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Default Mode Network Homeostasis and Alzheimer's Disease

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ABSTRACT

Recent decades have produced numerous findings challenging the amyloid cascade hypothesis of AD, leading to a widely accepted view that the etiology of AD is multifactorial. Despite this consensus, ongoing attempts have sought to unify AD's causal basis within broader explanatory frameworks. A leading candidate has been the connectome hypothesis, which invokes degenerative mechanisms selective for brain synapses. This hypothesis has itself been challenged by findings showing selective default mode network (DMN) vulnerability in AD, seen in altered functional connectivity metrics obtained years and even decades before the appearance of clinical symptoms. More recent proposals have sought to introduce functional notions that are closely aligned with clinical symptoms and are based on the known homeostatic tendency to preserve brain functional integrity. Homeostatic mechanisms are known to involve a plethora of processes that are operative at multiple levels, from molecular and cellular domains to circuit and network operation. Among these, DMN homeostasis is notable for contributing to global functional representations and sustaining autopoiesis (self-maintenance), which promotes dynamic interactions with a variable world. Emerging findings from AD pathophysiology, seen in sleep disturbances and memory related dysfunctions, suggest that higher order, DMN homeostasis may be affected in AD, which could offer a broader causal framework illuminating the interdependence of varied molecular instigators, cellular and circuit disruptors, and systemic failures.

Keywords

Alzheimer's disease, Default mode network, Brain homeostasis, Amyloid cascade hypothesis, Alzheimer's connectome hypothesis.

Introduction

Since Glenner and Wong's amyloid cascade hypothesis [1,2] in the early 1990s, the field of Alzheimer research has grown rapidly, with many thousands of papers devoted to virtually every aspect of the disease. Findings from these studies increasingly challenge the amyloid cascade hypothesis and contribute to a now widely accepted view that AD is multifactorial. Among other discoveries, individuals with very high amyloid burden can exhibit normal cognition, revealing that beta amyloid alone is insufficient for AD onset and progression. Still other findings challenge the centrality of neurofibrillary tangles. While neurofibrillary tangles are frequently observed in AD patients, the disease may also occur in their absence. Accordingly, it has become apparent that AD pathogenesis cannot be explained solely by abnormal amyloid-(A) or tau protein metabolism [3].

Based on many studies, a spectrum of alternate candidates has been identified. At molecular levels, lipid dysregulation leads to changes in sphingolipids and ceramides, which may be attributed to lipid specific metabolic enzymes like serine palmitoyltransferase (spt) or ceramide synthases**,** that could potentially affect synaptic function [4]**.** On a cellular level, mitochondrial dysfunction has been observed, providing yet another effect (or cause) of AD pathology [5]. Neuroinflammation, further, has constituted a systems level dysfunction [6,7], with its evident potential for exacerbating degenerative influences. Hence, notwithstanding the initial discoveries that led to the amyloid cascade hypothesis, these findings have since relocated beta amyloid plaques and neurofibrillary tangles from their formerly central role to prospective candidates among a much broader set of causal

instigators that lead to AD.

The wide variety of factors that have come to be identified as causal agents of AD suggests that individual factors should not be viewed in isolation, but rather as multiple contributors sharing interdependent features. Indeed, concern for interdependency has invited the question of how lower level features may be organized within the higher order symptomatic expression that has come to clinically define AD; that is, how lower level features underpin macroscopic effects that may alter brain structure and function and, therefore, the psychology and cognitive well-being of the AD patient. How these factors are integrated within the cognitive symptoms characterizing AD has thus become an increasingly important focus of research in AD pathogenesis, and clearly also fundamental to diagnostic assessment and treatment [3].

The focus on relating higher order cognition to lower level features has put an emphasis on brain organization and information distribution and how these aspects of brain operation may affect molecular and cellular features known to characterize AD [3]. In one proposal AD pathogenesis is theorized to specifically target synapses, with observed behavioral symptoms interpreted as the result of increasingly widespread synaptic dysfunction. In fact, findings from current studies are broadly consistent with a pathological influence restricted to synaptic contacts of the brain. This alignment is increasingly addressed in hypotheses that explore how AD affects the brain connectome, the organization of synaptic connections that underlie the brain's capacity for communication and information distribution [3,8]. *Specifically, these hypotheses attempt to harness the complexity of AD pathology within an overarching framework wherein the molecular and cellular changes in AD affect the network of contacts established between brain neurons.*

Whether a causal origin for AD is related to influences solely affecting synapse degeneration, however, is made uncertain by observations of network selectivity known to characterize AD. Affected brain regions notably lie chiefly within the default-mode network (DMN), a selective vulnerability that has led to the claim that AD is a DMN neuropathology [9]. Numerous techniques have been used to show that as AD progresses in severity, communication within the DMN becomes increasingly faulty. Functional connectivity studies, especially, reveal a selective but progressive change in connectivity across both cortical and subcortical loci [10], which precedes structural brain changes by several years [11]. The failure of the connectome hypothesis to explain AD's selective effect on the DMN suggests that factors beyond those involved in synaptic degeneration are also at play. Accordingly, despite having broader explanatory power than the amyloid cascade hypothesis, the AD connectome thesis remains limited in its ability to unify clinical with lower level physiological features within an etiological framework for AD pathology.

Importantly, despite its broad emphasis on neuronal connections, the connectome hypothesis conceptually divorces the synaptic structural organization from the brain's functional aspects, which notably underpin clinical observations; hence, it remains a low level cellular approach. This conceptual weakness has motivated a search beyond similar reductionist models [3] to functional considerations that are operative in brain performance, seen in the increasing interest directed to organismal level influences on brain function [12], which can exert downstream effects expressed during disease pathogenesis.

Crucially, organismal function is driven by global behaviors by which the organism is identified; that is, organismal behaviors both define the individual and determine the latent performance by which he interacts with his environment. Given the essential nature of these behaviors for survival, the brain possesses a rich array of mechanisms for sustaining functional integrity, from low level circuit maintenance, e.g., firing rates, to high level functional representations such as, the motor image. Indeed, homeostasis of brain functions is increasingly recognized as essential for preserving not only functional performance but also functional integrity amidst the brain's universal plasticity and exposure to external perturbations.

Global functional representations, especially, are cohesive representations of the body's actions built through integration of sensory and motor information. These guide performance and make sense of individual experience within the world [12]. Failure to preserve such global functional representations during AD degeneration [9,10], conversely, is likely to result in downstream cognitive dysfunctions, seen, for example in memory loss, one of AD's most characteristic clinical symptoms.

This paper will examine the role of functional homeostasis in sustaining global functional representations in normal and AD related pathology. First, evidence will be presented for preservation of physiological processes in circuit and network performance. Second, findings from sleep physiology, cortical map plasticity, and functional adaptations will be used to illustrate the presence of homeostatic systems that maintain and sustain higher order behavioral performance functions. Third, the paper will explore extant evidence for maintenance and restoration of global functional representations by the DMN, which are used to guide the individual's interactions with his environment. From the preceding survey, the paper will then develop the case for an overarching etiological framework in which AD pathogenesis flows from a failure in DMN homeostasis, particularly with regards to processes used to maintain global functional integrity.

Homeostatic Resilience in Network Function

Current studies reveal the presence of a plethora of lower and meso level homeostatic mechanisms designed to stabilize important cellular and circuit functional features, including the regulation of firing rates, establishment of FR set points, synaptic scaling, and maintenance of critical regimes and correlation structures [13,14]. Compelling evidence shows, for example, that adjustments in the strength of excitatory synapses of central neurons provide for activity stabilization by generating homeostatic set points that confine average firing rates of regular-spiking neurons to only

narrow ranges [15-17]. In other cases adjustments in the strength of excitatory synapses of central neurons enable activity stabilization [18-20]. For example, adjustment in the strength of all synapses of a neuron, a phenomenon termed synaptic scaling, is frequently observed. In other cases, such adjustments involve only a subset of synapses and can occur at either the presynaptic or postsynaptic side of the synapse, thereby modulating distinct aspects of circuit function. Both population and single-cell firing levels of the V1, primary somatosensory (S1), and auditory (A1) cortices in young animals, for example, initially drop and then rebound slowly to baseline, a phenomenon ascribed to homeostatic plasticity [21,22]. While the underlying features of most such mechanisms are unknown, several methods are thought to entail calcium ion channel insertion and/or removal to achieve equilibrium at targeted calcium levels [23]. Manipulations of mitochondrial function and energy metabolism are also proposed to modulate calcium levels, suggesting the presence of interactions between calcium targets and energy homeostasis [24].

Besides regulating firing rates and set points, cortical circuits provide for intermediate level controls that sustain information transmission by maintaining correlation structures across neuronal circuit members. For example, analysis of the pairwise activity of ensembles of V1 neurons in freely behaving rats reveal that correlations between neuron pairs increase in the light with respect to the dark, suggesting that interactions between neurons are enhanced in light conditions. In turn, enhanced interactions facilitate throughput of meaningful signals [25].

Mechanisms for such meso scale control are broadly organized into cellular building blocks targeting excitatory or inhibitory synapses, or intrinsic neuronal excitability [26,27]. Each of these building blocks can contain functionally diverse subclasses that operate over a variety of spatiotemporal scales and respond to distinct activity features. Many appear to be modular, as they can be independently activated and combined in various permutations, thereby generating a highly complex and discretely nuanced, response capability. Synaptic scaling, notably, is one of the most widely studied, homeostatic mechanisms for meso scale events. It can occur within a small locus of one or several synapses, or regionally, and involve pre and post synaptic mechanisms across a broad neuron population. Both forms are temporally distinguished, with local events taking place within a few hours and global synaptic scaling requiring days or weeks to develop [28].

Homeostasis and Higher-Order Cognition

Lower-level homeostatic mechanisms enable cortical microcircuits to restore responsivity in the face of circuit perturbations, preserving computational proficiency for task related performance [26]. Such mechanisms alone, however, do not provide oversight of higher order cognitive function. Given the centrality of cognition to organismal function and survival, it is thus likely that the nervous system would be endowed with a capacity for assessing the integrity of higher order cognition and restoring it when functioning abnormally. Indeed, Conant and Ashby [29] notably posited that ideal regulators model the systems they control, a claim they extended to embodied systems grounded in sense making and adaptivity, i.e., engaging autopoiesis and homeostatic renewal [30]. In cases of pathogenesis, higher order homeostasis can thus be expected to influence the disease state, shaping the overall spectrum of disease symptoms.

In line with this, several domains of investigation implicate higher order, homeostatic mechanisms used to monitor and restore cognitive function in the presence of ongoing perturbations and activity [31]. Among these are such disparate areas as sleep dependent synaptic homeostasis [32], cortical map plasticity and adaptive reorganization [33,34], and neural substrates for adaptive behavior [35,36]. Findings from these domains suggest that higher order homoeostasis is an inherent property of the central nervous system and yield insight into its mechanisms; in turn, they also reveal the potential of homeostatic mechanisms to affect the manifestation of higher order cognition in AD.

Sleep and Cognitive Homeostasis

The synaptic homeostasis hypothesis (SHY), a leading proposal for the physiology of sleep, conceives of sleep as a restorative process overseeing the brain's total synaptic strength [32]. During waking hours, overall synaptic strength increases due to learning processes. The increased synaptic strength, however, requires increased energy for maintenance, with the potential for saturating available supplies. This need incurs a corresponding demand to scale down overall synaptic strength. In response, the brain gates incoming stimuli during sleep in a brain wide process of reactivation. The expression of excitatory glutamatergic AMPA (Alpha-Amino-3- Hydroxy-5-Methyl-4-Isoxazole Propionic Acid) receptors, for instance, is reduced after sleep, when measured at the synaptic level [37,38].

Much evidence indicates that renormalization mechanisms use the slow oscillation to achieve down scaling of elevated synaptic strength acquired during wakefulness. Emerging from the massive interconnections of the cortical network [39], the slow oscillation generates sustained and patterned oscillatory activity even in the absence of sensory stimulation such as that of sleep or anesthesia. During sleep the entire cortex undergoes slow synchronized transitions between enhanced synaptic activity (Up states) and silence (Down states) at an approximate frequency of 1 Hz. (<100 ms) [40]. High density EEG recordings have revealed that the slow oscillation propagates as a wave traveling in an anteroposterior direction activating neurons in a stereotypical sequence during passage [41].

The complex spatiotemporal architecture of the slow oscillation provides a mechanism for essential intermediate level computations during slow-wave sleep, such as those related to learning or memory consolidation [32]. Supporting this claim, recent experiments demonstrate a link between ON states of the slow oscillation and sleep dependent sparing of neuronal populations during synaptic renormalization. Neurons directly involved in task dependent activity increase their firing rates slightly with sleep, whereas those indirectly involved undergo a substantial reduction in firing,

revealing the presence of a selective homeostatic process that occurs during sleep [42]. Additionally, ON states promote higher order processes like memory. The consolidation of memory during sleep via spindles and sharp wave ripples, for instance, occurs preferentially during ON states of the slow oscillation [43]. The spatial distribution of spindle events, further, can be modulated by prior learning with task-specific cortical regions exhibiting enhanced spindle density following training [44].

The participation of the slow oscillation in structuring memory consolidation reveals the presence of homeostatic processes involved in [45] generating the DMN. The DMN notably engages slow wave oscillation, and intracranial EEG recording studies of intra DMN synchronization show slow wave synchronization during memory encoding and recall [46]. Two features of the slow oscillation likely to support DMN homeostasis are the marked bistability of the firing rate and the regularity of the cycle duration. These features suggest that the slow oscillation represents a network firing rate equilibrium with a net intrinsic tendency to persist. Supporting this, partial blockage of inhibition in cortical slices does not lead to destabilization of the slow oscillation in cortical slices [47] underscoring the resilience of slow oscillations to exogenous perturbations and their suitability for structuring higher order networks.

Homeostatic Adaptive Reorganization of Cortical Maps: External Influences Modulating Higher Order Plasticity

Cortical maps are a fundamental organizational pattern adopted by the brain to represent sensory and motor information [48]. These topographical, higher order sensory and motor representations constitute dynamically maintained, functional mosaics that support perceptual and motor learning abilities [34]. Topographic organization within sensory pathways, for example, is posited to promote the comparison of information carried by distinct neuron groupings, probably through processing phenomena such as lateral inhibition and gain control.

Research accumulated over decades has revealed that sensory and experience dependent cortical plasticity drives the organization of these functional representations throughout life. Recent findings show, for example, that during early development the initial neural substrate is commonly organized across the entire cortex, exhibiting millimeter scale correlations, rather than being locally differentiated [49]. Later in development, sensory and motor information elicit the functional organization of neuron populations, tuning their responsivity for unique sources and patterns of input. More than 50 years ago, Hubel and Wiesel notably demonstrated that the absence of visual stimulation (within a critical developmental window) led to the absence of cortical ocular dominance columns, effectively causing cats reared under these conditions to become blind [50]. Subsequent studies have since confirmed that cortical map organization for all other modalities is linked to experience dependent input. Taken together, these results suggest that a common modular organization serves as a general, developmental cortical substrate on which area specific input elicits diverse functional behaviors.

In adults, the morphological and functional connectivity established during development is additionally subject to ongoing modification from sensory input and use dependent experience. Intensive athletic training, for instance, results in widespread organizational changes within cortical maps that involve sensory perception and motor control, thereby promoting new sensorimotor and cognitive skills. Moreover, following a peripheral nerve lesion, like that of amputation or spinal cord injury [51,52], cortical maps are substantially reorganized, revealing that they remain malleable beyond the critical periods of post-natal development. In subcortical and cortical somatosensory areas, this malleability entails changes in the spatial region occupied by neuronal receptive fields, and/or alterations in sensory sub-modalities such as proprioceptive and cutaneous sensitivities. Significantly, the events of reorganization are initiated within seconds of sensory deafferentation and evolve progressively over many weeks, so that neuronal areas deprived of their original input display novel sensory responses [34]. During this interval, functional capacity is transferred to distributed cortical areas and subcortical structures, enabling damaged functions to be restored and so constituting an adaptive strategy for functional compensation.

The formation and life-long reorganization of cortical maps is thus significant for the establishment, restoration, and reorganization of representation associated cortical function. Based on findings during development and adulthood, like those described above, there is a growing consensus that afferent input and use dependent, subject environment interactions actively promote adaptive behavior throughout life, refining and reshaping the anatomical and functional architecture of neural circuits [33]. Together, these findings suggest that the homeostasis of functional representations becomes increasingly dependent on external sources to drive the direction of cortical map plasticity, revealing a key dependence on the individual's interactions with his environment to shape the brain's sensory motor substrate for behavioral performance.

Functional Behavioral Substrates; Stabilizing functional plasticity

While the ubiquity of central nervous system plasticity is both widely recognized and invoked to explain the adaptive reorganization of cortical map representations [53-55], its presence has also raised questions regarding the stability of functional representations, such as 'what underlying mechanisms contribute to functional stability in the subject's interactions with a highly variable, environmental landscape' and 'how are these representations shared within a nervous system subject to ongoing plastic change'.

Insight into these questions has emerged from studies of spinal cord plasticity [35], where different motor behaviors share interneurons and control muscles via the same small numbers of motoneurons. Throughout life, various regimes and physical experiences modify motor performance, functions that are carried out via the interfacing of spinal cord pathways with their motor effectors. While the reliability of motor performance has traditionally been explained on the basis of dedicated spinal cord pathways formed during development, findings acquired over recent decades are

revealing that the spinal cord instead undergoes continual activity dependent change, much like cortical map representations in the brain [56,57], with new motor performances added and old ones modified. This means that the same structural scaffold supports an increasing diversity of functional configurations, as brain regions form and dissolve coalitions to execute different cognitive operations. Indeed, the revelation of such causal degeneracy implicates the presence of novel mechanisms that preserve function despite the addition of behaviors that would otherwise disrupt motor performance.

Much of the evidence revealing these mechanisms has been obtained through studies of the H-reflex (spinal stretch reflex), a spinal cord path conveying proprioceptive input to the spinal motor neurons [56,57]. This pathway is comprised of group 1a afferent fibers, their synaptic contacts on the motor neurons and the motor neurons themselves. Descending activity from the brain influences the pathway responses, modifying the H reflex so as to either increase or decrease its response [57], and affecting adaptive behaviors acquired through practice. Using this system, it has been shown that motor learning is contingent on plastic changes in both spinal cord and brain. Separation of the spinal cord and brain, for instance, shows that when the monkey triceps surae H-reflex is down-conditioned in one leg, the contralateral triceps surae H-reflex does not change [35]. However, when the animal is anaesthetized and complete transection of the thoracic spinal cord removes the brain's influence, the reflex on the down-conditioned side is larger than that of a na¨ive animal and the contralateral reflex is larger still, while retaining the overall reflex asymmetry created by the conditioning protocol. These unusual results reveal that substantial plastic changes in the brain are required to suppress spinal cord responses on both sides, and that the changes can selectively target a single limb. Besides showing that regulation of H reflex plasticity is distributed across the brain and spinal cord, these results additionally reveal that key performance features of the motor behavior are maintained despite the substantial changes incurred in its regulation.

Significantly, due to use of the same spinal circuitry, neural output for separate motor behaviors is necessarily combined, as is that of newly acquired motor behaviors. Consequently, when experience modifies neurons and synapses to create a new adaptive behaviour - and inevitably disturbs existing (i.e. old) adaptive behaviours that use these same neurons and synapses - adjustments to the neural substrate(s) must be 'negociated' (conceived as an equilibrium process) between functional units for the behaviors, termed 'heksors', to be retained. Specifically, physical variables (e.g., synaptic strengths, connectivity, etc) underpinning the key features and motor behaviors undergo continual change, while the functional features and/or behaviors themselves do not [35]. Hence, the functional stability of old and new behaviors is prioritized during acquisition of a new behavior. Taken together, the plasticity of the variables underpinning the two functional units implies a process of homeostasis in which functional representations serve to determine the circuit variables that permit retention of the old behavior and the incorporation of the new one; that is, the substrate of an adaptive behavior possesses homeostatic properties dictated by a functional prior [58], which supports its internal operation and interactions with other functional priors, thereby enabling retention of key performance features throughout life.

The Default Mode Network and Global Homeostasis

Higher order cognitive homeostasis

While the neural substrate for such priors is unknown [35], several approaches that have been used to explain bodily interactions with the environment, including action affordances (somato sensory engagement) [59], the motor image (covert action) [60], and the peripersonal space (bodily perception) [58], suggest that an analogous functional unit exists at the level of the whole individual. These approaches extend findings from individual behaviors to the 'subject' of experience in his interactions with the external world [58].

As the perceiver of experience is essentially linked to his physical body, these approaches exploit the body's interaction with the environment to establish a functional representation for the whole individual [58], which is referenced to the body's dynamic actions in the world. Action affordances, for example, are conceived in terms of the various motor activities the environment 'affords' to the body [59], thus implicating a functional prior that generates bodily representations of prospective motor activities vis a vis the body's range of free interactions with the environment. Consistent with this, animals are known to constantly update their body posture to meet behavioral demands imposed by the environment, with the posterior parietal cortex (PPC) and related networks maintaining awareness of the body's spatial configuration. Recent investigations, in fact, have shown the presence of strong tuning to head, neck, and back postures in the posterior parietal cortex and frontal motor cortex areas of ongoing behavior that can be decoded [61].

Homeostatic mechanisms used to maintain the individual's functional representation are likely to form core aspects of the brain's overall functional organization. Crucially, causal relations between brain structure and function are multiple [35]. The same structural pathways enable diverse functional arrangements [62,63]; hence, they reveal the presence of ongoing shifts in converging and diverging relationships between brain structure and function [64,65], much as occurs in the spinal cord. Such causal degeneracy implicitly reveals the need for a global functional representation, one that possesses mechanisms for its maintenance and restoration when perturbed.

The DMN and Global Representation

While early descriptions of the DMN as a task negative network suggested a role limited to switching between extrinsic and intrinsic functions – that is, limited to encoding internal thoughts that were suspended during external stimulus processing - it has become increasingly clear that the DMN is also intimately involved in other higher order forms of cognition, as well as in extrinsic activity [66], revealing a much broader role across multiple cognitive functions. These insights emerge from observations of DMN disengagement

involving such cognitive functions as self referential judgments, episodic memory, language and semantic memory, and social cognition. Among other findings, meta analyses show that DMN nodes are disproportionately engaged across cognitive domains [67]. Whereas the PCC and mPFC nuclei are differentially involved in self-other distinctions, the hippocampus is chiefly associated with episodic memory and the precuneus with visual imagery [66].

As such, these findings support an overall integrative role for the DMN in cognition [66]. In this capacity the DMN synthesizes an ongoing functional narrative, drawing on the various cognitive systems that together shape and unify the idiosyncratic experience of the individual [67]. Facilitating construction of the narrative is the DMN's structural organization, which features short path lengths and local and global hubs in the PCC [68,69] that could enable the DMN to intersect with other networks and promote global state changes. Significantly, dynamic causal modeling using human fMRI and intracranial EEG data reveal a sustained causal influence of the DMN on other brain networks. This, together with the known location of DMN nodes at the apex of a functional hierarchy, suggest that information is retrieved from multiple brain domains to construct a narrative unique to the individual [70].

Specifically, ongoing synthesis of incoming information over extended time scales [71] enables the DMN to build context dependent and idiosyncratic functional models of the individual as he interacts with the environment. This means that the DMN engages a process of 'sense-making' for the individual with respect to the world [71]. In line with this, the duration of integration increases progressively from lower to higher order cognition. Early sensory areas such as the visual cortex, for example, are influenced by context acquired over tens of milliseconds whereas those involving linguistic domains of the temporal cortex require longer intervals occurring over seconds [72]. Additionally, DMN responsivity is engaged by context and not by form, being relatively invariant to low level stimulus properties.

As with functional representations of discrete behaviors, context dependent modulation of the subject's functional representation (by the DMN) refines interactive behaviors for the individual, thereby promoting adaptive reorganization within the nervous system. Gibson notably posited the ecological theory of perception with its concept of affordances to explain how the generation of motor performance could optimize the subject's dynamic interactions with the world [59]. In the Gibson model, behavioral representations contained in memory are modulated by incoming input to generate prospective functional representations adapted to the ecological space. Like discrete behaviors, such prospective representations are likely to retain key performance features, thus requiring a stable functional prior capable of dictating the features needed and selected for retention. Taken together, the DMN actively and dynamically engages in persistent 'sense making' vis a vis the world to generate context dependent performance models as the ecological space unfolds over time.

Loss of DMN Homeostasis: A Framework for AD Pathogenesis

Conversely, the loss of this ability is likely to induce pathogenesis, including the deterioration of higher order cognitive functions, e.g., self-narratives in memory or motor imagery, as well as lower level features, e.g., circuit, cellular, and molecular properties, that support higher order cognition. More generally, AD related loss of DMN function can be expected to feature a reduced capacity for global integration and maintenance of the subject's global functional representation.

Studies of late life depression (LLD), for example, a highly recurrent and disabling condition, show persistent changes in DMN connectivity following LLD [73]. Compared to healthy subjects, remitted LLD participants exhibit lower connectivity within the somato-motor network and greater connectivity between the executive control and default mode networks (DMN). Robust differences in network functional connectivity are also observed between stable remitted and relapsed participants. Together, these results reveal a failure of homeostatic mechanisms to establish a stable DMN network in relapse patients and the generation of aberrant homeostatic properties in patients having prior psychiatric dysfunctions [73].

Extant studies reveal several connections that may bridge the chasm between clinical pathogenesis and the neural substrate for DMN homeostasis at circuit, cellular, and molecular levels. Sleep difficulties, particularly, have been linked to increased risk of AD and its related dementias and have been used as predictive biomarkers for the prognosis of cognitive decline [74-76]. Besides symptoms involving insomnia or sleep latency, there are marked influences on physiological features, such as sleep spindles and slow oscillations [77]. Sleep spindle density, duration, and amplitude display decreases not only with age but show even further decreases with AD. Slow oscillations also decline with respect to number and amplitude relative to healthy older adults [78]. In fact, changes in these features are emerging as sensitive biomarkers for neurodegenerative diseases like AD. Consistent with this, resting-state fMRI analyses show that default mode connectivity is related to spindle architecture and that this is highly correlated with AD clinical phenotype [79].

Significantly, such pathophysiology is linked to dysfunctional aspects of memory. AD related effects on coupling between spindles and the slow oscillation, for example, appear to hinder the brain's ability to retain recently learned material [74]. Whereas higher spindle density, faster down-to-up state transitions within slow oscillations, and the time delay between slow oscillations and nested spindles predict better memory performance in healthy controls, they fail to do so in early AD patients. Moreover, the tight coupling between spindles and slow oscillations seen in normal subjects contrasts with the irregular timing of AD subjects and their diminished ability to recall recently learned material (such as in verbal memory tasks). Spatial navigation originating from the hippocampal-entorhinal circuit is also affected in early AD indicating that AD pathogenesis additionally impairs hippocampal memory.

Memory and slow oscillation pathophysiology, in turn, implicate impaired homeostatic mechanisms affecting higher order cognition, particularly DMN roles in global integration and 'sense making', as well as network stabilization. AD related effects observed in spatial navigation, for instance, suggest that AD pathogenesis can affect cortical map plasticity and loss of the ability to integrate multimodal afferent sourcing [78]. The inability to engage in adaptive reorganization of cortical mapping, moreover, can be expected to impair use dependent functional refinements needed for adjusting to environmental conditions. At network levels, the diverse spindle architectures obtained from different clinical phenotypes [79] at risk for AD suggest the presence of effects on more global properties, including influences on functional representations that could act as priors for behavioral performance.

Significantly, targeted enhancement of homeostatic mechanisms could offer novel therapeutic options for restoring functional loss [80]. In silico models of AD incurred synapse loss, for example, demonstrate that loss of excitatory synapses diminishes network sensitivity to small perturbations, a general indication of loss of computational capacity. Recovery of sensitivity, in turn, depends on restoration of firing rate homeostasis through processes involving the upscaling of residual synapses.

Conclusion and Summary

Findings over recent decades have revealed limits in the ability of the amyloid cascade hypothesis to explain the causal roots of AD, which has led to the present consensus surrounding AD's multifactorial origin. Despite this consensus, ongoing efforts seek to construct a broad framework within which disparate elements can be unified and by which their interrelationship in AD pathogenesis can be determined. A favored notion has been AD's targeting of synapses, a thesis encapsulated in the connectome hypothesis of AD. Despite the appeal of this framework and its enhanced explanatory power for current pathogenic models, it has nonetheless been challenged by findings showing selective DMN vulnerability in AD, seen in altered connectivity readings measured years and even decades before the appearance of clinical symptoms. Efforts to explain selectivity based on reductionist paradigms like that of protein instigators, unfortunately, reintroduce multifactorial issues and, even more significantly, fail to account for the inherent organismal tendency to sustain functional integrity. Such homeostatic renewal is now known to operate at multiple levels, from molecular and cellular domains to circuit and network operation. Importantly, DMN homeostasis contributes to maintenance of global functional representations and provides for sense making in environmental contexts, thus stabilizing autopoiesis (self-maintenance) and promoting dynamic interaction with a variable world. Emerging findings of AD pathophysiology, seen in sleep disturbances and memory related dysfunctions, suggest that higher order, DMN homeostasis may be affected in AD, which could offer a broader causal framework illuminating the interdependence of varied molecular instigators, cellular and circuit disruptors, and systemic failures.

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