empirical findings. **(A)** Alternative models of right inferior frontal gyrus/anterior insula (rIFG/aIns) function. (i) Inhibitory control hypothesis. (ii) Intentional processing hypothesis [41]. **(B)** The inhibition condition of the classic Stop-Signal Task (SST; centre) activates a set of brain regions including much of the rIFG [18]. Activation tends to be strongest within a network including the right aIns/inferior frontal operculum and anterior cingulate cortex. Similar activations are observed during other conditions including when targets are passively monitored (left) or elicit a planned motor response (right). **(C)** Task-related activation throughout the rIFG/aIns volume attenuates sharply as the SST becomes more familiar [18]. **(D)** A set of brain regions is commonly recruited under a very broad range of cognitive conditions, indicating general involvement in cognition [43]. Multiple-demand cortex (MDC) includes the anterior insula/inferior frontal operculum (AIFO), the inferior frontal sulcus (IFS), anterior cingulate cortex and pre-supplementary motor area (ACC/pre-SMA), and inferior parietal cortex (IPC). It overlaps heavily with the rIFG/aIns. **(E)** The presentation of 'Continue' trials that do not require stopping (Co) and the presentation of stop trials (StC) are both associated with rIFG/aIns activation (right). The contrast between stopping and continuing shows specific activation in the pre-supplementary motor area rather than the rIFG/aIns, which is unrelated to whether slowing is observed on subsequent trials (low and high Co trial slowing) [23].