

Thesis title: “Spontaneous retrieval deficits in older adults with amnesic Mild Cognitive Impairment and periodontal disease: Searching for early cognitive markers of dementia”

PhD Candidate: Michał Wereszczyński

Review by Dr Scott Cole (York St John University)

Overall Appraisal of the PhD

In this PhD, the researcher focusses on one central important and novel question; can we establish a cognitive marker that will predict later diagnosis of dementia? One novel hypothesis, proposed in Kvavilashvili and Rummel (2020) suggested that high risks of developing dementia could be determined by measuring mind wandering. Specifically, in their Spontaneous Retrieval Deficit Hypothesis (SRD), Kvavilashvili and Rummel argue that in the prodromal stage of dementia, and certainly in pre-diagnostic stage, high risk individuals would show lower amounts of spontaneous mind wandering. This hypothesis was supported by a study of people in the prodromal stage of dementia (specifically Alzheimer’s Disease), who had memory problems (classed as amnesic Mild Cognitive Impairment or aMCI) (Niedźwieńska & Kvavilashvili, 2018). Niedźwieńska & Kvavilashvili showed that, in line with the SRD, those with aMCI had fewer instances of spontaneous mind wandering, compared to healthy age-matched controls. Another study by Gyurkovics et al., 2018 further supported the SRD, showing that early AD is associated with a reduction in mind wandering, compared to healthy aged controls.

However, it is important to clarify at this stage of the review that not all studies have found such differences. For example, O’Callaghan and colleagues (2019), did not find any differences in mind wandering between those with Alzheimer’s Disease (AD) and healthy controls, and Rasmussen and colleagues (2021) found more spontaneous utterances (memories and non-memories) in a film viewing task, in people with AD versus controls. Although there are methodological differences between the studies that have and have not found reductions in mind wandering in AD, it is important to highlight this variability in the literature.

As rightly identified by the PhD candidate though, O’Callaghan and colleagues (2019) did not distinguish spontaneous and deliberate thoughts and Rasmussen and colleagues (2021) relied on participants to choose whether or not to report any thoughts/comments, rather than probed and specifically asked about the thoughts. In studies relying on introspection, it is very important that recordings are taken in a timely manner, near when the mental experience occurs (Ericsson & Simon, 1980, Psychological Bulletin). For Rasmussen et al (2021) the memories and thoughts they recorded represented significant differences to the type of momentary experience sampling typical in mind wandering research (e.g., Stawarczyk et al., 2011). In their view, these memories were not equatable with mind wandering experiences. However, such conceptual differentiation is a matter of debate, with some arguing *for* (Cole & Kvavilashvili, 2019, 2021, Psychological Research) and some arguing *against* (Berntsen, 2021, Philosophical Transactions of the Royal Society B) that involuntary memories and spontaneous mind wandering can be subsumed under one

conceptual “category” or psychological “entity”. To my understanding, the candidate assumes that a general category of spontaneous thought is plausible and tractable.

The aims of the thesis are novel and well-founded, and the methods of the two studies were well justified. As is clear, there are very limited data on this hypothesis. The first study, published in the highly esteemed *Scientific Reports* (Wereszczyński & Niedźwieńska, 2022) examined whether and in which circumstances the reduction in mind wandering is found in AD. The specific task was based on a previous task used by Maillet & Schacter, but differed by differentiating highly familiar and low familiarity manmade and natural objects (although the stimuli were taken from the same database). Thought probes were irregular and fairly infrequent which is in line with other tasks in the literature (Plimpton et al., 2015; Smallwood et al., 2011). What differed from most mind wandering tasks was that the task did not require very frequent responding and continual attention (SART). The SART/ go/no go task requires participants respond on every trial (1-2 s) and is also less likely to trigger stimulus independent thoughts as the stimuli (numbers) are non meaningful (Maillet & Schacter, 2016, *Psych and Aging*). It was more aligned with tasks that had a low cognitive demand (vigilance task, Plimpton et al., 2015; Mazzoni, 2019). These choices increased the chances the participant was in a state that could facilitate wandering thoughts.

What would have been useful, and this relates to some points below (Study 2), is that the candidate would have engaged in a more conceptual discussion of mental time travel. There was little explanation of this concept in the Introduction of the thesis, and how it relates to past and especially future thinking. It was mentioned in page 20, but this seems late and a clearer outline of this concept and its brief history would have put other MW findings in a clearer conceptual context (both study 1 and 2 split thoughts by temporality). I will now review each study in turn.

Conclusions regarding this PhD

Throughout these 2 studies - both involving clinical aspects and thus a substantial endeavour for within a single PhD – the candidate used rigorous measures (measuring DNA of bacteria identified in Study 2), employed measures that reduced bias (e.g., blinding dentist from neuropsychological outcomes in Study 2) and good statistical techniques (controlling for extraneous variables in Study 1). These factors highlight that the candidate displays a very good understanding of designing and undertaking high quality neuropsychological studies. The candidate has now a good footing to now become an independent researcher.

The most positive aspects of these studies is their ability to explore completely new ground. This was partly the case for Study 1 where only a handful of prior studies existed and results were mixed, but was more concretely the case for Study 2 where, for the first time, periodontitis was used as a precursor to AD (based on models, some derived from neurobiological data from animal studies). This creativity and novelty translated to high impact studies that were published in a highly-regarded, general audience and prestigious Journal: *Scientific Reports (Nature)*. Although publication in this Journal does not automatically guarantee quality of its contents, it is highly suggestive of it, and is further

indicated by the fact that *both studies* were published in this Journal. The studies were consistently high quality. This research is likely to gather ground and more attention from scientific and general audiences, as this Journal has readers from across multiple disciplines, not just psychology.

This PhD is therefore an extremely valuable set of neuropsychological findings and data that indicate new methods of early detection which can be used for the specific targeting of health interventions. This PhD may prove to be a key “game changer” in dementia research, and I praise the novelty, creativity and rigour the candidate deployed to complete these studies.

Study 1

Study 1 was important in refining the methods of prior work, establishing the boundary conditions of mind wandering deficits, and replicating the prior studies showing deficits. The study compared 27 adults with aMCI with 27 healthy controls. The inclusion criteria for aMCI adults were rigorous and clearly explained. The findings replicated the finding that those with in the prodromal stage of dementia have a significantly reduced amount of spontaneous mind wandering compared to healthy older adults. More detailed analyses established that the finding was exaggerated and driven by spontaneous and past-related thoughts, in line with prior work (Niedźwieńska & Kvavilashvili, 2018). It is also an important study as it shows the same finding as Niedźwieńska & Kvavilashvili, 2018 and Gyurkovics et al., 2018 but with a different type of stimuli, one encountered more often in everyday life – visual objects.

Study 1 Queries

1. One aspect that requires more elaboration is the temporality question. Specifically, why did autobiographical memories show a greater difference between aMCI and healthy controls than future-oriented thoughts? The candidate mentions there are key similarities between the two, drawing upon data and theoretical work by Endel Tulving. However, the differences have been documented and evidenced, and the candidates own data may give clues as to how similar the past and future thoughts were, if at all.
2. Relatedly, how does the SRD Hypothesis relate to future oriented MW episodes. Are their hypotheses different for future versus past spontaneous thoughts?

Study 2

Study 2 - “Investigating the Relationship Between Periodontitis and Specific Memory Processes in the Search for Cognitive Markers of Alzheimer's Disease Risk” - extended logically from Study 1, by examining what may cause these mind wandering deficits in aMCI and later, AD. The approach was to examine mind wandering using the same sensitive techniques employed in Study 1, but this time, the candidate recruited a group of healthy community dwelling adults. The candidate had two main questions in Study 2 that utilised the idea that periodontitis is associated with alzheimer’s disease (which has been

convincingly stated using evidence from biomolecular studies): First, if periodontitis is associated with cognitive deficits which lead to AD, would mind wandering be negatively associated with gum disease or periodontitis? Second, considering the lack of robust and well designed neuropsychological studies of periodontitis and cognitive function, will the authors find a correlation between gum disease and memory, specifically, and no relationship between other cognitive functions and gum disease?

It is worth spending some time considering gum disease – measured here via subjective ratings, numbers of pathogens and a dentists' assessment based on standard criteria (CPITN) - and how that relates to dementia, since this second study rests on this assumption. In one model (by Kamer et al.) it is postulated that chronic oral inflammation starts a chain reaction which can end in glia cells of the brain producing amyloid tau fibre, which can start or speed the neuropathology linked with AD. The candidate outlines these neurobiological studies in the Introduction and Discussion of Study 2, and also mentions possible secondary contributors to AD such as poor dental health leading to poor diet.

Study 2 Queries

There are however some questions that remain unclear or in need of further explanation at the examination.

1. The first point is around measures; there were several measures of gum disease (see Methods, Study 2): For example, mean CPITN, number of sextants with specific codes (1,2,3,4), highest CPITN score. It was not always clear why one or other of these measures were used in the analysis. The same can be said for the different measures used in the CVLT. However, the fact that a multiple comparisons correction was employed means the probability of Type 1 Error is reduced. I note though that a good discussion of the relation between different measures of gum disease was presented in the Discussion of Study 2.
2. The second point worthy of further explanation is around the temporal direction of mind wandering thoughts. In Study 2, the significant effects of future MW survived after adding control variables (e.g., age) in hierarchical multiple regression analyses, whereas other measures of MW did not. Furthermore, the candidate highlights that periodontitis is related to "spontaneous retrieval" in particular. I believe there needs to be more explanation given to the concept of future oriented MW, and specifically what extent it relies on mnemonic processes/systems rather than more imaginary mental processes (e.g., thinking of visiting the Moon). Perhaps the candidate has evidence from the content of MW thoughts that may answer some of these questions. There also need to be more consideration of why there were smaller effects of future MW versus past MW in Study 1, but stronger effects of future MW in Study 2. How and why do these effects differ? Is this an important question?

This study represents the cutting-edge of dementia research because early detection of AD is now agreed as the most important question in this area. To give an example, the latest pharmaceuticals that have been developed and shown to be effective at slowing the disease require that people at high risk of developing AD are identified early. The candidate's

research represents an early step into identifying these high risk individuals and also suggests a way to non-invasively and easily test for cognitive precursors (i.e., mind wandering). This will all help in the overall global goal of reducing the prevalence of AD and slowing its course.

Stylistic Corrections and Small Corrections

Study 2, line 277. Should some of these beta values have a direction. All seem to indicate positive relations between dependent and predictors, but surely some are negative?

Study 2, a brief rationale of why the 5th trial was used is required, perhaps in a footnote