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Dementia and the Default Mode

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Abstract

Changes in regional activity levels and network connectivity occur across the lifespan within the default mode network (DMN) of resting brain function. Changes with age are noted in most components of the DMN, especially in medial frontal/anterior cingulate and posterior cingulate/precuneus regions. Individuals with age-related disease such as mild cognitive impairment (MCI) and Alzheimer's disease (AD) demonstrate additional default-related changes particularly in posterior cingulate/precuneus and hippocampal regions. As these regions are areas of known pathologic change in both normal aging and age-related disease, examining DMN activity may allow future studies to more fully assess the relationship between pathology and function in these regions. The ability to form this structure-function link could allow us to determine critical factors involved in the decline or preservation of function in the presence of age-related neuropathology.

Keywords

functional imaging; brain function; mild cognitive impairment; MCI; Alzheimer's Disease; AD; age; PET; fMRI; human

The default mode of brain activity

Functional neuroimaging has historically been used to determine patterns of regional activity associated with the performance of various cognitive operations. Recently, however, interest has moved toward studies of activity during passive or resting states of brain function. Much of the work in this area stems from pivotal studies by Shulman [1] and Raichle et. al. [2] where intrinsic activity attributed to a baseline state or 'default mode' was first proposed.

In a meta analysis of positron emission tomography (PET) data collected during both verbal and non-verbal visual processing, Shulman et. al. [1] noted that task-related deactivations, or decreases in cerebral blood flow (CBF) during task performance, occurred commonly across all studies. These deactivations were noted when task conditions were contrasted with a low level, often resting-state, condition which led the investigators to propose that active networks of brain activity were present during the baseline state. Several resting state networks have subsequently been defined, including those thought to be involved in functions ranging from visuoperception to executive function [2–4], yet the earliest and most extensively studied is the default mode network (DMN).

From the early studies [1,2], a specific set of regions were defined that exhibited greater activity during the resting state than during task performance. The areas included medial frontal/anterior cingulate, inferior temporal, posterior cingulate/precuneus and inferior

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parietal regions. Subsequent studies also identified medial temporal regions associated with this network [5,6], and together these areas remain the most consistently observed regions in studies of default mode function.

Previous functional neuroimaging studies have used two principal ways of examining DMN activity. The traditional approach is to contrast a low level condition (rest with eyes closed, rest with eyes open and fixed on a cross hair, or passive viewing) with a higher level cognitive activation task. With this method, regions in the DMN emerge as deactivations during higher level task performance. The spatial pattern of the task-related deactivations and the degree of deactivation can then be used as measures of comparing default function across subject populations, disease states, etc.. The underlying assumption with this method is that measures of deactivation allow one to assess the ability of the given study group to inhibit or turn off default-related activity during task performance.

The second approach of examining DMN activity involves isolating networks of brain activity that occur during the resting state alone. This has generally been done using one of two methods: independent component analysis and/or network connectivity analysis. Using the independent component approach, coherent spatiotemporal patterns of activity that occur during the resting state are identified, and the component related to the DMN is typically defined by the characteristic regional pattern of activity [4,6]. Using network connectivity approaches, an *a priori* region is usually chosen and regions with similar temporal time courses of activation are then determined [7,8]. With both methods, inferences can then be made regarding the spatial extent and relative magnitude of activity of DMN regions during the resting state alone, and the connectivity approach also allows for the assessment of the interaction between regions.

The functional role of the DMN is a topic of much debate, with some questioning the interpretation of the default mode as a measure of true baseline activity and in relation to cognitive operations [9,10]. The spatial pattern of default mode activity, however, originally prompted the theory of a baseline or default network involved in self-referential processes [1,11], spontaneous or stimulus-independent thought [2] and random episodic memory processes [6,12]. More recent theories propose that fundamental intrinsic processes such as information consolidation and stabilization may be related to activity in default mode regions [13–15]. Although there is evidence from both humans and animals that lend support to these theories, the exact function of the DMN remains unclear.

With the undecided nature of DMN function, is the study of this network a useful tool in the field of aging and age-related dementia? There is little doubt of the popularity of DMN studies in the current literature, likely because it is an easily produced, readily identified, and consistent pattern of brain activity. To the study of aging and dementia, however, the DMN offers a functional glimpse into regions of particular interest. From the disease prospective, many DMN regions are particularly vulnerable to neuropathologic cellular [16] and structural [17] change in mild cognitive impairment (MCI) and Alzheimer's disease (AD). The hippocampus, for example, demonstrates marked volume loss in both MCI and AD [18,19], and the posterior cingulate and precuneus demonstrate a pattern of early metabolic decreases that are a hallmark of AD [20,21]. Activity in these regions can be readily elicited during simple resting state scans, a benefit in the study of individuals with compromised or differential cognitive ability.

Default mode activity with age

DMN activity appears to be relatively consistent in younger individuals. The same general pattern of resting state activity is seen in frontal, cingulate, temporal and parietal regions when contrasted with a variety of task modalities [2,3] and across multiple imaging sessions

[4,22]. A similar pattern is also seen in both men and women [23]. Other data, however, suggests that changes within this network do occur across the lifespan.

Several age-related changes in the DMN have been noted. First, the network of regions involved may be larger in the older compared to the younger brain. In addition to those typically observed in young individuals, several regions in the inferior, middle and orbital frontal cortex, as well as medial and lateral temporal cortex show resting-state activity in older adults that is not apparent in the young [24]. Second, the magnitude of activity in some regions associated with the DMN changes as a function of age. Deactivation of the DMN during task performance is decreased in older individuals compared to younger and middle-aged individuals in medial frontal/anterior cingulate and posterior cingulate/precuneus regions [25–27]. Additionally, other studies have shown age-related decreases in resting-state activity levels alone within default mode regions [28] and decreases in the functional connectivity between these regions [29] when comparing young and older individuals.

Together, these findings suggest that changes occur in the pattern of activity and perhaps the processes related to the default mode from young adulthood to older age. The spatial increase in default-related regional activity suggests that the older brain may recruit areas beyond those typically used in the younger brain during default mode processes, a finding commonly observed in functional imaging studies and often attributed to functional reorganization in the aging brain [30,31]. In addition, the reduced deactivation or increased activity in regions commonly associated with the default mode during task performance has been interpreted as an inability of the older brain to inhibit or shift resources from default mode processes to those involved in the task at hand [25,26].

Although changes are observed when comparing young and older individuals, what happens to default mode activity as older people continue to age? In normal aging, we have shown that the major components of the DMN such as medial frontal/anterior cingulate, hippocampal and posterior cingulate regions retain relatively stable rest-specific activity levels over a period of 8 years in older individuals [32], also illustrating that the pattern of activity in these regions is reliable and reproducible over this time period (regional activity test-retest correlations r=0.51–0.68). These findings are important as they suggests that activity levels in some DMN regions may plateau in normal aging. This is likely not the case with pathologic aging, as some suggest that alterations in DMN activity may be a marker of incipient disease as detailed in the next section.

Default mode activity in MCI and AD

Several lines of evidence suggest that regions associated with the DMN may be predisposed to altered patterns of functional activity in pathological aging. In individuals with mild cognitive impairment (MCI), often considered a prodromal stage of Alzheimer's disease (AD), neuropathologic features are already present in some default-associated regions of the brain.

On the cellular level, the presence of neuropil threads (NT), neurofibrillary tangles (NFT) and amyloid accumulation in the brain are hallmarks of AD and are also prominent in individuals with MCI [16,33]. In AD, these pathologic features appear early in the hippocampus [34,35], and increase in severity as the disease progresses [36,37]. The posterior cingulate/precuneus regions are also affected with NFTs and diffuse amyloid accumulation, but usually at later stages than the hippocampus [36,38]. Interestingly though, of the two regions, the posterior cingulate/precuneus is one of the earliest brain areas to show amyloid β accumulation with *in vivo* fibrillar amyloid tracers [39].

Tissue loss is another neuropathologic change noted in both MCI and AD. For example, studies have shown that the regional volumes of lateral temporal [40–42], hippocampal [18,19,40,43], posterior cingulate [40–43] and precuneus [44] regions are decreased in MCI relative to normal agers. Of these regions, two of the earliest and ultimately most affected DMN areas in both MCI and AD are the hippocampus and posterior cingulate/precuneus. Volume loss or atrophy of the hippocampus can be observed between groups [18,19,40,43] and longitudinally in the same individuals over time [45,46]. Like the hippocampus, the posterior cingulate/precuneus areas also exhibit volumetric changes in MCI and AD [40,41]. Whereas some have shown that the greatest overall volumetric changes occur in medial temporal and precuneus regions in AD [40,44], higher rates of longitudinal tissue loss in both the hippocampus [47,48] and posterior cingulate/precuneus [49,50] may also predict the conversion from MCI to AD.

With the presence of these cellular and structural abnormalities, it is not surprising to observe functional alterations in these regions. Indeed, studies of the DMN have shown that there are changes in regional activity in both MCI and AD. In individuals with MCI, medial frontal, posterior cingulate and parietal regions exhibit decreased resting-state activity relative to normal agers [51]. Individuals with AD also show decreased activity levels [24] and decreased resting-state network activity coherence [52] in the hippocampus. Examination of task-related deactivations also shows altered patterns of activity. Individuals with MCI and AD show reduced deactivation of medial frontal, posterior cingulate and precuneus regions during task performance [53–55], and some studies have shown that the levels of reduced deactivation may be related to degree of disease state in these individuals [53,54].

Default mode activity and prediction of future outcomes

It is clear that early identification of at-risk individuals is of utmost importance, as disease-modifying treatments are likely to be most effective before the onset of clinical symptoms in individuals who will eventually develop AD. To this end, some investigators have used the DMN to examine functional activity in those at increased genetic risk for AD. Cognitively normal individuals carrying the APOE ε4 allele show smaller task-related deactivations of DMN regions relative to APOE ε4 non-carriers [56–58]. APOE ε4 carriers also show increased coactivation of medial frontal, retrosplenial, and hippocampal regions during the resting state alone [59]. These findings suggest that the DMN might be useful in predicting future outcomes in those at genetic risk for AD.

Other studies have examined the relationship between amyloid accumulation and DMN activity. A connection between amyloid accumulation and the DMN was originally made by Buckner and colleagues [60], who noted that the spatial pattern of fibrillar amyloid tracer Pittsburgh compound B (PIB) binding in young and older individuals was similar to that seen in studies of the default mode. Subsequent studies have examined the relationship between amyloid burden and the conversion from normal aging to cognitive impairment and dementia. Sperling and colleagues [61] found that DMN deactivations declined as a function of age in non-demented individuals, and that increased amyloid accumulation or PIB binding correlated with the functional imaging signal in medial frontal, posterior cingulate and precuneus regions of the DMN. Additionally, Morris et. al. [62] showed that age and cortical PIB binding were the primary predictors of time to conversion from normal aging to dementia over a 2.4 year follow up in the same individuals. While it is likely that multiple factors play a role in the decline to AD, these studies suggest that amyloid accumulation may be a critical component in the conversion process.

Several other key questions also remain in the study of age-related cognitive decline and dementia. For example, why do some individuals with the beginnings of cognitive decline eventually progress to dementia while others do not? How do some individuals with dementia-related neuropathology retain normal cognitive and functional abilities while others do not? Katzman [63] and Stern [64,65] propose that both brain and cognitive reserve processes play important roles in the progression to dementia related to accumulating neuropathology. The brain reserve theory suggests that structural features such as brain size and number of neurons play a role in the ability of the brain to function in the presence of increasing neuropathology [63], while the cognitive reserve theory proposes that the ability to effectively cope with neuropathology is also related to the ability to successfully maintain cognitive processes and/or use effective compensatory mechanisms [64,65]. DMN studies examining factors related to reserve show that measures of cognitive reserve [66] and related measures of intelligence [67] may mediate both regional activity and the interaction between regions within this network.

The link between structure, function and neuropathology is still not fully understood, however. Examination of the default mode network will allow for the study of brain activity levels within regions of known AD pathology to further assess these structure-function relationships. This is particularly important in individuals at-risk of or progressing to dementia, as preventing functional loss is an ultimate goal in the treatment of AD. Studies of the DMN may also be useful in determining factors which promote preservation of function in the presence of neuropathologic change, an important avenue of research in the field of age-related disease and dementia.

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