**Paper accepted for publication in Trends in Cognitive Sciences on 19 January 2020.**

# Deficits in Spontaneous Cognition as an Early Marker of Alzheimer's Disease

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**Keywords:** Default Mode Network, mind-wandering, prospective memory, involuntary memory, spontaneous retrieval, mild cognitive impairment, posterior cingulate cortex

**Abstract**

In the absence of pharmacological cure, finding the most sensitive early cognitive markers of Alzheimer's disease (AD) is becoming increasingly important. In this paper, we review evidence showing that brain mechanisms of spontaneous, but stimulus-dependent, cognition overlap with key hubs of the default mode network (DMN), which become compromised by amyloid pathology years before the clinical symptoms of AD. This leads to the formulation of a novel hypothesis, which predicts that spontaneous, but stimulus-dependent conscious retrieval processes, generally intact in healthy ageing, will be particularly compromised in people at the earliest stages of AD. Initial evidence for this hypothesis is presented across diverse experimental paradigms (e.g., prospective memory, mind-wandering), and new avenues for research in this area are outlined.

**Trends**

- The DMN was originally assumed to be involved in internally generated spontaneous thoughts, due to the high level of activity during "rest".
- Recent fMRI findings indicate that the DMN, and most notably the PCC, is involved in the manifestation of spontaneous cognitions triggered by stimuli in the environment.
- Years before the diagnosis, AD-related amyloid accumulation appears to compromise key hubs of the DMN, especially the PCC, associated with spontaneous stimulus-driven cognitive phenomena.
- The spontaneous retrieval deficit hypothesis posits that patients with aMCI and AD should demonstrate significant disruptions in bottom-up, cue-driven spontaneous cognitive processes. Evidence across prospective memory and mind-wandering studies supports this hypothesis.
- Tasks assessing spontaneous, but stimulus-dependent conscious retrieval processes may be a good diagnostic means for detecting early stages of AD.

**Glossary**

**Alzheimer's disease (AD):** A progressive and irreversible neurodegenerative disease, affecting primarily older population, which is characterized by significant impairments in episodic memory and other cognitive abilities, leading to a loss of functional independence.

**Default mode network (DMN):** A widely distributed functional network along the brain's midline that is important for self-referential information processing. It is characterized by high activations when people are engaged in processing internal thoughts and deactivations when individuals perform attentionally demanding experimental tasks.

**Intrusive memories:** Memories that repeatedly intrude upon consciousness, often against one's will, are hard to control, and may disrupt one's ongoing activities. Although they can be sometimes about positive events, they are predominantly negative and disturbing, and constitute a core symptom of the Post-Traumatic Stress Disorder.

**Involuntary autobiographical memories:** Memories of past events that pop into mind without any deliberate intention to recall anything, often when a person is engaged in some mundane everyday activities (e.g., driving, brushing teeth) and in response to easily identifiable triggers. They may refer to positive, negative, or completely neutral events such as remembering one's first romantic kiss, failing an exam, or buying food in a supermarket.

**Involuntary (or spontaneous) future thinking:** Involves mental representations about the future, which may come to mind unintended (unexpectedly) while being engaged in other habitual activities, and in response to irrelevant stimuli in the environment. They can refer to planned events (e.g., buying a train ticket tomorrow), plausible future events (e.g., a trip to Japan) or hypothetical scenarios and wishful thinking (e.g., winning the lottery).

**Involuntary semantic memories:** Fragments of semantic knowledge (e.g., someone's name, image of Big Ben, or a familiar song) that pop into mind unexpectedly, without any accompanying contextual information (e.g., memory of when we last heard the song). Research on mind-pops has focussed mainly on 'earworms' – when a song or a tune gets stuck in one's mind and repeatedly occurs over a period of time. Identifying triggers for these semantic mind-pops is more difficult than for other types of involuntary memories.

**Mild cognitive impairment (MCI):** Characterized by subjective and objective impairments in memory and cognitive abilities, without the loss of functional independence characteristic of AD. It is considered a transitional (prodromal) stage between normal ageing and AD, with MCI individuals having a higher risk of developing AD than normally ageing adults. Amnestic MCI is characterized by impairments specifically in memory and can be further sub-divided into single domain (memory impairment only) and multiple domain (impairments in memory and other cognitive functions) amnestic MCI.

**Mind-wandering:** This has mainly been defined as task-unrelated and stimulus-independent thinking, which occurs spontaneously while the person is supposed to be attending to a particular ongoing task. However, recent studies indicate that task-unrelated thoughts can sometimes be instigated deliberately or occur in response to incidental stimuli. Moreover, the dynamic nature of freely moving thoughts versus thoughts that are constrained by particular goals or concerns of the individual has also been stressed in the literature.

**Prospective memory:** Involves remembering previously intended actions at a particular time (e.g., making a phone call at 2:00 pm), or in response to a particular target event (e.g., passing on a message to a friend) in the future, termed time- and event-based prospective memory, respectively. Research has suggested that event-based prospective memory tasks vary in their reliance on spontaneous retrieval (e.g., effortlessly remembering to pass on a message when seeing a colleague) versus strategic monitoring (e.g., searching a crowded room to deliver a message to a particular person), while time-based tasks involve mainly self-initiated monitoring processes (e.g., checking elapsed time in the absence explicit target events or cues).

**Early Diagnosis of Alzheimer's Disease**

The number of older adults diagnosed with **Alzheimer's disease (AD)** (see Glossary) is growing rapidly. In the absence of pharmacological cure, attention has shifted towards identifying people at risk of developing AD (e.g., those with **mild cognitive impairment - MCI**), who are likely to benefit most from early disease management and care [1]. Consequently, finding cognitive markers with higher sensitivity and specificity for detecting early AD is becoming increasingly important [2,3]. Various cognitive tests assessing episodic memory recall have been traditionally used for early AD diagnosis [4,5], and several new tasks, measuring binding [3,6] and spatial navigation [6,8] processes, are being developed in an effort to increase diagnostic accuracy. Despite these efforts, most currently used tests involve deliberate encoding and retrieval processes [4,9], in which people use attentionally demanding (i.e., effortful) strategies to enhance recall. Such executive control processes are mediated by areas of the dorsolateral prefrontal cortex (PFC), which become substantially compromised at later stages of the disease [10-12] and are also subject to large ageing effects [7,13]. Therefore, more theory-driven cognitive approaches are needed to map particular cognitive processes to the neuropathological changes occurring at the earliest stages of the disease to answer the important question about which memory systems or processes are selectively impaired early in the course of the AD (*cf.* [2,7,14]) while not being affected by typical ageing processes.

In this paper, we formulate a novel hypothesis, based on recent evidence emerging from several different, but related strands of research. According to this hypothesis, the earliest accumulation of amyloid pathology in key areas of the **brain's default network** (**DMN**) is linked to significant disruptions in a distinct class of cognitive phenomena, that were relatively neglected until recently and, unlike currently used cognitive tests, are characterised by spontaneous retrieval processes.

**Brain Mechanisms of Disrupted Spontaneous Cognition in Early Stages of Alzheimer's Disease**

The first signs of neuropathological changes of AD tend to occur in posterior parts of the cortex, with anterior and dorsolateral PFC remaining relatively intact [10,11], resulting in disproportionate temporo-parietal atrophy in early stages of the disease [15,16]. The pathology involves the accumulation of tau-positive neurofibrillary tangles in medial temporal lobe (MTL) structures, spreading from the entorhinal cortex to the hippocampus [17], and the formation of β-amyloid plaques in the medial prefrontal and posteromedial cortices, especially in the posterior cingulate cortex (PCC) and adjacent areas [18,19]. These neuropathological processes, especially the β-amyloid accumulation, may progress insidiously with a slow presymptomatic course for many years before clinical symptoms are evident [1]. The preferential β-amyloid accumulation in PCC and adjacent areas with increased age, in comparison to orbitofrontal and dorsolateral PFC, has been also reported in a lifespan sample of healthy adults aged 18-89 [12].

Importantly, the PCC, MTL, and medial PFC, are anatomically and functionally strongly interconnected and form part of the brain's DMN [20,21]. Historically, DMN activity has been linked to **mind-wandering**, which involves spontaneous (i.e., unintentional) shifts of attention from the external world to one's inner thoughts, ideas and musings [22,23]. Therefore, the DMN has been often conceptualized as the network that is predominantly involved in stimulus-independent spontaneous processing [20,21,24,25]. However, spontaneous cognitions have also been studied in several other research areas and include phenomena such as **involuntary autobiographical memories** [26,27], **spontaneous future thinking** [28,29], some aspects of **prospective memory** [30,31], **intrusive memories** [32], as well as **involuntary semantic memories** or mind-pops [33,34]. What these seemingly diverse phenomena share with mind-wandering episodes is that thoughts, memories, or intentions come to mind spontaneously without any deliberate intention to think about them. Importantly, behavioural studies of these spontaneous phenomena indicate that very often they arise in response to easily identifiable cues, in other words, they appear to be stimulus-dependent [26,28,32,35-37] (for examples, see **Box 1**).

In this paper, we will first review available evidence from fMRI studies, which show that these diverse cognitive phenomena are mediated by the same DMN areas as stimulus-independent mind-wandering, which has significant implications for our understanding of the DMN and its functions. Moreover, by showing that the key DMN regions involved in conscious spontaneous cognitive phenomena overlap with the main areas of brain pathology in AD and MCI, we will formulate a novel hypothesis, which predicts that spontaneous (i.e., unintentional and effortless), but stimulus-dependent explicit retrieval processes, which are generally preserved in healthy ageing [36,38,39], will be significantly compromised at the earliest stages of AD. This hypothesis is highly counterintuitive, because it challenges current theories of cognitive ageing [40,41], which predict that both typical and atypical ageing predominantly impair performance on difficult cognitive tasks, relying on deliberate (i.e., intentional and effortful) control processes, whereas performance on easy tasks mediated by spontaneous retrieval with strong environmental support (i.e., bottom-up cuing) are relatively spared. However, we will review emerging evidence from several behavioural studies across diverse experimental paradigms that provide strong initial support for this hypothesis.

**Stimulus-Dependent and Stimulus-Independent Spontaneous Cognitions**

In recent years, there has been a dramatic shift towards studying thoughts and memories that come to mind spontaneously without any deliberate intention to recall them [39,42] (**Box 1**). Several experimental paradigms have been used to capture and measure these seemingly transient phenomena under controlled laboratory conditions. Studies of mind-wandering typically involve having participants engaged in a monotonous ongoing task while assessing the frequency with which their mind wanders off (see **Box 2**). The key assumption is that because participants are deliberately trying to concentrate on an ongoing task, any reports of mind-wandering would be indicative of spontaneous shifts of attention from ongoing stimuli to one's inner thoughts. Moreover, the use of predominantly abstract stimuli (e.g., single digits, letters or shapes) has led to the assumption that mind-wandering is an internally generated stream of thoughts that is not dependent on incidental stimuli in the environment. However, both assumptions have been challenged by recent findings. For example, studies have shown that on several occasions, participants report engaging in task-unrelated thoughts deliberately [36,37,43]. Furthermore, the existence of irrelevant cue words has been shown to be instrumental in eliciting reported involuntary thoughts about the past or the future during undemanding vigilance tasks [26,37,44-46]. This dovetails nicely with findings from numerous diary studies of involuntary autobiographical memories and future thinking [35,47] and experience sampling studies of mind-wandering [36,48], which have all confirmed the importance of incidental external triggers in eliciting spontaneous cognitions in everyday life.

Consequently, in addition to intentional versus unintentional mind-wandering [43], an important distinction between stimulus-dependent and stimulus-independent mind-wandering has been proposed [49]. Moreover, stimulus-independent mind-wandering appears to occur only in a minority of thought probes (20-25%), indicating that when participants are exposed to meaningful incidental stimuli, stimulus-dependent mind-wandering is the norm rather than the exception, both in the laboratory [37] and in everyday life [36]. In fact, being stimulus-dependent does not mean that the occurrence of a thought is less spontaneous than during instances of stimulus-independent thoughts. For example, during a boring lecture one may suddenly find themselves thinking about an upcoming holiday in Spain without any noticeable trigger or because the word 'Spanish' was mentioned by the speaker. What matters is that at the time of the thought popping up, there was no deliberate intention or desire to think about this particular holiday.

Such stimulus-dependent, but spontaneous retrieval processes are also often involved in event-based prospective memory tasks, where participants have to remember to do something in the future in response to a particular target event. In so-called focal prospective memory tasks, remembering an intended action is easy and often based on spontaneous retrieval processes upon encountering the target, for example, remembering to pass a message to a colleague when having a lunch with her. Seeing the colleague may result in the intention to pass her the message to pop to mind and this type of spontaneous "reminding" [50] can occur even before having the lunch in response to other incidental cues (e.g., someone mentioning the colleague's name at a meeting) [51]. By contrast, non-focal prospective memory tasks are more demanding because they require actively searching or monitoring for the target event, for example, passing a message to a colleague in a busy conference room [52] (**Box 3**). Importantly, in line with Craik's theory of cognitive ageing [40], healthy older adults typically show substantial impairments in remembering such strategic and attentionally demanding non-focal tasks, while age effects are smaller or absent in focal prospective memory tasks [53], which strongly rely on environmental support and spontaneous retrieval processes [54].

**Spontaneous Cognitions and the Default Mode Network: Review of fMRI Studies**

Neural activations during low-task demands, known to be conducive to mind-wandering, converge on key hubs of the DMN along the brain's midline, including anterior medial PFC, PCC, and the inferior parietal lobule (IPL) [20,55]. The PCC appears to play a key integrative role in the DMN, as it shows functional correlations with other regions of the network [56]. Moreover, the strong reciprocal anatomic and functional connections between the PCC and the hippocampus, may also partially explain its involvement in self-referential processes, including remembering past episodes/autobiographical events and constructing future mental projections (see [20,57]).

Links between mind-wandering and increased DMN activity have been demonstrated in several studies (for meta-analyses, see [58,59). Individuals reporting a greater tendency to experience task-unrelated thoughts exhibited higher activity in the core DMN regions during repetitive tasks in the scanner (e.g., [60,61]). However, the involvement of brain regions outside the DMN, most notably the dorsal anterior cingulate cortex and dorsolateral PFC, has also been reported [58,62]. The additional recruitment of these executive areas of PFC could be due to the difficulty of separating the spontaneous onset of mind-wandering episode from the maintenance of a train of thought in one's mind [63], or because participants engage in task-unrelated thoughts intentionally on a substantial minority of trials [43].

Several studies have conducted a more targeted investigation of brain activations involved in the actual onset of reported mind-wandering episodes while participants were completing a task in the scanner (e.g., [62,64,65]). For example, one key study [65] showed that levels of activation were significantly higher during brief intervals immediately preceding the reports of task-unrelated thoughts (i.e., both off-task thoughts and thoughts about external distractions) compared to task-related thoughts (both on-task and task-related evaluative thoughts) in several DMN regions, including the medial PFC, PCC/precuneus, and left posterior IPL/occipital cortex.

However, these studies did not distinguish spontaneous (unintentional) and intentional shifts of attention (or mind-wandering), and it is possible that some instances of off-task thoughts were initiated deliberately [43]. Several studies, therefore, examined mind-wandering in experienced meditators who had to concentrate on their breathing in the scanner and press a button when detecting spontaneous shifts of attention away from breathing because, unlike participants in standard laboratory tasks of mind-wandering, they would be less likely to start deliberately thinking about something else while meditating. Using this method, a recent study [66] showed that posterior parts of the DMN, including the MTL, PCC and posterior IPL, yielded significant activations just *before* the reported occurrence of *unintentional shifts of attention* to task-unrelated thoughts. In contrast, activations in anterior parts of the DMN, including medial and lateral PFC, temporopolar cortex and dorsal anterior cingulate cortex, were observed while participants were keeping the task-unrelated thought in mind (see also [67,68]). This contrasting pattern of activations emphasizes the importance of distinguishing the moment when the spontaneous cognition springs to mind and its subsequent maintenance in the mind in the form of a freely moving train of thoughts [22,63]. It is also in line with the findings of a meta-analysis [69] showing that activations of medial parts of the rostral PFC were associated with tasks involving mentalizing and reflecting on one's internal states.

Although studies, reviewed above, have mostly conceptualized mind-wandering as stimulus-independent, some studies have demonstrated DMN involvement in stimulus-dependent task-unrelated thoughts such as thoughts about external distractions (e.g., [65,68]). These findings are important because they suggest that the DMN may support the spontaneous occurrence of task-unrelated mental representations in general, irrespective whether they are triggered by irrelevant stimuli or internally generated (see also [70,71]). Strong additional support for this idea comes from fMRI studies of event-based prospective memory tasks, in which successful retrieval depends on encountering a target event in the ongoing activity. While in focal prospective memory tasks, encountering the cue often elicits spontaneous associative retrieval processes, retrieval in non-focal tasks relies primarily on active monitoring for the target(s) while performing an unrelated ongoing task [72] (see **Box 3**). Results of a recent meta-analysis of 22 studies, with 38 individual experiments and 461 activation foci, showed that different brain activations in focal and non-focal prospective memory tasks emerged only at the time of their retrieval [73]. Specifically, higher activations in non-focal than focal tasks were observed only in the left lateral anterior PFC (BA 10) and anterior cingulate cortex, while higher activations in focal tasks were found in the PCC, ventral parietal regions (i.e., posterior IPL and supramarginal gyrus), and the cerebellum (see also [74,75]). Importantly, such transient bottom-up prospective memory cue-related activations in PCC and ventral parietal areas were also reported in a study [76] with a different design, where participants did not need to perform the prospective memory task in some blocks of trials, but still encountered the previously relevant prospective memory cues.

Several studies on involuntary episodic memories (e.g., [77-79]) and intrusive memories [80,81] have provided further evidence on the role of the PCC, together with inferior parietal and MTL areas, in spontaneous stimulus-dependent retrieval processes. In those studies, while PCC was reliably involved in both voluntary and involuntary memory recall, dorsolateral PFC was active only during voluntary recall, suggesting that for voluntary recall to succeed, the additional recruitment of executive areas of PFC may be necessary [77,78].

Taken together, the review of fMRI studies provides converging evidence for the idea that the PCC and posterior parietal regions, like the IPL, may play an important role, together with MTL, in spontaneous, bottom-up retrieval processes across a variety of domains that can be classed under the umbrella of spontaneous cognitive phenomena. The role of anterior parts of the DMN such as the medial PFC in this process is currently less clear. Given its important role in endogenous mentalizing processes [69], it is possible that this region is involved in more top-down idea generation rather than stimulus-dependent retrieval processes [82,83].

**Disruptions of the Default Mode Network in Alzheimer's Disease**

The strong involvement of posterior parts of the DMN, especially the PCC, in eliciting a variety of involuntary cognitive phenomena is particularly interesting in relation to AD, which is characterized by pathological changes in brain regions overlapping with parts of the DMN, most prominently the hippocampus and PCC. Multiple lines of research support the notion that the earliest and most consistent extracellular β-amyloid depositions tend to occur in key hubs of the DMN, including the PCC, lateral parietal, and medial prefrontal regions [18,19,70,84], before they spread to the MTL and other subcortical structures. The initial β-amyloid accumulation in these regions is accompanied by disruptions in resting state functional connectivity, reductions in glucose metabolism, and cell atrophy [18,19,85,86]. These neuropathological processes are most pronounced in the PCC/retrosplenial cortex area [87,88], which has dense functional and anatomic connections with MTL structures, like the hippocampus [56,89]. Moreover, amyloid burden in these areas has been shown to result in disruptions in resting state connectivity even in cognitively normal asymptomatic older adults [90,91].

There is growing consensus that the β-amyloid accumulation in the key DMN regions may initiate a cascade of other downstream events, including accelerated aggregation of neurofibrillary tangles in the entorhinal cortex and hippocampus [1,92,93], which spread to cortical regions at the later stages of the disease [10,17,94]. Metabolic changes and cell atrophy in the PCC, due to amyloid burden, is comparable to or even stronger than changes occurring in the hippocampus due to tau accumulation [95,96] and may be related to brain or hippocampal atrophy in both healthy and MCI individuals [97-99]. Moreover, amyloid burden is detected in about 20% of healthy older adult samples [12,99], and it occurs years or even decades before the formal clinical diagnosis is made [19,100]. Most importantly, the presence of amyloid burden in cognitively normal and MCI individuals increases the likelihood of conversion to MCI and AD [101-103]. Although the evidence about relations between amyloid burden and impaired cognitive performance in healthy older adults has been somewhat mixed, a meta-analysis of 64 studies found a small, but significant correlation with episodic memory scores (accounting for less than 2% of total variance), while relations with semantic and working memory, processing speed and visuospatial function were not significant [104] (for similar findings, see [105]).

**The Spontaneous Retrieval Deficit Hypothesis**

Based on recent findings regarding the involvement of core regions of the DMN in spontaneous cognitive processes, and the same regions being preferentially compromised by amyloid depositions in preclinical AD (e.g., [12,18,84-85]), we have recently proposed the spontaneous retrieval deficit hypothesis [106,107]. This new hypothesis stipulates that the earliest (prodromal and even preclinical) stages of AD, characterised by amyloid accumulation in core DMN regions along the brain's midline, should be associated with significant disruptions in spontaneous, stimulus-dependent (bottom-up) retrieval processes that rely primarily on the PCC and its reciprocal interactions with the hippocampus (**Figure 1, Key Figure**). Because spontaneous retrieval processes often occur without additional recruitment of anterior and dorsolateral PFC, which get compromised at later stages of the disease [10-12], they may offer a unique possibility of detecting brain pathology in amyloid-positive individuals years before the AD diagnosis.

Currently, all dominant theoretical approaches on early cognitive markers of AD associate the deficits in long-term episodic memory tasks (e.g., free and cued recall, story recall, spatial navigation) with the neuronal and synaptic loss in the MTL [4-5,108], due to initial accumulation of tau protein in the entorhinal cortex and hippocampus [10,15-17]. However, tau aggregation is commonly observed in the brains of normally ageing individuals and is not specific to AD [10,109]. Moreover, healthy older adults' performance in episodic memory tasks is substantially impaired when compared to younger adults (for reviews see [9,40]), which can lead to diagnostic uncertainty during the earliest stages of the disease [2]. Most importantly, all currently used neuropsychological tests rely on deliberate, effortful and top-down retrieval processes, mediated by executive and attentional control regions in the PFC, which can partially compensate impaired task performance in both healthy older adults [9,110,111] and people with MCI [112,113].

The novelty of the spontaneous retrieval deficit hypothesis lies in its emphasis on β-amyloid accumulation as a key driver of functional, metabolic, and structural changes in brain areas outside hippocampus, and linking these changes to disruptions in a new class of cognitive operations, which rely on spontaneous retrieval processes. Indeed, the measurement of spontaneous retrieval processes requires new experimental paradigms (see Boxes 2-4) and performance on these tasks relies predominantly on MTL and PCC regions without additional recruitment of anterior and dorsolateral PFC. Although spatial navigation tasks are highly promising early cognitive markers of AD [7,8], because of their strong reliance on retrosplenial cortex (a structure that is adjacent to PCC and often considered as part of PCC [114,115]), they nevertheless share some similarities with standard episodic memory tasks. Indeed, they often involve intentional and strategic encoding and retrieval processes, which engage control areas of PFC [116-118], and despite some variability across tasks, by and large, show typical ageing effects [118-119].

**Review of Evidence for the Spontaneous Retrieval Deficit Hypothesis**

So far, the strongest evidence in support of the spontaneous retrieval deficit hypothesis derives from research on prospective memory and mind-wandering. Research on prospective memory has consistently demonstrated significant impairments at prodromal (MCI) and very early stages of AD [120], with some studies finding prospective memory scores to have higher discriminative power of detecting early stages of AD than standard episodic memory and attention tests [121-123]. However, only a handful of studies have directly compared performance on well-defined focal and non-focal prospective memory tasks in people with MCI and AD, which is important for assessing the spontaneous retrieval deficit hypothesis, because these tasks rely on spontaneous (and effortless) and deliberate (and effortful) strategic processes, respectively.

One of the first such studies [123] used a within-subjects manipulation of focal and non-focal prospective memory (see **Box 3, Figure I**) and showed that patients with very mild AD were disproportionately more impaired than healthy controls in a focal event-based task, mediated by spontaneous retrieval processes, than in a more effortful and demanding non-focal task. In the non-focal task, both healthy controls and AD patients exhibited low levels of performance and slower reaction times to ongoing task trials (compared to trials in the control block with no prospective memory task), indicating the presence of strategic monitoring processes in this condition, while no slowing was detected in the focal prospective memory condition. Using the same paradigm [124], these initial findings were replicated and extended on a sample of single- and multiple-domain amnestic MCI (aMCI) patients, suggesting that aMCI primarily penalized spontaneous retrieval processes [124]. More recently, the group by prospective memory cue-focality interaction was replicated in a sample of single-domain aMCI patients using a newly developed prospective memory task with pictorial material (pictures of famous people) and manipulating prospective memory cue-focality between- rather than within-subjects [106].

Additional evidence for the spontaneous retrieval deficit hypothesis comes from research on mind-wandering. The first such study [125] used an adapted version of the go/no-go task with thought probes (see **Box 2, Figure I**) and showed that patients with very mild to mild AD reported significantly fewer instances of task-unrelated thoughts and performed worse than controls on the go/no-go task. Importantly, this initial finding was recently replicated and extended in aMCI patients [107]. Considering that to properly assess the spontaneous retrieval deficit hypothesis in relation to mind-wondering, it is necessary to minimise group differences in the ongoing task performance (cf. [126]), this study employed thought probes during an easier (modified) version of the standard vigilance task, developed to study involuntary thoughts about the past and future [26,37], and distinguished spontaneous mind-wandering from deliberate shifts in attention (**Box 4**). The results showed that aMCI individuals reported significantly fewer spontaneous task-unrelated thoughts than healthy older adults, most notably thoughts about past events (i.e., involuntary autobiographical memories). Moreover, in both participant groups, the majority of spontaneous thoughts were reported as triggered by irrelevant words randomly presented during the ongoing task. These findings suggest that while irrelevant cues elicited the recall of involuntary autobiographical memories in typically ageing adults, this automatic bottom-up retrieval in response to environmental cues was disrupted in aMCI. Importantly, when a group of younger adults also completed this vigilance task, and rates of their mind-wandering and involuntary memories were compared to those in healthy older adults, no significant age effects emerged [127].

Contrary to the findings reported in [125] and [107], a recent study [128], in which thought probes were employed during a cognitively undemanding shape expectations task (see [126]), revealed no group differences in the frequency of on- and off-task thoughts between patients with probable AD and healthy controls (although subtle, non-significant differences were observed in the contents of thoughts along the continuum of on-task versus off-task thoughts). However, in contrast to [107], this study did not examine whether participants' off-task thoughts were spontaneous or intentional, and, second, participants were not exposed to meaningful cue words during the ongoing task. These discrepant findings suggest that not all spontaneous retrieval processes are disrupted at early-stage AD, but those processes of spontaneous retrieval that are cue-driven. This notion accords well with the results from prospective memory studies [106,123,124] in which significant disruptions were manifested in conditions where the exposure to focal cues failed to elicit thoughts about the prospective memory task in aMCI and AD patients, but not in healthy older adults.

**Concluding Remarks and Future Perspectives**

Evidence reviewed in this paper suggests that one of the key DMN hubs, the PCC, which is characterized by amyloid pathology many years before the official diagnosis of AD, is also crucially involved in spontaneous and effortless retrieval processes in response to task-relevant (in case of prospective memory) or task-irrelevant (in case of mind-wandering) stimuli. Although the hippocampus has also been thought to be involved in rapid and obligatory spontaneous retrieval (and encoding) processes [129,130], this involvement is probably achieved by its reciprocal connections with the PCC [56]. For example, a recent study [131] did not find any reductions in the rate of mind-wandering in amnesic patients with hippocampal lesions (although the lesions affected the contents of task-unrelated thoughts reported by patients).

The findings that spontaneous stimulus-dependent retrieval processes are significantly disrupted at the earliest (or prodromal) stages of AD, but are minimally affected by normal aging (in contrast to effortful retrieval processes), can potentially transform the current theoretical understanding of the most effective early cognitive markers of the disease and how they map onto the earliest neuropathological changes in the brain [2,13]. They may also have significant practical implications by helping researchers develop new and simple cognitive tests to assess spontaneous stimulus-driven retrieval processes, which may be used clinically for detecting and predicting the conversion to AD and even to MCI among individuals with subjective cognitive decline (cf. [132]). Given that currently used episodic memory tasks rely on effortful retrieval processes, which are also sensitive to normal ageing effects, the development of tasks based on spontaneous retrieval processes would be an attractive prospect for clinicians. The findings call for more systematic investigations of the spontaneous retrieval deficit hypothesis in MCI and mild AD and the examination of possible disruptions in spontaneous cognitions other than prospective memory and mind-wandering (see **Outstanding Questions**). One particularly important avenue for future research involves studying the relationship between amyloid burden, atrophy in posterior parts of the DMN and measures of spontaneous cognition. It is, for example, possible that relatively weak amyloid-cognition associations reported in previous studies [104,105] are due to researchers using standard tests of episodic memory rather than the tasks based on spontaneous retrieval processes.

Our review of the fMRI research on spontaneous cognitive phenomena also has important implications for understanding of the DMN and its functions. DMN has been consistently linked with task-unrelated thoughts or mind-wandering, which has been conceptualized as internally generated and independent of external stimuli (hence the terms self-generated or stimulus-independent thoughts) [22,23]. However, the idea that DMN activity is exclusively associated with stimulus-independent processes has been challenged by the latest evidence reviewed in this paper (see also [133,134] for further evidence and discussion), showing that the PCC, a core DMN region, is crucially involved in the manifestation of spontaneous thoughts in response to stimuli encountered in the environment. It is possible that other parts of the DMN, such as the medial PFC, support the occurrence of spontaneous task-unrelated thoughts in the absence of meaningful cues in the environment. For example, in a recent study [135], which employed ongoing tasks with numerical stimuli, patients with ventromedial PFC lesions experienced significantly fewer mind-wandering episodes (and marked absence of thoughts about the future) than patients with lesions outside the DMN and healthy controls. Furthermore, preliminary findings from another study [136] showed that (meaningful) verbal cues enhanced mind-wandering frequency in ventromedial patients (although they still did not reach the frequency levels displayed by matched controls). These novel insights call for more systematic investigations of the role of key DMN hubs in eliciting stimulus-dependent and stimulus-independent spontaneous thoughts (see also [137] for further discussion).

Future research will also be useful in informing current debates on the nature and definitions of mind-wandering, where some researchers consider mind-wandering as an umbrella term for a broad range of cognitive phenomena (including both intentional and unintentional forms of mind-wandering) [138] while others are calling for a narrower definition of the phenomenon (e.g., [139]). Clarifying the boundary conditions of mind-wandering, what constitutes its core aspects, and how they relate to the DMN are important questions that will occupy the minds of cognitive scientists in the decades to come

**Acknowledgments**

Work presented in this paper was supported by a Marie Sklodowska-Curie Intra-European Fellowship within the 7th European Commission Framework Program (FP-7) for Research and Innovation (under grant agreement no 623230).

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**Box 1: Spontaneous or involuntary cognitions**

The study of spontaneous cognitions in the form of explicit conscious mental representations, which pop into mind when one is not deliberately trying to think about them, has grown exponentially in the past 10-15 years. The terms 'spontaneous' and 'involuntary' have been used interchangeably in different fields of research to denote the absence of intention when experiencing such thoughts. There is increased realisation that rather than being rare phenomena, involuntary or spontaneous cognitions are ubiquitous in everyday life and may even represent a basic mode in which our cognitive system typically operates [50,140]. The common aspect of these diverse phenomena is that they tend to occur while people are engaged in undemanding daily tasks (e.g., travelling by bus, washing up) [26,33,36] and, often, in response to incidental cues in the environment [26,35-37]. For example, when driving past a particular post-office, one can suddenly experience a spontaneous recall of a previously formed intention to buy some stamps while in town (i.e., manifestation of spontaneous prospective memory retrieval), or how they bought foreign currency from this post-office last year (involuntary autobiographical memory). One may also start thinking about possible future trips (spontaneous future thinking) or find herself humming a tune from a post-office advert on TV (involuntary semantic mind-pop).

Considering that the person was engaged in an unrelated activity at the time these thoughts came to mind (e.g., driving and listening to the radio), they could be construed as brief episodes of task-unrelated but stimulus dependent mind-wandering [29,37]. For example, thinking about possible future trips or the need to buy some stamps may be construed as mind-wandering about the distant or immediate future [29,141], while having an involuntary autobiographical memory about buying foreign currency at the post-office – as mind-wandering about one's past [36,37]. Considering that these diverse phenomena consist of single thoughts rather than chains of freely flowing thoughts, characteristic of mind-wandering [22], one could argue that they may actually constitute the building blocks from which mind-wandering episodes are constructed from (see Figure I below). This proposition calls for more research examining the precise contents of mind-wandering episodes to investigate similarities and differences between mind-wandering and these other related cognitive phenomena [29,37,141].

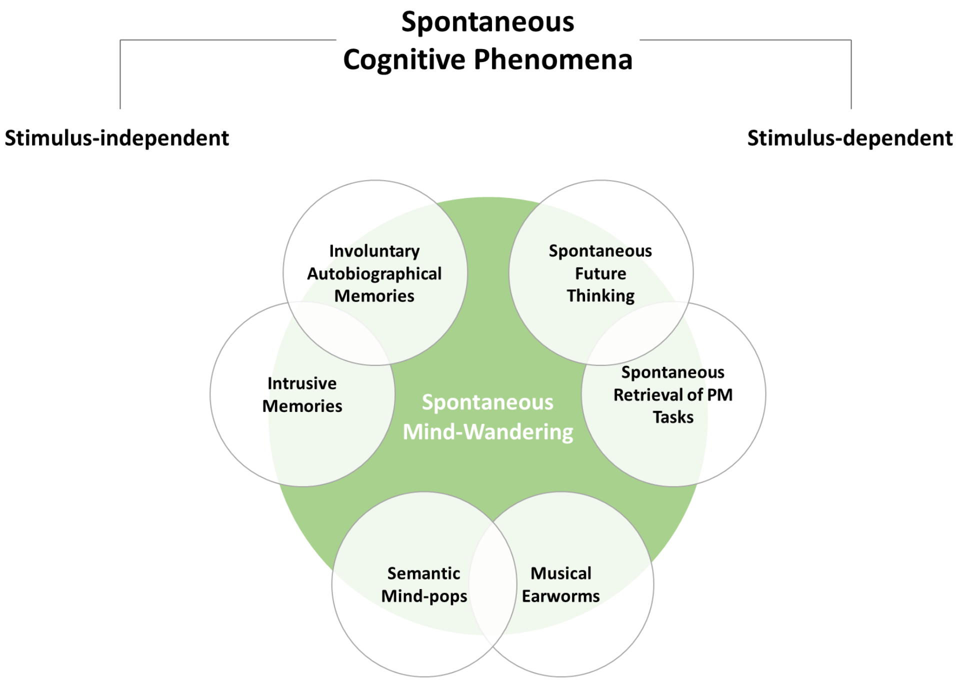



**Figure I. Spontaneous cognitive phenomena and mind-wandering.** The idea that spontaneous cognitive phenomena may constitute the raw cognitive material or building blocks of freely flowing spontaneous (unintentional) mind-wandering episodes, is represented by a circle depicting spontaneous mind-wandering and smaller circles of spontaneous cognitive phenomena which partially overlap with each other and with spontaneous mind-wandering. The area of spontaneous mind-wandering not covered by smaller circles depicts other possible types of spontaneous task-unrelated thoughts, for example, thinking about one's current situation (relationship problems), more abstract atemporal thoughts (does God exist?) or nonautobiographical events (moon landing in 1969). This indicates that the content of mind-wandering is broader than any one of the specific spontaneous cognitive phenomena. In addition, any particular episode of mind-wandering can involve rapid transitions between these different types of thought content [22,137]. The diagram also indicates that the spontaneous cognitive phenomena and mind-wandering can be stimulus-independent (i.e., a thought pops into mind without any noticeable trigger) or stimulus-dependent (i.e., thoughts that occur in response to a cue) [49]. Cues can be incidental stimuli in the external environment as well as internal states (e.g., feeling hungry may trigger thoughts about family dinner next Sunday) or preceding thoughts (e.g., thinking about a friend may trigger memories of your last trip together) [36,37,51].

**Box 2: Paradigms for studying mind-wandering**

In mind-wandering research, participants are typically asked to concentrate on carrying out a non-demanding monotonous ongoing task. In addition, in some studies, they have to evaluate whether they are on- or off-task during intermittent stop trials (probe-caught method), and in other studies they have to stop themselves to report a task-unrelated thought when they experience it (self-caught method) [23,142]. Although several different ongoing tasks have been used (e.g., simple vigilance, reading, and choice reaction time tasks), the most frequently used task is the sustained attention to response task (SART). In this go/no-go task, participants are presented with single digits (1 to 9) in the centre of the screen for a brief duration (e.g., 250 msec), followed by a visual mask (e.g., for 900 msec). Participants have to respond to each digit by pressing a key ("go" trials) and withhold their response on infrequent "no-go" trials when they see a target digit (e.g. 3).

Although the SART enables researchers to obtain behavioural measures of mind-wandering (e.g., speeded reaction times and commission errors), the primary focus has been on participants' self-reported instances of mind-wandering. Due to problems in noticing when one's mind starts to wander [143], most studies have used the probe-caught method in which participants are asked to report on the nature of their thought, just prior to being stopped, by choosing from response options provided on the screen. There has been a huge variability in the number and contents of response options provided (for a review see [142]). Typically, participants have been asked to report whether, or to what extent, their thoughts have been on- or off-task, and if the latter option is chosen whether they were aware or unaware of their mind being off-task (called zone-outs and tune-outs, respectively). However, more fine-grained response options have been used in some studies [65], distinguishing on-task thoughts from so-called task-related interference or evaluative thoughts about the task (e.g., "this task is so boring") and task-unrelated mind-wandering from thoughts about external distractions (e.g., "what is the noise outside?").

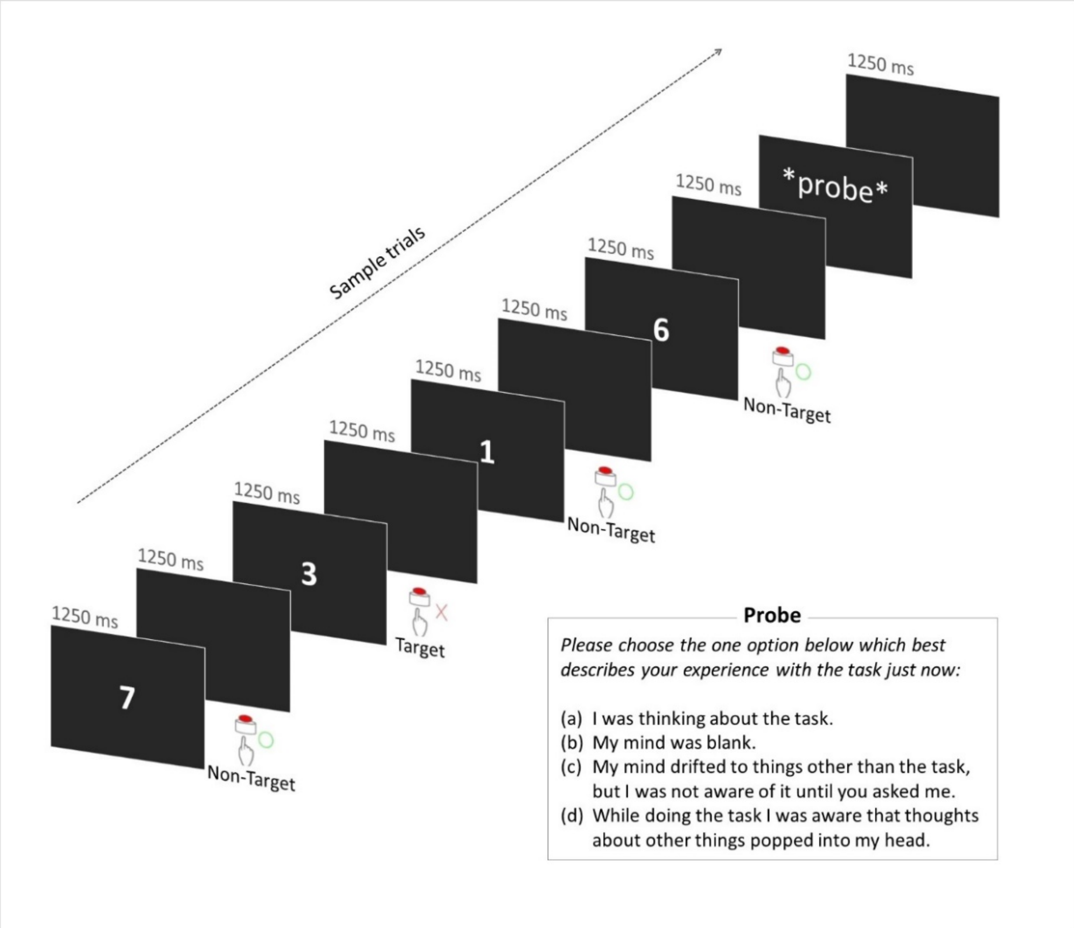



**Figure I. The sustained attention to response task.** The SART version with thought probes used in [125] to study mind-wandering in patients with very mild to mild AD and healthy controls. Compared to standard versions of SART, the presentation speed of trials and interstimulus intervals was slower, and each trial was followed by a blank screen (rather than a mask) to facilitate the performance of the clinical sample.

**Box 3: Prospective memory paradigms**

In the standard prospective memory paradigm [52], participants are engaged in an ongoing task (e.g., rating words for pleasantness, making word/non-word judgments in the lexical decision task, etc.). In addition, they have to remember to carry out an intended action (e.g., press a particular key on the keyboard) whenever they encounter a particular target event or cue (e.g., the word "office" or words beginning with the letter "S"). Thus, while concentrating on the ongoing task trials, which participants believe to be the focus of the study, those cues should act as reminders of the prospective memory task and signify that the relevant action can be carried out.

According to the multiprocess theory, the retrieval of intention at the right moment may be mediated by spontaneous retrieval processes (i.e., intention simply pops into mind) or by more strategic monitoring processes for the target event while performing the ongoing task [30]. Accordingly, a distinction between focal and non-focal tasks has been drawn [52,144]. In focal tasks, the processing involved in ongoing trials overlaps with the processing of key features of prospective memory target, which encourages spontaneous retrieval (e.g., when participants rate words for meaning in the lexical decision task and they have to respond to a particular word, such as "office" or "tortoise"). In non-focal tasks, there is little overlap (e.g., when rating words for meaning, but having to respond to a word starting with "S" or when seeing a particular syllable, like "ras") and, hence, it is less likely that participants spontaneously remember the prospective memory task when encountering the word. Ample behavioural evidence suggests that non-focal tasks are more difficult to remember as they require the deployment of attentionally demanding monitoring processes throughout the ongoing task. For example, participants slow down on the ongoing task in non-focal tasks in comparison to a control condition with no prospective memory component, while with focal tasks slowing is much reduced or non-existent [52]. Moreover, participants slow down on target word trials in comparison to non-target word trials even when the prospective memory task has been cancelled or postponed [52, Exp.5;54]. This indicates that previously relevant target words still manage to spontaneously elicit thoughts about the past prospective memory task (see also [76]). Different versions of the paradigm have been used to study focal and non-focal prospective memory in patients with AD and MCI, with most studies [123,124] using verbal cues (Figure I), while pictures of famous people were used in [107] as target events in focal and non-focal prospective memory tasks.

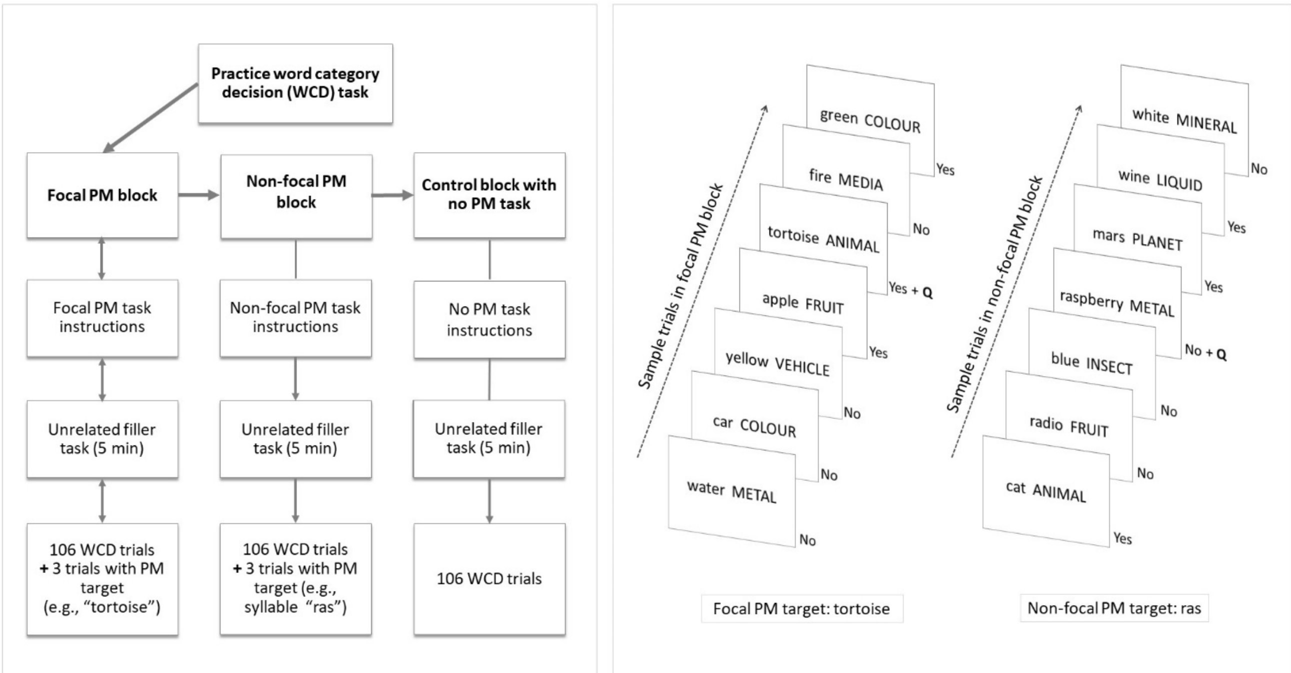



**Figure I. Focal and non-focal prospective memory paradigm.** (A) The paradigm used to study focal and non-focal prospective memory in patients with very mild AD and healthy controls [123]. Participants completed three separate blocks of ongoing word-category decision (WCD) task (in counterbalanced order) after a brief practice session. In the focal block, participants had to also press the Q key if they saw the word "tortoise" while completing the WCD task (which occurred 3 times). In the non-focal condition, they were instructed to press the Q key when they encountered the syllable "ras". In the control condition, no prospective memory task was given. (B) Shows example trials in the focal and non-focal blocks of the ongoing WCD task. In each trial, participants had to judge by pressing 'Yes' or 'No' button, whether the word on the left in lowercase letters was a member of the category presented on the right in uppercase letters. PM targets always appeared as exemplar items of the left rather than category words on the right.

**Box 4. Paradigm for studying stimulus-dependent mind-wandering**

The paradigm was originally developed to elicit and measure retrieval times of involuntary autobiographical memories in the laboratory [26] and was subsequently extended to study involuntary future thoughts [28] and spontaneous thoughts about the past, present and future [37]. It involves exposing participants to irrelevant cue words while they are engaged in a repetitive, cognitively undemanding, vigilance task (e.g., detecting very infrequent target slides with vertical lines among hundreds of non-target slides with horizontal lines), and using either self-caught or probe-caught methods to capture task-unrelated involuntary thoughts or memories (e.g., [26,28,37,145]; Figure I). More specifically, participants have to either stop every time they realize that they were having an involuntary thought or memory, or they are randomly stopped and asked to report what goes through their mind at that moment, and the reported thoughts are classified later in terms of their temporal focus (e.g., past, present and future) and the content. Results of such studies have shown that participants experience several involuntary thoughts during the vigilance task, the majority of which are reportedly triggered by irrelevant cue words presented on the screen [28,37,46].

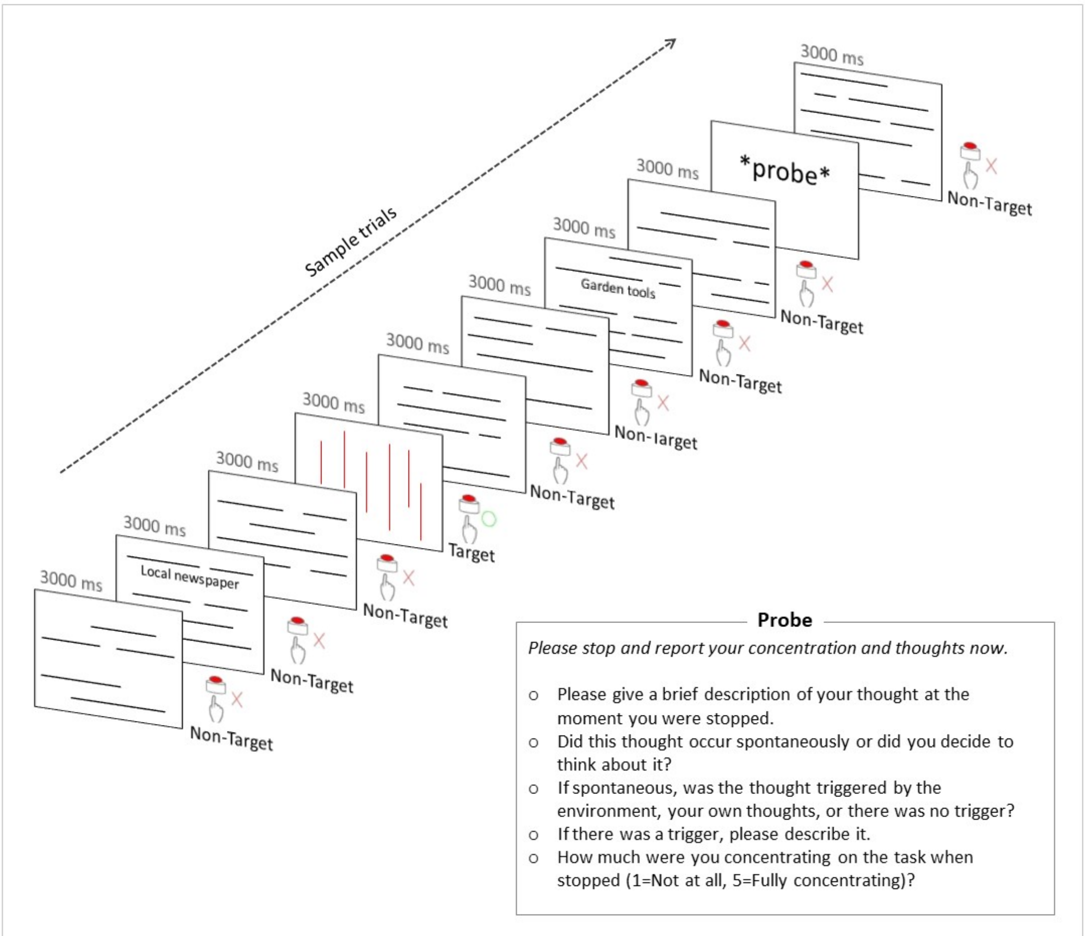
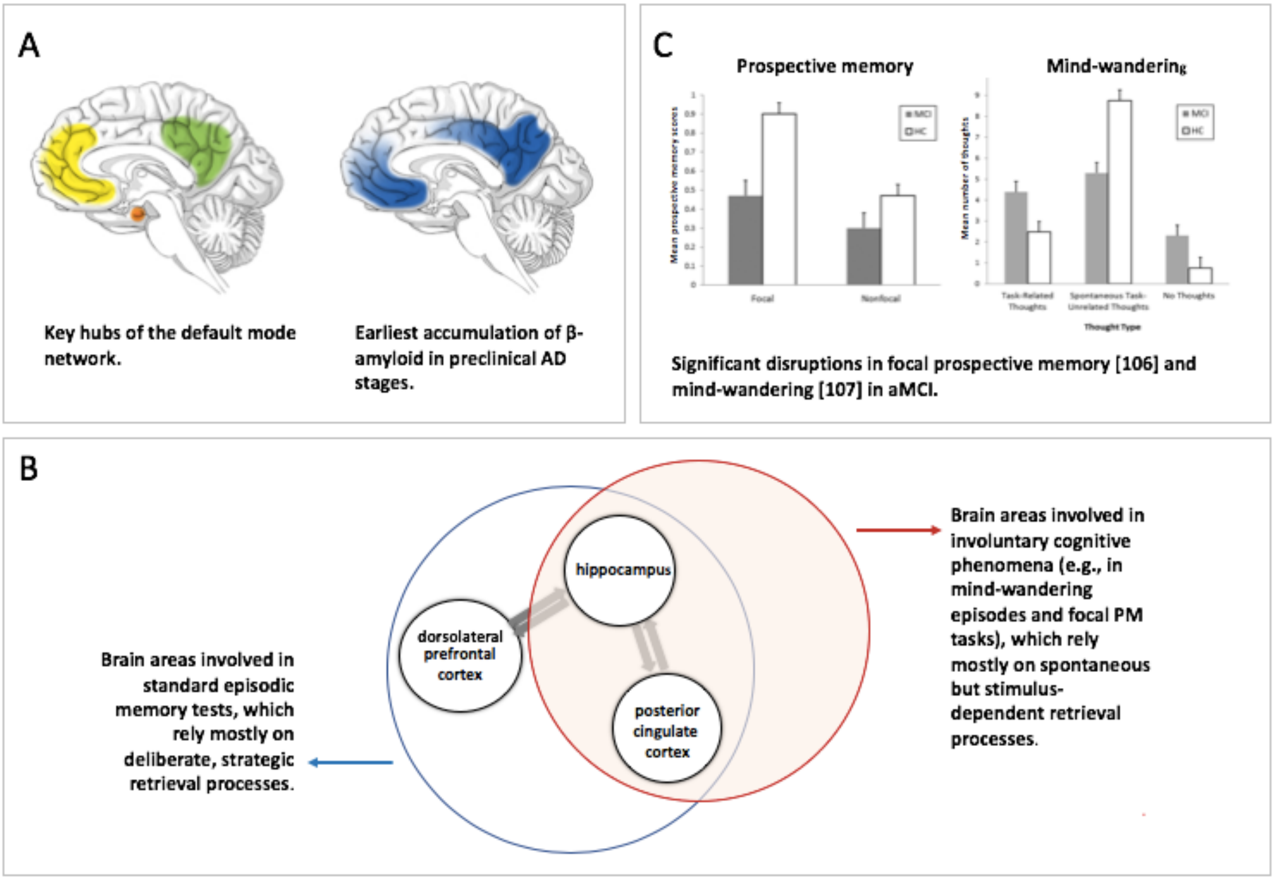



**Figure I. The vigilance task.** The version of the vigilance task [26,37], which was recently used by [107] to study mind-wandering in aMCI patients. Participants were presented with a continuous stream of 589 non-target slides (black horizontal line patterns). The infrequent target slides (*N*=11) with vertical lines were presented in red colour to help participants with target detection. On 200 slides participants were presented with cue phrases, which were irrelevant to the detection of target slides, but have shown to elicit spontaneous task-unrelated thoughts in previous studies [26,37]. To assess participants' thoughts during this easy and monotonous task, participants were randomly stopped 12 times and asked to report what was going through their mind at that moment, and whether the thought had popped into their mind spontaneously (and if yes, what was the trigger) or whether they had deliberately decided to think about it.

**Key Figure. Overview of the spontaneous retrieval deficit hypothesis**




(A) Key hubs of the default-mode network (DMN) include the posterior cingulate cortex (PCC, in green) and the anterior medial prefrontal cortex (PFC, in yellow) (left panel). Recent evidence has revealed a strong involvement of posterior regions of the DMN in various types of spontaneous cognition. The PCC appears to be crucially involved in the process of eliciting involuntary thoughts, often in response to incidental triggers in the environment or in one's thoughts [65,71,73,76,80]. This finding is of particular interest in relation to AD, because key hubs of the DMN, especially the PCC, are compromised by amyloid burden during very early prodromal and preclinical stages of the disease (right panel). (B) Based on this overlap, we propose a new hypothesis which predicts that individuals at risk of developing AD should exhibit disproportionate impairments in stimulus-dependent spontaneous retrieval processes (subserved by PCC and hippocampal activity), which are not affected by typical ageing, compared to more effortful tasks relying on strategic retrieval processes, which additionally recruit executive and control areas of dorsolateral PFC and are subject to large typical ageing effects. (C) In line with this hypothesis, recent findings confirm that under certain task conditions (i.e., when the ongoing task difficulty is matched between patients and healthy controls), patients with aMCI and very mild AD exhibit significant disruptions in spontaneous but stimulus-dependent retrieval processes across PM [106,123,124] and mind-wandering [107] paradigms, whereas group differences in more difficult and effortful tasks may be less pronounced (e.g., in non-focal PM condition as shown in the left side of the panel).