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Review

Anticorrelation emerges within a dynamic and competitive neural landscape

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Default network anticorrelation with other neurocognitive networks has been a topic of ongoing and expanding interest in neuroscience. Advances in anticorrelation research have moved beyond debates regarding methodological artifact to reveal a more comprehensive view of brain function. We review neurocognitive, anatomical, computational, neuromodulatory, and dynamical approaches to the study of anticorrelation. We argue that anticorrelation is a robust feature of network organization, revealing a latent principle of network competition.

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Introduction

Functional magnetic resonance imaging (fMRI) and analysis of spontaneous oscillations in blood-oxygen-level-dependent (BOLD) signal have catalyzed insights into macroscale functional network architecture [1]. Much of this work has emphasized oscillation synchrony amongst brain regions, typically measured as the positive product-moment correlation coefficient (or other measures of covariance) [2]. Nevertheless, in one of the first studies to examine spontaneous BOLD activity, Fox et al. signaled the importance of negative correlations, or '*anticorrelation*', between large-scale patterns of network activity [3]. The anticorrelation between networks was speculated to underlie segregation of neuronal processes subserving opposing goals or competing representations [3].

The default (mode) network (DN) is perhaps the most reliable observation to emerge from human neuroimaging (*c.f.* [4]). Some of the first metabolic positron emission tomography (PET) studies of human cognitive processes during visual tasks implicated a distributed set of regions with suppressed activity [see [4] for review]. These very regions demonstrated high BOLD synchrony, and anticorrelation with (a) the inferior parietal sulcus, frontal eye fields (FEF), the motion-sensitive complex, as well as (b) the dorsal anterior cingulate cortex (ACC) and anterior insula. Collectively, these regions are referred to as the 'task-positive network' (TPN), subdivided into the (a) dorsal attention network (DAN) and (b) salience network (SN) [5,6]. Initially, Fox et al. suggested network antagonism as a tool for functional differentiation [3], wherein the loci of task demand may dissociate network function, split by internal (DN) versus external (DAN/SN) orientation [7,8]. Further research demonstrated multiple subnetworks, unimodal (visual; somatomotor) and distributed (fronto-parietal control) [9], each with unique topographies and patterns of anticorrelation [10–13], suggesting anticorrelation is a more fundamental feature of brain dynamics, rather than a phenomenon limited to the DN.

The Achilles' heel of anticorrelation research was revealed by limitations of BOLD signal preprocessing. Murphy et al. demonstrated that global signal regression 'mathematically mandated' the introduction of artefactual anticorrelations [14]. Researchers tackled the replication of anticorrelation with diverse acquisition, regression, and correction methods, yielding inconsistent results: some methods eliminated anticorrelation effects altogether [15,16] while others found them robust and reliable [17–20]. In 2017, Murphy and Fox jointly published guidelines for global signal regression implementation [21] without a definitive consensus on anticorrelations as chiefly biological or artefactual observations.

The expansion of anticorrelation research underscores the necessity of resolving both its origin and functional

role; tackling this requires a broader framework and interdisciplinary approach. Undergirding anticorrelation is a central premise: rising activity in one region, mirrored by a decline in another, reflects a competitive dynamic between functional systems. In fMRI, this opposition is often inferred from BOLD signal deviations above and below baseline, but critics argue that vascular artifacts confound such interpretation [22]. This competitive relationship between regions and networks has not been limited to the study of anticorrelation. Rather, many other aspects of network competition have included phase coherence [23], inhibition-excitation ratio [24–26], and integration/segregation metrics [27,28]. Our goal is to highlight the contributions of anticorrelation as one of many fundamental facets of a singular core concept: network competition. To this end, we review how neurocognitive, anatomical, neuromodulatory, computational, and dynamical approaches have advanced our understanding of network competition.

Neurocognitive approaches to anticorrelation have yielded promise as potential biomarkers and intervention targets for psychiatric disorders. Anatomical evidence points to anticorrelation as an indirect, meso-scale, and macro-scale phenomenon. This is supported by neuromodulatory approaches, which demonstrate changes in inhibition and excitation patterns, spurring greater integration or segregation within and between networks. Computational neuroscience complements this approach, examining the ways inhibition and excitation ratios underpin these processes, demonstrating anticorrelation as a necessary and emergent phenomenon of neural flexibility. Dynamic approaches underscore the undulating nature of anticorrelation, inhibition, and segregation, emphasizing the variable changes between these states as a crucial component of their significance. We aim to show that these insights reveal a dynamic landscape of regions and networks constantly cooperating and competing at different scales.

Neurocognition

Anticorrelation has been primarily observed from a neurocognitive perspective, with a major emphasis on fMRI. Research into regional brain activity has demonstrated that canonical networks underlie experimentally manipulable behaviors. Core DN regions — the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobule — have been linked to self-referential processing, autobiographical memory, and internally directed thought [4,29]. Conversely, the DAN and SN have been posited to reflect an opposing axis of cognition, and anticorrelation with the DN (see Figure 1) [5,6]. Early accounts of DN-DAN/SN antagonism showed a suppression of DN activity when individuals engage in externally-oriented goal-directed tasks [3,30,31]. This DN suppression has been related to better task performance [32,33], suggesting that inhibiting DN processes enables more efficient cognitive engagement.

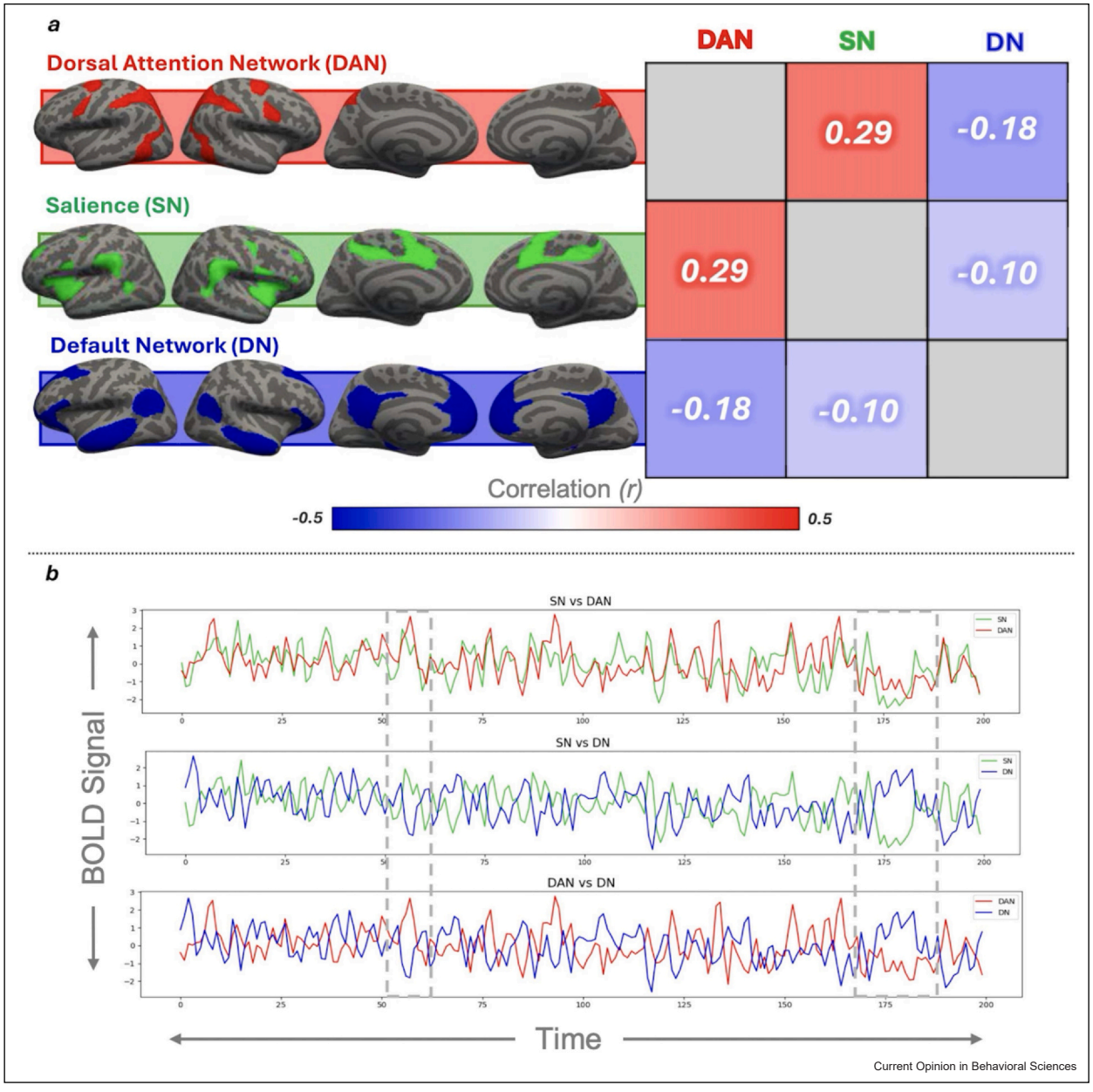
The validity of neurocognitive approaches to anticorrelation has surfaced in clinical and therapeutic settings. Traumatic brain injury patients have shown localized TPN lesions propitiate ripple effects, degrading the DN proportionally [34–36]. Disruption to DN-anticorrelation balance is ubiquitous across neuropsychiatric dysfunction, including major depressive disorder, schizophrenia, ADHD, and anxiety disorders [37–39]. The commonality of antagonism-disruption has led to a proposed framework of precision functional mapping [40]. Treatment options like mindfulness meditation, cognitive-behavioral therapy, and neurofeedback have all been associated with changes in DN–anticorrelation balance, often restoring more typical anticorrelation patterns [40–42]. Further, interventions normalizing DN overactivity or boosting TPN engagement have been shown to benefit conditions characterized by excessive internal focus, like depression or obsessive-compulsive disorder [43,44]. This growing evidence for anticorrelation highlights the need for further translational research for clinical impact.

Anatomy

Investigation into the anatomical basis of connectivity has revealed an asymmetry: positively correlated regions show direct structural connections where anticorrelated regions largely do not [45,46]. One study used diffusion tensor imaging to show that white matter connectivity tends to increase with functional correlation strength [47]. This finding has also been demonstrated at the synaptic level. Antidromic and orthodromic stimulation — used to assess direct, mono-, and polysynaptic connections by evoking action potentials in both forward and reverse directions — were applied between the ACC sulcus and two targets: medial FEF (positively correlated) and lateral FEF (negatively correlated) [48]. Only the positively correlated pair showed direct synaptic connectivity. This asymmetry suggests two possibilities: anticorrelation may lack direct structural support, instead arising from peripheral mechanisms like vasodilation, or it may reflect *indirect* structural pathways.

Vascular artifacts, such as CO_2-driven blood flow changes, can create spurious anticorrelations in resting-state fMRI by eliciting differential BOLD responses across brain regions due to variations in vascular reactivity or timing [49]. Yet, two major issues hamper this interpretation. First, anticorrelation appears highly correspondent to task-evoked activation. Further, negative BOLD responses — a defining feature of anticorrelation — provide better task specificity than the positive BOLD response during cognitive tasks [50], and suppressed regions can predict activation patterns based on their cortical geometry [86]. This corroborates Fox et al., suggesting that

Figure 1



Anticorrelation. (a) Three canonical resting-state networks—dorsal attention (DAN), salience (SN), and default (DN) — plotted alongside a correlation matrix plotted from 154 young adults (see Spreng et al. [87] for details). Numbers on the matrix indicate correlation values between two networks; warm correlation colors indicate positive correlation, cool indicate negative correlation. **(b)** Time courses from a single subject showcasing disjunction between correlation and anticorrelation. The *y*-axis contains BOLD signal and the *x*-axis represents 3s TRs across a ten-minute scan. Gray dashed boxes highlight regions where clear differences occur between positively correlated and negatively correlated pairings. Note the overall difference where DN-DAN and DN-SN are highly anticorrelated, with instances of specially pronounced negative connectivity. Conversely, the DAN-SN time courses are largely correlated and lack the instance of pronounced anticorrelation exhibited by the DN. TR, Repetition Time.

anticorrelation supports segregation of neuronal processes subserving opposing goals or competing operations. Second, it is not obvious that a vascular component undermines anticorrelations as markers of network competition because it is unclear to what extent this noise may indeed be signal — especially when negative BOLD is so tightly coupled to active neuronal inhibition [51,52]. Indeed, research has demonstrated that a common source of perceived noise used for regression — ventricular cerebrospinal fluid — demonstrates anticorrelations that track differences in cognitive abilities [53]. This suggests that early intuitions about what constitutes a source of noise

may be some of the very mechanisms underpinning network competition in unexpected ways.

Anticorrelation may be better framed as anatomically grounded, but indirect. Global network properties, such as specific connectivity motifs and common efferent and afferent pathways, significantly influence inter-areal relationships, suggesting that negative functional relationships may also emerge from higher-order network architectures rather than direct anatomical links [54,55]. Anatomical findings suggest that anticorrelations may be better construed as emergent outcomes of competition within a dynamic neural landscape, rather than dissociable, morphologically-driven events. New discoveries in neuromodulation, computational modeling, and dynamics support this perspective.

Neuromodulation

The evidence for indirect modulation through inhibitory and excitatory mechanisms dovetails with a growing literature on the role of neurotransmitter and neuromodulatory systems in sculpting large-scale network states. The clearest direct link to excitation and inhibition falls to the brain's main chemical workhorses — glutamate and Gamma-Aminobutyric acid (GABA) — which can be studied through the use of pharmaceutical agonists. PET or magnetic resonance spectroscopy (MRS) (a method that measures specific chemical concentrations by detecting their distinct resonance frequencies), combined with fMRI, can be employed to map regional receptor densities for these neurotransmitters in conjunction with local changes in BOLD response. The robustness linking glutamate and GABA with excitation and inhibition, respectively, enables computational modeling of excitation-inhibition ratios based on local changes of these neurotransmitters that are biologically derived. One such study examining excitation-inhibition ratios tested their model against a pharmacological fMRI that included benzodiazepine — a GABA agonist [56]. It found that increased GABAergic signaling from the introduction of benzodiazepine skewed the excitation-inhibition ratio, in favor of inhibition [56]. Another study combining spectroscopy with fMRI demonstrated that in vivo GABA concentrations have an outsized impact on evoking anticorrelations, compared to glutamate [57]. Taken together, these studies suggest that inhibitory changes at the molecular level can evoke large changes in inhibition and excitation ratios in the brain, which in turn may be important for anticorrelation to emerge.

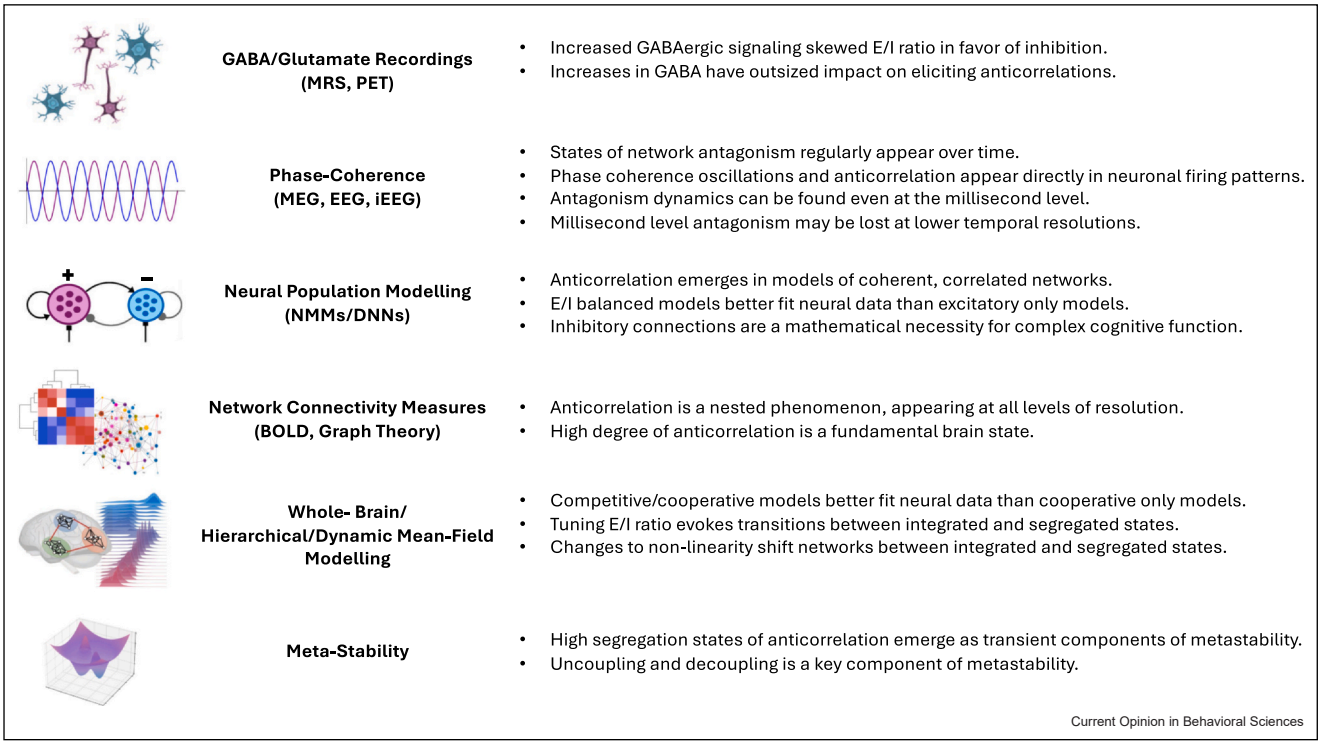
Neuromodulators — like acetylcholine and norepinephrine — indirectly orchestrate rhythms of synchrony and discordance, integration and segregation, of brain networks [58,59]. Acetylcholine, released from the basal forebrain, has been shown to desynchronize cortical activity, shifting the brain from synchronized, quiescent patterns, to active, stimulus-responsive states [60]. Similarly, norepinephrine from the locus coeruleus enhances the brain's sensitivity to salient external cues, facilitating rapid transitions between network configurations [58,61]. These neuromodulators affect the gain of various networks, effectively 'turning up' one functional constellation while 'damping down' another, creating conditions for anticorrelations to emerge. Manipulating neuromodulatory tone — baseline neuromodulatory activity — can alter cortical states and functional connectivity patterns. For example, stimulating the basal forebrain induces cortical desynchronization, altering the interplay between networks associated with internally versus externally directed attention [60,62]. This suggests that anticorrelation may reflect a mediation between competing cognitive functions through the use of inhibitory control, allowing contextually appropriate regions and networks greater access to metabolic resources.

The relationship between neuromodulation and large-scale functional dynamics has been synthesized in integrative reviews and computational frameworks that highlight how fluctuations in neuromodulator levels support flexible network reconfiguration [59,63]. By altering the gain, excitability, and synchronization of neuronal ensembles, neuromodulators establish the conditions under which anticorrelations become more pronounced. Taken together, the neuromodulatory evidence suggests that, rather than directly wiring one region negatively to another, neuromodulators set the stage for indirect, feedback-driven inhibitory or competitive interactions that instantiate distributed anticorrelation activity patterns across the cortex.

Computational Modeling

One of the main computational models employed in studying neural systems are neural mass models (NMMs) (for a brief summary of modeling methods and outcomes, see Figure 2). These models employ equations to characterize the activity of neuronal groups by incorporating biologically linked variables like membrane potential, firing rate, or inhibitory/excitatory propensities. These equations can then be used to model neuronal population behaviors at the circuit, network, or whole-brain level, and can then be cross-validated with real data to see how tweaking certain variables makes the models more or less biologically plausible. Early NMMs revealed three criteria sufficient for simulating resting-state activity: structurally-bound connectivity, noise, and spontaneous fluctuations. An attempt to use these parameters to artificially synthesize DN coherence found anticorrelations to be an emergent property [64]. Subsequent studies incorporated other biological features, including delays, local oscillatory dynamics, and

Figure 2



An integrative summary of the core findings pertinent to network competition. GABA/Glutamate recordings (through MRS and PET can be used to model the proliferation and balance of the brain's main inhibitory and excitatory neurotransmitters. Phase coherence capitalizes on electrophysiological recordings from MEG, EEG, and iEEG to capture antagonistic relationships through in-phase and anti-phase dynamics. Neural population modeling, through methods like NMMs and DNNs, can model and tweak excitatory/inhibitory (E/I)) ratio balance to determine how changes in these variables modulate the system's behavior and how these changes map onto neural data. Network connectivity measures, often drawing on BOLD often draw on correlation and graph theoretical measures to show the canonical feature of anticorrelation as a competition metric. Expanded mean-field modeling (whole-brain, hierarchical, and/or dynamic) highlights the tensions between integration and segregation at multiple temporal and hierarchical scales. Metastability introduces a necessary push-pull tension to the brain as a dynamical system to maintain balance and flexibility. These are all nested components at different spatial and temporal scales, all featuring a competition-cooperation tension.

nonlinear coupling, advancing a more mechanistic understanding of anticorrelations as manifestations of network-level excitatory and inhibitory forces [65,66].

This incidental emergence of anticorrelation in network modeling raises a question about the inevitability of network antagonism: are inhibitory or negative connections a neurobiologically necessary feature? In an ironic twist, harking back to Murphy's 'mathematical mandate', it was shown, first, anticorrelations are mathematically necessary for any neural system capable of universal approximation [67]. Universal approximation is the ability, given sufficient time and resources, for a neural network to learn any continuous function or pattern. Humans are universal approximations, and negative connectivity is thus mathematically necessary [67]. Recent modeling work further supports this conclusion by showing that excitatory-inhibitory models better capture neural data than excitatory-only models [56,68]. Similar results were found in parallel models comparing cooperative-only to competitive-cooperative dynamics, favoring the latter [25].

Anticorrelations have been shown to emerge at both the local and global scale, with mediators between these found at the mesoscale with regions like the FEF, DAN, and SN more broadly [69]. Moreover, the brain — both locally and globally— fluctuates between states of anticorrelation and states of high integration, with the latter mediating the transition to the former [69]. Inhibition and excitation begin largely as microscale phenomena, pooling to collectively elicit changes in the integration and segregation of neural populations and networks at the mesoscale, which, in turn, fosters metastability of brain states at the macroscale. Segregation — a necessary prerequisite for anticorrelation — tracks the degree to which neural populations cluster, facilitating more specialized functions. In doing so, neural populations display greater intraregional connectivity and weaker interregional

connectivity by tuning the inhibition-excitation ratio. Inhibition-excitation balance has been shown to optimize the brain's flexibility in state transitions [70]. By modulating inhibition-excitation balance, the brain maintains a dynamic tension between integration and segregation; this ongoing capacity to transition without stabilizing in a single state is what characterizes the property of metastability (*c.f* [71]). Taken together, this outlines a scale-nested phenomenon, in which microscale inhibition/excitation fluctuations modulate mesoscale segregation–integration dynamics, giving rise to macroscale metastable transitions among large-scale brain states. These nested dynamics reflect an ongoing tension between cooperative (excitatory/integrative) and competitive (inhibitory/segregative) interactions that underpin the brain's adaptive flexibility.

Attempts to delineate the link between inhibition, segregation, and metastability have drawn heavily on NMM work, using these as springboards for hypotheses to determine how feedback and feedforward inhibition change brain metastability in such a way that anticorrelations emerge [72]. While useful, NMMs are often too narrow in scope to encompass the level of dynamism and complexity of macroscale, whole-brain systems over time. Hierarchical and dynamic mean field modeling (MFM) methods pool across many NMMs to connect broader spatial and temporal scales. MFM demonstrates that tuning the gain of local excitatory and inhibitory circuits sparks transitions between integrated and segregated states [73]. Further, mesoscopic network modeling showed that in cortical macrocolumns, excitation and inhibition spontaneously segregate — not at the level of individual neurons, but across the mesoscale — such that highly connected hub nodes become dominantly inhibitory, while peripheral nodes remain excitatory [74]. Other work using dynamic MFM has shown that by tuning non-linearity, this can shift networks between integrated and segregated states, with anticorrelations emerging as transient phenomena in a metastable dynamic landscape [75]. Taken together, these findings indicate that anticorrelation emerges from the competitive network dynamics that facilitate metastable brain states, or is a core feature in maintaining them.

Dynamics

Anticorrelations were originally observed in static resting-state studies, with connectivity averaged over relatively long timescales, leading to the interpretation that the DN-DAN anticorrelation was stable [1–3]. Correlation measures, whether negative or positive, are inherently linear, but the fluctuations of brain networks are not, making anticorrelation an important but insufficient method of capturing functional relationships. Phase coherence emerges from a small subset of slow-wave oscillations, one of which is characterized by DN-antagonism [55]. These slow-wave patterns of phase coupling and decoupling at local levels coalesce to propagate emergent, non-random fluctuations with integration and segregation as a global property of metastability [76]. An accumulation of evidence now demonstrates that states of network antagonism fluctuate substantially over time and context [77,78], and the presence or absence of anticorrelation depends on fluctuating phases of dynamic connectivity [79].

Electrophysiological methods, including electroencephalography (EEG), magnetoencephalography (MEG), and intracranial EEG (iEEG), have been an asset to the dynamic study of anticorrelation directly and with high temporal resolution. The detection of anticorrelation relationships in electrical activity undermines the case that they are solely artifacts of vascular or preprocessing methods unique to BOLD. Intracranial recordings show that temporal fluctuations in connectivity, including anticorrelations, are reflected in directly observed neuronal firing patterns [80]. Moreover, one iEEG study examining DN-DAN transitions with internal and external attention tasks demonstrated a pronounced low-frequency band anticorrelation based on temporal task-switching [81].

Unique features of anticorrelation dynamics are revealed with temporal resolution at the millisecond level. EEG microstate analysis showed that the brain spontaneously shifts through four transient topographies mirroring anticorrelation states found in fMRI, but demonstrated that these states were brief, lasting only around 100 ms [82]. Observations of iEEG data indicate that the anticorrelations of three major networks (SN, DAN, and DN) were time-lagged by up to a few hundred milliseconds, further corroborating an indirect, intermediary link observable at high temporal resolution [80]. The finding that anticorrelations wax and wane over short timescales aligns with findings that networks like the DN and DAN are not perpetually locked in opposition. Rather, these networks dynamically reconfigure according to task demands, internal states, and spontaneous cognitive fluctuations [83,84]. Static estimates of anticorrelation have laid the foundation for examining dynamic transitions between phase coupling and uncoupling, integration and segregation, and periods when networks may cooperate or compete [30,85].

Conclusion

Contemporary anticorrelation research has provided ample evidence that anticorrelation is a robust and reliable feature of brain network organization. We have found that anticorrelation is part of a nested system overarchingly defined by network competition. Yet a more detailed, mechanistic understanding of what

causes neuronal populations, regions, and networks to switch between cooperation and competition is needed. Future directions must address network competition at different resolutions when taking inhibition, segregation, anticorrelation, and anti-phasic relationships and metastability into account. Then, the dynamics of anticorrelation may more directly inform brain health and emergent psychopathologies.

Data Availability

The data are open access and referenced in text.

Declaration of Competing Interest

The authors declare no conflicts.

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