## Cognition and the Middle-Aged Brain

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# Summary

Studies using functional magnetic resonance imaging (fMRI) to examine brain activation during tasks requiring memory and learning processes have demonstrated age-related activation changes in older adults (60 + years old). As cognitive ageing has already begun during the 20s, we can also expect age-related activation changes to be present in middle age (40 - 60 years). Yet, very few studies have used fMRI to examine brain activation during learning and memory in middle-aged adults. Moreover, few studies have considered individual differences in cognitive decline or the effects of factors commonly encountered by middle-aged adults that may exacerbate or ameliorate ageing effects. The main objective of this thesis was to investigate learning and memory-related performance and brain activation in middle-aged adults with regard to demand, fatigue and caffeine effects. In a field dominated by studies comparing retired old adults to young university students, this thesis provides novel insight into ageing effects within the young to middle-aged working population. In particular, we focus on a group of professionals in a cognitively demanding occupation, namely school teachers. Professionals working fulltime in highly demanding occupations represent a particularly difficult group with regard to recruitment for scientific investigation. However, as this thesis demonstrates, the ageing professional is worthy of our attention.

**Chapter 1**, the introduction, outlines the rationale, aims and methodologies in relation to studies comprising the present thesis. The chapters in this thesis were written based on data from two fMRI studies. In the first study, young and middle-aged school teachers were scanned in a control condition and cognitive fatigue condition (requiring the sustained performance of cognitively demanding tasks). In both conditions participants completed a working memory (WM) task (chapter 2), episodic memory task (chapter 3) and resting state measurement (chapter 4). Chapter 5 is also based on data from the first study and examines the interaction between individual differences in the cortisol response and fatigue. In the second study, a group of middle-aged professionals were scanned following consumption of a cup of coffee (compared to placebo) during the WM task (chapter 6). In chapter 7 we combine data from the first and second study (using the control and placebo conditions respectively) to investigate differences between low- and high-performing middle-aged adults during episodic memory encoding. Finally, in Chapter 8, we reflect on the scientific and practical implications of the findings, possible directions for future research, and discuss some methodological considerations.

In **Chapter 2** we examined the effects of age group (young vs. middle-aged school teachers) and induced cognitive fatigue (control vs. fatigue condition) on brain activation during WM encoding and maintenance. Middle-aged adults showed greater encoding activation than young adults in the left dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex, regardless of WM load or fatigue condition. This activation difference appeared to fulfil a neural compensatory function, supporting a higher level of performance in middle-aged adults (performance accuracy was statistically equivalent in young and middle-aged

adults). An interaction was found between age group and fatigue condition effects in the dorsomedial prefrontal cortex. This effect reflected greater load-dependent activation in middle-aged than young adults in the control condition, but a lack of difference between the age groups in the fatigue condition due to increased activation from the control to fatigue condition in the young group. Greater age and fatigue-related DMPFC recruitment in middle-aged and young adults respectively, appeared to reflect less effortful, neurally inefficient processing.

In **Chapter 3** we investigated differences between young and middle-aged school teachers during successful memory encoding. Results showed age-related brain activation differences underlying statistically equivalent behavioural performance including: 1) greater activation in middle-aged than young teachers in bilateral prefrontal cortex areas and 2) differential fatigue effects in the left anterior cingulate cortex and left hippocampal formation, with middle-aged teachers showing an activation decrease in the fatigue compared to control condition, whereas no change was evident in young teachers. Findings demonstrate ageing effects typically found in older adults, specifically the increased recruitment of neural resources, in middle age and indicate that ageing may also be associated with greater resource depletion following sustained task performance.

In **Chapter 4** we examined resting state functional connectivity (RS FC) in young and middle-aged school teachers in the control and induced fatigue conditions. We focused on the executive control (ExN), left and right fronto-parietal (FPN) and default mode network (DMN). RS FC was reduced in middle-aged compared to young adults in the left inferior (part of the ExN) and middle frontal gyrus (part of the DMN). Sustained cognitive performance increased subsequent RS FC between the ExN and a lingual/parahippocampal cluster, and between the left FPN and a right calcarine/precuneus cluster. In these cluster, FC strength correlated positively with the perceived amount of effort during the intervention. Furthermore, sustained cognitive performance affected subsequent RS FC between the ExN and the right temporal superior gyrus differently in young and middle-aged adults. Results suggest that effects of age on RS FC are already present at middle age. Sustained cognitive performance increased RS FC between task-positive networks and other brain regions, although a change in RS FC within the networks was not found.

In **Chapter 5** we investigated the relationship between individual differences in acute fatigue and endogenous cortisol changes elicited by the sustained performance of cognitively demanding tasks (fatigue condition). School teachers provided salivary cortisol measurements and subjective fatigue ratings, and were scanned during memory encoding and recognition tasks in the fatigue and control conditions. A group of 15 'responders' (showing a significant cortisol increase) were compared to 12 'non-responders' (with age included in the analysis as a covariate). Responders showed higher subjective fatigue and reduced encoding and recognition activation than non-responders in the fatigue condition. An interaction in the right hippocampus during encoding reflected decreased activation in responders, but somewhat increased activation in non-responders in the fatigue compared to control condition. Moreover, decreased hippocampal activation in responders was associated with increased subjective fatigue. Findings are consistent with a central role for the hippocampus in differences between responders and non-responders and also implicate the right hippocampus in individual differences in induced cognitive fatigue effects.

In **Chapter 6** we aimed to determine the effect of caffeine (compared to placebo) on WM load-related activation during encoding, maintenance and retrieval. Healthy, male, habitual caffeine consumers aged 40 to 61 years were scanned in a non-withdrawn state following a workday during which caffeinated products were consumed according to individual normal use. Acute caffeine administration was associated with increased load-related activation compared to placebo in the left and right DLPFC during WM encoding, but decreased load-related activation in the left thalamus during WM maintenance. These findings are indicative of an effect of caffeine on the fronto-parietal network involved in the top-down cognitive control of WM processes during encoding and an effect on the prefrontal cortico-thalamic loop involved in the interaction between arousal and the top-down control of attention during maintenance. Therefore, the effects of caffeine on WM may be attributed to both a direct effect of caffeine on WM processes, as well as an indirect effect on WM via arousal modulation. Behavioural and fMRI results were more consistent with a detrimental effect of caffeine on WM at higher levels of WM load, than caffeine-related WM enhancement.

In **Chapter 7** we investigated age-related differences in episodic memory encoding performance and brain activation between young and middle-aged professionals. Furthermore, we investigated differences within the middle-aged group between a low-performing subgroup and a high-performing subgroup. Results are in accordance with findings from previous studies comparing young and old adults. Middle-aged adults showed greater recruitment of the bilateral DLPFC during encoding than young adults, with the age-related increase in activation in the right DLPFC evident to a greater extent in low- than in high-performing middle-aged adults. These findings contribute to on-going discussion regarding the nature of age-related prefrontal over-recruitment; findings corroborate the suggestion that over-recruitment of the right DLPFC does not serve a compensatory function in the support of a higher level of performance in ageing adults and may instead represent an age-related decline in neural efficiency.

Finally, in the concluding remarks (**Chapter 8**) we discuss some scientific and practical implications of the finding that age-related brain activation differences during learning and memory tasks are evident in middle-aged adults. We conclude that fMRI is a valuable tool for the investigation of ageing effects in middle age, since effects at the behavioural level are subtle. However, factors encountered during daily life should also be considered in ageing studies to gain a better understanding of mechanisms underlying cognitive decline and facilitate the development of interventions aiming to optimise workday performance and quality of life in middle-aged adults.