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Spontaneous retrieval deficits in older adults with amnestic Mild Cognitive Impairment and periodontal disease: Searching for early cognitive markers of dementia

Doctoral Dissertation

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Contents

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Declaration of authorship

I hereby declare that the work presented in this thesis is my own work. Two papers describing the outcomes of my research are presented in *the Overview of the research program* section.

I confirm that I am the first (leading) author of each paper, and none of the papers has been submitted as a requirement to obtain a different degree. The co-authors indicated and confirmed their contribution to the presented papers. The authors' contribution confirmations are attached to each paper.

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Abstract

The novel Spontaneous Retrieval Deficit (SRD) hypothesis predicts that people in the earliest stages of Alzheimer's Disease (AD) are particularly affected in spontaneous retrieval (e.g., mind-wandering) rather than deliberate retrieval measured by most of the currently used neuropsychological tests. The purpose of this Ph.D. was to test the robustness of the spontaneous retrieval deficit in groups with an elevated risk of developing AD, and to investigate whether the deficit can be detected even in groups that are selected according to noncognitive criteria, i.e., people with periodontal disease. In Study 1, 27 individuals with amnestic Mild Cognitive Impairment (aMCI) and 27 healthy controls were compared on mind-wandering while performing a novel task during which they were exposed to either highly meaningful or unmeaningful pictures. In line with the SRD hypothesis, a substantial reduction in mind-wandering was found among aMCI individuals. Importantly, the reduction was found with exposure to highly meaningful stimuli, but not to unmeaningful stimuli, supporting our expectation that the deficit is particularly pronounced in bottom-up and stimulus-dependent spontaneous processing. Study 2 investigated, for the first time, the relationship between spontaneous retrieval and periodontitis. Sixty community-dwelling dementia-free older adults varying in periodontal health completed a battery of neuropsychological tests and the same task as in Study 1, during which mind-wandering was evaluated. Periodontal health was assessed subjectively, and objectively, in terms of periodontitis-related changes in periodontal tissue, and periodontitis bacteria. In line with predictions, the objective and subjective symptoms of poorer periodontal health were associated with less mind-wandering, further supporting the SRD hypothesis. The findings from the Ph.D. research allow us to clarify the SRD hypothesis by showing which specific type of spontaneous retrieval best demonstrates very subtle signs of cognitive change, and show that these signs can be detected even before the prodromal stage of AD.

Streszczenie

Zgodnie z nową hipotezą Deficytów Spontanicznego Wydobycia (DSW), bardzo wczesne stadia choroby Alzheimera cechuje przede wszystkim osłabienie procesów poznawczych opartych na spontanicznym wydobyciu (np. zmniejszone błądzenie myślami). Celem pracy było zbadanie stabilności tego deficytu w grupach obarczonych ryzykiem choroby, oraz tego, czy występuje on również w grupach zagrożonych chorobą, ale wyselekcjonowanych na podstawie poza-poznawczych kryteriów, tj. u osób z paradontozą. W Badaniu 1, 27 osób w fazie prodromalnej choroby Alzheimera, czyli z amnestycznym Łagodnym Zaburzeniem Poznawczym, oraz 27 zdrowych osób starszych porównano pod względem błądzenia myślami (liczby spontanicznych myśli) podczas wykonywania nowego zadania eksperymentalnego, w którym wyświetlano im zdjęcia o wysokim lub niskim znaczeniu. Zgodnie z hipotezą DSW, w grupie klinicznej ogólnie zaobserwowano mniej spontanicznych myśli. Co więcej, DSW zaobserwowano jedynie po ekspozycji na zdjęcia posiadające znaczenie, co wskazuje, że deficyt jest szczególnie widoczny w przetwarzaniu spontanicznym, ale zależnym od bodźców (typu dół-góra). W Badaniu 2 analizowano, po raz pierwszy, relację pomiędzy DSW a paradontozą. Sześćdziesiąt osób starszych bez demencji, ze zróżnicowanym stanem zdrowia przyzębia, zbadano baterią testów neuropsychologicznych oraz narzędziem mierzącym błądzenie myślami, jakiego użyto w Badaniu 1. Stan przyzębia oceniano subiektywnie i obiektywnie, uwzględniając wywołane paradontozą patologiczne zmiany w tkance oraz obecność bakterii wywołujących chorobę. Zgodnie z przewidywaniami, silniejsze obiektywne i subiektywne objawy paradontozy wiązały się z redukcją błądzenia myślami, co stanowi nowy rodzaj danych potwierdzających hipotezę DSW. Wyniki przedstawionych badań pozwalają doprecyzować hipotezę DSW, pokazując, który konkretnie rodzaj procesów spontanicznego wydobycia najlepiej ujawnia bardzo subtelne oznaki zmian poznawczych oraz wskazują, że oznaki te można uchwycić jeszcze przed fazą prodromalną choroby.

1. Introduction

1.1 The need to develop methods for the early diagnosis of Alzheimer's disease

According to the United Nations report "World Population Ageing 2019"(United Nations Department of Economic and Social Affairs, 2019), the number of people over 65 years of age in the world will increase by 120 percent in 2050. Although it is good news that shows the growing effectiveness of modern medicine and health education in increasing global life expectancy, such trends are also related to a number of challenges that future societies will need to face. One of them is the growing number of people affected by age-related neuropsychological disorders, e.g., Alzheimer's disease (AD). It is estimated that currently every 3 seconds someone in the world is diagnosed with dementia – statistical predictions show that by 2050 there will be 131,5 million individuals worldwide suffering from dementia (Prince et al., 2015). If the solution to this problem is not developed in the near future, it will not only be the source of private tragedies of millions of people affected by the disease, but it will also be a trigger for potential economic and social turbulences. According to the World Alzheimer Report 2015 (Prince et al., 2015), the projected worldwide cost of treating and caring for people with dementia will reach the threshold of 2 trillion dollars in 7 years (close to the current GDP of Italy).

Given the scale of the problem, continued research is needed on the development of treatments for AD, but there are currently no effective drugs for the disease. Therefore, in the near future, it is also important to develop inexpensive early detection methods, because in the absence of an effective drug, it is the only way to increase the benefits of early disease management and reduce the cost of care (Sperling et al., 2014)**.** Studies have shown that the first cerebral pathological changes related to AD occur even up to 20 years before the clinical diagnosis of dementia (Jansen et al., 2015). It suggests that subtle markers of cognitive deterioration may be detectable decades before the disease is diagnosed using conventional

methods. It also suggests that researchers in this field should focus on identifying cognitive functions that deteriorate first in the disease process so that such subtle changes can be used as an early risk indicator of neurodegeneration. The recently developed Spontaneous Retrieval Deficits hypothesis (Niedźwieńska & Kvavilashvili, 2018) is one of such attempts.

1.2 Spontaneous Retrieval Deficits Hypothesis

The novel Spontaneous Retrieval Deficits (SRD) hypothesis stipulates that spontaneous (i.e., unintentional and effortless) retrieval processes, which are generally preserved in healthy ageing (Mullet et al., 2013; Rubin & Berntsen, 2009; Warden et al., 2019) will be significantly compromised in the earliest stages (prodromal and even preclinical) of AD. The hypothesis also predicts that cognitive tasks based on spontaneous retrieval will be more sensitive to early cognitive deterioration than tasks relying on deliberate and effortful encoding and retrieval processes.

It is a counterintuitive claim, as it seems that such effortless processes would decrease later than more demanding strategic functions. This may be the reason why clinicians have been using cognitive tests that involve strategic encoding and retrieval processes to detect AD. However, recent neuropsychological studies on AD etiology have shown that structures responsible for involuntary, effortless retrieval degenerate much earlier than structures in the prefrontal cortex that are responsible for strategic processing - see Kvavilashvili et al., (2020) for a review of evidence. Aggregation of tau-positive neurofibrillary tangles in the medial temporal lobe (Braak & Braak, 1991) and the presence of senile plaques in the posterior cingulate cortex (Buckner et al., 2008) were observed earlier than changes in the prefrontal lobe. The medial temporal lobe and the posterior cingulate cortex are interconnected and are part of the Default Mode Network of the brain (Raichle, 2015), which is associated with effortless spontaneous cognition (Christoff et al., 2016). As the authors of the hypothesis suggest (Niedźwieńska & Kvavilashvili, 2018), the fact that neurodegenerative changes are

found in these structures earlier than those in the prefrontal cortex, which is linked to deliberate cognition, may be an argument for considering spontaneous retrieval deficits as the earliest markers of dementia.

Many functions associated with involuntary cognition are associated with default mode network activities, such as mind-wandering (Niedźwieńska & Kvavilashvili, 2018) or prospective memory (Niedźwieńska et al., 2017). These phenomena are experienced repeatedly throughout the day, usually while performing undemanding tasks (Schlagman & Kvavilashvili, 2008). Although they seem to vary greatly, they all share a similar mechanism: they occur without the intention and effort of the person (Kvavilashvili et al., 2020). Importantly, for each of these functions, there have been documented deficits in individuals with prodromal and early AD, providing empirical evidence for the SRD hypothesis (Chi et al., 2014; Gyurkovics et al., 2018; McDaniel et al., 2011; Niedźwieńska et al., 2017; Niedźwieńska & Kvavilashvili, 2018).

Mind-wandering is the main phenomenon associated with involuntary cognition. The term refers to the situation where people, during a certain activity, start thinking about something not related to the ongoing activity, without their intention to do so (Schooler et al., 2011). Mind-wandering was the first spontaneous function that was linked to the activity of Default Mode Network of the brain and triggered the current discussion on spontaneous cognition (Kvavilashvili et al., 2020). Many studies explored the relationship between mind-wandering and age-related cognitive changes in healthy older adults (e.g., Krawietz et al., 2012; Maillet & Schacter, 2016). An interesting methodological approach to this issue is the study of Maillet and Schacter (2016), in which they compared mind-wandering between young and older adults. Participants were asked to complete the task, in which they were asked to decide whether the object presented on the screen was natural or man-made. Once in a while, the task stopped without warning, and the participants were asked if they had

experienced any thoughts before the appearance of the question. If the answer was confirmative, they answered more questions to determine whether their thought was spontaneous, and whether it was triggered by any of the shown pictures. In addition to comparing an overall number of spontaneous thoughts between the groups, the authors conducted an additional analysis in which they divided the participants' thoughts into two categories: stimuli-dependent thoughts that were triggered by one of the presented pictures, and stimuli-independent thoughts. Interestingly, the proportion of stimuli-dependent thoughts in all spontaneous thoughts experienced by older adults was higher, compared to younger adults. Maillet and Schacter (2016) suggest that since initiating stimuli-independent thoughts is likely to require more resources, reduced cognitive resources in older adults make them more dependent on external cues in generating thoughts.

Mind-wandering was also investigated in the context of the SRD hypothesis (Niedźwieńska & Kvavilashvili, 2018). Participants were asked to complete the vigilance task, during which the thought-triggering cues appeared (with positive, negative, or neutral emotional valency). Once in a while, the task stopped, and participants were asked if they had experienced any thoughts just before they were stopped. The results showed that individuals with amnestic Mild Cognitive Impairment (aMCI), which is a prodromal stage of AD, reported significantly less spontaneous, task-unrelated thoughts than healthy adults, and the vast majority of spontaneous thoughts were triggered by cues presented on the screen. The authors interpret these results as supporting the SRD hypothesis and suggest that spontaneous retrieval deficits may be particularly pronounced in stimulus-dependent spontaneous processing. In another study in this area (Gyurkovics et al., 2018) involving older individuals in an early stage of AD, participants completed a simple go-no-go task, which was occasionally stopped by the screen with questions about thoughts that participants might have experienced. Similarly to the study of Niedźwieńska & Kvavilashvili (2018), participants in

an early stage of AD demonstrated a reduced number of task-unrelated thoughts compared to healthy older adults.

1.3. The need to develop sensitive methods for measuring spontaneous retrieval

Given that a certain amount of behavioral evidence has accumulated in favor of the SRD hypothesis over the past few years (see Kvavilashvili et al., 2020 for the review), it seems that, although there is still much to uncover in this matter, it is the right time to start switching from testing the hypothesis per se to testing the robustness of the effect, and developing new methods able to detect spontaneous retrieval deficits in vulnerable groups in the earliest stages of dementia. Furthermore, it is important to determine a specific type of spontaneous processing (top/bottom, or bottom/top) in which the deficits are most pronounced to clarify the characteristics of the tasks that should be used to detect them. The final stage would be to introduce the SRD hypothesis into clinical practise.

To determine the parameters that the task must meet in order to best capture the effect of spontaneous retrieval deficits, it is necessary to compare studies in which the effect was found and those in which it was not. In studies that showed deficits in mind-wandering in clinical groups (Gyurkovics et al., 2018; Niedźwieńska & Kvavilashvili, 2018), experimental tasks shared number of similarities: a) the main ongoing task was very undemanding; b) it included thought-probes, i.e., participants were asked to answer the questions about their thought content in the indicated moments; c) the distinction was made between off-task thoughts and on-task thoughts. Furthermore, the task used by Niedźwieńska & Kvavilashvili (2018), required participants to determine whether the thought they had experienced was deliberate or spontaneous.

In contrast, two studies did not find reduced mind-wandering in clinical groups (O'Callaghan et al., 2019; Rasmussen et al., 2021). In O'Callaghan et al.'s study (2019), people with probable AD and healthy controls did not differ in the frequency of on- and off-

task thoughts reported during a shape expectations task. In Rasmussen et al.'s (2021) study, participants watched an audiovisual material that presented popular activities, people, and songs of their youth, and the comments that the participants had made during the film and shortly after were recorded. Individuals with mild to moderate AD did not have less comments related to autobiographical memories, compared to the control group.

However, unlike Niedźwieńska & Kvavilashvili (2018), neither of these studies investigated whether off-task thinking (O'Callaghan et al., 2019) or comments about the film (Rasmussen et al., 2021) were based on spontaneous or intentional thoughts. Since there is empirical evidence to show that participants deliberately engage in task-unrelated thoughts (Plimpton et al., 2015; Seli et al., 2016; Warden et al., 2019), not all trials with off-task thoughts can be considered spontaneous retrieval. Therefore, the lack of deficits may be due to the fact that the reduction in spontaneous task-unrelated thoughts in clinical groups may be obscured by the unreduced number of deliberate thoughts in the early stages of AD. In Rasmussen et al.'s (2021) study, contrary to the studies that found reduced mind-wandering in aMCI and early AD (Gyurkovics et al., 2018; Niedźwieńska & Kvavilashvili, 2018), there were no thought-probes, but participants commented on the film whenever they felt like doing it. Therefore, the study may have measured inhibition control rather than spontaneous retrieval efficiency, as AD participants, due to reduced inhibition, may have felt less reluctant to share their thoughts.

An important factor that could have contributed to the lack of group differences in mind-wandering in the study by O'Callaghan et al. (2019) was that, unlike Niedźwieńska & Kvavilashvili (2018), the ongoing task during which thought-probes were administered did not include meaningful stimuli. The results of previous studies suggest that, when exposed to meaningful stimuli, which can serve as thought-evoking cues, participants most often report stimulus-dependent thoughts, i.e., thoughts directly related to the stimuli present in the

environment (Plimpton et al., 2015; Warden et al., 2019). Given this observation, it is important to consider the distinction between stimulus-dependent and stimulus-independent thoughts when analysing mind-wandering data. This distinction is supported by fMRI studies that show that the posterior cingulate cortex, a key hub of the Default Mode Network, is crucially involved in the manifestation of spontaneous thoughts in response to stimuli encountered in the environment (Beck et al., 2014; Lamichhane et al., 2018; Spreng et al., 2018). Based on the distinction between stimulus-independent and stimulus-dependent mind-wandering, the SRD hypothesis stipulates that aMCI and very mild AD cause deficit mainly within the spontaneous, but bottom-up and cue-driven, retrieval processes for which the presence of meaningful cues is essential (Kvavilashvili et al., 2020; Plimpton et al., 2015). *One of the goals of my project was to investigate whether the quality of stimuli present in the environment influences the size of reduction in mind-wandering in clinical groups, which would provide evidence for the claim that the deficit is most pronounced in bottom-up spontaneous processing.*

Taking into account the characteristics of the studies that managed and did not manage to capture the spontaneous retrieval deficit in clinical groups, it is possible to list the optimal parameters of the experimental task that would maximise the chance of detecting the deficit. First, the difficulty of the ongoing task should be low and matched between patients and healthy controls to exclude the possibility that cognitive resources, which may be needed for spontaneous processes, will be much more limited among patients. Second, there should be stimuli in the environment that have the potential to serve as cues to trigger spontaneous thoughts. Third, the experimenter must distinguish between spontaneous and intentional task-unrelated thoughts. Fourth, thought-probes must be used during which participants are directly asked what they were thinking about, to avoid the impact of group differences in reluctance to share inner thoughts. *Another goal of my project was to verify whether the task*

that meets all the criteria listed above would successfully capture the spontaneous retrieval deficit in the clinical groups.

1.4. The need to test the SRD hypothesis in new groups at risk of dementia

So far, all studies on the SRD hypothesis have focused on individuals with aMCI or early AD (see Kvavilashvili et al., 2020 for the evidence). Although the spontaneous retrieval deficit can be captured in these groups, they are selected from the population of older adults based on the criteria of their cognitive capacity. To show even more clearly the robustness of the deficit and provide stronger evidence for the SRD hypothesis, it is necessary to show that the deficit also emerges in groups with the documented elevated risk of dementia, but not selected according to cognitive criteria. One of such groups are individuals with periodontal disease.

In recent years, there has been a rapid shift towards investigating the link between periodontitis and AD (Asher et al., 2022; Tonsekar et al., 2017). This interest is fully justified as, unlike AD, periodontitis can be successfully treated. Sufficient evidence for the triggering role of periodontitis in the process of dementia development would allow clinicians to successfully assess and reduce the risk of AD indirectly, by treating gum diseases. A substantial part of the research in this area consists of longitudinal studies (e.g., Chen et al., 2017; Choi et al., 2019; Ide et al., 2016; C. Y. Lee et al., 2020; Y. L. Lee et al., 2017; Tzeng et al., 2016). In one of these studies, 60 older adults were evaluated in terms of dementia and periodontitis. At 6 months of follow-up, people with baseline periodontal disease showed significantly higher cognitive decline than people without baseline gum disease (Ide et al., 2016). Similar results were observed in a study with much longer follow-up (10 years) and a large international sample (30 thousand participants): baseline periodontitis significantly increased the risk of developing AD (Chen et al., 2017). According to one of the most common explanations of the relationship between periodontitis and AD, chronic exposure to

periodontitis-related pathogens, and the inflammatory state in the gum that is caused by them, trigger the autoimmune response of microglial cells in the central nervous system, leading to neurodegeneration (Wu & Nakanishi, 2014). Claims about the triggering role of peripheral gum inflammation in AD etiology are supported by numerous studies that show a significant relationships between AD and the level of antibodies of periodontitis (Kamer et al., 2009; Noble et al., 2014; Sparks Stein et al., 2012) .

Despite the data that confirm the relationship between periodontitis and AD, there is still no clear answer to how periodontitis pathogens could trigger brain inflammation. One postmortem study showed that brain tissue from AD-affected people, in contrast to healthy adults, included periodontitis pathogens, suggesting that infection may somehow cross the blood-brain barrier (Poole et al., 2013). The hypothesis of the brain „invaded" by bacteria has been repeated in many theoretical models regarding this issue (Kamer et al., 2008). One of them applied the transgenic mouse model, in which AD mice were infected with periodontitis (Ishida et al., 2017). Then, the speed of cognitive deterioration was compared between AD mice infected with periodontitis and AD mice without periodontitis. Infected mice cognitively deteriorated significantly faster, which, according to the authors, may be linked to inflammation.

The next goal of my project was to investigate, for the first time, whether people with a high number of symptoms of periodontal disease will show reduction in spontaneous retrieval (as measured by reduced mind-wandering) when compared to people with a low number or no symptoms of periodontitis. Such a result can provide strong support for the SRD hypothesis by demonstrating that the spontaneous retrieval deficit is detectable even in groups that are selected according to noncognitive criteria, and thus proving its robustness and effectiveness in early detection of very subtle changes in individuals with an elevated risk of dementia. So far, there has been only some support for the relationship between

periodontitis and spontaneous retrieval coming from the two studies that analysed the relationship between periodontitis and prospective memory (Bergdahl et al., 2007; Manchery et al., 2021). Poorer periodontal health was associated with poorer event-based prospective memory, but not with the other type of prospective memory (time-based). The analyses of prospective memory mechanisms (McDaniel & Gilles, 2000, 2007) suggest that performance in event-based tasks can be based on the spontaneous retrieval of intended actions, whereas time-based tasks require strategic and effortful retrieval.

2. Overview of the research program

The main objective of the research was to test the robustness of the spontaneous retrieval deficit in groups with an elevated risk of developing AD and to provide stronger support for the SRD hypothesis. Specific objectives were: (1) to provide further support for the SRD hypothesis by showing that if a cognitive task meets certain criteria, it is capable of showing the spontaneous retrieval deficit, measured by reduced mind-wandering, in the prodromal stage of AD, i.e., aMCI, (2) to demonstrate that the size of this deficit will depend on the quality of stimuli present in the environment, and therefore support the claim that the deficit is particularly pronounced in bottom-up and stimulus-dependent processing, (3) to demonstrate the spontaneous retrieval reduction in a group of individuals at a higher risk of dementia, but not selected on the basis of neuropsychological criteria, i.e., people with a high number of periodontal disease symptoms, and therefore show that the deficit can be detected even before the neuropsychological diagnosis of cognitive deterioration is made.

To accomplish these objectives, two studies were conducted.

2.1. Preview of Study 1

Study 1, presented in our paper published in *Scientific Reports* (Wereszczyński & Niedźwieńska, 2022), served to achieve the first two specific objectives. We expected that, if the task used meets certain criteria (described in Introduction), aMCI individuals will report

less mind-wandering than healthy older adults. Based on Niedźwieńska & Kvavilashvili (2018), we also expected that thoughts about the past, compared to thoughts about the future and present, would most strongly demonstrate the reduction of mind-wandering in aMCI. Furthermore, we expected that this reduction would be larger after exposing participants to highly meaningful stimuli than after exposing them to unmeaningful stimuli.

In the first step of the project, we modified a very easy categorisation task that had been created by Maillet and Schacter and used to measure mind-wandering in healthy adults (Maillet & Schacter, 2016). We modified the task to be able to develop two versions of it: one version with highly meaningful stimuli, i.e., pictures rated by participants as highly familiar based on their personal experience, and the other version with unmeaningful pictures, i.e., rated by participants as highly unfamiliar.

In the proper study, 54 participants (27 with aMCI and 27 without it) completed both versions of this task during which they were asked to decide whether the objects depicted in the pictures on the computer screen were artificial (man-made) or natural: In one version, objects were highly meaningful to participants; in the other version they were unmeaningful. The task included thought-probes during which participants described their thought content the moment before they were stopped, and then used several dimensions to clarify the nature and content of their thought, if they had any.

We took special care for the clinical group to meet all the diagnostic criteria for aMCI, described by Petersen (2004). For this purpose, a battery of neuropsychological tests (Hopkins Verbal Learning Test, California Verbal Learning Test, Addenbrooke's Cognitive Examination III) and questionnaires was administered in individual sessions. The inclusion criteria for the aMCI group included: (a) the presence of a subjective memory complaint; (b) objective memory impairment evidenced by a score at or below 1.5 SD of the mean of peers on at least one test of the neuropsychological screening battery evaluating episodic memory;

(c) not meeting the criteria of DSM-5 for dementia, (d) preserved general cognitive function as confirmed by a normal score on the Mini-Mental State Examination (normality cut-off score: 24) (Measso et al., 1993) ; (e) maintained activities of daily living or slight impairment in instrumental activities of daily living, confirmed by no more than one item showing deterioration in the Instrumental Activities of Daily Living subscale of the Nurses' Observation Scale for Geriatric Patients; (f) absence of severe depression.

We grouped responses in thought-probes into: spontaneous task-unrelated thoughts (mind-wandering); spontaneous task-related thoughts; deliberate thoughts; no thoughts. The vast majority of spontaneous task-unrelated thoughts in both groups were stimulus-dependent.

The main findings were in line with our expectations. The aMCI group in general experienced significantly fewer spontaneous task-unrelated thoughts (less mind-wandering) than healthy older adults. There were also significantly more “no thoughts” probes in the aMCI group than in the control group. Furthermore, aMCI individuals reported significantly fewer spontaneous task-unrelated thoughts (less mind-wandering) than healthy controls when participants were exposed to highly meaningful stimuli, but not when exposed to unmeaningful stimuli. Finally, the reduction in mind-wandering in aMCI was most pronounced for past-oriented, spontaneous, task-unrelated thoughts (involuntary autobiographical memories).

Reference: Wereszczyński, M., Niedźwieńska, A. (2022). Deficits in spontaneous and stimulus-dependent retrieval as an early sign of abnormal aging. *Scientific Reports*, *12*, 9643. https://doi.org/10.1038/s41598-022-13745-6 (see Attachment 1)

2.2. Preview of Study 2

Study 2 is presented in our second paper that is currently in press in *Scientific Reports* (Wereszczyński, Śmigiel, Tomaszewska, Niedźwieńska, in press). The manuscript in Attachment 2 is a revised version of the paper that has been accepted for publication.

Study 2 served to achieve the third specific objective of the project. We wanted to show reduced spontaneous retrieval among people who have an elevated risk of dementia, but are not selected according to neuropsychological criteria, i.e., those with a high number of periodontitis symptoms, and thus demonstrate that the deficit can be detected before the neuropsychological diagnosis of cognitive deterioration. Based on the evidence already collected on the spontaneous retrieval deficit in the prodromal stages of AD, and studies showing the relationship between AD and periodontitis (see meta-analyses: Asher et al., 2022; Tonsekar et al., 2017), we expected that cognitively healthy older adults, without any cognitive deficits related to dementia or other diseases, but with poor periodontal health, would show reduced mind-wandering. The additional objective of Study 2 was to analyse the relationship between periodontitis and episodic memory to find out whether periodontitis is primarily related to AD that, in the earliest stages, manifests itself primarily as memory deficits, rather than other types of dementia, which, in the earliest stages, show deficits in other cognitive domains (Auning et al., 2011; Lindau et al., 2000; Román, 2003). We expected that poorer periodontal health would be associated with lower performance on the episodic memory test, rather than on the measure that targets various cognitive abilities, other than memory.

To achieve these goals, 60 dementia-free community-dwelling older adults performed the Man-made/Natural Task with though-probes (the same as in Study 1), to measure a level of their mind-wandering. They also completed a measure of various cognitive abilities (Addenbrooke's Cognitive Examination III, from which the memory index was excluded) and a comprehensive test of episodic memory (California Verbal Learning Test). We took special care to have a very comprehensive assessment of the subjective and objective periodontal health of the participants. Subjective oral health was measured by the periodontitis symptom list filled in by the participants. The objective examination was conducted by a qualified

dentist in a specialist dental clinic and included two types of evaluation: a) the number and severity of visible periodontitis-related changes in periodontal tissue, scored for each tooth sextant with the Community Periodontal Index of Treatment Needs (CPITN), which ranges from 0 (healthy periodontium) to 4 (pathological gingival pockets indicating the need for complex treatment); b) the number and type of periodontitis bacteria present in the oral cavity. The bacteria samples collected in the dental clinic were sent to a specialised biomolecular laboratory in Germany where the number and type of periodontitis pathogens present within the periodontium were examined with PET plus.

In line with predictions, the objective and subjective symptoms of poorer periodontal health were associated with less mind-wandering, further supporting the SRD hypothesis. There has been a moderate positive correlation between the number of periodontitis-free sextants (CPITN 1) and the number of spontaneous, task-unrelated thoughts. Negative associations with mind-wandering were also found for the mean CPITN and the highest CPITN (for both indices, a higher value indicated poorer periodontal health). Importantly, the number of subjective periodontitis symptoms reported by the participants was also negatively associated with the number of spontaneous task-unrelated thoughts. Furthermore, after the median split according to the number of each periodontitis pathogen, individuals with a high number of *Tannerella forsythia,* which was one of the most common pathogens in our sample, showed significantly less mind-wandering, compared to individuals with a low number of this pathogen. Finally, again in line with predictions, poorer periodontal health was associated with worse episodic memory, as demonstrated by numerous associations between the episodic memory scores and the number of different types of periodontitis pathogens, as well as between the episodic memory scores and CPTIN 4. In contrasts, no relationships were found between periodontitis measures and the measure of various cognitive abilities from which memory was excluded.

Reference: Wereszczyński, M., Śmigiel, A., Tomaszewska, I. and Niedźwieńska, A. (in press). Investigating the Relationship Between Periodontitis and Specific Memory Processes in the Search for Cognitive Markers of Alzheimer's Disease Risk. *Scientific Reports* (see Attachment 2)

3. General discussion

3.1. Implications from Study 1

The primary goal of the Study 1 was to provide new behavioral evidence to support the SRD hypothesis, which we were able to achieve.

Above all, in line with the SRD hypothesis, aMCI individuals experienced much less spontaneous task-unrelated thoughts than HC. Second, we demonstrated the robustness of the spontaneous retrieval deficit by showing, for the first time, that it applies to tasks using pictorial stimuli. Third, Study 1 was the first to demonstrate that the quality of external stimuli that could facilitate spontaneous processing affected the size of the spontaneous retrieval deficit: the reduction of mind-wandering was found with exposure to highly meaningful stimuli, but not to unmeaningful pictures. This finding shows that the deficit is most pronounced in spontaneous, but the bottom-up and cue-driven, processes. Finally, again in line with predictions, the deficit was most apparent in past-oriented, spontaneous, task-unrelated thoughts. For these involuntary autobiographical memories, the reduction in aMCI was significant for both highly meaningful and unmeaningful stimuli, but different in size: it was much larger for highly meaningful pictures.

It is interesting to note that future-oriented thoughts, although much less frequent than present-oriented thoughts, demonstrated the reduction of mind-wandering in aMCI, albeit much smaller than that for autobiographical memories. This finding is consistent with the results of both neuroimaging research (Botzung et al., 2008; Lavallee & Persinger, 2010; Viard et al., 2011) and behavioural studies (Berntsen & Jacobsen, 2008; D'Argembeau &

Van der Linden, 2006; D'Argembeau & Van Der Linden, 2004; El Haj et al., 2015) that show that past-oriented and future-oriented thoughts are based on overlapping cognitive processes. Our finding is thus in line with the results of previous research in suggesting that future-oriented and past-oriented thoughts can be considered two aspects of the same phenomenon, i.e., mental time travel, which is the ability to mentally re-experience autobiographical events and pre-experience possible future occurrences (Tulving, 2002).

Unexpectedly, we found an increase in the number of spontaneous task-unrelated thoughts in aMCI individuals for unmeaningful stimuli, as compared to highly meaningful pictures. However, when only past-oriented, spontaneous, task-unrelated thoughts were taken into account, mind-wandering no longer significantly differed after the exposure of aMCI participants to unmeaningful stimuli versus highly meaningful stimuli. This suggests that present-oriented thoughts may have been primarily responsible for this unexpected increase (future-oriented thoughts were scarce). Such an interpretation is supported by the fact that the type of stimuli did not influence the number of present-oriented, spontaneous, task-unrelated thoughts, either in the between-groups or within-groups comparisons.

3.2. Implications from Study 2

The most important findings of Study 2 are several significant associations between measures of mind-wandering and periodontitis, across subjective and objective indices of oral health, which should be highlighted – all in the expected direction. Importantly, all but one of these associations remained significant after adjustment for age, education, and general cognitive function (measured by MMSE scores). This finding, when considered together with the fact that quite a few relationships between periodontitis and the California Verbal Learning Test were no longer significant after adjustment for MMSE scores, serves as an argument for the advantage of mind-wandering as an early marker of cognitive decline, as it appears to be less dependent on general cognitive function.

As for the bacteria analyses, although no significant relationships were found between the number of periodontitis pathogens and mind-wandering, the between-group comparisons after the median split showed significantly fewer mind-wandering for picture-related thoughts oriented either toward the past or future, in the group with an elevated number of *Tannarella forsythia*. This is in line with previous studies (Niedźwieńska & Kvavilashvili, 2018), including our Study 1, in which individuals with aMCI had the spontaneous retrieval deficit primarily within these two types of mind-wandering: stimulus-related thoughts that were oriented either toward the past or future.

Importantly, we also found many significant associations between episodic memory indices and periodontitis status, objectively measured by both CPITN and pathogens. Furthermore, a significant part of these associations remained significant after adjustment for age, education, and general cognitive function. At the same time, no relationship was found between periodontitis and the test measuring various cognitive abilities, other than memory. These findings support the claim that periodontal health is particularly related to episodic memory and may help to gain a clearer understanding of the association between oral health and dementia.

3.3. Limitations and future directions

A possible limitation of Study 1 was the use of captioned pictures in the Man-made/Natural Task, rather than pictures alone. Although thought-probes explicitly asked participants whether they had any picture-related thoughts, and no participant mentioned captions, participants might have difficulty distinguishing between caption-induced thoughts and picture-induced thoughts. This limitation does not change the fact that Study 1 extended the behavioural data in support of reduced mind-wandering in aMCI to the type of stimuli that had not been used in previous supportive studies. However, it may lead to a slightly different theoretical interpretation of this reduction. If thoughts were caption-induced, then semantic-

to-autobiographical memory priming may have been involved (Mace et al., 2019; Mace & Unlu, 2020). This priming takes place when processing semantic information (prime) leads to activation of relevant autobiographical knowledge structures, which increases the likelihood of evoking related memories. Mace et al. suggest that low-frequency prime words are weakly associated with the personal experience of participants and therefore may activate very few autobiographical memories (Mace et al., 2019; Mace & Unlu, 2020). Therefore, it may be argued that the reduced number of involuntary autobiographical memories in the MCI group was due to impaired spreading of activation between semantic representations of verbal primes and related autobiographical memories. Future research may test this theoretical interpretation of differences between aMCI and healthy ageing. However, it should be noted that even this alternative interpretation puts emphasis on those deficits in aMCI that are related to automatic/spontaneous processes in memory.

As for Study 2, one limitation can be weak to moderate associations between periodontitis status and mind-wandering, and periodontitis status and episodic memory. Furthermore, these associations were found only for some measures of mind-wandering and episodic memory. The lack of stronger associations may be due to the characteristics of the sample that consisted of high-functioning, well educated, and community-dwelling older adults with a restricted range of periodontal health indices. Since participants were able to take care of their dental health, the sample did not include many of those with highly developed periodontal disease. This explanation is in line with the results of previous studies suggesting that the relationship between oral health and cognitive function is stronger for groups with a lower overall and a wider range of oral health status (e.g., residents of nursing homes), compared to high-functioning, community-dwelling older adults (Manchery et al., 2021; Zenthöfer et al., 2014). To ensure greater variance in periodontitis status, future studies

on the relationship between periodontitis and specific memory processes can recruit both high functioning community-dwelling adults and residents of nursing homes.

It should be noted that the pattern of our results in Study 2 suggests that mind-wandering was more associated with CPITN scores and subjective evaluation of periodontal symptoms, while episodic memory was more associated with the number of pathogens and CPITN scores, with most associations found with the number of sextants most severely affected by the disease (CPITN 4). It may be due to the fact that the three measures of oral health applied in our study provide somewhat different types of information on oral health status. The number of bacteria represents the current scale of infection with certain types of periodontitis pathogens, while CPITN describes the visible changes in the structure of the gums caused by periodontitis over the years. These changes are caused by gingivitis, but can remain observable even after the gingivitis infection is treated or decreased (Järvensivu, 2004). This reasoning is supported by our additional analyses in which a significant relationship was found between the number of bacteria and the number of CPITN 4 sextants, but not the other three CPITN codes that indicated better oral health, or the number of periodontitis symptoms listed by the participants. Therefore, the pattern of relationships may suggest that mind-wandering is more related to cumulative changes caused by well-managed disease over the years, while episodic memory is more related to the most severe changes in the gums caused by poorly managed periodontitis. Future studies may address this issue more directly.

Since Study 2 was a single-assessment cross-sectional study, only further longitudinal research can clearly indicate the causal direction behind the relationships that we demonstrated. Of particular interest would be the use of prospective longitudinal studies to investigate how simple tasks relying on spontaneous retrieval will compare with standard neuropsychological tests currently used, in terms of early detection of MCI and predicting

conversion rates to AD. Finally, future studies may investigate the relationship between deficits in spontaneous cognitions and biological markers of AD (e.g., amyloid plaques or the ApoE4 gene).

3.4. Contribution and perspectives

Our studies provide several important contributions to the search for early cognitive markers of the preclinical and prodromal stages of AD. Although the SRD hypothesis has been supported by the results of several behavioral studies, it needs further verification and elaboration to be able to improve the current diagnostic methods of neurodegenerative disorders. Study 1 provides strong new support for this hypothesis, and shows that it is the spontaneous, but bottom-up and cue-driven processes, for which meaningful environmental stimuli are crucial, that are very promising early markers of the disease. As for practice, our findings may help researchers develop new and simple cognitive tests to assess spontaneous, stimulus-driven processes, which may be used clinically to detect early cognitive deterioration and predict the conversion to AD. In addition to meeting the criteria listed in the Introduction, e.g., undemanding ongoing task, thought probes, distinguishing between spontaneous and deliberate thoughts, such tests should provide patients with highly meaningful environmental stimuli. Our findings suggest that, for healthy older adults, in contrast to individuals with aMCI, such an environment stimulates spontaneous task-unrelated thoughts in general, and past-related thoughts in particular.

Study 2 is the first study to focus directly on measuring the relationship between periodontitis and mind-wandering. Most research on the link between AD and periodontitis was based on a traditional, sometimes superficial, neuropsychological assessment. My project is not only the first to describe people with periodontitis in terms of a cognitive process that has never been investigated in this group, i.e., spontaneous retrieval. It also integrates data from psychological tools and modern biomolecular tests. Data collected in this manner enable

further improvement of modern neuropsychological diagnostic methods and may significantly enrich current knowledge on the etiology of AD.

Furthermore, Study 2 is an important voice in the discussion of the relationship between dementia and periodontitis. A particular link between periodontitis and memory ability suggests that periodontal health may be primarily related to an elevated risk of Alzheimer's type dementia, the early stages of which, unlike other types of dementia, manifest with memory impairment (Auning et al., 2011; Lindau et al., 2000; Román, 2003). This conclusion is supported by the results of biomolecular studies that have shown associations between periodontitis and specifically AD, e.g., the presence of periodontitis bacteria's DNA in cerebrospinal fluid from individuals with probable AD (Dominy et al., 2019) or increased production of β-amyloid and tau protein in mice' brain after chronic oral exposure to periodontitis pathogen (Ilievski et al., 2018).

Therefore, our results, by showing the associations of periodontitis with memory ability and the specific memory process, expand the accumulating data that show that periodontitis is particularly related to the elevated risk of AD, which has important implications for early identification of AD risk and clinical practise. It suggests that the presence and severity of periodontitis should be considered when projecting the probability of progression to AD in preclinical groups or when developing questionnaires and clinical inventories designed to assess such risk. As for clinical practise, it shows the importance of taking special care of gingival health in individuals with an elevated likelihood of progression to AD as a means of reducing the risk of progression.

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Deficits in spontaneous and stimulus-dependent retrieval as an early sign of abnormal aging

Michał Wereszczyński & Agnieszka Niedźwieńska

Research on early cognitive markers of Alzheimer's disease is primarily focused on episodic memory tests that involve deliberate retrieval. Our purpose was to provide clear evidence to support a novel Spontaneous Retrieval Deficit hypothesis, which predicts that people at pre-clinical stages of dementia, including those with amnestic Mild Cognitive Impairment (aMCI), are particularly impaired on tasks based on spontaneous retrieval. We compared 27 aMCI individuals and 27 healthy controls on mind-wandering while performing a task during which there were exposed to either highly meaningful or unmeaningful pictures. The substantial reduction in mind-wandering among individuals with aMCI was found with exposure to highly meaningful stimuli, but not to unmeaningful pictures, and it was most pronounced for past-oriented thoughts, i.e., involuntary autobiographical memories. Those findings provide strong support for this novel hypothesis, and show that it is the spontaneous, but bottom-up and cue-driven processes, for which meaningful environmental stimuli are crucial, that are very promising early markers of the disease.

With increased life expectancy, the number of older adults diagnosed with Alzheimer's disease (AD) continues to grow[1]. Impairment of declarative memory, one of the key symptoms indicating AD, is associated with cerebral pathological changes which may start years, or even decades, before the clinical diagnosis of dementia[2,3]. In the absence of effective drug treatment, research has increasingly focused on identifying individuals most at risk of developing AD who could most likely benefit from early disease management and care[4]. One such group are those with various forms of Mild Cognitive Impairment, the most prevalent being amnestic MCI (aMCI). It manifests in subjective and objective memory deficits, as evidenced by the performance on episodic memory tests, without the loss of functional independence that is characteristic of AD[4]. Individuals with aMCI have increased yearly conversion rates to AD (10–15%) and are more likely than normally aging adults to have brain pathology characteristic of AD[3,5].

A novel hypothesis has been recently formulated which stipulates that spontaneous (i.e., unintentional and effortless) retrieval processes, which are generally preserved in healthy aging[6–8], will be significantly compromised in individuals with aMCI, and at the earliest stages of AD[9]. It also argues[9] that cognitive tasks that are based on spontaneous retrieval may be more sensitive to early cognitive deterioration than tasks that rely on deliberate and effortful encoding and retrieval. Deliberate processes are mediated by executive and attentional control regions in the prefrontal cortex which become substantially compromised at later stages of AD. Since all currently used neuropsychological tests of episodic memory rely on deliberate memory processes, the hypothesis, if confirmed, can transform the current theoretical understanding of the most effective early cognitive markers of the disease.

The spontaneous retrieval deficit hypothesis (the SRD hypothesis) is based on the results of the neuroimaging studies showing that, during the etiology of AD, neurological structures of the Default Mode Network (DMN) tend to degenerate much earlier than other parts of the central nervous system (see [9], for a review of evidence). The first signs of neuropathological changes within AD tend to occur in posterior parts of the cortex, with the anterior and dorsolateral prefrontal cortex remaining relatively intact[10,11], resulting in disproportionate temporoparietal atrophy in the early stages of the disease[12,13]. The pathology involves the accumulation of tau-positive neurofibrillary tangles in medial temporal lobe structures, spreading from the entorhinal cortex to the hippocampus[14], and the formation of β-amyloid plaques in the medial prefrontal and posteromedial cortices, especially in the posterior cingulate cortex and adjacent areas[15,16]. These neuropathological processes, especially β-amyloid accumulation, may progress insidiously, for many years, along a slow pre-symptomatic course before clinical symptoms are evident[4].

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Importantly, the posterior cingulate cortex, medial temporal lobe, and medial prefrontal cortex are anatomically and functionally strongly interconnected and form part of the DMN[17,18]. DMN activity has been traditionally linked to mind-wandering, which involves spontaneous shifts of attention from the external world to one's inner thoughts[19,20]. Links between mind-wandering and increased DMN activity have also been demonstrated in several fMRI studies (see[9], for a review of evidence). Mind-wandering share similar characteristics with several other phenomena of spontaneous cognitions such as, for example, involuntary autobiographical memories[21,22], or those aspects of prospective memory that involve effortlessly remembering previously intended actions in response to a particular target event[23,24]. What these phenomena share with mind-wandering episodes is that thoughts and memories come to mind spontaneously and effortlessly, without any deliberate intention to think about them.

A few recent behavioural studies support the SRD hypothesis by showing the deficit of spontaneous retrieval in individuals with aMCI, and at early stages of AD, in prospective memory[25–27] and mind-wandering[28,29]. Niedźwieńska and Kvavilashvili[28] used thought probes alongside an easy vigilance task, during which cue phrases, irrelevant to the ongoing task, were frequently presented. Participants with aMCI reported significantly fewer spontaneous task-unrelated thoughts than healthy older adults, especially thoughts about past (i.e., involuntary autobiographical memories). Importantly, the vast majority of spontaneous thoughts were triggered by irrelevant cue phrases. The decrease in the frequency of task-unrelated thoughts were also found among patients with very mild to mild AD, as compared with healthy controls, while performing the Sustained Attention to Response Task, with thought probes[29].

However, two behavioral studies did not find support for the SRD hypothesis[30,31]. Patients with probable AD and healthy controls did not differ in the frequency of on- and off-task thoughts reported during a shape expectations task[30]. However, by contrast to[28], this study also did not examine whether participants' off-task thoughts were spontaneous or intentional, and, second, participants were not exposed to meaningful stimuli during the ongoing task. With regard to the first issue, it has been shown that participants report engaging in task-unrelated thoughts deliberately[8,32,33], and therefore not all task-unrelated thoughts qualify as spontaneous cognitions. As to the second issue, an important distinction between stimulus-independent and stimulus-dependent mind-wandering has been proposed[9,34]: i.e., thoughts may occur without any noticeable trigger or pop into mind in response to a cue which could be an incidental stimulus in the external environment. Distinguishing stimulus-dependent mind-wandering is supported by empirical evidence showing that when participants are exposed to meaningful incidental stimuli, stimulus-dependent spontaneous thoughts is the norm rather than the exception, both in the laboratory[32] and in everyday life[8]. FMRI studies also show that the posterior cingulate cortex, a key hub of the DMN, is crucially involved in the manifestation of spontaneous thoughts in response to stimuli encountered in the environment[35–37]. Based on the distinction between stimulus-independent and stimulus-dependent mind-wandering, the SRD hypothesis stipulates that aMCI and very mild AD primarily penalise spontaneous, but bottom-up and cue-driven, retrieval processes for which the presence of meaningful cues is essential[9] (see also[32]).

The other study, which did not find support for the SRD hypothesis, asked participants to watch an audio-visual material which presented common activities, famous actors and popular songs from the period corresponding to participants' youth[31]. The experimenter recorded participants' commentaries that they were making, unprompted, during the film and briefly after that. Although participants with mild to moderate AD shared more commentaries relating to autobiographical memories, as compared with healthy controls, again the experimenter did not examine whether their commentaries were based on thoughts that had entered their mind spontaneously or whether they had deliberately decided to think about them. Importantly, in contrast to all previous studies that examined mind-wandering in aMCI and mild AD by using thought probes[28,29], participants were not systematically asked to reveal their thoughts. Therefore, the study may have measured inhibitory control rather than spontaneous retrieval efficiency, and a lower number of commentaries in healthy controls may have reflected a greater reluctance to share their thoughts. This explanation is partially in line with the authors' suggestion that deficits in inhibitory control made patients less able to hold back emotion-expressive behavior when being exposed to emotionally arousing material[31].

Therefore, we suggest that discrepant findings regarding the SRD hypothesis may be due to the fact that previous studies have used tasks that, to varying degrees, meet the criteria that are necessary to capture group differences in spontaneous and cue-driven retrieval processes. First, the ongoing task difficulty needs to be low and matched between patients and healthy controls to exclude the possibility that cognitive resources, which could be disposed for spontaneous processes, will be much more limited among patients. Second, there should be stimuli in the environment that have the potential to serve as cues to trigger spontaneous thoughts. Third, the experimenter needs to distinguish between spontaneous and intentional task-unrelated thoughts. Fourth, thought probes need to be used during which participants are directly asked what they were thinking about, to avoid the impact of group differences in reluctance to share inner thoughts.

The first goal of our study was to test the SRD hypothesis while using a task that meets all the necessary criteria to capture spontaneous and cue-driven retrieval processes. Second, we tested the robustness of the spontaneous retrieval deficits by investigating whether they generalise to situations when individuals are exposed to potential cues that are different in their nature to the ones used so far. Since behavioral evidence for the SRD hypothesis comes from the studies that used verbal[28] or digital[29] stimuli, we used pictures as potential cues. Third, to test the prediction that it is spontaneous, but bottom-up and cue-driven, retrieval processes that are impaired in aMCI, and that it is meaningful cues that are essential for eliciting such processes, we investigated, for the first time, whether highly meaningful stimuli would better enable to demonstrate spontaneous retrieval deficits in aMCI, compared to unmeaningful stimuli.

To accomplish these goals, we used a task of distinguishing between natural and man-made objects, visually presented[6], with participants with aMCI and matched healthy older controls. Both groups were given thought

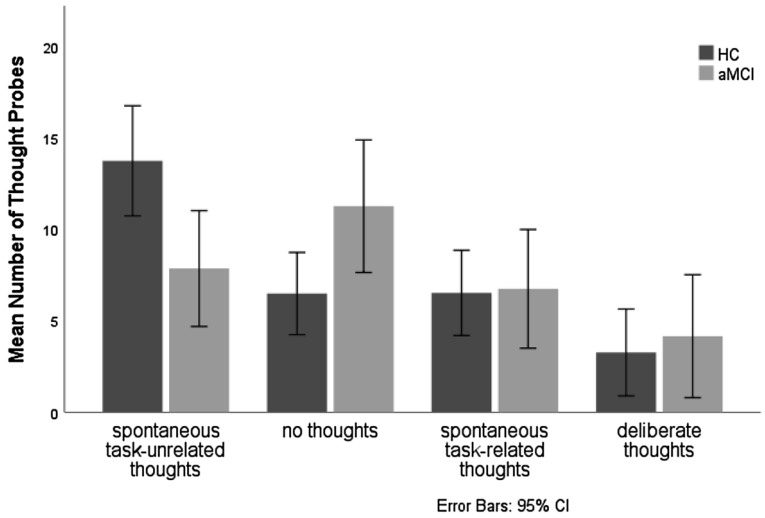

Figure 1. Mean number of thought probes as a function of response type (spontaneous task-related thoughts vs. spontaneous task-unrelated thoughts vs. deliberate thoughts vs. no thoughts) and group (aMCI participants vs. healthy controls).

probes. We developed two versions of the task: one with highly meaningful pictures, i.e., rated by participants as highly familiar based on their personal experience, and the other version with unmeaningful pictures, i.e., rated by participants as highly unfamiliar based on their personal experience. Strictly speaking, unmeaningful objects were not completely unknown to participants, but, judging by the familiarity ratings, they had not been present, or had been present very rarely, in participants' individual past, and therefore had no, or very little, personal meaning to them.

In line with the SRD hypothesis, we expected that aMCI participants would report significantly fewer spontaneous task-unrelated thoughts than healthy controls (HC). We also expected that the reduction of spontaneous thoughts in aMCI would manifest more strongly with exposure to highly meaningful stimuli, compared to exposure to unmeaningful stimuli. Based on[28], we also expected thoughts about past, compared to thoughts about future and present, to most strongly demonstrate the reduction of spontaneous thoughts in aMCI.

Results

The alpha level adopted for determining significance of the results was set at 0.05. The effect size was measured by partial eta squared, η_p^2 (small 0.01, medium 0.06, large 0.16) or Cohen's d (small 0.20, medium 0.50, large 0.80)[38].

Types of responses recorded during the task. To test the SRD hypothesis, and based on participants' answers whether they had any thought at a thought probe, and if yes, whether it was related to the experience of doing the Man-made/Natural Task, and whether it was spontaneous or deliberate, we grouped participants' responses into: (1) spontaneous task-unrelated thoughts; (2) spontaneous task-related thoughts (3) deliberate thoughts; (4) no thoughts. The vast majority of spontaneous task-unrelated thoughts in both groups were stimulus-dependent (91% in aMCI and 81% in HC).

To assess the hypothesis that aMCI participants would report significantly fewer spontaneous task-unrelated thoughts than HC, the mean number of thought probes in each of the 4 response types (spontaneous task-related, spontaneous task-unrelated, deliberate, no thoughts) were entered into a MANOVA with group (HC vs aMCI) as a between-subject factor. There was a significant main effect of group [F (3, 50) = 3.075, p = 0.036; η_p^2 = 0.156] (Fig. 1). As expected, participants with aMCI experienced significantly fewer spontaneous task-unrelated thoughts than HC [F (1, 52) = 7.672, p = 0.008; η_p^2 = 0.129]. There were significantly more "no thoughts" probes in aMCI individuals than in HC [F (1, 52) = 5.299, p = 0.025; η_p^2 = 0.092]. No other group differences were significant (all group comparisons in "Supplementary Material").

Spontaneous task-unrelated thoughts as a function of stimulus type. To assess the hypothesis that spontaneous retrieval deficits in the aMCI group would be particularly pronounced with exposure to highly meaningful stimuli, as compared with exposure to unmeaningful stimuli, the mean number of thought probes with spontaneous task-unrelated thoughts was entered into a 2 group (HC vs. aMCI) by 2 stimulus type (highly meaningful vs. unmeaningful) mixed ANOVA with the repeated measure on the second factor. There was a significant main effect of group [F (1, 52) = 7.678, p = *0.00*8; η_p^2 = 0.129], and a significant group by stimulus type interaction [F (1, 52) = 9.728, p = *0.00*3; η_p^2 = 0.158] (Fig. 2). As predicted, aMCI participants reported significantly fewer spontaneous task-unrelated thoughts than HC when exposed to highly meaningful stimuli [F (1, 52) = 14.412, p = *0.00*0; η_p^2 = 0.217], but not when exposed to unmeaningful stimuli [F (1, 52) = 2.135, p = *0.15*0; η_p^2 = 0.039]. The number of spontaneous task-unrelated thoughts did not significantly differ for highly meaningful and unmeaningful stimuli in HC [F (1, 52) = 3.645, p = *0.06*2; η_p^2 = 0.066], but aMCI participants had more

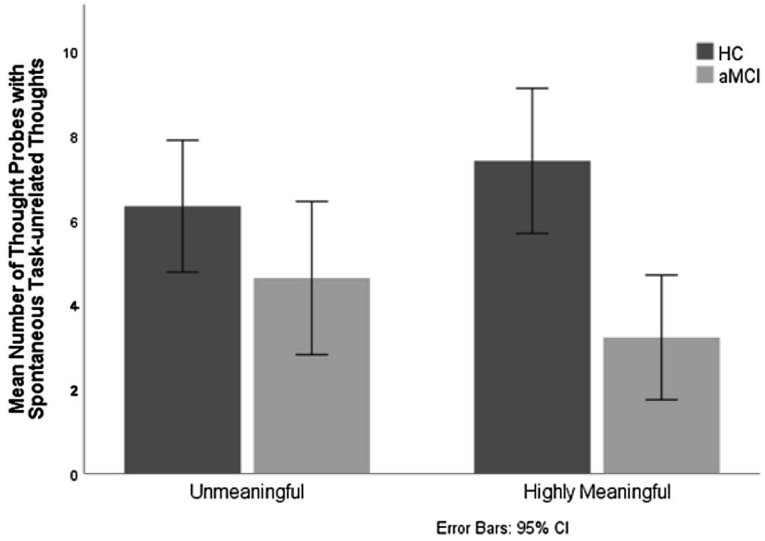

Figure 2. Mean number of thought probes with spontaneous task-unrelated thoughts as a function of stimulus type (highly meaningful vs unmeaningful) and group (aMCI participants vs. healthy controls).

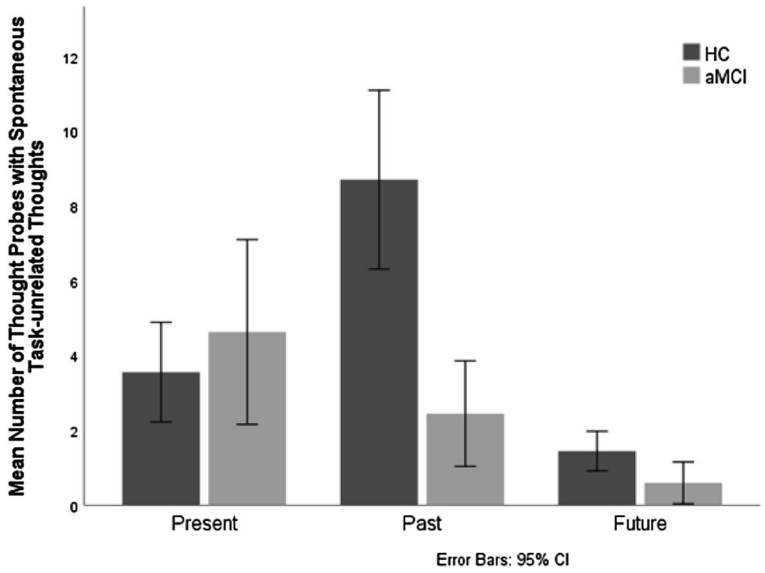

Figure 3. Mean number of thought probes with spontaneous task-unrelated thoughts as a function of temporal orientation (present vs. past vs. future) and group (aMCI participants vs. healthy controls).

spontaneous task-unrelated thoughts for unmeaningful stimuli compared to highly meaningful stimuli [F (1, 52) = 6.258, $p = 0.016$; $\eta_p^2 = 0.107$] (all comparisons in "Supplementary Material").

Spontaneous task-unrelated thoughts as a function of thought temporality. To assess the hypothesis that thoughts about past events (i.e. involuntary autobiographical memories) would most strongly demonstrate the reduction of spontaneous thoughts in participants with aMCI, the mean number of spontaneous task-unrelated thoughts was entered into a 2 group (HC vs. aMCI) by 3 temporal orientation (future vs. past vs. present) mixed ANOVA with the repeated measure on the second factor. There were significant main effects of group [F (1, 52) = 8.041, $p = 0.006$; $\eta_p^2 = 0.134$] and temporal orientation [F (2, 51) = 33.78, $p = 0.000$; $\eta_p^2 = 0.570$]. These effects were qualified by a significant group by temporal orientation interaction [F (2, 51) = 9.50, $p = 0.000$; $\eta_p^2 = 0.272$] (Fig. 3). As predicted, aMCI participants had significantly fewer past-oriented thoughts than HC [F (1, 52) = 21.482, $p = 0.000$; $\eta_p^2 = 0.292$]. This difference was also significant for future-oriented thoughts, with much smaller effect size [F (1, 52) = 5.136, $p = 0.028$; $\eta_p^2 = 0.090$] (all group comparisons in "Supplementary Material").

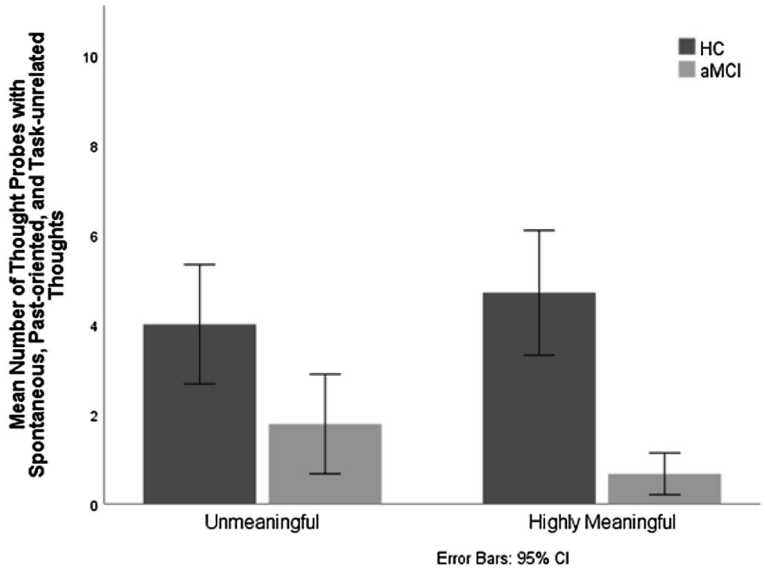

Figure 4. Mean number of thought probes with spontaneous, past-oriented, and task-unrelated thoughts as a function of stimulus type (highly meaningful vs unmeaningful) and group (aMCI participants vs. healthy controls).

Man-made/natural task	aMCI (n = 27)[a]	Healthy controls (n = 27)	*t*	*df*	*p*	*d*
Accuracy	0.91 (0.12)	0.96 (0.02)	− 1.94	52	0.057	0.58
Response time (ms)	2096.05 (542.15)	1889.65 (345.41)	1.66	52	0.101	0.45
Invalid answers	32.37 (41.30)**	10.14 (8.14)	− 2.98	52	0.008	0.71
Interest[b]	7.96 (2.08)	6.84 (3.04)	1.54	50	0.129	0.43

Table 1. Mean (standard deviation) accuracy, response time, invalid answers and interest ratings for the man-made/natural task in participants with aMCI and healthy controls, and results of independent samples T-test. *aMCI* amnestic Mild Cognitive Impairment. Differences between aMCI and HC are indicated by ** $p < 0.01$. [a]Except for the interest ratings that were not provided by two participants (one in each group). [b]Task interest ratings were made on a 10-point scale (1 = very boring; 10 = very interesting).

Past-oriented thoughts (involuntary autobiographical memories) as a function of stimulus type. Since the reduction of spontaneous task-unrelated thoughts in aMCI was most strongly pronounced in involuntary memories, we conducted additional analyses to investigate whether the quality of stimuli influenced the size of the reduction in memories in the same way as it was predicted, and indeed found, for spontaneous task-unrelated thoughts overall. Therefore, the mean number of thought probes with past-oriented, spontaneous and task-unrelated thoughts was entered into a 2 group (HC vs. aMCI) by 2 stimulus type (highly meaningful vs. unmeaningful) mixed ANOVA with the repeated measure on the second factor. There was a significant main effect of group [F (1, 52) = 21.482, $p = 0.000$; $\eta_p^2 = 0.292$], and a significant group by stimulus type interaction [F (1, 52) = 5.348, $p = 0.025$; $\eta_p^2 = 0.093$] (Fig. 4). Individuals with aMCI had significantly fewer past-oriented thoughts than HC for both highly meaningful and unmeaningful stimuli, but, as it could be expected, the effect size of this difference was much bigger for highly meaningful stimuli [F (1, 52) = 31.991, $P = 0.000$; $\eta_p^2 = 0.381$] compared to unmeaningful stimuli [F (1, 52) = 6.952, $p = 0.011$; $\eta_p^2 = 0.118$]. No other effects were significant (all comparisons in "Supplementary Material").

Potential confounds to spontaneous retrieval deficits. It may be argued that the Man-made/Natural Task was easier, and therefore more boring, for HC, compared to aMCI individuals, which made them mind-wander more. In a similar vein, the Man-made/Natural Task may have been more difficult for aMCI individuals, and therefore they did not have enough cognitive resources left for spontaneous processes. However, the data indicate otherwise (Table 1). Both groups performed at ceiling on the Man-made/Natural Task, and they did not differ on any of the performance measures (the percentage of correct answers out of all answers provided and mean response time), except for the number of invalid answers caused by pressing the wrong keyboard button or missing an answer. Furthermore, the groups expressed the same level of interest in the task. However, to exclude this alternative explanation of group differences in mind-wandering, we investigated whether the level of performance on the Man-made/Natural Task influenced the pattern of group differences in the number of

spontaneous task-unrelated thoughts. The mean number of spontaneous task-unrelated thoughts was entered into a one-way ANCOVA, with group as a between-subject factor and the three measures of performance on the Man-made/Natural Task as covariates. None of the covariates was significant: mean response time [F (1, 49) = 0.196; $p = 0.660$; $\eta_p^2 = 0.004$]; number or invalid answers [F (1, 49) = 0.915; p = 0.344; $\eta_p^2 = 0.018$]; percentage of correct answers [F (1, 49) = 2.702; $p = 0.107$; $\eta_p^2 = 0.052$]. The main effect of group was significant [F (1, 49) = 7.003; $p = 0.011$; $\eta_p^2 = 0.125$], such that aMCI participants continued to mind-wander less, after controlling for performance on the Man-made/Natural Task. This speaks against the task difficulty as being a potential confound to spontaneous retrieval deficits.

It may also be argued that the group differences in cognitive functions, other than memory retrieval, may explain less mind-wandering in aMCI. Again, to exclude this alternative explanation, we investigated whether other cognitive functions, as measured by the Addenbrooke's Cognitive Examination-III (ACE-III), influenced the pattern of group differences in the number of spontaneous task-unrelated thoughts. The mean number of spontaneous task-unrelated thoughts was entered into a one-way ANCOVA, with group as a between-subject factor and a composite score on the ACE-III, which included the attention, fluency, language and visuospatial abilities subscales, as a covariate. The covariate was not significant [F (1, 51) = 0.126 $p = 0.724$; $\eta_p^2 = 0.002$]. The main effect of group was significant [F (1, 51) = 6.282; $p = 0.015$; $\eta_p^2 = 0.110$], such that aMCI participants continued to mind-wander less, after controlling for performance on the ACE-III. This speaks against the differences in other cognitive functions as being potential confounds to spontaneous retrieval deficits.

The aMCI group and HC did not differ in their ratings of how difficult the task of categorizing thoughts was for them ($p = 0.265$).

Discussion

A recently formulated SRD hypothesis stipulates that tasks based on spontaneous retrieval are most compromised in aMCI and at early stages of AD, and are better early cognitive markers of the disease, compared to tasks that rely on deliberate episodic memory processes[9]. This hypothesis is highly counterintuitive because it challenges current theories of cognitive aging[39,40] which predict that both typical and atypical aging predominantly impair performance on difficult cognitive tasks that rely on deliberate and strategic processes. It also speaks against the current practice of the dementia diagnosis which involves neuropsychological tests based on strategic encoding and retrieval processes. However, recent neuropsychological studies have shown that the structures responsible for spontaneous retrieval degenerate much earlier during the dementia development than those mediating strategic memory processes[10,11,14–16].

The primary goal of the present study was to provide more conclusive behavioral evidence to support the SRD hypothesis. To this aim, we compared individuals with aMCI and healthy controls in terms of mind-wandering while performing the task that met all the criteria to capture spontaneous stimulus-dependent retrieval, and included either highly meaningful or unmeaningful pictorial stimuli. Several important findings emerged from this comparison that provide very strong support for the SRD hypothesis.

Most importantly, in line with the SRD hypothesis, individuals with aMCI experienced significantly less spontaneous task-unrelated thoughts than HC. Second, we demonstrated the robustness of the spontaneous retrieval deficits by showing that, for the first time, for pictorial material. Third, the present study is the first to demonstrate that the quality of stimuli in the environment, which could potentially trigger spontaneous thoughts, impacts the size of the spontaneous retrieval deficits. This finding unequivocally supports the claim that the deficits involve spontaneous, but the bottom-up and cue-driven, processes. As predicted, the reduction in spontaneous task-unrelated thoughts was found with exposure to highly meaningful stimuli, but not to unmeaningful pictures. Finally, in accordance with[28] and our hypothesis, the deficits were most pronounced for past-oriented, spontaneous, task-unrelated thoughts (involuntary autobiographical memories). For such thoughts the deficits were significant for both highly meaningful and unmeaningful stimuli, but varied in size: they were much larger for highly meaningful pictures.

Unexpectedly, we found an increase in the number of spontaneous task-unrelated thoughts in aMCI individuals for unmeaningful stimuli, as compared with highly meaningful pictures. When only past-oriented, spontaneous, task-unrelated thoughts were taken into account, mind-wandering no longer significantly differed after the exposure of aMCI participants to unmeaningful stimuli versus highly meaningful stimuli. This suggests that present-oriented thoughts may have been primarily responsible for this unexpected increase (future-oriented thoughts were scarce). Such interpretation is supported by the fact that the type of stimuli did not influence the number of present-oriented, spontaneous, task-unrelated thoughts, either in the between-groups or within-groups comparisons. This explanation is also in line with the studies showing that, in the absence of meaningful stimuli, people tend to experience primarily future- and present-oriented thoughts[41,42] in which the deficits are less pronounced compared to involuntary autobiographical memories (see[28] and the present findings). Interestingly, although future-oriented thoughts were much less frequent than present-oriented thoughts in the present study, it is future-oriented thoughts that demonstrated the reduction of mind-wandering in aMCI, albeit a much smaller reduction than that for autobiographical memories. This finding is in line with the results of both neuroimaging research[43–45] and behavioral studies[46–49] showing that past-oriented and future-oriented thoughts are based on overlapping cognitive processes. These studies suggest that future-oriented and past-oriented thoughts can be considered two aspects of the same phenomenon, i.e., mental time travel which is the ability to mentally re-experience autobiographical events and pre-experience possible future occurrences[50].

A possible limitation of our study was using captioned pictures in the Man-made/Natural Task, rather than pictures alone. Although thought probes explicitly asked participants whether they had any picture-related thoughts, and no participant mentioned captions, participants might have difficulties in distinguishing between caption-induced thoughts and picture-induced thinking. This limitation does not change the fact that we

extended behavioral data in support of reduced mind-wandering in aMCI to the type of stimuli that had not been used in previous supportive studies. However, it may lead to a slightly different theoretical interpretation of this reduction. If thoughts were caption-induced, then semantic-to-autobiographical memory priming may have been involved[51,52]. This priming takes place when processing semantic information (prime) leads to activation of relevant autobiographical knowledge structures which increases the likelihood of evoking related memories. Mace et al.[51] consider semantic-to autobiographical priming a specific type of associative priming, occurring between two separate memory systems (semantic and autobiographical). It has been demonstrated in relation to involuntary autobiographical memories, and interestingly, all primed memories were associated only with high-frequency prime words[51,52]. Mace et al.[51,52] suggest that low-frequency prime words are weakly associated with participants' personal experience, and therefore may activate very few autobiographical memories. It is likely that, in the present study, caption words for unmeaningful objects were lower in frequency, compared to captions for highly meaningful objects. Therefore, it may be argued that the reduced number of involuntary autobiographical memories in the MCI group was due to impaired spreading of activation between semantic representations of verbal primes and related autobiographical memories. It may be further argued that low-frequency caption words, corresponding to unmeaningful objects, were less able to demonstrate this impairment because they had equally poor associations with participants' personal experience in both aMCI group and healthy older adults. Future research may test this theoretical interpretation of differences between aMCI and healthy ageing. However, it should be noted that even this alternative interpretation puts emphasis on those deficits in aMCI that are related to automatic/spontaneous processes in memory.

As for practice, our findings may help researchers to develop new and simple cognitive tests to assess spontaneous, stimulus-driven processes, which may be used clinically for detecting early cognitive deterioration and predicting the conversion to AD. In addition to meeting the criteria listed in the Introduction, e.g., undemanding ongoing task, thought probes, distinguishing between spontaneous and deliberate thoughts, such tests should provide patients with highly meaningful environmental stimuli. Our findings suggest that, for healthy older adults, in contrast to individuals with aMCI, such an environment stimulates spontaneous task-unrelated thoughts in general, and past-related thoughts in particular.

Method

Participants. A total of 27 healthy older adults and 27 aMCI participants were recruited. To ensure sufficient power, we performed the a priori power analysis on GPOWER 3.1[53]. The effect size calculation was based on mind-wandering reported by Niedźwieńska and Kvavilashvili[28] (f = 0.718). With an alpha level of 0.05 and the minimum power of 0.95, 28 participants were necessary to find a statistically significant effect in the model. However, in the study of Maillet and Schacter[6], in which the Man-made/Natural Task was originally used to compare young adults with healthy older adults, older adults reported much more "no thoughts" trials (~ 20%), compared to the task used in the reference study of Niedźwieńska and Kvavilashvili (6%)[28]. This suggested that the Maillet and Schacter task might have been less powerful in eliciting mind-wandering. Although the substantially modified version of the Maillet and Schacter task was used in the present study, to avoid the risk of not having enough power to capture the difference in mind-wandering between aMCI individuals and HC, we recruited about twice as many participants as calculations indicated were necessary.

All participants were recruited from among inhabitants of local nursery houses and members of senior social clubs. All research was performed in accordance with the Declaration of Helsinki. The study was approved by Psychology Research Ethics Committee at the Jagiellonian University. Participants provided written informed consent to take part in the study. For all participants, exclusion criteria included: (a) head/brain injuries, (b) history of cerebrovascular disease, (c) current alcohol or substance dependence, (d) medical, neurological, or psychiatric disorders resulting in cognitive dysfunctions, (e) age less than 65 years. Fluency in Polish and adequate vision and hearing were also required. Exclusion criteria were assessed in the initial interview screening. Participants who passed the screening, completed a battery of experimental and standardized neuropsychological tests.

aMCI participants. Participants were assigned to the clinical group using the inclusion criteria that satisfied the diagnostic criteria of aMCI[54,55] (a) presence of a subjective memory complaint; (b) objective memory impairment evidenced by a score at or below 1.5 *SD* of the mean of age-matched peers on at least one test of the neuropsychological screening battery assessing episodic memory (see the Neuropsychological evaluation section); (c) not meeting the Diagnostic and Statistical Manual of Mental Disorders' (DSM-5) criteria for dementia (American Psychiatric Association, 2013), (d) preserved general cognitive function as confirmed by a normal score on the Mini-Mental State Examination (MMSE)[56] (normality cut-off score: 24)[57]; (e) maintained activities of daily living or slight impairment in instrumental activities of daily living, as confirmed by no more than one item showing deterioration in the Instrumental Activities of Daily Living (IADL) subscale of Nurses' Observation Scale for Geriatric Patients (NOSGER)[58,59]; (f) absence of severe depression, as confirmed by a score below 10 on the Geriatric Depression Scale 15[60].

Healthy controls (HC). Inclusion criteria for the HC group were: (a) a score within or above 1.5 *SD* of the mean of age-matched peers on each test of the neuropsychological screening battery assessing episodic memory; (c) a score ≥ 27 on the MMSE; (d) no impairment in instrumental activities of daily living, as confirmed by minimum score in the Instrumental Activities of Daily Living (IADL) subscale of Nurses' Observation Scale for Geriatric Patients (NOSGER)[58,59]; (e) absence of severe depression, as confirmed by a score of below 10 on the GDS 15.

Table 2 shows demographic details of the final sample. A series of independent samples t-tests revealed no significant group differences between aMCI and HC on the demographic variables, except for MMSE scores, which were lower in aMCI individuals than in HC ($p = 0.000$; $d = 1.74$).

	aMCI (n = 27)	HC (n = 27)
Sex	10 males	10 males
Age (SD)	79.44 (8.18)	77.77 (7.71)
Years of education (SD)	11.66 (2.54)	12.68 (3.10)
Health at present (SD)	3.14 (0.86)	3.37 (1.00)
Health compared to peers (SD)	3.70 (0.95)	3.59 (0.84)
GDS	3.85 (2.82)	3.07 (1.66)
MMSE	26.59 (1.18)***	28.59 (1.11)

Table 2. Demographic characteristics as a function of group (aMCI vs HC). Health at present (1 = poor, 5 = excellent); Health compared to peers (1 = significantly worse, 3 = same, 5 = significantly better). *aMCI* amnestic Mild Cognitive Impairment, *HC* Healthy Controls. Differences between aMCI and HC are indicated by *** $p < .001$.

	aMCI (n = 27)	HC (n = 27)	*d*
Episodic memory			
CVLT: immediate recall 1–5	31.55 (9.64)***	45.11 (8.56)	1.48
CVLT: short delay recall	5.51 (2.62)***	9.18 (2.70)	1.40
CVLT: long delay recall	5.18 (2.14)***	10.18 (2.40)	2.19
CVLT: recognition	13.88(2.24)*	15.00 (1.10)	0.63
HVLT: immediate recall 1	3.07 (1.688)**	5.33 (1.41)	1.45
HVLT: immediate recall 2	5.59 (1.96)***	7.37 (1.59)	0.99
HVLT: immediate recall 3	6.11 (1.80)***	8.14 (1.91)	1.09
HVLT: delayed recall	3.29 (2.35)***	6.77 (2.62)	1.38
HVLT: recognition	9.88 (1.88)**	11.03 (0.93)	0.77
Other cognitive functions			
ACE-III: attention	16.22 (1.52)*	17.11 (0.97)	0.69
ACE-III: fluency	8.29 (2.65)***	11.12 (1.93)	1.22
ACE-III: language	22.12 (4.46)**	25 (1.41)	0.87
ACE-III: visuospatial	13.48 (1.92)*	14.62 (1.36)	0.68

Table 3. Mean scores on neuropsychological test battery in participants with aMCI and healthy controls. For each test, a high score indicates a better performance. *aMCI* amnestic Mild Cognitive Impairment, *HC* healthy controls, *CVLT* California Verbal Learning Test, *HVLT* Hopkins Verbal Learning Test. Differences between aMCI and HC are indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Measures. *Neuropsychological evaluation.* The episodic memory tests included the Hopkins Verbal Learning Test (HVLT)[61,62] and California Verbal Learning Test (CVLT)[63,64]. HVLT consists of three immediate recall tests, one delayed recall test and one delayed recognition test. CVLT includes five immediate recall tests, one short delay recall test, one long delay recall test and one delayed recognition test. Attention, executive functions, language and visuospatial abilities were tested with the Addenbrooke's Cognitive Examination-III (ACE-III)[65]. Significant group differences were obtained for all neuropsychological tests, with aMCI participants scoring lower (see Table 3). The effect sizes for episodic memory tests were markedly higher than for the tests measuring other cognitive functions i.e. attention, language, fluency and visuospatial.

Mind-wandering evaluation. Participants completed a computer-based Man-made/Natural Task, which was a modified version of the task developed by Maillet and Schacter[6]. The task consisted of a 242-slide presentation of pictures showing natural objects (e.g., flower) and man-made objects (e.g., car). Below each picture there was a caption corresponding to it**.** Participants were asked to decide whether the depicted object was artificial or natural. Each stimulus was presented for 4 s, followed by a blank screen for 4 s. Every 6–10 stimulus slides, the task stopped and thought probe questions appeared on the screen. Participants were asked to describe their thought content the moment before the question appeared on the screen by choosing one of the following answers: (a) I did not have any thoughts; (b) I had a thought triggered by one of the pictures I saw; (c) I had a thought unrelated to the task or any of the pictures I saw; (d) I was thinking how I feel about doing this task. If participants had stimuli-related thoughts, they were additionally asked which picture had triggered the thought. Participants were then asked whether the thought they had was spontaneous or deliberate. Finally, they were asked whether the thought they had were about the past, present or the future. The categories of thoughts and the thought probing procedure were adapted from Maillet and Schacter[6] (see also[28,32] for similar thought probing). Thought

probes were presented 1.5 s after preceding stimulus slides, since the results of Maillet and Schacter [6] suggest that such interval slightly increases the probability of evoking stimulus-related thoughts in healthy adults.

Stimulus presentation and the response collection were controlled by Inquisit 5 software running on a 14″ foldable notebook. Pictures measured on average 600 px (height) × 600 px (width) at a viewing distance of 60 cm, and were presented on a white background in the center of the screen. They were generated in a random order, which was then the same for each participant. To simplify the recording of thought probes for Polish older adults who may not be very familiar with using the computer, all participants were giving their answers orally, rather than typing them into the computer as in Maillet and Schacter[6]. The experimenter manually recorded participants' responses.

We developed two versions of the Man-made/Natural Task. All participants completed the two versions in one session, in a counter-balanced order, without any break between the versions. Each version consisted of 121 blocked pictures of either very familiar objects (the block with highly meaningful stimuli) or unfamiliar objects (the block with unmeaningful stimuli). There were 15 thought probes in each block.

Stimuli-pictures were obtained from the same base as used by Maillet and Schacter[6], i.e., Bank of Standardized Stimuli[66,67]. The base consists of stimuli that were assessed on different dimensions by a high number of participants, as part of normalization studies. One of these dimensions was familiarity, which was measured with the question: "Rate the level to which you are familiar with the object" on a 5-point scale (1 = very unfamiliar; 5 = very familiar).

For the present study, 300 pictures with the highest scores of familiarity and 300 pictures with the lowest scores of familiarity were chosen from the base. To select the pictures that would be most familiar/unfamiliar to Polish older adults, the pilot study was conducted in which 29 Polish older adults of age 60 + (MA = 67.65; SD = 4.60; 9 Males) were asked the same question about familiarity in relation to each picture chosen form the base. A total of 121 pictures with the highest mean familiarity (M = 4.42; SD = 0.20) and 121 pictures with the lowest mean familiarity (M = 2.81; SD = 0.29) were selected for the final set. Due to the predominance of pictures showing man-made objects among the pictures rated as most familiar and most unfamiliar, pictures with natural objects accounted for 1/3 of stimuli in each version of the Man-made/Natural Task.

Procedure. Participants were tested individually in two sessions, up to 5 weeks apart, with each session lasting approximately one hour. Sessions took place on the premises of the nursing houses and senior social clubs, in quite separate rooms. The screening interview, NOSGER-IADL, MMSE, ACE-III, CVLT and Geriatric Depression Scale 15 were administrated in Session 1. The Man-made/Natural Task and HVLT were completed in Session 2.

At the beginning of Session 2 participants completed the short-delay HVLT tasks. They were then briefly introduced to the Man-made/Natural Task. Participants were asked to press "S" on the keyboard if the object on the screen was man-made, and press "N" if it was natural. They were also informed that we are interested in what types of thoughts people experience while performing such tasks. Therefore, the slide presentation would occasionally stop, at which point they would be prompted to report their thoughts at the exact moment they were stopped. Participants were briefly informed about the thoughts they might experience during the task and what options they would have to categorize them, i.e., no thoughts, picture-triggered off-task thoughts, picture-unrelated off-task thoughts, and thoughts about the experience of performing the task. This was followed by training, during which participants were given examples of thoughts from various categories and asked what category they would choose. If they made the wrong choice, they were explained why it should be a different category. The exemplary thoughts were, among others: *I used to work as a bus-driver* after seeing the picture of a bus; *I have a doctor appointment tomorrow*, with a no picture related to such fact; *I wonder if I have chosen the right answer*. The training continued until the participant was able to correctly categorize all types of thoughts. Participants were then explained the difference between spontaneous thoughts (thoughts that pop into mind without your intention) and deliberate thoughts (something you deliberately chose to think about). Finally, participants were briefly informed about the types of off-task thinking they could experience, i.e., that it could be related to something that: (a) was happening in the present, at any point in the course of the task (e.g., *I love my family*); (b) had happened in the past, before starting the task (e.g., *I went to Spain last year*); (c) would happen in the future, after completing the task (e.g., *I'm going to eat delicious supper today*). This was followed by short practice with two 10-slides trials and two thought probes. After practice, participants completed the long-delay HVLT tasks and then both versions of the Man-made/Natural Task. When the procedure was completed, participants were asked to rate how interesting the task of classifying pictures was (1 = very boring; 10 = very interesting), and how difficult the task of categorizing thoughts was (1 = very difficult; 10 = very easy).

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Author contributions

M.W. and A.N. designed the study, developed methodology, conducted statistical analyses and prepared the manuscript. M.W. administrated the project, conducted experimental sessions, prepared the data and wrote the original draft. A.N. conducted reviewing & editing and provided conceptual feedback.

Competing interests

The authors declare no competing interests.

Additional information

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Kraków, 30.06.2023

Author's contribution statement

I hereby declare that my contribution to the publication: Michał Wereszczyński and Agnieszka Niedźwieńska (2022). „ Deficits in spontaneous and stimulus-dependent retrieval as an early sign of abnormal aging " published in Scientific Reports, included: Conceptualization, Methodology, Resources, Funding acquisition, Project administration, Investigation, Formal analysis, Data curation, Writing original draft and Writing review & editing.

Michał Wereszczyński

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Mgr Michał Wereszczyński

Kraków, 29.06.2023

Author's contribution statement

I hereby declare that my contribution to the publication: Michał Wereszczyński and Agnieszka Niedźwieńska (2022) „ Deficits in spontaneous and stimulus-dependent retrieval as an early sign of abnormal aging ” published in *Scientific Reports*, included: Supervision, Conceptualization, Methodology, Formal analysis, Writing original draft and Writing review & editing

Niedźwieńska

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Attachment 2

Investigating the Relationship Between Periodontitis and Specific Memory Processes in the Search for Cognitive Markers of Alzheimer's Disease Risk

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Abstract

The Spontaneous Retrieval Deficit (SRD) hypothesis argues that individuals in the preclinical stages of Alzheimer's disease (AD) are particularly impaired in spontaneous retrieval, which manifests in reduced mind-wandering. Our main purpose was to provide novel evidence to support the SRD hypothesis by investigating, for the first time, the relationship between mind-wandering and periodontitis, the latter being the risk factor for AD. The second objective was to address the lack of deeper understanding of the relationship between oral health and specific cognitive abilities by investigating whether periodontitis would be primarily associated with memory. Sixty community-dwelling dementia-free older adults completed neuropsychological tests that focused on various cognitive abilities and a computerised task, during which mind-wandering was evaluated. Periodontal health was assessed subjectively, and through an oral examination by a qualified dentist that focused on visible periodontitis-related changes in gingival tissues and the number of periodontitis bacteria. In line with our predictions, objective and subjective symptoms of poorer periodontal health were associated with less mind-wandering, providing further support for the SRD hypothesis. Again in line with predictions, poorer periodontal health was associated with worse episodic memory, with no relationship between periodontitis and the measure targeting various cognitive abilities, from which memory was excluded.

Alzheimer's disease (AD) is a major cause of dementia and one of the leading causes of death in the elderly age group[1]. Cerebral pathological changes associated with the disease can precede clinical symptoms by up to 20 years[2]. Given the lack of an effective cure, research has progressively focused on identifying people at risk of developing AD among which early intervention can delay and even prevent the emergence of clinical syndrome[3,4].

Recently, a novel hypothesis has been formulated that argues that spontaneous (i.e., unintentional and effortless) retrieval processes, which are relatively well preserved in healthy ageing[5–7] **,** will be significantly compromised during the prodromal and early stages of AD[8]. The spontaneous retrieval deficit (SRD) hypothesis is highly counterintuitive because it challenges current theories of cognitive ageing[9,10], which predict that both typical and atypical ageing predominantly impair performance in difficult cognitive tasks dependent on deliberate and strategic processes. However, the hypothesis is based on the results of neuroimaging studies showing that, during the etiology of AD, the neurological structures of the Default Mode Network (DMN) tend to degenerate much earlier than other parts of the central nervous system (see[8] for a review of evidence).

The first signs of neuropathological changes within AD tend to occur in the posterior parts of the cortex, with the anterior and dorsolateral prefrontal cortex remaining relatively intact[11,12], resulting in disproportionate temporoparietal atrophy in the early stages of the disease[13,14]. The pathology involves the accumulation of tau-positive neurofibrillary tangles in the structures of the medial temporal lobe, spreading from the entorhinal cortex to the hippocampus[15], and the formation of β-amyloid plaques in the medial prefrontal and posteromedial cortices, especially in the posterior cingulate cortex and adjacent areas[16,17]. These neuropathological processes, especially β-amyloid accumulation, may progress for decades before the onset of dementia[2].

Importantly, the posterior cingulate cortex, the medial temporal lobe, and the medial prefrontal cortex form the key hubs of DMN[18,19]. DMN activity has traditionally been associated with mind-wandering, which involves spontaneous shifts of attention from the external world to one's inner thoughts[20,21]. Links between mind-wandering and increased DMN activity have also been demonstrated in several fMRI studies (see[8] for a review of evidence). Mind-wandering shares similar characteristics with several other phenomena of spontaneous cognitions such as, for example, involuntary autobiographical memories[22,23] or those aspects of prospective memory that involve effortlessly remembering previously intended actions in response to a particular target event[24,25]. What these phenomena share with mind-wandering episodes is that thoughts and memories come to mind spontaneously and effortlessly, without any deliberate intention to think about them.

Spontaneous retrieval, when measured during simple cognitive tasks, can provide a promising alternative to the neuropsychological tests of episodic memory currently used to detect an increased risk of AD. Since spontaneous retrieval is not affected by deliberate strategies to enhance recall and, during examination, participants are not aware of what exactly is being measured, such tasks may have a particular advantage for testing highly functioning dementia-free older adults. In such groups, high education and well-developed learning strategies can mask very early signs of cognitive change in standard neuropsychological tests.

A few recent behavioural studies support the SRD hypothesis by showing the deficit of spontaneous retrieval in amnestic Mild Cognitive Impairment (aMCI), which is the prodromal stage of AD, and in early stages of AD[26–29]. Amnestic MCI manifests itself in subjective and objective memory deficits, as evidenced by neuropsychological tests that measure episodic memory, without the loss of functional independence characteristic of AD[3]. Behavioural evidence of spontaneous retrieval deficits in the prodromal and early stages of

AD has been found in prospective memory[27,30,31] and mind-wandering[26,28,29] (details of behavioural evidence from prospective memory studies in[8]). In mind-wandering studies, thought probes are used alongside very easy cognitive tasks, e.g., deciding whether lines presented on the computer screen are horizontal or vertical, or whether presented pictures show natural or man-made objects. In each probe, participants are asked whether they had any thought at the time they were stopped, and if so, whether it was related to the ongoing task, and if it was spontaneous or deliberate. Participants with aMCI reported significantly less mind-wandering, as measured by the number of spontaneous task-unrelated thoughts, than healthy older adults[28,29]. At the same time, the aMCI groups did not outperform healthy older adults on ongoing tasks, and they continued to mind-wander less after controlling for the ongoing task performance. Studies involving the aMCI groups also suggested that the type of thoughts analysed, i.e., whether related to environmental stimuli or not, and whether oriented toward the past, present, or future, can matter for how strongly the spontaneous retrieval deficit manifests itself[28,29].

The primary objective of our study was to provide more evidence to support the SRD hypothesis by investigating, for the first time, the relationship between mind-wandering and one of the factors that appears to increase the risk of cognitive decline and AD, namely periodontitis (see meta-analyses of longitudinal studies on periodontitis as a risk factor for AD[32,33]). We expected that cognitively healthy older adults (i.e., without cognitive deficits related to dementia or other diseases), but with poorer periodontal health, would show reduced spontaneous retrieval, that is, less mind-wandering. Although the relationship between mind-wandering and periodontitis has not been investigated for far, the results of only two studies on periodontal health and prospective memory can be interpreted in terms of the link between periodontitis and spontaneous retrieval deficits[34,35]. In both studies, poorer periodontal health was associated with poorer event-based prospective memory, but not with

the other type of prospective memory (time-based)[34]. The analyses of prospective memory mechanisms[36,37] suggest that performance in event-based tasks can be based on spontaneous retrieval of intended actions, whereas time-based tasks require strategic and effortful retrieval.

Several pathophysiological mechanisms could explain the negative impact of poor oral health on cognitive function and its role in the development of AD. For example, Dominy et al.[38] have identified *Porphyromonas gingivalis*, an organism associated with chronic periodontitis, in the brain of patients with Alzheimer's disease, and suggested that this microorganism may play a vital role in the disease pathway. A widespread view is that the relationship between AD progression and infection with periodontitis bacteria may occur through the inflammatory pathway, where people with periodontitis are systemically affected by chronic oral inflammation[39–41]. According to the most established model of Kamer et. al.[41–43], periodontitis pathogens or pro-inflammatory cytokines produced in the immune response to infection can enter the central nervous system (through systemic circulation or through the neural pathways) where they may trigger an immune reaction of glia cells. The model holds that chronic inflammation within the brain stimulates glia cells to produce β-amyloid, tau-fibre and pro-inflammatory molecules that, by inducing autoimmune reaction, cause neurodegeneration. Claims about the triggering role of peripheral gum inflammation in AD etiology are supported by numerous studies that show a significant relationship between AD and the level of periodontitis antibodies[43–45]. Diet and nutrition could also explain the link. Older people with tooth loss, particularly edentulism, could suffer from impaired masticatory function and consequently poor nutritional status[46].

A straightforward argument can also be presented for the opposite direction of causality behind the link between oral health and cognitive function, i.e., how cognitive decline could negatively impact oral health through behavioural changes such as reduced attention to oral hygiene or inadequate use of dental health services. However, a recent large-

124 scale longitudinal study[47] shows that the relations between oral health and cognitive function
125 are indeed bidirectional.

126 The second goal of our study was to investigate whether periodontitis is primarily
127 associated with memory ability. It has recently been suggested[34,48] that existing studies on the
128 relationship between oral health and cognitive function provide little insight into the nature of
129 cognitive difficulties that are associated with poor periodontal health. This is due to the fact
130 that many of these studies used brief screening measures of general cognitive function rather
131 than comprehensive tests that target specific cognitive abilities. The distinction between
132 specific cognitive abilities is critical to inform the mechanisms underlying the association
133 between oral health and cognition. For example, individuals in early stages of AD show
134 deficits primarily in episodic memory, while individuals in early stages of other types of
135 dementia (i.e., cardio-vascular, frontal-temporal, or lewy bodies) show deficits mainly within
136 other cognitive domains[49–51]. Therefore, if episodic memory is primarily related to periodontal
137 health, this may suggest that we need to look for explanations that associate periodontitis with
138 AD, rather than other types of dementia. A recent systematic review of Nangle et al.[48]
139 suggests that memory is in fact one of few cognitive abilities that may be specifically related
140 to periodontal health.

141 To achieve these goals, we performed a neuropsychological assessment that targeted
142 various cognitive abilities in a group of 60 dementia-free community-dwelling older adults.
143 The assessment included, among other tests, a comprehensive episodic memory test
144 (California Verbal Learning Test)[52]. Periodontal health was subjectively evaluated with the
145 list of symptoms, and then objectively through an oral examination conducted by a qualified
146 dentist in a specialist dental clinic. The objective evaluation involved calculating: (1) the
147 Community Periodontal Index of Treatment Needs (CPITN), and (2) the number and type of
148 periodontitis pathogens present within the periodontium. Mind-wandering was evaluated

during a very easy Man-made/Natural Task[5,29]. Participants were repeatedly stopped to report whether they had any thought at the time they were stopped and, if so, if it was related to the Man-made/Natural Task, and whether it was spontaneous or deliberate.

In line with the SRD hypothesis, we expected that poorer periodontal health would be associated with less mind-wandering, that is, less spontaneous, task-unrelated thoughts. Based on the results of a systematic review on how oral health can be related to specific cognitive abilities in older adults[48], and data suggesting that periodontitis increases the risk of AD rather than the risk of other types of dementia[44,45], we expected that poorer periodontal health would be associated with a lower performance on the episodic memory test, rather than on the measure targeting various cognitive abilities (Addenbrooke's Cognitive Examination III), from which memory was excluded.

The novelty of our approach was twofold. First, it provided a new way of testing the SRD hypothesis, by going beyond the spontaneous retrieval deficits in aMCI and early stages of AD, and measuring spontaneous retrieval in cognitively healthy older adults in relation to the risk factor for AD. Second, it addressed the concern of a lack of deeper insight into the relationship between oral health and cognitive function, by investigating links between oral health and the specific cognitive domain (memory) and the specific cognitive process (spontaneous retrieval).

Results

The alpha level adopted to determine the significance of the results was set at 0.05. Pearson's coefficients were used to measure correlations between periodontitis status and mind-wandering, and then periodontitis status and tests targeting episodic memory and other cognitive abilities. The strength of the correlations was interpreted according to Cohen's criteria (0.1=small; 0.3=moderate; 0.5=large)[53]. The correlations and t-test results were controlled for multiple comparisons using the Benjamini- Hochberg procedure[54] (False

Discovery Rate = .25). Only those correlations and t-test results that remained significant after the correction are reported, except for tables that present all correlations. When significant associations were established, hierarchical multiple regression models were performed to adjust for background factors that included age, years of education, and MMSE scores.

Periodontitis Status and Mind-Wandering: Testing the SRD Hypothesis

There have been 261 valid sextants in the sample, with 10 % of sextants with CPITN 1, 24% with CPITN 2, 46 % with CPITN 3, 20 % with CPITN 4, and only one sextant with CPITN 0, excluded from the analyses. Periodontitis pathogens were detected in the entire sample with *Capnocytophaga gingivalis* in 93% of the participants, *Tannerella forsythia* in 86%, *Treponema denticola* in 75%, *Peptostrep. (Micromonas) micros* in 71%, *Porphyromonas gingivalis* in 50%, and *Fusobacterium nucleatum* in 41%. Three pathogens were very rare in the sample, thus reducing the number of participants for correlation analyses to 12 or less (*Eubacterium nodatum* detected in 20% of the participants, *Aggregatibacter actinomycetemcomitans* 18%, and *Prevotella intermedia* 13%). Therefore, these three pathogens were excluded from the analyses (see Table 1 for the means of all CPITN indices, the number of periodontitis pathogens, and the number of subjectively evaluated periodontitis symptoms).

Based on the participants' responses to whether they had any thought in a thought probe, and if so, if it was related to the experience of doing the Man-made/Natural Task, and whether it was spontaneous or deliberate, we calculated the number of spontaneous task-unrelated thoughts (the amount of mind-wandering). In line with the literature, these thoughts were further divided into: (a) picture-related vs. picture-unrelated (i.e., whether related to pictures presented as part of the Man-made/Natural Task or not), (b) present vs. past vs. future oriented (see Table 1 for the mean number of each type of spontaneous task-unrelated thoughts).

Table 2 shows zero-order correlations between periodontitis status and mind-wandering measures. In line with our predictions, periodontitis status, measured objectively and subjectively, was significantly related to several types of spontaneous task-unrelated thoughts during the Man-made/Natural Task, and for each of these types of thoughts, poorer periodontal health was related to fewer mind-wandering, and better periodontal health was related to more mind-wandering. For objective measures of periodontitis status, there has been a moderate positive correlation between the number of sextants with CPITN 1 (the more sextants with CPITN 1, the better periodontal health) and the number of spontaneous, task-unrelated thoughts that were picture-unrelated and present-oriented. This type of spontaneous task-unrelated thoughts was also negatively related to the mean CPITN, which was the sum of CPITN codes divided by the number of valid sextants (small correlation), and the highest CPITN code among valid sextants (correlation close to moderate). For the subjective measure of oral health, the number of periodontitis symptoms reported by the participants was negatively associated with the number of spontaneous task-unrelated thoughts that were picture-related and oriented either toward the future (moderate correlation) or past (small correlation).

Table 3 shows the results of hierarchical regression analyses predicting mind-wandering from background variables (age, years of education, and MMSE scores) and CPITN scores. The amount of mind-wandering, as measured by the number of spontaneous, task-unrelated thoughts that were picture-unrelated and present-oriented, remained positively associated with the number of CPITN 1 sextants (β=0.348; p<0.05), and negatively associated with the mean CPITN (β=-0.201; p<0.05) and the highest CPTN (β=-0.282; p<0.05; Table 3). For each of these measures of periodontitis status, the addition of the periodontitis status score as a second step in the regression model contributed uniquely and significantly (see Table 3). Table 3 also shows the results of hierarchical regression analyses that predict mind-wandering

from background variables (age, years of education, and MMSE scores) and the number of periodontitis symptoms chosen by the participant on the list of symptoms. The number of symptoms remained negatively associated with the amount of mind-wandering that was picture-related and future-oriented (β=-0.316; p<0.05), and this number contributed significantly when added as a second step in the regression model (Table 3). However, the number of symptoms was no longer a significant predictor of mind-wandering that was picture-related and oriented toward past.

The correlation analyses did not show significant associations between mind-wandering measures and the number of each type of periodontitis pathogen (p_s>.144). However, since the number of pathogens, as a measure of periodontal health, met the criteria under which the dichotomised indicator performs as well as or better than the original continuous indicator[55,56], for each pathogen we a posteriori assigned participants to two groups: one group with a high number of bacteria (above the median for the sample) and the other group with a low number of bacteria (below the median for the sample). The groups were then compared on mind-wandering measures. Significant group differences were found for *Tannerella forsythia*, which was one of the most common pathogens in our sample. In line with our predictions, individuals with a high number of bacteria showed less mind-wandering that was picture-related and past-oriented (M=3.60, SD=4.02) than those with a low number of bacteria (M=6.43, SD=5.53) (t=-1.754; p<.05; d=.453). Similarly, individuals with a high number of bacteria showed less mind-wandering that was picture-related and future-oriented (M=1.23, SD=1.59) than those with a low number of bacteria (M=2.33, SD=3.04) (t=-2.271; p<.05; d=.586). The cutoff number of *Tannerella forsythia* for group assignment was 15500, and the groups did not differ in age, education, or gender (p_s>0.170).

Periodontitis Status and Episodic Memory

The periodontitis status measures were not significantly associated with performance in Addenbrooke's Cognitive Examination III (ACE-III) (see Table 4), neither with performance in several subtests that evaluated attention, fluency, visuospatial abilities and language, nor with the total ACE-III score, from which the memory subtest was excluded (CPITN scores: p_s>.080; number of symptoms subjectively: p_s>.152; number of pathogens p_s>.100). This pattern was in line with our predictions.

There was a significant correlation between one measure of periodontitis status (the number of CPITN 1 sextants) and another test measuring general cognitive function, namely MMSE (r=.261; p<.05; Table 4). However, it did not contradict our predictions since MMSE includes episodic memory tasks. Furthermore, the relationship between the CPITN 1 sextants and MMSE did not remain significant after adjustment for age and education in a two-step hierarchical regression analysis, with MMSE as a dependent variable and the CPITN 1 sextants as a predictor.

The CPITN scores and the California Verbal Learning Test (CVLT). Four significant correlations were found between the number of sextants with CPITN 4, which are the sextans most severely affected by periodontitis, and the CVLT indices (see Table 4). In line with our predictions, these relationships were negative for recall measures, and positive for the number of intrusion errors. Furthermore, and also in line with our predictions, the mean CPITN was positively associated with the number of intrusion errors from five learning trials, and negatively associated with long delay free recall. Except for a moderate correlation between the CPITN 4 sextants and the number of intrusion errors in the fifth trial, all of these correlations were small.

Table 5 shows the results of hierarchical regression analyses predicting episodic memory performance from background variables (age, years of education, and MMSE scores)

and CPITN scores. For all but one of the CVLT indices that were significantly associated with the CPITN 4 sextants in the correlation analyses, the number of CPITN 4 sextants remained a significant predictor: free recall in the fifth trial, β=0.254; p<0.05; intrusions in the fifth trial, β=0.428; p<0.001; intrusions in trials 1-5, β=0.276; p<0.05. Adding the number of CPITN 4 sextants as a second step in the regression model contributed significantly for all these episodic memory measures (see Table 5). In contrast, mean CPTIN was no longer related to episodic memory, for any of the two CVLT indices that were significantly associated with it in the correlation analyses.

Periodontitis symptoms, subjectively evaluated, and CVLT. The number of symptoms chosen by the participant on the list of symptoms was not significantly associated with any of the episodic memory test indices (p_s>.072).

The number of periodontitis pathogens and CVLT. Seven significant associations were found between the number of different types of pathogen and CVLT indices (see Table 6). In line with our predictions, these relationships were negative for recall measures, and positive for the number of intrusion errors. Most of the correlations were moderate, except for one small correlation between free recall in trials 1-5 and *Tannerella forsythia* and one large correlation between the fifth trial intrusions and the number of *Fusobacterium nucleatum.*

Table 7 shows the results of hierarchical regression analyses predicting episodic memory performance from background variables (age, years of education, and MMSE scores) and the number of bacteria. Three pathogens remained significantly associated with the fifth trial intrusions: *Tannerella forsythia*, β= 0.475; p<0.001; *Peptostrep. (Micromonas) micros*, β= 0.329; p<0.05; *Fusobacterium nucleatum*, β=0.755; p<0.001, and the addition of the number of these pathogens as a second step in the regression model contributed significantly (see Table 7). Two pathogens remained significantly related to intrusions in trials 1-5: *Peptostrep. (Micromonas) micros,* β=0.300; p<0.05; *Fusobacterium nucleatum,* β=0.294;

$p<0.05$, and adding the number of these pathogens as a second step in the regression model contributed significantly (see Table 7). One of the two recall measures that were significantly associated with the number of pathogens in the correlation analyses, namely the recall in the fifth trial, remained significantly related to the pathogens (*Treponema denticola,* β=-0.276; $p<0.05$).

Discussion

A novel SRD hypothesis argues that individuals in the preclinical stages of AD are particularly impaired in tasks based on spontaneous retrieval, and thus these tasks are sensitive to very early signs of cognitive decline. Our first objective was to provide more evidence to support the SRD hypothesis by showing, for the first time, the relationship between poorer periodontal health, which is considered a risk factor for AD, and reduced spontaneous retrieval, as measured by fewer mind-wandering. Our second objective was to provide evidence that poorer periodontal health is particularly associated with worse episodic memory. Therefore, we expected to show the relationship between periodontitis and performance on the comprehensive episodic memory test, rather than the association between periodontitis and the measure of general cognitive function from which memory was excluded. We confirmed the expected relationships.

The Spontaneous Retrieval Deficit Hypothesis: Relationship between Periodontitis and Mind-wandering

We found several significant associations between measures of mind-wandering and periodontitis, across subjective and objective indices of oral health, and all were in the expected direction. Importantly, all but one of these associations remained significant after adjustment for age, education, and general cognitive function (as measured by MMSE scores). The latter finding, together with the fact that quite a few relationships between periodontitis and the California Verbal Learning Test were no longer significant after

adjustment for MMSE scores, supports our argument about the advantage of mind-wandering as an early marker of cognitive decline. Specifically, compared to cognitive processes captured by neuropsychological tests, including the episodic memory test that we used, mind-wandering is less dependent on general cognitive function.

Although correlation analyses did not show significant associations between the number of periodontitis pathogens and mind-wandering, due to median-split we did find fewer mind-wandering, picture-related and oriented either toward the past or future, in the group with an elevated number of *Tannarella forsythia*, which was one of the most common pathogens in our sample. Given the exploratory nature of these findings, they should be interpreted with caution. However, it should be noted that they are in agreement with the results of the correlation analyses between mind-wandering and other periodontitis measures. They are also in line with previous studies in which individuals with aMCI had spontaneous retrieval deficits primarily within the same two types of mind-wandering: stimulus-related thoughts that were oriented either toward the past or future[28,29].

Taken together, our findings significantly expand previous data on reduced mind-wandering in aMCI and early stages of AD, and provide novel evidence to support the SRD hypothesis by showing the relationship between spontaneous retrieval and the risk factor of AD, namely periodontitis.

Relationship between Periodontitis and Episodic Memory

We found many significant associations between episodic memory indices and periodontitis status, objectively measured by both CPITN and pathogens, and a substantial part of them remained significant after adjustment for age, education, and general cognitive function. All associations were in the expected direction, and they were stronger for the number of pathogens than CPITN. At the same time, no relationship was found between periodontitis and the tests measuring specific cognitive abilities, other than memory, or a general index of

cognitive function (Addenbrooke's Cognitive Examination III) from which memory was excluded. These findings unequivocally support the claim that periodontal health is particularly related to episodic memory, and may help to gain a clearer understanding of the association between oral health and dementia.

A particular link between periodontitis and memory suggests that periodontal health may be primarily related to an elevated risk of Alzheimer's type dementia, the early stages of which, unlike other types of dementia, manifest with memory impairment[49–51]. This conclusion is supported by the results of biomolecular studies that have shown associations between periodontitis and specifically AD, e.g., the presence of periodontitis pathogens within brain tissue from individuals with AD in post-mortem assessment[57]; the presence of periodontitis bacteria's DNA in cerebrospinal fluid from individuals with probable AD[38]; a decreased ability to learn and memorise following intracellular accumulation of β-amyloid after chronic exposure to the periodontitis pathogen that was demonstrated in the animal model[58], and increased production of β-amyloid and tau protein in mice' brain, which is AD-specific pathology, after chronic oral exposure to periodontitis pathogen[59].

Our results thus expand the accumulating data that suggest that periodontitis is primarily related to the elevated risk of AD, by showing its relationship with episodic memory in general and spontaneous retrieval in particular. It has important implications for research on early identification of AD risk, as well as clinical practise. The data suggest that the presence and severity of periodontitis should be considered when projecting the probability of progression to AD in preclinical groups or when developing questionnaires and clinical inventories designed to assess such risk. Regarding clinical practise, they show the importance of taking special care of gingival health in individuals with an elevated likelihood of progression to AD as a means of reducing the risk of progression.

Limitations and Future Directions

Despite encouraging findings, the present study has some limitations that will need to be addressed in future research, such as weak to moderate associations between periodontitis status and mind-wandering, and periodontitis status and episodic memory. Furthermore, these associations were found only for some measures of mind-wandering and episodic memory. The lack of stronger associations may be due to the characteristics of the sample that consisted of high functioning, well educated, and community-dwelling older adults with a restricted range of periodontal health indices. Since participants were able to take care of their dental health, the sample did not include many of those with highly developed periodontal disease. This explanation is in line with the results of previous studies suggesting that the relationship between oral health and cognitive function is stronger for groups with a lower overall, and of a wider range, oral health status (e.g., residents of nursing homes), compared to high functioning, community-dwelling older adults[34,60]. To ensure a greater variance in periodontitis status, future studies on the relationship between periodontitis and specific memory processes can recruit both high functioning community-dwelling adults and residents of nursing homes.

It should be noted that the pattern of our results suggests that mind-wandering is more consistently associated with CPITN scores and subjective evaluation of periodontal symptoms, while episodic memory is more consistently associated with the number of pathogens and CPITN scores, with the majority of the associations found with the number of sextants most severely affected by the disease (CPITN 4). It may be due to the fact that the three measures of oral health applied in our study provide somewhat different types of information on oral health status. The number of bacteria represents the current scale of infection with certain types of periodontitis pathogens, while CPITN describes the visible changes in the structure of the gums caused by periodontitis over the years. These changes are

caused by the gingivitis infection, but can remain observable even after the gingivitis infection is treated or decreased[61]. Therefore, it is possible to have a low number of periodontitis bacteria due to the applied gingivitis treatment and, at the same time, to have visible moderate changes in gum structure caused by periodontitis over the years. Similarly, the chosen symptoms show what kind of periodontitis symptoms the participant has experienced during the course of the disease, even if they do not have gingivitis or an elevated number of bacteria at the time of examination, due to the previously applied treatment. This reasoning is supported by our additional analyses in which a significant relationship with the number of bacteria was found for the number of CPITN 4 sextants, but not for the other three CPITN codes or the number of symptoms. Therefore, the pattern of relationships may suggest that mind-wandering is more related to cumulative, but not very severe, changes caused by well-managed disease over the years, while episodic memory is more related to the most severe changes in the gums caused by poorly managed periodontitis. Future studies may address this issue more directly.

Finally, since our investigation was a single-assessment cross-sectional study, further longitudinal examination is needed to be able to unequivocally determine the causality and directionality behind the relationships that we demonstrated. Of particular interest would be the use of prospective longitudinal studies to investigate how simple tasks relying on spontaneous retrieval will compare with standard neuropsychological tests currently used, in terms of early detection of MCI and prediction of conversion rates to AD. Future studies may also investigate the relationship between deficits in spontaneous cognitions and biological markers of AD (e.g., amyloid plaques or the ApoE4 gene).

Method

Participants

A total of 60 participants (M_{age}=72.52; SD=4.15; 86% women) who lived independently in the community, with varying periodontal treatment needs were recruited. To ensure sufficient power, we performed the a priori power analysis on GPOWER 3.1[62]. Since there were no published studies on the relationship between periodontal health and spontaneous retrieval, as measured by mind-wandering, the calculation of the effect size was based on the relationship found by Manchery et al.[34] (*r*=-.51) between periodontal health and an event-based prospective memory task. According to theoretical explanations of prospective memory[36,37], performance on event-based prospective memory tasks, in contrast to performance on the other type of prospective memory tasks (time-based), can be based on spontaneous retrieval of intended actions. With an alpha level of .05 and a minimum power of .95, 39 participants were necessary to find a statistically significant effect for a zero-order correlation. However, Manchery et al.[34] found the relationship between objectively measured periodontal health and prospective memory among older adults living in a retirement village, and suggested that this link may be weaker among older adults who live independently in the community, among which oral health is generally much better, so the range of oral health indexes is relatively restricted. Therefore, to avoid the risk of not having enough power to capture the relationship between oral health and mind-wandering, we recruited more participants than the calculations indicated were necessary.

The participants were members of senior social clubs or volunteers in the community, and they all received 150 PLN (approximately 34 USD) for their participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Bioethics Research Committee at Jagiellonian University (Opinion number: 1072.6120.76.2022). Participants provided their informed written consent to take part in the study. For all

participants, inclusion criteria were: (a) no head/brain injuries, (b) no history of cerebrovascular disease, (c) no current dependence on alcohol or substances, (d) no medical, neurological, or psychiatric disorders resulting in cognitive dysfunctions, (e) age more than 65 years, (f) not meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders' (DSM-5) for dementia[63], (g) preserved general cognitive function as confirmed by a normal score on the Mini-Mental State Examination (MMSE)[64] (normality cut-off score: 24)[65] – MMSE scores in the sample ranged from 25 to 30, (h) maintained activities of daily living as confirmed by a maximum score on the Instrumental Activities of Daily Living (IADL) subscale of the Nurses' Observation Scale for Geriatric Patients (NOSGER)[66,67] (i) absence of severe depression, as confirmed by a score below 10 on the Geriatric Depression Scale 15[68] . Fluency in Polish and adequate vision and hearing were also required. Inclusion criteria were evaluated in the initial interview screening.

Measures

Neuropsychological evaluation. A Polish version of the Mini-Mental State Examination[64] was used in the initial screening for dementia. To measure episodic memory, a Polish version[69] of the California Verbal Learning Test (CVLT)[52] was used. During CVLT, the experimenter reads a list of 16 nouns aloud over five learning trials. After each trial, the participant is asked to recall as many words as possible. After the fifth trial, a distractor list, with new 16 words, is presented. Free recall of the original list is tested immediately (short delay), and again after 20 minutes (long delay). We calculated four free recall measures for which a higher score indicated better performance: (a) the number of words recalled after the fifth trial, (b) the number of words recalled across all five trials, (c) the number of words recalled after the short delay, and (d) the number of words recalled after the long delay. Furthermore, the number of intrusion errors (recalling words that were not present on the original list) was calculated after the fifth trial, for all five trials together, after the short delay

474 and the long delay, with a higher score indicating poorer performance. Attention, executive
475 functions, language and visuospatial abilities were tested with Addenbrooke's Cognitive
476 Examination III (ACE-III)[70]. There were three tasks in the attention subscale (maximum score
477 – 18), two verbal fluency tasks in the executive function subscale (max. 14), seven tasks in
478 the language subscale (max. 26), and five tasks in the visuospatial abilities subscale (max.
479 16). For all these subscales, a higher score indicated better performance. ACE-III also
480 included five memory tasks, but the memory subscale was excluded from the total ACE-III
481 score.

482 ***Oral health evaluation.*** An eight-item list of warning signs of periodontal disease was
483 developed. The list of symptoms was based on[71] and symptoms published by the Centres for
484 Disease Control and Prevention of the United States[72]. Participants were asked to confirm or
485 deny experiencing any of the symptoms on the list (YES/NO answer). The list included: (a)
486 swollen gums, (b) redness of the gums, (c) bleeding gums during brushing or spontaneously,
487 (d) exposure of tooth necks, (e) migration of teeth, (f) loosening of teeth, (g) sore gums while
488 brushing, (h) unpleasant smell from the mouth, (i) unpleasant taste in the mouth, (j) recurrent
489 gingivitis, and (k) hypersensitivity of teeth to extreme temperatures.

490 To capture possible associations between gingival health and cognitive functioning
491 rather than diagnose participants with periodontitis, we measured the number and severity of
492 symptoms of periodontal disease. Two types of oral examination were performed in one
493 specialist dental clinic by the same single examiner who was a qualified dentist and had no
494 access to the data about the participants collected during the neuropsychological evaluation
495 session. As the first type of oral examination, gingival health was evaluated using the
496 Community Periodontal Index of Treatment Needs (CPITN) recommended by the WHO[73].
497 The index could range from 0 to 4, with: 0 for healthy periodontium, 1 for gingival bleeding
498 on probing (gingivitis infection), 2 for the presence of subgingival calculus (i.e., 0-2 indicated

no symptoms of periodontitis), 3 for the presence of at least one pathological gingival pocket 4-5mm (symptom of periodontitis), and 4 for at least one pathological gingival pocket 6mm or more (symptom of severe periodontitis) indicating the need for complex treatment[74]. The index was calculated for each tooth sextant as the tooth score with the highest CPITN. Sextants with less than 2 teeth were excluded from the calculations. We analysed CPITN scores at various levels. First, we analysed the number of sextants with each CPITN code per participant. Since CPITN codes 3 to 4 indicate the presence of pathological gingival pockets, i.e., sextants considered to be severely affected by the disease[75], the higher the number of sextans with these CPITN codes, the poorer the gingival health. In contrast, CPITN codes 0 to 2 indicate a lack of pathological gingival pockets, and therefore, the higher the number of sextans with these CPTN codes, the better the gingival health. Second, for each participant, we calculated the mean CPITN score (i.e., the sum of CPITN codes divided by the number of valid sextants), and the highest CPITN score. For both indices, a higher score indicated poorer gingival health.

As the second type of oral examination, the number and type of periodontitis pathogens present within the periodontium were examined with PET plus (MIP Pharma®, Germany). During the examination procedure, the dentist placed, for 20 seconds, a special sterile dental filter in the periodontal pockets, or in the area of the periodontium, if the participant was healthy. One pooled sample per participant was collected from four sextants with the deepest pathological gingival pockets. If pocket depths did not exceed 3mm in the individual (which was the case only for 4 participants), the sample was taken from four different sextants with the deepest pockets within the normal limit (i.e., < 3mm). If there were fewer than four sextants present, the sample was taken four times from the available sextants. After that, the filter was secured in a special transport sample, and then sent to the MIP Pharma® specialistic biomolecular laboratory in Germany by ordinary mail. In the

laboratory, the sample was analysed using the real-time polymerase chain reaction (PCR) method to isolate the DNA of bacteria. The test was designed to detect nine types of periodontitis bacteria: *Aggregatibacter actinomycetencomitans, Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Eubacterium nodatum, and Capnocytophaga gingivalis,* which are the most prevalent periodontitis pathogens[76–79]. We analysed the number of detected pathogens for each participant, separately for each type of bacteria.

Mind-Wandering Evaluation. Participants completed a computer-based Man-made/Natural Task, which was originally developed by Maillet and Schacter[5], and then modified and used to test the SRD hypothesis by Wereszczyński and Niedźwieńska[29]. The task consisted of a 242-slide presentation of pictures showing natural objects (e.g., flower) and man-made objects (e.g., car). Below each picture was a caption corresponding to it**.** Participants were asked to decide whether the object depicted was artificial or natural. Each stimulus was presented for 4 seconds, followed by a blank screen for 4 seconds. Every 6 to 10 stimulus slides, the task stopped and thought probe questions appeared on the screen. Participants were asked to describe their thought content the moment before the question appeared on the screen by choosing one of the following answers: (1) I didn't have any thoughts; (2) I had a thought triggered by one of the pictures I saw; (3) I had a thought unrelated to the task or any of the pictures I saw; (4) I was thinking how I feel about doing this task. It is important to note that the last category (task-related thoughts) would predominantly include so called task-related interference[5,80], i.e., concerns about task performance (e.g., *Oh no! I've chosen wrong answer!*) or opinions about the task itself (e.g., *This task is very easy*). Such thoughts may sometimes include references to the pictures, but only to the pictures as parts of the task, and they will still be expressing, for example, concerns about the task performance (e.g., *The tree is natural but I have chosen that it's man-*

549 *made!*) or opinions about the task itself (e.g., *Pictures take too long to change*). In contrast,
550 thoughts from the second category (picture-related thoughts) would be direct associations
551 with the pictures, without any reference to the task, e.g., *My friend is a mechanic* after seeing
552 the picture of a car.

553 If participants had stimuli-related thoughts, they were additionally asked which picture
554 had triggered the thought. The participants were then asked whether the thought they had was
555 spontaneous or deliberate. Finally, they were asked if the thought they had was about the past,
556 present, or future. The categories of thoughts and the thought probing procedure were adapted
557 from Maillet and Schacter[5] and Wereszczyński and Niedźwieńska[29] (see also[28,81] for similar
558 thought probing).

559 The presentation of the stimuli and the response collection were controlled by Inquisit
560 5 software running on a 14" foldable notebook. Pictures measured on average 600 px (height)
561 x 600 px (width) at a viewing distance of 60 cm, and were presented on a white background
562 in the centre of the screen. They were generated in random order, which was then the same for
563 each participant. Since older Polish adults may not be very familiar with using the computer,
564 all participants gave their answers orally, rather than typing them into the computer, and the
565 experimenter manually recorded the responses of the participants.

566 Stimuli-pictures were obtained from the same base as used by Maillet and Schacter[5],
567 that is, the Bank of Standardised Stimuli[82,83]. The base consists of stimuli that were assessed
568 on different dimensions by a large number of participants, as part of normalisation studies.
569 One of these dimensions was familiarity, measured by the question: "Rate the level to which
570 you are familiar with the object" on a 5-point scale (1=very unfamiliar; 5=very familiar). For
571 the study by Wereszczyński and Niedźwieńska[29], 300 pictures with the highest familiarity
572 scores and 300 pictures with the lowest familiarity scores were chosen from the base, and then
573 piloted among older Polish adults to obtain those that would be most familiar and most

574 unfamiliar for a Polish sample. Since Wereszczyński and Niedźwieńska[29] showed that mind-
575 wandering was much more likely when older adults were exposed to highly familiar pictures,
576 compared to when they were exposed to highly unfamiliar pictures, a total of 242 pictures
577 with the highest mean familiarity (M=4.16; SD=0.34) were selected for the final set in the
578 present study. Due to the predominance of pictures showing man-made objects among the
579 pictures rated as most familiar, pictures with natural objects accounted for 1/3 of the stimuli.
580 As should be with a cognitive task, during which mind-wandering is evaluated, the
581 performance of the participants on the Man-made/Natural Task, as measured by the
582 percentage of correct answers out of all answers provided, was at ceiling (M=96.45,
583 SD=2.19). The performance was not associated with any of the mind-wandering measures
584 (p_s>.223).
585 **Procedure**
586 Participants were individually tested in two psychological evaluation sessions (each
587 approximately 1 hour long) on separate days, and in one dental examination session
588 (approximately 0,5 hour long) which took place between psychological evaluation sessions.
589 The screening interview, NOSGER-IADL, MMSE, ACE-III, and the Geriatric Depression
590 Scale 15 were administered at the first psychological evaluation session. The Man-
591 made/Natural Task and CVLT were completed in the second.
592 At the beginning of the second psychological evaluation session, participants
593 completed short-delay CVLT tasks. They were then briefly introduced to the Man-
594 made/Natural Task. The procedure of administering the task was the same as in
595 Wereszczyński and Niedźwieńska[29], and its description is based on their paper. Participants
596 were asked to press ‘S’ on the keyboard if the object on the screen was man-made, and to
597 press ‘N’ if it was natural. They were also informed that we are interested in what types of
598 thoughts people experience while performing such tasks. Therefore, the slide presentation

would occasionally stop, at which point they would be prompted to report their thoughts at the exact moment they were stopped. Participants were briefly informed about the thoughts they might experience during the task and what options they would have to categorise them, i.e., no thoughts, picture-triggered off-task thoughts, picture-unrelated off-task thoughts, and thoughts about the experience of performing the task. This was followed by training, during which participants were given examples of thoughts of various categories and asked what category they would choose. If they made the wrong choice, it was explained why it should be a different category. The exemplary thoughts were, among others: *I used to work as a bus driver* after seeing the picture of a bus; *I have a doctor appointment tomorrow*, with no picture related to this fact; *I wonder if I have chosen the right answer*. The training continued until the participant was able to correctly categorise all types of thoughts. The participants were then explained the difference between spontaneous thoughts (thoughts that pop into mind without your intention) and deliberate thoughts (something you deliberately chose to think about). Finally, participants were briefly informed about the types of off-task thinking they could experience, i.e., that it could be related to something that: (a) was happening in the present, at any point in the course of the task (e.g., *I love my family*); (b) had happened in the past, before starting the task (e.g., *I went to Spain last year*); (c) would happen in the future, after completing the task (e.g., *I am going to eat delicious supper today*). This was followed by a short practise with two 10-slide trials and two thought probes. After practising, participants completed the long-delay CVLT tasks and the Man-made/Natural Task.

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Author Contributions

M.W. and A.N. designed the project and developed methodology. M.W. administrated the project, carried out the study and performed data analyses. I.T. provided feedback on medical issues and administrated the medical documentation of the study. A.Ś performed medical assessments and prepared database with oral health data. M.W. and A.N. wrote the manuscript with input from all authors. All authors approved the submitted version.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

The authors declare no competing financial or non-financial Interest

Table 1

Summary of mean results for demographic variables, mind-wandering, neuropsychological tests, and oral examinations

Variable		Mean	SD
Age		72.517	4.152
Education (years)		16.083	2.757
Mind-wandering: Spontaneous task-unrelated thoughts			
Picture-related:	Present	6.333	5.190
	Past	5.017	5.000
	Future	1.783	2.471
Picture-unrelated:	Present	0.417	0.979
	Past	0.017	0.129
	Future	0.217	0.865
Geriatric Depression Scale 15		2.467	2.281
MMSE		28.117	1.519
Addenbrooke's Cognitive Examination-III			
Attention		17.400	0.785
Fluency		11.850	1.938
Visuospatial functions		15.750	0.541
Language		25.783	0.454
Total (excluding memory)		70.783	2.484
California Verabal Learning Test			
Trial 5: free recall		11.150	2.385
Trial 5: intrusion errors		0.267	1.205
Trials 1-5: free recall		47.717	10.064
Trials 1-5: intrusion errors		1.333	2.398
Short delay free recall		9.33	3.317
Short delay free recall intrusion errors		0.25	0.541
Long delay free recall		9.90	3.203
Long delay free recall intrusion errors		0.57	1.267
Community Periodontal Index of Treatment Needs (CPITN) scores			
Sum of sextants with CPITN 1[1]		.43	.810
Sum of sextants with CPITN 2		1.03	1.235
Sum of sextants with CPTIN 3		2.02	1.479
Sum of sextants with CPTIN 4		0.85	1.162
Mean CPITN[2]		2.781	0.618
Highest CPITN[3]		3.42	0.671
The number of periodontitis symptoms evaluated subjectively		3.950	2.727
The number of periodontitis pathogens			
Porphyromonas gingivalis		900595,5	2310386
Treponema denticola		204062	439252,2
Tannerella forsythia		125645,2	283586,5
Peptostrep. (Micromonas) micros		6108,333	13017,13
Fusobacterium nucleatum		4891,167	14331,26
Capnocytophaga gingivalis		32865,33	45195,72

[1] There was only one sextant rated CPITN 0 across all participants, so sextans with code 0 are not included; [2]Sum of CPITN codes divided by number of valid sextants; [3] The highest CPITN code among valid sextants

Table 2

Testing the relationship between poorer periodontal health and fewer mind-wandering with zero-order correlations between Community Periodontal Index of Treatment Needs (CPITN) scores and mind-wandering measures

	Mind-wandering: Spontaneous task-unrelated thoughts					
	Picture-related			Picture-unrelated		
	Present	Past	Future	Present	Past	Future
Community Periodontal Index of Treatment Needs (CPITN) scores						
Sum of sextants with CPITN 1[1]	.078	.027	-.045	**.324***	-.07	.081
Sum of sextants with CPITN 2	-.137	-.11	-.053	-.138	-.11	-.134
Sum of sextants with CPTIN 3	.194	0	.117	-.052	.087	.13
Sum of sextants with CPTIN 4	.028	-.026	-.088	-.168	.243	-.085
Mean CPITN[2]	.105	.009	-.03	**-.277***	.152	-.086
Highest CPITN[3]	.037	-.083	-.047	**-.294***	.114	-.1
The number of periodontitis symptoms evaluated subjectively	.056	**-.261***	**-.351****	-.036	.002	-.11

** p < 0.05, ** p < 0.01; Values that remained statistical significant after Benjamini–Hochberg correction in bold; [1] The higher the number of sextans with CPITN 1 to 2, the better the gingival health; the higher the number of sextans with CPITN 3 to 4, the poorer the gingival health; [2] Sum of CPITN codes divided by number of valid sextants; a higher score indicates poorer gingival health [3] The highest CPITN code among valid sextants; a higher score indicates poorer gingival health*

Table 3
Hierarchical multiple regression analyses predicting mind-wandering from age, education, MMSE scores and CPITN scores[1]

	Mind-wandering Picture-Unrelated About Present[2]		Mind-wandering Picture-Unrelated About Present[2]		Mind-wandering Picture-Unrelated About Present[2]		Mind-wandering Picture-Related About Past[3]		Mind-wandering Picture-Related About Future[4]	
	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2	β
Step 1	.079		.079		.079		.280***		.111	
Age		.083		.083		.083		-.011		-.227
Education		-.138		-.138		-.138		.207		-.080
MMSE		.265		.265		.265		.388*		.194
Step 2	.106*		.081*		.079*		.035		.097*	
Age		.139		.142		.076		-.003		-.213
Education		-.203		-.150		-.149		-.139		-.096
MMSE		.196		.252		.242		.385***		.148
CPITN 1 sextants		.348*	Mean CPITN	-.292*	Highest CPITN	-.282*	Sum of symptoms	-.190		-.316*
Total R^2	.184*		Total R^2	.159*	Total R^2	157*	Total R^2	.315***	.208*	

*p < 0.05, ** p < 0.01, *** p <0.001*; [1]Analyses include only those mind-wandering measures that were significantly related with CPITN scores; [2] Spontaneous task-unrelated thoughts that were picture-unrelated and present-oriented; [3] Spontaneous task-unrelated thoughts that were picture-related and past-oriented; [4]Spontaneous task-unrelated thoughts that were picture-related and past-oriented

Table 4
Testing the relationship between poorer periodontal health and poorer episodic memory with zero-order correlations between the Community Periodontal Index of Treatment Needs (CPITN) scores and neuropsychological tests

	CPITN					
	Sum of sextants with:				Mean CPITN[1]	Highest CPITN[2]
	CPITN 1	CPITN 2	CPITN 3	CPITN 4		
MMSE	**.261***	-.047	-.001	-.028	-.100	-.082
Addenbrooke's Cognitive Examination (ACE-III)						
Attention	.096	.021	.023	.03	.042	.129
Fluency	.15	-.069	.06	.088	.067	.166
Visuospatial functions	.058	-.063	-.101	.236	.07	.152
Language	.121	.104	.081	.194	-.013	.134
Total (excluding memory)	.182	-.042	.047	.165	.079	.228
California Verbal Learning Test (CVLT)						
Trial 5: free recall	.168	.056	.038	**-.279***	-.17	-.135
Trial 5: intrusion errors	-.103	-.063	-.136	**.440*****	.228	.112
Trials 1-5: free recall	.215	.106	.022	**-.256***	-.234	-.145
Trials 1-5: intrusion errors	-.128	-.135	-.097	**.268***	**.280***	.197
Short delay free recall	.185	.101	-.025	-.185	-.24	-.14
Short delay free recall intrusion errors	-.174	.267*	.143	-.074	-.058	-.058
Long delay free recall	.252	.151	.000	-.109	**-.264***	-.13
Long delay free recall intrusion errors	-.062	-.11	-.159	.105	.184	.196

**p<.05, ** p<.01, *** p <.001; Values that remained statistical significant after Benjamini–Hochberg correction in bold; [1]Sum of CPITN divided by number of valid sextants; [2]Highest CPITN among valid sextants; For the number of sextants CPITN 1-2, higher score indicates better gingival health; For the rest of CPITN indices, higher score indicates poorer gingival health; For the CVLT recall, higher score indicates better memory; For the CVLT intrusion errors, higher score indicates worse memory*

Table 5

Hierarchical multiple regression analyses predicting California Verbal Learning Test (CVLT) scores from age, education, MMSE scores and the Community Periodontal Index of Treatment Needs (CPITN) scores[1]

	CVLT Trial 5: Free recall		CVLT Trial 5: Intrusion errors		CVLT Trials 1-5: Free recall		CVLT Trials 1-5: Intrusion errors			CVLT Long delay free recall		CVLT Trials 1-5: Intrusion errors	
	Δ R^2	β	Δ R^2	β	Δ R^2	β	Δ R^2	β		Δ R^2	β	Δ R^2	β
Step 1	.165*		.043		.294***		.027		Step 1	.220**		.027	
Age		-.014		.124		-.163		.146	Age		-.109		.146
Education		-.121		.135		-.177		.004	Education		.031		,004
MMSE		.398**		-.094		.469***		-.049	MMSE		.424**		-.049
Step 2	.062*		.174***		.043		.073*		Step 2	.040		.062	
Age		-.009		.115		-.159		.140	Age		-.067		.094
Education		-.066		.042		-.131		-.056	Education		.023		.014
MMSE		.386**		-.074		.459***		-.036	MMSE		.415**		-.038
CPITN 4		-.254*		.428***		-.213		.276*	Mean CPITN		-.206		.256
Total R^2	.227**		.217**		.337***		.100		Total R^2	.260**		.089	

*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; [1]Analyses include only those episodic memory measures that were significantly related to CPITN scores

Table 6
Testing the relationship between poorer periodontal health and poorer episodic memory with zero-order correlations between the number of detected pathogens per specie and neuropsychological tests

	Number of pathogens from specie:					
	Porphyromonas gingivalis	Treponema denticola	Tannerella forsythia	Peptostrep. (Micromonas) micros	Fusobacterium nucleatum	Capnocytophaga gingivalis
MMSE	-0,223	-0,134	-0,158	0,069	-0,058	0,061
Addenbrooke's Cognitive Examination (ACE-III)						
Attention	-0,202	-0,015	-0,206	0,018	-0,115	-0,057
Fluency	-0,125	-0,099	-0,091	0,090	-0,105	-0,045
Visuospatial functions	0,088	0,034	0,146	0,139	0,025	0,115
Language	-0,070	-0,008	0,042	0,126	-0,051	-0,215
Total (excluding memory)	-0,155	-0,076	-0,096	0,129	-0,122	-0,067
California Verbal Learning Test (CVLT)						
Trial 5: free recall	-0,055	**-0,305***	-0,21	-0,193	-0,168	0,052
Trial 5: intrusion errors	0,135	-0,069	**0,484*****	**0,340****	**0,765*****	-0,059
Trials 1-5: free recall	-0,092	-0,238	**-0,265***	-0,232	-0,193	0,051
Trials 1-5: intrusion errors	0,009	0,090	0,214	**0,306***	**0,300***	0,163
Short delay free recall	-0,260*	-0,192	-0,242	-0,062	-0,18	0,091
Short delay free recall intrusion errors	-0,169	0,198	-0,123	-0,021	0,014	-0,084
Long delay free recall	-0,155	-0,213	-0,159	-0,024	-0,126	0,028
Long delay free recall intrusion errors	-0,016	-0,007	-0,042	-0,011	-0,092	-0,043

**p<.05, ** p<.01, *** p <.001; Values that remained statistical significant after Benjamini–Hochberg correction in bold; For the CVLT recall, higher score indicates better memory; For the CVLT intrusion errors, higher score indicates worse memory*

Table 7

Hierarchical multiple regression analyses predicting California Verbal Learning Test (CVLT) scores from age, education, MMSE score and the number of pathogens[1]

	CVLT Trial 5: Free recall			CVLT Trial 5: Intrusion errors		CVLT Trials 1-5: Free recall			CVLT Trial 5: Intrusion errors		CVLT Trials 1-5: Intrusion errors			CVLT Trial 5: Intrusion errors		CVLT Trials 1-5: Intrusion errors	
	Δ R^2	β		Δ R^2	β	Δ R^2	β		Δ R^2	β	Δ R^2	β		Δ R^2	β	Δ R^2	β
Step 1	.165***		Step 1	.043		.294***		Step 1	.043		.027		Step 1	.043		.027	
Age		-.014	Age		.124		-.163	Age		.124		.146	Age		.124		.146
Education		-.121	Education		.135		-.177	Education		.135		.004	Education		.135		.004
MMSE		.398***	MMSE		-.094		.469***	MMSE		-.094		-.049	MMSE		-.094		-.049
Step 2	.073*		Step 2	.217***		.032		Step 2	.103*		.085*		Step 2	.567***		.086*	
Age		.003	Age		.069		-.142	Age		.059		.087	Age		.108		.140
Education		-.152	Education		.147		-.182	Education		.102		-.026	Education		.102		-.009
MMSE		.369***	MMSE		-.034		.446***	MMSE		-.130		-.081	MMSE		-.051		-.032
Td[2]		-.276*	Tf[3]		.475***		-.182	Pm[4]		.329*		.300*	Fn[5]		.755***		.294*
Total R^2	.238**		Total R	.260**		.326***		Total R^2	.146		.113		Total R^2	.610***		.113	

*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; [1]Analyses include only those episodic memory measures that were significantly related to the number of pathogens; [2]*Treponema denticola;* [3]*Tannerella forsythia;* [4]*Peptostrep. (Micromonas) micros;*[5]*Fusobacterium nucleatum*

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In this revision the authors have successfully addressed the two areas of concern by this reviewer including a more detailed description of the sites and method of plaque collection and use of the CPTIN index without the need for intra examiner calibration for the one dental examiner.

Reviewer 2
The authors should be commended for the substantial revisions made to the manuscript to address my and the other Reviewer's previous concerns. I believe that these revisions have strengthened the manuscript, and thus, I do not have further recommended revisions. I look forward to seeing future research from these authors.

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I hereby declare that my contribution to the publication: Michał Wereszczyński, Aleksandra Śmigiel, Iwona Tomaszewska and Agnieszka Niedźwieńska (2023). „The relationship between periodontal health and specific memory processes: Searching for cognitive markers of Alzheimer's disease risk"[1] under review in *Scientific Reports* , included: Conceptualization, Methodology, Resources, Funding acquisition, Project administration, Investigation, Formal analysis, Data curation, Writing original draft and Writing review & editing.

Michał Wereszczyński

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Mgr Michał Wereszczyński

[1] Please note that during the process of revising the manuscript we were asked to change the original title of the manuscript: „The relationship between periodontal health and specific memory processes: Searching for cognitive markers of Alzheimer's disease risk" into the title: "Investigating the Relationship Between Periodontitis and Specific Memory Processes in the Search for Cognitive Markers of Alzheimer's Disease Risk". The co-authors prepared their declarations of contribution when the manuscript had still the original title.

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Aleksandra Śmigiel

Lek. dent. Aleksandra Śmigiel

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Dr hab. n. med. Iwona Tomaszewska

Kraków, 29.06.2023

Author's contribution statement

I hereby declare that my contribution to the publication: Michał Wereszczyński, Aleksandra Śmigiel, Iwona Tomaszewska and Agnieszka Niedźwieńska (2023) „The relationship between periodontal health and specific memory processes: Searching for cognitive markers of Alzheimer's disease risk" under review in *Scientific Reports*, included: Supervision, Conceptualization, Methodology, Formal analysis, Writing original draft and Writing review & editing

Niedźwieńska

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