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The role of default network deactivation in cognition and disease

Alan Anticevic[1,2,3], Michael W. Cole[4], John D. Murray[5,6], Philip R. Corlett[1,3], Xiao-Jing Wang[5,6,9], and John H. Krystal[1,2,3,7,8]

[1] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06510, USA
[2] National Institute on Alcohol Abuse and Alcoholism (NIAAA) Center for the Translational Neuroscience of Alcoholism (CTNA), Yale University, New Haven, CT 06519, USA
[3] Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, Department of Psychiatry, Yale University, New Haven, CT 06519, USA
[4] Department of Psychology, Washington University in St. Louis, St. Louis, MO, 63130, USA
[5] Department of Physics, Yale University, New Haven, CT 06520, USA
[6] Department of Neurobiology and Kavli Institute of Neuroscience, Yale University School of Medicine, New Haven, CT 06510, USA
[7] Psychiatry Services, Department of Psychiatry, Yale–New Haven Hospital, New Haven, CT 06510, USA
[8] Clinical Neuroscience Division, Veterans Affairs (VA) National Center for Post-Traumatic Stress Disorder (PTSD), VA Connecticut Healthcare System, West Haven, CT 06516, USA
[9] Center for Neural Science, New York University, 4 Washington Place, New York, NY 10003, USA

A considerable body of evidence has accumulated over recent years on the functions of the default-mode network (DMN) – a set of brain regions whose activity is high when the mind is not engaged in specific behavioral tasks and low during focused attention on the external environment. In this review, we focus on DMN suppression and its functional role in health and disease, summarizing evidence that spans several disciplines, including cognitive neuroscience, pharmacological neuroimaging, clinical neuroscience, and theoretical neuroscience. Collectively, this research highlights the functional relevance of DMN suppression for goal-directed cognition, possibly by reducing goal-irrelevant functions supported by the DMN (e.g., mind-wandering), and illustrates the functional significance of DMN suppression deficits in severe mental illness.

Brief history of the default-mode network (DMN)

Non-invasive neuroimaging, especially functional MRI (fMRI), has enabled the characterization of large-scale neural systems involved in human cognitive processes. A set of regions that has been identified via functional MRI (fMRI) and includes hubs around the anterior and posterior medial cortex, bilateral temporal lobes, as well as superior frontal and parietal cortices, is characterized by high activity when the mind is not engaged in specific behavioral tasks and low activity during focused attention on the external environment. These regions are collectively termed the 'default mode network' (DMN) [1,2]. Leading hypotheses regarding DMN function postulate its involvement in self-referential processing [3], which is typically in opposition to externally-oriented goal-directed cognition. Indeed, a distinctive feature of large-scale distributed neural networks, involving

Glossary

Anti-correlation: hypothesized as a fundamental property of large-scale neural systems whereby signals in a set of regions are negatively correlated with signals across another set of regions. This property has been identified and extensively replicated in resting-state neuroimaging studies of the BOLD signal [14]. Example anti-correlated systems are the default-mode network and the fronto-parietal control network [4].

Biophysically-based computational modeling: a branch of mathematical modeling of neural function based on biologically realistic principles of neural function [36].

Cingulo-opercular network (CON): a set of brain regions typically associated with maintenance of a cognitive set over an extended period during performance of externally focused cognitive tasks [100].

Default mode network (DMN): a set of brain regions identified as anti-correlated with the fronto-parietal regions typically associated with cognitive control and also deactivated during demanding cognitive tasks directed towards external stimuli [4]. DMN function has been largely linked to self-relevant, internally directed information processing.

Dorsal attention network (DAN): a set of brain regions typically associated with focused attention on external stimuli [99].

Externally-directed cognition: a set of cognitive processes that involve representing an external source of information in the service of a goal or action. A prototypical example is working memory [101,102], which involves encoding, manipulating, and retrieving information in the service of some goal, and is typically associated with activity in a distributed network encompassing fronto-parietal cortical regions. Overall, externally-directed cognitive processes are most typically associated with the FPCN, DAN, and CON [100,103].

Fronto-parietal control network (FPCN): a set of brain regions most typically implicated in executive, top-down cognitive control processes [47].

Internally-directed cognition: a set of cognitive processes that involve self-relevant information processing and spontaneous cognition, such as autobiographical memories. These processes are most typically associated with the DMN [26].

Ketamine: a non-competitive N-Methyl-D-aspartate (NMDA) receptor antagonist. Ketamine has been successfully used as a pharmacological model of schizophrenia because it transiently and safely invokes the cardinal symptoms associated with this illness. At doses used to produce psychotomimetic effects, ketamine is hypothesized to selectively block NMDA receptor conductances on inhibitory γ-Aminobutyric acid (GABA) expressing neurons [104]. Therefore, it is hypothesized that ketamine's effects may induce a state of cortical disinhibition, induced by a lack of inhibitory interneuron function [95].

Schizophrenia: a severe psychiatric syndrome that is most typically associated with symptoms such as delusions and hallucinations, but is also characterized by severe cognitive and affective disturbances [69].

the DMN, is functional 'antagonism' [4]. This antagonism was initially observed in task-based neuroimaging studies [5–10] that documented reduced activity across DMN regions during task conditions relative to a resting baseline. Given the nature of the fMRI signal and the potential sources of error, initial concerns arose that these deactivations were spurious [11,12]. Two decades later, there is compelling evidence that nearly every cognitive task involves the modulation of these specific deactivated regions [1,2]. Nonetheless, research in the field continues to emphasize the functional relevance of task-positive deflections in blood-oxygenation-level-dependent (BOLD) signals, perhaps due to the long-standing hypothesis that neural computations function mainly in the service of stimulus processing. Recently, the focus has shifted toward the functional importance of task-based deactivation [13]. In this review, we highlight recent findings that allow a deeper understanding of such task-based deactivations.

In parallel with task-based studies, there has been an explosion of research that exploits resting-state functional connectivity fMRI (rs-fcMRI) to characterize the large-scale organization of neural networks via analyses of temporally correlated BOLD signals [14]. Seminal work by Biswal, Fox, Greicius, Raichle and colleagues (among others) delineated an anti-correlated system-level organization of the human brain [4,14–16], illustrating that large-scale distributed networks exhibit negatively correlated signal over time (see Glossary). These rs-fcMRI investigations identified functional networks with striking correspondence to findings from task-induced deactivation studies [9], which have been extensively replicated across sites [14], within subjects [17,18], and across species [19]. This approach also delineated the DMN, complementing studies of cortical deactivation [1,2,20]. Although some controversies remain related to data analysis and potential sources of artifact [21,22], this anti-correlated organization appears to be a fundamental property of the mammalian central nervous system [23–25].

Building on these insights, there has been intensive study of the role of the DMN in higher cognition [26,27], with an emphasis on internally-directed thought [3]. Based on the anti-correlated architecture of the human brain, there is also increasing evidence that DMN deactivation is functionally relevant for cognitive performance. Here, we summarize evidence in support of the view that DMN suppression supports certain types of goal-directed cognitive processes [28]. We also detail recent evidence that demonstrates the functional relevance of failures in the relationship between task-positive and default networks in pharmacological models of psychoses and two exemplar psychiatric disorders, depression and schizophrenia. This review draws on multiple complementary approaches, including cognitive and systems neuroscience [29,30], electrophysiology [31], clinical neuroscience [32–35], computational neuroscience [36], and emerging pharmaco-fMRI studies [37,38].

Functional relevance of DMN deactivation: can the DMN signal be thought of as a source of distraction?

Before we discuss DMN deactivation, it is important to consider briefly what functions DMN activation might reflect [13]. As noted, the prevailing hypotheses suggest that it supports computations necessary for self-referential thought (i.e., internal mentation, daydreaming, etc. [1,2,39–44]; for a review, see [3,45]). The dominant proposal argues that the DMN may enable internal construction of mental models that support self-referential computations [3,42]. This set of functions seems to contrast with externally-oriented goal-directed thought. Thus, by its nature, DMN activity could conflict with computations necessary for externally-oriented processes, reflected in the divergent architecture of the DMN and control networks [23]. Although there is a general consensus that the DMN is anti-correlated with an external attention system (EAS) [46], it is important to briefly distinguish between several sub-networks that appear to be antagonistically coupled with the DMN [46,47]: (i) the dorsal attention network (DAN); (ii) the cingulo-opercular network (CON); (iii) and the fronto-parietal control network (FPCN). This distinction is important because there is evidence to suggest that the DMN and the FPCN network positively couple during certain self-referential, cognitively demanding tasks [28,48]. Nevertheless, here we focus on the role of DMN suppression in support of externally-oriented cognition.

Several studies have found that lower DMN activity is associated with more successful performance across a number of stimulus-driven goal-directed cognitive tasks [29,30,37,49,50]. Building on an earlier meta-analysis [9], Shulman and colleagues showed that a node proximal to the DMN (i.e., the right temporo-parietal junction, TPJ) was suppressed during correct performance of a demanding visual search task [50]. Deactivation of regions considered to be part of the DMN during encoding of novel information has been shown to enhance subsequent retrieval of learned information [30]. Similarly, less DMN suppression is associated with less efficient stimulus processing during attention lapses [51]. In addition, in a set of regions that overlap considerably with the DMN, a weaker signal during working memory (WM) encoding predicts better performance [29] (Figure 1a), a finding that was recently replicated [37]. These findings suggest that lower DMN activity on a trial-by-trial basis is associated with better cognitive performance, indicating that DMN suppression is functionally important. One hypothesis [13] suggests that such suppression during externally focused cognition might be necessary for adaptive disengagement from certain distracting cognitive operations, such as mind-wandering [40], possibly imposing a filter.

However, deactivations within parts of the DMN may depend on task characteristics [52], on the basis of which the DMN can be subdivided into nodes that deactivate indiscriminately ('the core DMN') and regions whose deactivation depends on task demands. This suggests functional heterogeneity [53], which in part challenges the hypothesis that that the entire DMN is suppressed in response to any cognitive demand. Notwithstanding the possibility of functional heterogeneity, the core observation of functionally relevant DMN suppression has been replicated and extended by a number of studies [49,52,54–56]. Animal electrophysiology adds converging evidence: non-human primates exhibit reliable suppression of neuronal
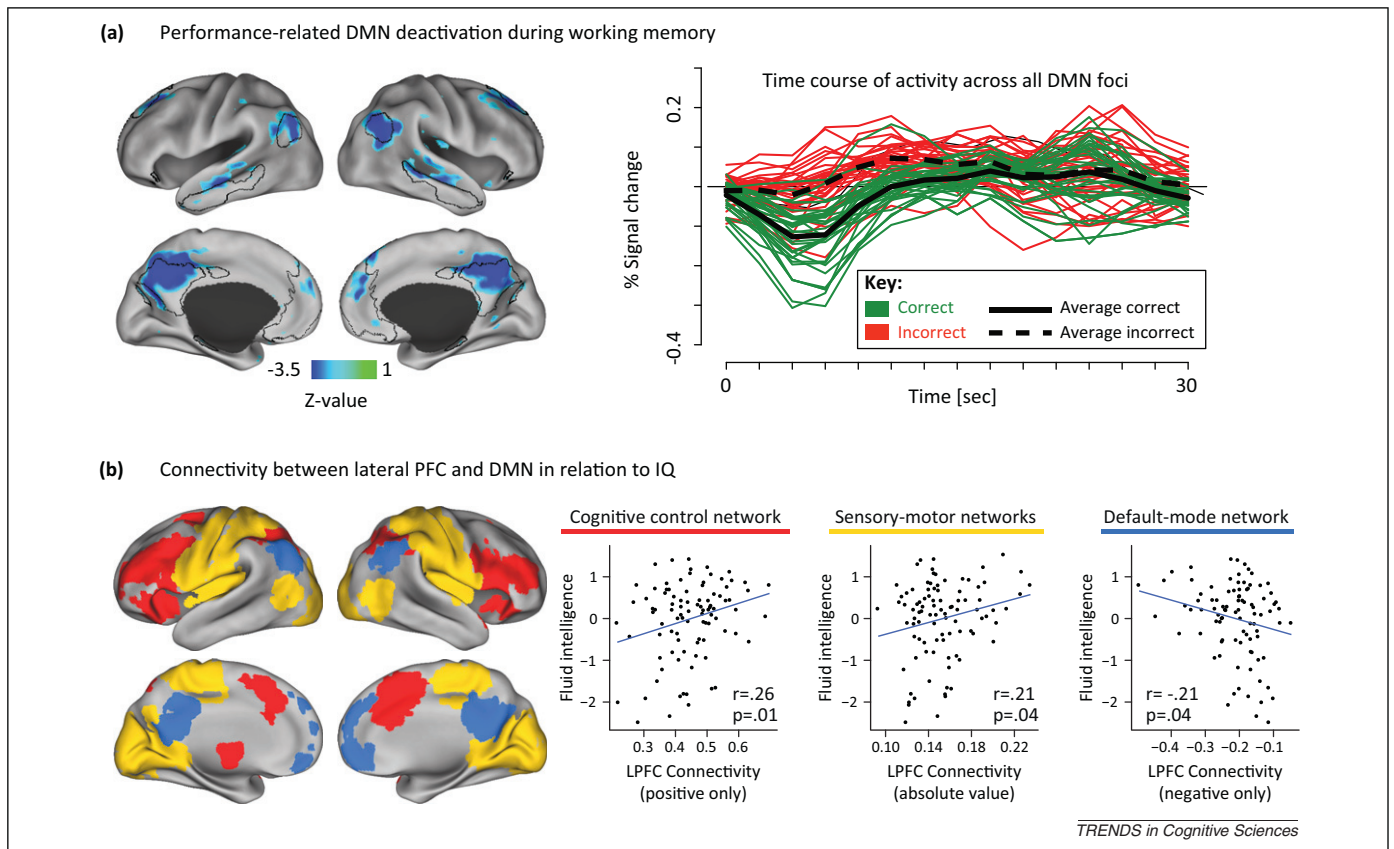
Figure 1. Functional relevance of DMN suppression. **(a)** The left panel shows regions closely corresponding to the DMN that were identified as exhibiting a weaker signal for correct relative to incorrect trials while healthy adults performed a delayed object working memory task (black borders mark the DMN as originally defined by Fox and colleagues [4]). The top right panel shows the signal extracted from all the identified foci displayed in the functional map. For each region a green line indicates correct trials, whereas a red line marks incorrect trials. Average correct vs incorrect signals for all DMN regions are shown in solid vs dashed black lines, respectively. **(b)** Functional connectivity between three *a priori* defined large-scale networks (red, control; yellow, sensory-motor; blue, default mode network) and a lateral-prefrontal node that was stringently identified as being involved in cognitive control. The panels on the right show individual differences in IQ (assessed using Raven's progressive matrices) and connectivity for a large sample of college-age adults (N=94). Both sensory and control network connectivity strength was positively associated with IQ, whereas DMN network connectivity was inversely correlated with IQ, such that higher IQ individuals evidenced stronger anti-correlation. Adapted, with permission, from [29] and [67].

firing rates in the posterior cingulate node of the DMN during performance of demanding attention and WM tasks [31]. Furthermore, higher firing in the posterior cingulate DMN node is associated with higher error rates and slower task performance [31].

Recently, an EEG-fMRI study found that increased θ oscillations were associated with suppression of the DMN and successful WM performance [49]. As discussed later, increased θ power may reflect top-down modulation of the DMN via control signals [57]. More evidence for the top-down vs bottom-up mechanisms in DMN function was provided by a recent elegant experiment [58] that selectively manipulated task-relevant vs task-irrelevant distraction during WM, while measuring functional connectivity between stimulus-selective visual regions (faces vs scenes) and the DMN as well as the FPCN. The authors reported that, depending on task demands, DMN coupling with visual cortex was predictive of task performance. Specifically, they found that the DMN is functionally correlated with stimulus-selective visual regions only in the presence of task-irrelevant distraction, postulating that: '...suppression of externally generated distracting information (that is, suppression of visual cortical activity) is intimately coupled with the suppression of internally generated distracting information (that is, suppression of default network

regions)'. Moreover, this connectivity finding highlights the fact that there may be competition for computational resources between the DMN and FPCN with sensory regions (Box 1). This may be one mechanism that in part underlies the antagonistic relationship between the DMN and control regions.

Emerging task-relevant effects clearly support the conclusion that DMN suppression is functionally important for successful operation of certain cognitive processes, such as focused attention and WM. Group differences in the capacity to suppress the DMN may also be meaningful. Indeed, a recent study identified greater deactivation of key DMN nodes in experienced meditators relative to non-meditators [59], suggesting that DMN suppression may reflect a state that could be refined with practice. Future studies should ascertain whether such meditation practice leads to better performance on externally directed cognitive tasks. By contrast, older adults exhibit deficits in filtering external distraction [60–62] and are less able to suppress the DMN during cognitive tasks [3,63–65]. Thus, the capacity to 'tune' DMN activity may have clinical significance.

The ability to suppress the DMN may be related to individual differences in cognitive control. To examine this possibility, Cole *et al*. recently identified a portion of the

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Box 1. Is there competition for computational resources between anti-correlated systems?

What is the function of the antagonistic relationship between control systems and the DMN? One possibility is that this relationship may result from competition for control of shared computational resources between distributed networks. For both networks, their associated computations are likely to entail coordination with additional brain regions. For example, visual cortex is differentially coupled with each network according to task demands [58]. Visual WM or selective attention robustly activate the task-positive fronto-parietal dorsal attention network (DAN), whose activity is often found to be anti-correlated with that of the DMN [28,48]. Engagement in such attention-demanding tasks is also associated with positive coupling between the DAN and parts of visual cortex [58]. Interestingly, cognitive functions linked to DMN activation similarly entail coordination between visual cortex and the DMN. In some mental processes, parts of visual cortex and elements of the DMN are positively coupled [30,58,105], and other processes that activate the DMN cause suppression of visual cortex [106]. Therefore, DMN influence on visual cortex may disrupt its coordination with the DAN, interfering with cognitive processing. Similarly, DAN influence on visual cortex may interfere with the DMN recruiting or suppressing it. Therefore, for optimal cognitive processing, it may be beneficial for the DAN and DMN to have a reciprocally antagonistic relationship. Activation of one network would suppress the other in order to limit the other's interference in the coordination of shared neural resources relevant for supporting ongoing computations.

In addition to competition for use of sensory computational resources, the DMN and DAN appear to compete for positive coupling with brain networks involved in cognitive control, such as the cingulo-opercular network or the fronto-parietal control network (FPCN) [48]. In this sense, although the FPCN is typically conceptualized as anti-correlated with the DMN, it may actually positively couple with the DMN when organizing internal self-relevant thought [48]. Moreover, the antagonistic DAN-DMN architecture provides a substrate for control networks to flexibly perform circuit selection. The FPCN may exert cognitive control by biasing the competition between the DMN and DAN in order to guide selection of the active network according to task demands. Thus, there may be a dynamic interplay for computational resources between these distributed systems, with the FPCN positioned to integrate information depending on present demands [47].

Box 2. What causes lack of DMN suppression in mental illness?

The DMN is increasingly implicated in mental illness by functional connectivity studies. In this review we take a different perspective on the DMN – namely, we explore the possibility that the lack of DMN suppression represents a mechanism whereby certain cognitive deficits and/or symptoms may be exacerbated in neuropsychiatric illness. If the functional relevance of DMN suppression for goal-directed cognition can be established, what does this suggest about a failure in the ability to accomplish such suppression? As noted in the main text, there is strong evidence for lack of DMN suppression in neuropsychiatric disease, in particular schizophrenia. Such DMN over-activity during goal-directed cognition may in part contribute to cognitive deficits observed in this illness. That is, it is not sufficient to consider only lack of task-positive signals during cognitively demanding tasks as the only neural signature of cognitive deficits in schizophrenia. Nevertheless, although the DMN signal, if left unsuppressed, may compromise optimal goal-directed cognitive function, it still remains unresolved whether the ability to adequately suppress the DMN (or lack thereof) could be explained by FPCN deficits alone. Therefore, there is an interesting 'chicken or egg' problem: it is not clear whether the lack of DMN suppression adds a unique source of variance or whether the success of DMN suppression can be explained purely by considering FPCN activity. This problem highlights the issue of causality in the interaction of large-scale anti-correlated distributed neural systems. We argue that it is crucial to conceptualize such anti-correlated networks as a complex dynamical system, where the state of each network is critical when considering its impact on other networks. For instance, elevated DMN signals may adversely impact the ability to recruit the computations necessary for externally focused goal-directed cognitive tasks, because it may suppress activity of such regions [37]. In turn, if there exist primary deficits in the ability to recruit computations supported by the FPCN, this may result in inadequate suppression of DMN signals at times when such deactivation is critical. Nevertheless, regardless of the causal direction, if unconstrained during certain goal-directed cognitive processes, the DMN signal could interfere with goal-directed cognitive function, which may be exacerbated in neuropsychiatric conditions presenting with cognitive impairment. We discuss a biophysically-realistic computational model that offers a hypothetical framework for this mechanism [37] (Box 3).

FPCN, lateral prefrontal cortex (PFC), in a sample of college-age adults that was associated with cognitive control and was highly globally connected with the rest of the brain [66,67]. A follow-up analysis examined resting-state connectivity of this region with three major cortical networks and its relationship with general fluid intelligence (Figure 1b) [67]. This study found that the PFC-DMN relationship was predictive of intelligence. Strikingly, the DMN-FPCN relationship was negative: individuals with higher intelligence exhibited more negative PFC-DMN coupling. These findings suggest that individual differences in the relationship between control regions and the DMN may be related to cognitive control and the ability to modulate DMN suppression (although it remains unclear whether variability in this relationship is completely explained by activity in the FPCN; Box 2).

The evidence reviewed in this section suggests that DMN suppression serves a vital function in the context of goal-directed cognition and cognitive control. Put simply, DMN suppression appears to be a mechanism through which the brain suppresses certain internal activity (e.g. mind-wandering) to optimize externally-directed cognitive function. This observation suggests that such cognitive

function would be impaired if DMN suppression was compromised, which is indeed the case in patients with neuropsychiatric disorders.

The role of DMN suppression in mental illness

A growing body of work using rs-fcMRI implicates the DMN in cognitive impairments and symptoms associated with neuropsychiatric disorders, such as schizophrenia and depression (see [3,68]), both of which impact cognitive function. Schizophrenia is a disabling disorder associated with delusions and hallucinations [69], cognitive impairment [70], social isolation, and emotional dysfunction [71]. Lack of DMN suppression in schizophrenia has been observed when affected individuals perform demanding cognitive tasks [32–35,72–79]. Studies have reported deficits in DMN suppression during the performance of the 'n-back' WM task in schizophrenia patients, even before the DMN literature evolved [75]. This finding was subsequently replicated both in schizophrenia patients and, to a lesser extent, in first-degree relatives of patients with schizophrenia and found to be associated with worse task performance [35], as well as extended to schizoaffective disorder [74]. A recent study showed that, even when matched to
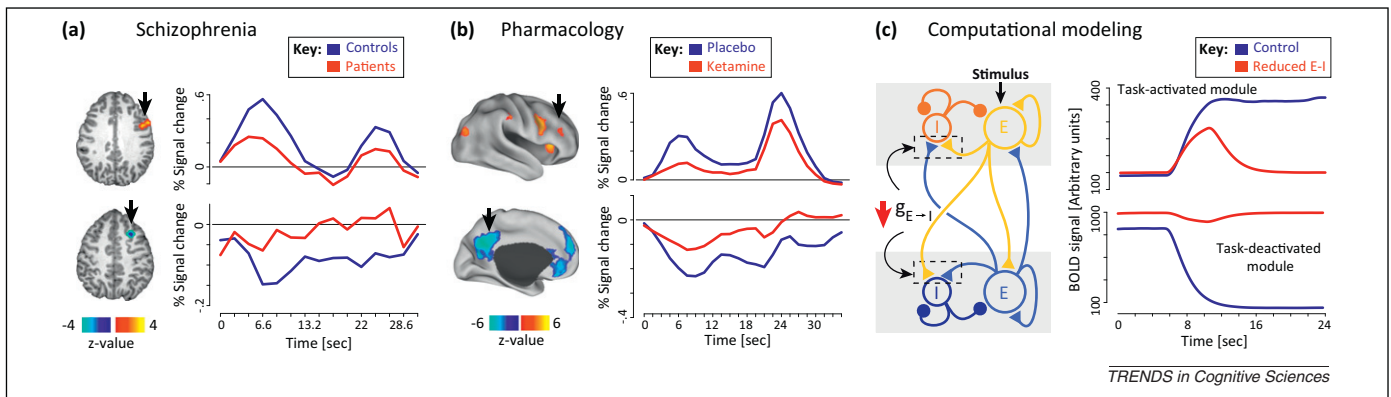
Figure 2. DMN deactivation findings across clinical, pharmacological and computational approaches. **(a)** A set of regions (2 example foci shown) was identified, where patients (red) failed to show sustained activation (top), as well as appropriate suppression (bottom) during delayed WM, relative to healthy controls (blue) [32]. This finding was present even in the context of matched performance. **(b)** Regions closely corresponding to the FPCN and the DMN were modulated by an NMDA-receptor antagonist ketamine (red) relative to a placebo control condition (blue) [37]. Two regions with a similar pattern of modulation as observed in schizophrenia are highlighted. **(c)** A computational model of WM, comprised of task-activated (top) and task-deactivated (bottom) modules that highlights a possible mechanism for deactivation (Box 3), followed by results. The model was tested on whether 'disinhibition' via reduced NMDA receptor conductance onto GABA cells (E-I) (small red arrow) would resemble activation/deactivation BOLD findings under ketamine and observations in schizophrenia. Adapted, with permission, from [32] and [37].

healthy individuals for WM performance, schizophrenia is associated with reduced suppression of DMN nodes during encoding and maintenance of delayed WM [32] (Figure 2a). This challenges the notion that DMN suppression deficits in schizophrenia are purely a result of suboptimal task engagement [80]. Nonetheless, cognitively relevant DMN suppression in schizophrenia warrants further investigation. Moreover, PFC activation is associated with DMN suppression in healthy individuals, but not in schizophrenia [32,33]. Together, these findings support the hypothesis that DMN suppression may be compromised in schizophrenia during performance of cognitively demanding tasks and contribute to cognitive impairment observed in this illness. DMN suppression deficits possibly exemplify additional forms of cortical circuit dysfunction associated with schizophrenia, adding to task-related cortical activation deficits that underlie cognitive impairment (Box 2). These findings tempt one to speculate that DMN suppression deficits compromise task-relevant signal processing, given that the weaker DMN signal may reflect the suppression of cognitive operations carried out by the DMN [5,7–9,13].

Lack of DMN suppression has also been reported in depression. Sheline and colleagues found that depressed individuals fail to reduce DMN activity while reappraising negative images [81] (see also [82]). Unlike schizophrenia, where lack of DMN suppression has been identified during cognitively demanding tasks, DMN suppression deficits in depression have been linked to negative rumination [83]. Therefore, a failure to suppress DMN nodes (in particular medial prefrontal cortex in depression) may be representative of a regime that manifests as negative internal thought, rather than as a primary inability to engage executive resources (as hypothesized in schizophrenia), which is perhaps linked to aberrant automatic emotion processing [81,84]. In the framework of dynamical systems, such a regime may constitute a robust 'attractor state' in which the neural system is not readily dislodged from, and thus returns to, this stable state [85]. Indeed, as recently hypothesized [86], in depression there may be hyper-activity in medial prefrontal nodes, in turn inducing a hypo-function of

control-related regions (due to antagonistic architecture of the two systems) without primary abnormalities in control regions. Nonetheless, a hyper-active DMN in depression may result in detrimental effects on cognitive performance [87]. However, it may be that DMN over-activity persists – possibly due to heightened rumination – even in the absence of cognitive engagement. Although impaired DMN suppression may manifest across neuropsychiatric conditions, the emergent property of DMN dysfunction could possibly occur due to dissociable pathophysiological mechanisms across diagnoses, a hypothesis that warrants direct prospective investigation (Box 4).

In the following section, we review human pharmaco-fMRI studies to identify mechanisms that might contribute to DMN dysfunction. We focus on schizophrenia as one candidate disorder, where there is emerging understanding of the underlying neural mechanisms that may compromise DMN suppression [37]. We hope that similar mechanistic understanding will help to elucidate DMN abnormalities across other neuropsychiatric conditions.

Pharmacological neuroimaging studies: identifying the synaptic mechanisms of DMN suppression

In order to fully understand the clinical significance of DMN abnormalities, it will be important to understand the synaptic mechanisms underlying DMN suppression and suppression failures. Recently, Mayer and colleagues hypothesized that DMN suppression involves long-range projections onto inhibitory interneurons [52]. Dysfunction in inhibitory mechanisms and optimal functional antagonism across circuits has been implicated in cognitive impairment [88,89]. However, there have been few direct tests of this hypothesis. One strategy that may enable progress in this area is pharmacological neuroimaging (ph-fMRI) [90], whereby pharmacological agents are employed to explore specific synaptic mechanisms that contribute to DMN suppression.

Recent studies have implicated monoaminergic mechanisms in DMN suppression. Minzenberg and colleagues found that the stimulant modafinil enhances DMN suppression and is related to successful WM performance [38].

A subsequent study also found that at rest increased dopamine is associated with stronger positive FPCN-DMN coupling and stronger negative DAN-DMN coupling [91]. Related findings have been observed with the $5HT_{2A/2C}$ receptor agonist psychedelic hallucinogen, psilocybin, which at rest increases DMN suppression [92]. These investigations implicate possible monoaminergic modulation of cortical inhibition in the drug effects on DMN suppression.

Building on this work, Anticevic *et al.* [37] addressed the impact of disrupting glutamatergic neurotransmission by blocking *N*-methyl-D-aspartate (NMDA) receptors on DMN suppression. They found that the NMDA receptor antagonist, ketamine, disrupted FPCN activation and DMN deactivation during performance of delayed WM [37]. Critically, ketamine effects on the BOLD signal during delayed WM were very similar to observations in schizophrenia (Figure 2). This study also showed that less DMN suppression predicted worse WM performance within subjects, replicating prior findings [29]. Interestingly, subjects with the least DMN suppression showed more severe negative symptoms associated with schizophrenia following ketamine. As noted, one mechanism for DMN suppression may involve an active inhibition of regions not engaged in ongoing goal-directed cognition [13]. This hypothesis was formalized in a biophysically-realistic computational model of WM [93] that also implements an explicit pharmacological manipulation [94] of hypothesized ketamine effects [95]

and sheds light on the possible mechanisms underlying DMN suppression via long-range inhibition (Box 3 and Figure 2c). The modeling simulations were consistent with the proposal that local excitation/inhibition balance (E/I balance) may be one critical property that mediates the interaction between task-based activation and suppression. These simulations were in line with the pharmacological manipulation of the NMDA receptor via ketamine and observations in schizophrenia (Figure 2a-c). Thus, the findings of this work support the hypothesis that long-range inhibition may be critical for FPCN/DMN modulation.

Taken together, these early ph-fMRI studies illustrate one path for probing the synaptic mechanisms that underlie the relationship between the FPCN and the DMN, a strategy that also enables the exploration of the beneficial or maladaptive effects of modulating the functional antagonism of these networks.

Concluding remarks

In this review, we discussed evidence that reveals the functional relevance of DMN suppression and its importance in goal-directed externally-oriented cognition. Furthermore, we highlighted two neuropsychiatric conditions that exhibit a potential failure to suppress DMN signals, which impacts symptoms and cognition, possibly due to different pathophysiological mechanisms. Based on pharmacological studies, we discussed the role of both fast and slow neurotransmission in optimal modulation of DMN suppression. Finally, we outlined a computational modeling framework for DMN suppression during cognitive

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Box 3. Synaptic mechanisms of DMN suppression

In the main text, we highlight evidence that there may exist an antagonistic relationship between regions involved in externally-directed cognition (i.e., the DAN/FPCN) and regions involved in self-relevant thought (i.e., the DMN). We also discussed recently emerging pharmacological neuroimaging studies that highlight how modulating both fast and slow neurotransmission can affect the interplay among these systems. Anticevic *et al.* [88] explicitly manipulated the NMDA receptor component of glutamatergic neurotransmission via ketamine administration in the context of WM performance. This resulted in an attenuation of both task-positive and task-negative signals in WM-related regions, similar to prior observations in schizophrenia [32,35] (Figure 2a, b). This finding was extended by implementing a leading hypothesis for ketamine's effects at the synaptic level – namely, cortical disinhibition – within a well-validated biophysically plausible computational model of WM [37]. The model consists of two modules: a task-activated module that is a recurrent microcircuit capable of WM computations and a task-deactivated module that represents the DMN and is characterized by high baseline firing rate and deactivation at task onset [31]. To capture the observed anti-correlation during task performance, the modules interact reciprocally through net inhibitory long-range projections. Disruption of NMDA conductance onto GABAergic interneurons (i.e., E-I conductance) closely reproduced the BOLD effects observed following ketamine administration, which also matched prior observations from an independent WM study involving patients with schizophrenia [32] (Figure 2). These modeling results suggest that local disinhibition renders the DMN-type microcircuit hyperactive and therefore less sensitive to the long-range suppressive input from the task-activated WM-related microcircuit. Thus, the already high-firing task-deactivated module cannot be silenced at task onset. These modeling simulations demonstrate that it is vital to consider the complex dynamics between these large-scale neural systems because a given neuropathology (or pharmacological manipulation) can impact both systems due to its downstream synaptic effects (namely cortical disinhibition [89]).

Box 4. Outstanding questions

- What regions/mechanisms mediate the suppression of the DMN? Is it an emergent property of system dynamics or are there key cortical/subcortical nodes that may mediate the relationship?
- Is the anti-correlation between DMN and task-positive networks always present? What are the mental states that occur when they anti-correlate vs correlate and why is the anti-correlation so important functionally?
- Is it possible that anti-correlation reflects internal competition for shared computational resources?
- What are the common vs unique synaptic mechanisms for the failure of DMN suppression across different neuropsychiatric conditions (e.g., schizophrenia vs depression)?
- Are individual differences in the ability to accomplish DMN suppression completely explained by variance related to the activation of regions responsible for cognitive control?
- Is DMN suppression equally functionally relevant across cognitive domains? Is attention the key variable? Future studies should systematically examine, in the same sample of subjects, which tasks require performance-relevant DMN suppression and to what extent.
- Do DMN suppression deficits across neuropsychiatric conditions reflect separable processes (e.g., excessive rumination in depression vs compromise of executive function in schizophrenia)? Prospective studies should directly compare patients diagnosed with schizophrenia vs depression to examine whether similar effects emerge across relevant cognitive/emotional manipulations.
- What is the dynamical nature of the DMN and of spontaneous activity in the brain in general? Can it be captured theoretically using the presently available theory of deterministic chaos or stochastic processes? Alternatively, is a new mathematical theory needed in order to understand the complex spatiotemporal dynamical patterns of the DMN system?

operations and articulated the role of optimal inhibitory microcircuit function for coordinated DMN suppression.

Further characterization of circuit mechanisms behind these observations will be critical in order to elucidate the role of DMN signals both in healthy cognition and neuropsychiatric illness (Box 4). At the theoretical level, it will be informative to characterize quantitatively the dynamical nature of the DMN and capture its complexity via neural circuit modeling, possibly with the help of chaotic dynamics theory [96–98]. Using the complementary approaches of experimentation and computational theory will provide a powerful cross-disciplinary approach in this exciting area of basic and clinical neuroscience in the coming years.

Disclosure statement

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