NEUROMODULATION ON WORKING MEMORY AMONG OLDER ADULTS AND PERSONS WITH MILD COGNITIVE IMPAIRMENT (MCI)

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CERTIFICATE OF ORIGINALITY

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ABSTRACT

Background

Working memory decline is one common complaint in aging and mild cognitive impairment (MCI). There are emerging evidences of using non-invasive neuromodulatory techniques including transcranial direct current stimulation (tDCS) to modulate memory function behaviourally and neurally. This provides a tool to investigate the question of how neuroplastic the aging brain is by observing how it might be responsive to the cortical modulation induced by the electrical stimulation and to further examine how the MCI condition would further impact on this neuroplasticity.

Objectives

This study aimed to investigate how single-session electrical stimulation might modulate working memory function by altering the associated neural mechanisms among a group of healthy older adults and compared them with a group of persons with MCI. Our focus was placed on the match-mismatch discriminative process (denoted by N200) and attentional allocation process (denoted by P300) essential to the working memory function.

Methods

Ten minutes of 1-mA anodal HD-tDCS was applied at dorsolateral prefrontal cortex on 18 healthy older adults (mean age = 63.1 ± 2.6, 10 males), 18 persons with MCI (mean age = 68.3 ± 7.1, 5 males), and 22 younger adults (mean age = 19.7 ± 1.6, 9 males). Electroencephalogram (EEG) data was recorded while a standard working memory task (digit two-back) was performed before and after HD-tDCS. The stimulation effect was examined using repeated measure ANOVAs to analyse the mean amplitude of N200 and P300 indexing key processes in two-back task and the behavioural performance between the younger and healthy older adults, and between the two older adult groups.

Results

In the behavioural pilot study conducted to test the time-course of the after-effect of the HD-tDCS, a greater enhancement in the working memory performance in the young participants after anodal stimulation was observed approximately at 30 minutes post-stimulation, concurring with previous evidence of the HD-tDCS after-effect on motor cortex peaking at 30 minutes after stimulation. In the main study, the stimulation generally improved the accuracy and quickened the response in the

younger and the healthy older adult participants but no significant change was observed in the group of persons with MCI. The stimulation induced a less negative-going frontal N200 for target stimuli in the younger adults but induced a more positive-going frontal P300 for non-target in the healthy older adults. Both changes were associated with faster response in the respective groups after stimulation. No change in the N200 was observed for non-target in the younger adults and also generally for the older adults. The P300 in the younger adults did not change after stimulation and this component for target in older adults was not modulated by the stimulation too. The frontal P300 in the group of persons with MCI also became more positive-going but for target stimuli and associated with poorer accuracy rate.

Conclusion

The short-lifting electrical stimulation enhanced the discrimination process (denoted by N200) for target stimuli in the younger participants. In contrast, the same stimulation resulted in enhancing the attentional allocation process (denoted by P300) for non-target in the older participants. Despite similar post-stimulation modulation effects were revealed for the MCI participants, the increases in the P300 positivity did not seem to influence the task performance. The match-mismatch discriminative process for target in the younger participants was less negative-going after the stimulation, suggesting that target stimuli were less perceived as non-targets by them, which was found beneficial to the task performance. No significant modulation of the discriminative process was found in the older participants. The enhanced attentional allocation and hence the task performance among the older participants could be due to the intact compensatory neural capacity among the older participants in response to the excitatory effects brought by the electrical stimulation. This is in contrary to the MCI participants in which the enhanced attentional attention from the same stimulation resulted in poorer task performance. These findings tend to suggest reduced compensatory neural capacity among the MCI participants as they were likely to recruit and exhaust the compensatory mechanism earlier than their healthy counterparts given that MCI condition marks a further deterioration from normal aging. The observed compensatory neural capacity in older participants in response to the electrical stimulation points towards the potential for external stimulation such as tDCS to augment cognitive reserves in the older adults.

PUBLICATIONS ARISING FROM THE THESIS

Oral

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Poster

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CHAPTER 1 INTRODUCTION

Memory decline is one of the common complaints in aging. Behavioural studies often showed that older adults performed poorer in recall or recognition compared to younger adults (Craik & Rose, 2012). Cognitive rehabilitation for older people as well as those with pathological cognitive aging such as mild cognitive impairment (MCI) often focuses on the retrieval stage such as use of memory aids. However, memory decline may begin with deterioration in the encoding of required information for later processing (Craik & Rose, 2012; Friedman, Nessler, & Johnson, 2007) and working memory during encoding thus plays an important role (Craik & Rose, 2012; Grady, 2012).

It had been evidenced that, relative to the young adults, older adults were impaired in discriminative processing of stimuli indexed by event-related potential (ERP) signature N200 (Daffner et al., 2011), and utilized higher top-down attentional allocation indexed by frontal P300 in working memory (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi, Geerligs, Lorist, & Maurits, 2013).

There are emerging evidences of using non-invasive neuromodulatory techniques including transcranial direct current stimulation (tDCS) to modulate memory function behaviourally and neurally (Bennabi et al., 2014; Berryhill & Jones, 2012; Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013; Meinzer, Lindenberg, Antonenko, Flaisch, & Floel, 2013; Meinzer et al., 2015). tDCS modulates cortical excitability and neural plasticity by delivering weak electric current to the scalp to enhance or inhibit excitability of underlying cortical regions (Nitsche et al., 2005; Priori, 2003; Wassermann & Grafman, 2005). High-definition tDCS (HD-tDCS) is a recent modification of the conventional tDCS to improve the spatial focality of the electric field induced (Borckardt et al., 2012; Datta et al., 2009; Dmochowski, Datta, Bikson, Su, & Parra, 2011; Edwards et al., 2013; Garnett & den Ouden, 2015; Kuo et al., 2013; Villamar, Volz, et al., 2013). This provides a tool to investigate the question of how neuroplastic the aging brain is by observing how it might be responsive to the cortical modulation induced by the electrical stimulation and to further examine how the MCI condition would further impact on this neuroplasticity. These questions would be relevant in the light that the age-related and the MCI-related neural changes in working memory differs. They are also questions that stimulates both research and clinical interests to

find out how pliable aging brain is in terms of its activity being changed by external means (e.g. electrical stimulation) and how the pathological brain as in the case of MCI condition would respond in similar manner as the aging brain.

Hence, this study aimed to investigate how HD-tDCS, as an external stimulation, would enhance working memory by modulating the neural processes associated with working memory, namely the match-mismatch discriminative processing (denoted by N200) and attentional allocation (denoted by P300). Specifically, the interests were in the differences between older adults and persons with MCI. This allows better understanding of aging effect and MCI on influencing neuroplasticity which underpin working memory function as well as cognitive function as a whole.

To this end, anodal HD-tDCS was applied on prefrontal cortex of younger participants (YG), healthy older participants (OG) and participants with MCI (MG), and their behavioural and electrophysiological responses on a working memory task performed before and after the stimulation were recorded and examined. The whole study was divided into two parts: comparison between the younger participants and the healthy older participants, and the comparison between healthy older participants and those with MCI. It was expected that the match-mismatch discriminative process (N200) would be enhanced in the YG and the OG, thus narrowing the age-related differences after stimulation. As the N200 was enhanced, the need to utilize the top-down attentional allocation indexed by frontal P300 by the OG would be assumed to be reduced; hence the frontal P300 was hypothesized to be less positive-going in OG and narrowing the difference with YG after stimulation. Behaviourally, the task performance in the two groups as well as in the MG was expected to improve after stimulation. It remained exploratory as to whether N200 and P300 in MG would respond similarly to the stimulation as OG.

It was hoped that the findings from this study would better inform how age- and MCI-related effects influence the neuroplasticity and cognitive reserve underlying working memory relative to the healthy brain.

The thesis reports the study and consists of seven chapters, including the current introduction. Chapter 2 is the literature review on working memory with its neuroimaging and electrophysiological evidences as well as aging effect and the influence of MCI. The background to tDCS as well as the newly developed HD-tDCS is

described in Chapter 2 too. Chapter 3 describes the behavioural pilot study that was conducted to verify the time-course of HD-tDCS effect after stimulation (aftereffect) as there was evidence that the time-course differed between conventional and HD-tDCS. The chapter reports the pilot study as a standalone study with its background, methods, results and discussion. Chapter 4 describes the research methodology as well as the data analysis method employed in the study. Chapter 5 reports the results of the study in two parts: the results between the young adults and healthy older adults to establish a model for the age-adjusted modulation of discriminative processing and attentional allocation associated with working memory functions by the HD-tDCS, and that between healthy older adults and persons with MCI to elucidate possible differentiation of the modulation effects due to the MCI on the aged brain. Discussion of the behavioural and ERP findings from the two parts of the study is covered in Chapter 6. The final chapter covers the limitations and possible future investigations before concluding the thesis.

CHAPTER 2 LITERATURE REVIEW

2.1 WORKING MEMORY

Working memory refers to the process of maintaining a recently-experienced information transiently in mind when it no longer exists in the external environment; and that the information can be subjected to operations for the purpose of goal-directed behaviour (D'Esposito, 2007). In the conceptualization of working memory, one approach is store- or component-based such as the Baddeley's multicomponent model (Baddeley, 1992, 2000, 2012; Baddeley & Hitch, 1974) where working memory is understood as composed of the "phonological loop", the "visuospatial sketchpad", and the episodic buffers as temporary stores within long-term memory (LTM) and the "central executive" as the central controller. Another approach, which is receiving emerging prominence, is Cowan's embedded-process model (Cowan, 1988, 1999) where working memory is conceptualized as activated states within the LTM to varied extent by virtue of attentional selection of mental representations (Cowan, 1988, 1999; D'Esposito & Postle, 2015; Oberauer, 2002, 2009).

2.1.1 Embedded-processes model of working memory

The embedded-processes model (1988, 1999) conceptualizes working memory as an elevated state of activation of long-term memory (LTM) representation via attention. Within the activated LTM is a subset of representations that are in the focus attention or in short, FoA (Cowan, 1999), which is a small and limited state corresponding to task-relevant information held at any moment in time using top-down attentional control via the central executive (Cowan, 1988, 1999). The central executive directs the process of voluntary attention during which items are placed intentionally in the FoA (Cowan, 1988, 1999). Oberauer (2002, 2009) extended the model by narrowing the FoA into one-element focus embedded in the region of direct access which is equivalent to the subset of activated representations in Cowan's version of the model. The one-element FoA serves to select a single representation for active processing, ready for the next cognitive operation (Oberauer & Hein, 2012).

The embedded-process model of working memory elegantly links the role of attention with working memory as well as incorporates top-down modulation (the central executive) on attention and working memory. Grady (2012) reviewed evidences of aging cognition to be often implicating declining attention (Madden et al.,

2007; Thomsen et al., 2004; Townsend, Adamo, & Haist, 2006) and changes in the frontal cognitive control (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Velanova, Lustig, Jacoby, & Buckner, 2007; West, Murphy, Armilio, Craik, & Stuss, 2002), the embedded-process model of working memory would provide a relevant framework to examine both the aging effect as well as to compare MCI-related influence on the neuroplastic change and cognitive reserves in working memory.

2.1.2 Neural mechanism of working memory

2.1.2.1 *Persistent neuronal activity*

The concept of working memory as a functional activated state as outlined by the embedded-process model (Cowan, 1988, 1999) paralleled with the findings that working memory had been associated with persistent, sustained neuronal activity. Persistent neuronal firing during retention interval when performing tasks that required retaining information for a short duration of time (Curtis, Rao, & D'Esposito, 2004; Fuster & Alexander, 1971; Kubota & Niki, 1971) was observed, demonstrating the ability of neurons to generate persistent activity in the absence of external stimuli, particularly though not limited to the prefrontal cortex. This could be corresponding to the activated representations for active task-relevant processing in the region of direct access and focus of attention in the embedded-process model (Oberauer, 2002, 2009). In two-back task, one has to maintain two digits actively (the last digit seen and the digit seen in two trials ago) while encoding and processing the currently-presented probe. The active maintenance of the two digits would correspond with the persistent neuronal activity observed in working memory tasks during retention period.

2.1.2.2 *Neuroanatomy*

2.1.2.2.1 *Dorsolateral and ventrolateral prefrontal cortex*

The early work by Cohen (1997) on human subjects showed that dorsolateral PFC (DLPFC), posterior and inferior frontal cortex and posterior parietal cortex were modulated by memory load but it was anterior frontal cortex (including DLPFC) that was sustained throughout the trial, suggesting its role in active maintenance of information.

Evidences, however, are showing that sustained activity in the DLPFC and VLPFC might reflect more than maintenance alone but also associated with manipulation of

working memory content (Blumenfeld, Lee, & D'Esposito, 2014; Blumenfeld & Ranganath, 2006; Postle et al., 2006).

Blumenfeld and Ranganath (2006) recorded event-related fMRI to examine PFC activity in participants when they performed two types of WM tasks: trials that required the participants to sub-vocally rehearsed a list of three words during a memory delay periods (rehearse trial) vs. trials that required them to mentally rearrange a list of three words according to the weight of the objects that the words referred to (reorder trial), and a surprise recognition test followed after the delay period. The authors found that although the delay-period activations at both bilateral DLPFC (Brodmann's area, BA 9 and 46) and VLPFC (BA 6, 44, 45, 47) were increased during reorder trials relative to rehearse trials, it was left DLPFC activity that was correlated with subsequent memory performance specifically during reorder trials whereas left posterior VLPFC (BA 6 and 44) activity was correlated with subsequent memory on both reorder and rehearse trials (Blumenfeld & Ranganath, 2006). Due to the marginal statistical difference between two areas, the authors suggested that their difference might be "graded rather than absolute" (Blumenfeld & Ranganath, 2006, p. 920).

Studies on DLPFC suggested that its activation during delay-period was associated with attentional selection (Rowe & Passingham, 2001; Sakai, Rowe, & Passingham, 2002) which might complement the evidence that DLPFC was associated with manipulation (Blumenfeld & Ranganath, 2006) since it would require focus of attention or attentional selection. Rowe and Passingham (2001) attempted to differentiate the sustained brain activity in DLPFC, specifically BA 46, as related to maintenance from the selection of item in working memory by having young participants view three red dots presented sequentially at different location of screen and to attend to their order; a probe then followed after the delay period for them to respond. In selection trials, the probe was a number indicating the first, second or third dot was the target for response and the participants had to move the cursor to the location of the target dot using joystick. In control trials, the probe was a "X" and the participant was required to move the cursor the location of the "X" (Rowe & Passingham, 2001). Increased activation related to maintenance of the spatiotemporal information during the delay-period relative to the baseline were bilateral superior frontal sulcus (BA 8), intraparietal cortex (IPC) and precentral gyrus but not at BA 46;

the activation related to selection was found at bilateral middle frontal gyrus (BA 46, 9/46) together with inferior frontal gyrus, orbitofrontal PFC, precuneus, IPC and striate cortex (Rowe & Passingham, 2001). The authors suggested that maintenance was associated with BA 8 (superior frontal sulcus) and IPC, whereas selection between the items within WM was associated with BA 46 and BA 9/46 in PFC (or DLPFC) and this involved focussing of attention on one remembered item among the others as reflected by the task used in the study (Rowe & Passingham, 2001).

Sakai et al. (2002) further examined the brain activity during the delay period by removing the opportunity of rehearsal; the participants viewed a sequence of 5 spatial location indicated by red squares, after an unfilled delay-period, they were presented with a distractor task by viewing a sequence of 5 blue dots followed by a recognition judgment task on the blue dots before they were tested on the memory of the order of the red squares (distractor-plus trial). This was contrasted with distractor-minus trial where there was no distractor task and the delay-period was followed immediately by the memory test on the red squares; as well as contrasted with a control task where the participants were presented with the same red squares array and after the unfilled delay-period, they were required to press a button with index finger if the square in the centre was indicated by an arrow and press a button with middle finger if a square at the corner was indicated by an arrow (Sakai et al., 2002). The authors found significant activation in middle frontal gyrus (BA 46) during delay-period on correct distractor-plus trials but not error trials which correlated with improved performance, indicating that it was corresponded with resistance to distraction; in addition to the significant activation in posterior part of superior frontal sulcus (BA 8) and IPC in both correct and error trials which the coupling between them was associated with resistance to distraction (Sakai et al., 2002). Moreover, activity in BA 46 was associated with tighter coupling between BA 8 and IPS, suggesting the modulatory role of BA 46 on the posterior brain region (Sakai et al., 2002). The findings suggested attentional selection might be achieved by repeated top-down signal from BA 46 to the posterior association areas where the memory representations are held and enhancing the representation in face of distraction that occurred after the delay in this study; or alternatively that the activity of BA 46 reflected elaboration or manipulation of the maintained information which led to better memory performance (Sakai et al., 2002).

Put together, sustained activity at DLPFC during working memory task likely reflected attentional selection in the process of manipulating and/or maintaining the information in working memory.

Albeit not restricted to working memory alone, memory studies on VLPFC suggested its role associated with currently-relevant information held in memory (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Hampshire, Duncan, & Owen, 2007; Toepper et al., 2010). Hampshire et al. (2007) found that activation in bilateral VLPFC and the pre-SMA only for target stimulus when participants viewed target image followed by a sequence of non-target images before they responded if the last image seen was the target image. In contrast, all stimuli produced activation in anterior right DLPFC extending to the posterior of frontopolar cortex, and non-target stimuli that belonged to the same category as the target activated areas midway between DLPFC and VLPFC (Hampshire et al., 2007). The findings suggested that VLPFC is associated with processing currently-relevant information, and that the dorsal and anterior frontal regions represented deliberate focusing of attention when the difference between the target and the non-target was small (Hampshire et al., 2007).

It was often observed in studies on DLPFC and VLPFC that they often work in tandem (Blumenfeld, Nomura, Gratton, & D'Esposito, 2013; Blumenfeld & Ranganath, 2006; Hampshire et al., 2007; Toepper et al., 2010). For example, Toepper et al. (2010) found that while both DLPFC and VLPFC were activated in the participants when they performed the Corsi block test (CBT), it was only DLPFC (specifically BA 9) that was activated by the suppression CBT (BST) contrasted with CBT and DLPFC activity was higher in BST than in CBT but there was no difference in VLPFC activities in the two conditions. These observations led the authors to suggest the role of VLPFC in simple mnemonic operation that requires maintenance of information whereas DLPFC represents higher-level operations such as inhibition in this case.

Putting together the evidences of the functions of DLPFC and VLPFC, they echoed the arrangement of the two regions along the rostral-caudal axis observed by Blumenfeld et al. (2013) whereby the VLPFC appeared to subserve 1st order processes such as selection, maintenance of information whereas DLPFC subserves higher-order processes such as manipulation, monitoring, maintenance with focused attention.

2.1.2.2.2 *Other cortical areas*

Other cortical regions which are also consistently found to be activated during working memory are PPC including IPS/IPL, primary and associative areas and inferior temporal region (Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Roth, Serences, & Courtney, 2006; Toepper et al., 2010). Apart from activities in DLPFC and VLPFC, Toepper et al. (2010) observed activity in posterior parietal cortex (PPC, BA 7) as well as premotor (BA 6) cortex related to task-relevant information and activity related to inhibition (to suppress distractor) in PPC. Roth 2006 found overlapped activities in primary motor, frontal, IPL, IPS, primary visual, associative visual during updating, refreshing and maintenance in working memory task. Bunge et al. (2003) found that while VLPFC, DLPFC, parietal and temporal cortices were involved in rule retrieval at the cue presentation, the activity was only sustained during delay (i.e. maintenance) in posterior VLPFC and parietal cortices when the participants learnt 4 cue-rule association and responded accordingly in the trials. In summary, the PPC is likely to be associated with inhibition related with attention such as to suppress distractor; and representations held in working memory are associated with primary and associative cortices largely depending on the modality of the stimuli involved in the task.

2.1.2.2.3 *Top-down modulation from DLPFC and VLPFC*

Importantly, it was frequently observed that DLPFC and/or VLPFC interacted with the other involved cortical regions by exerting a top-down control such as attentional selection (Rowe & Passingham, 2001; Sakai et al., 2002), integrating representations from other cortices as well as maintaining task-relevant higher-order information (Burgess, Dumontheil, & Gilbert, 2007; Stuss & Alexander, 2007) such as rules (Bunge et al., 2003; Riggall & Postle, 2012; Warden & Miller, 2010), information about stimuli (Stokes et al., 2013) and object category (Meyers, Freedman, Kreiman, Miller, & Poggio, 2008). This implies that the two lateral PFC regions could exert a top-down control to bias the activities in primary and associative areas to sustain or reactivate the relevant sensory information or representations when the external stimuli are absent (Fuster, 2000; Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005; Miller & D'Esposito, 2005; Postle, 2005; Ranganath, Cohen, Dam, & D'Esposito, 2004); as well as the LTM representations at inferior temporal cortex (Bunge et al., 2003; Eriksson, Vogel, Lansner, Bergstrom, & Nyberg, 2015; Ranganath, 2006; Ruchkin,

Grafman, Cameron, & Berndt, 2003). The top-down control could also be in the form of rehearsal or reactivation of representation through reverberation of signals between the lateral PFC and the other cortices in the absence of the external stimuli (Eriksson et al., 2015; Gazzaley et al., 2005). Gazzaley and his colleagues (2005) recorded fMRI and event-related potential (ERP) from participants as they viewed pairs of faces or natural scenes and were required to remember faces but ignore scenes, or remember scenes but ignore faces, or passively view the faces and scenes. The data revealed an increased fusiform face area (FFA) activity and earlier N170 (face-selective ERP) in remember-face condition relative to passive-viewing condition, and conversely a suppressed FFA activity and delayed N170 in remember-scene condition relative to passive-viewing condition; demonstrating that there are at least two types of top-down signals with one serving to enhance task-relevant information and the other to suppress task-irrelevant information (Gazzaley et al., 2005).

In essence, working memory involves sustained activity at DLPFC which likely reflects attentional selection or allocation in the process of manipulating and/or maintaining the information (Rowe & Passingham, 2001; Sakai et al., 2002) whereas the neighbouring VLPFC processes currently-relevant information (Badre et al., 2005; Hampshire et al., 2007; Toepper et al., 2010). Together, both DLPFC and VLPFC provides top-down modulation (Burgess et al., 2007; Rowe & Passingham, 2001; Sakai et al., 2002; Stuss & Alexander, 2007) to posterior parietal cortex which is associated with inhibition such as suppressing distractor (Bunge et al., 2003; Toepper et al., 2010), as well as to other primary and associative cortices (Fuster, 2000; Gazzaley et al., 2005; Miller & D'Esposito, 2005; Postle, 2005; Ranganath et al., 2004), and the inferior temporal cortex (Bunge et al., 2003; Eriksson et al., 2015; Ranganath, 2006; Ruchkin et al., 2003), to sustain or reactivate the relevant sensory information or representation when the external stimuli are absent.

Putting it together, in the light of declining attention (Madden et al., 2007; Thomsen et al., 2004; Townsend et al., 2006) and changes in the frontal cognitive control (Persson et al., 2007; Velanova et al., 2007; West et al., 2002) observed in the older adults, stimulating DLPFC would allow us to examine the age-related influence on neuroplastic changes as their weakening attentional allocation and top-down cognitive control would be modulated, and subsequent comparison with persons with MCI. Aging

effect and MCI-related influence on working memory will be discussed in later sections (Section 2.4 and 2.5).

2.1.2.3 *Event-related potential (ERP)*

Event-related potential (ERP) is a technique of measuring brain electrical activities associated with specific event or mental process and its signature can be denoted by polarity (negative- or positive-going), latency (in terms of milliseconds), and amplitude in microvolt (Kappenman & Luck, 2012; Luck, 2005).

ERP studies on working memory might examined early and late processes; however the early processes such as visual processing and attention would be exogenous (Finnigan, O'Connell, Cummins, Broughton, & Robertson, 2011; Keeser et al., 2011; Lai, Lin, Liou, & Liu, 2010). As mentioned earlier, the key area of investigation in this thesis is to examine the age-related influence on neuroplastic changes induced by external enhancement in light of their weakening attentional allocation and top-down cognitive control, and to compare with the MCI-related influence. As such, the processes in working memory that are of interest here would be the later ones. The foci were the process of distinguishing the probe to be a target or a non-target, and the process of allocating attention to maintain and process the representation in working memory. These two processes would be intimately related to the declining attentional allocation (Madden et al., 2007; Thomsen et al., 2004; Townsend et al., 2006) and top-down cognitive control (Persson et al., 2007; Velanova et al., 2007; West et al., 2002) observed in aging brain and involving the frontal region (Grady, 2012). As there are evidences of frontal brain region being implicated in persons with MCI (Alichniewicz, Brunner, Klünemann, & Greenlee, 2012; Dannhauser et al., 2008; Lou et al., 2015), the foci would also serve as a platform for comparison with the MCI-related influence.

In relation to distinguishing the probe to be a target or a non-target, the frontocentral negativity N200 occurring at around 270 ms after onset stimulus would be relevant as it is often associated with mismatch detection and processing in working memory task (Daffner et al., 2011; Du et al., 2008; Folstein & Van Petten, 2008; Gajewski & Falkenstein, 2014; Yi & Friedman, 2011). If the probe was not any of the items in the representations held and maintained, it would elicit a larger N200, reflecting a mismatch process that served to distinguish targets from non-target (Du et al., 2008; Folstein & Van Petten, 2008; Yi & Friedman, 2011) and this component would be more

negative-going for non-targets that were previously in the representation than those that were never held in the representation (Yi & Friedman, 2011). Yi and Friedman (2011) examined how no-longer-relevant-information in working memory might influence interference and had participants viewed an array of 4 digits, followed by a cue for 2 digits out of the 4, before a probe appeared which can be a positive probe (target digit), a negative probe (non-target digit that is not from the array), and a lure (non-target digit that is one of the 2 cued digits). The authors found that both the negative probe and the lure elicited a N200 that was more negative-going than by positive probe; and N200 elicited by the lure was in turn more negative-going than that by the negative probe, reflecting mismatch processing and involving interference resolution (Yi & Friedman, 2011) which goes beyond template matching into cognitive control as reviewed by Folstein and Van Petten (2008).

With regards to P300, Berti (2016) found that the frontal P300 was more positive-going in switch trials than when the trials repeated but there was no difference in this component between the task conditions of processing and replacing the items held in working memory; indicating that the frontal P300 indexes the process of attention allocation to select information in working memory. Shucard, Tekok-Kilic, Shiels, and Shucard (2009) examined the topography of P300 as modulated by the encoding and maintenance stages of working memory and observed that P300 was maximal at parietal region during encoding stage but was more frontally distributed during maintenance stage. Put together, this frontal P300 reflecting attentional allocation would correspond well to the focus of attention within the region of direct access influenced by the central executive in the embedded-processes model of working memory (Cowan, 1988, 1999; Oberauer, 2013) and likely involve the top-down signalling from DLPFC/VLPFC modulating and reverberating the representations held in the posterior primary and associative cortices when the stimuli was absent from the external environment (Fuster, 2000; Gazzaley et al., 2005; Miller & D'Esposito, 2005; Postle, 2005; Ranganath et al., 2004).

2.2 WORKING MEMORY TASK: N-BACK TASK

The n-back task is a classic and popular working memory task (Dobbs & Rule, 1989) which involves viewing a continuous presentation of stimuli and judging if each currently-presented stimulus and the stimulus presented *n* trials ago matches (target)

or mismatches (non-target). These tasks require online monitoring, updating, and manipulation of remembered information (Owen, McMillan, Laird, & Bullmore, 2005).

2.2.1 Neuroanatomy

Owen et al. (2005) conducted a meta-analysis on primary studies of n-back task revealed that the DLPFC, VLPFC, frontal poles, medial and lateral PPC, as well as lateral and medial premotor cortex and dorsal cingulate, were robustly activated during n-back task that required identifying stimuli (vs. spatial location) of verbal stimuli (vs. object). This corroborated with the observations from neuroimaging studies on working memory mentioned earlier on the lateral PFC (Blumenfeld et al., 2013; Blumenfeld & Ranganath, 2006; Hampshire et al., 2007; Toepper et al., 2010), the primary and associative cortices, and the PPC and IPS/IPL (Bunge et al., 2003; Roth et al., 2006; Toepper et al., 2010).

2.2.2 ERP markers

In n-back task, the participant has to view a continuous presentation of stimuli and judging if each currently-presented stimulus and the stimulus presented n trials ago matches (target) or mismatches (non-target). The N200 in n-back task occurred around 200 – 350 ms after stimulus onset and was elicited at the frontocentral sites (Daffner et al., 2011; Patel & Azzam, 2005; Riis et al., 2008). Similar to the observation of N200 found in studies using different working memory paradigm mentioned earlier (Du et al., 2008; Folstein & Van Petten, 2008; Yi & Friedman, 2011), the amplitude of N200 becomes more negative-going when there is a mismatch between a stimulus held in the working memory or mental template and a stimulus presented, that is, a non-target (Daffner et al., 2011; Folstein & Van Petten, 2008; Gajewski & Falkenstein, 2014), reflecting a mismatch process that served to distinguish targets from non-target. The latency of N200 was observed to be earlier for target relative to non-target in the Young (Daffner et al., 2011).

The frontal P300, a positivity occurring at around 300 – 600 ms after stimulus onset, is another ERP marker often examined in n-back task. It had been associated with attentional allocation to select information in working memory based on the presented stimulus (Daffner et al., 2011), on potentially task-relevant stimuli (Keeser et al., 2011; Wild-Wall, Falkenstein, & Gajewski, 2011), and to discriminate between target and non-

target (Deiber et al., 2015). The latency of frontal P300 was observed to be earlier for non-target than target (Gajewski & Falkenstein, 2014).

Putting it together, in working memory tasks, such as n-back task, it was revealed that DLPFC, VLPFC, frontal poles, medial and lateral PPC, as well as lateral and medial premotor cortex and dorsal cingulate, were robustly activated (Owen et al., 2005) which corroborated with the above-mentioned neuroimaging evidences on working memory. Electrical activities during the n-back task involve the fronto-central N200 that reflects match-mismatch processing that serve to distinguish the targets from non-target (Daffner et al., 2011; Gajewski & Falkenstein, 2014), as well as the frontal P300 that is associated with attentional allocation to select relevant information within the working memory representations (Daffner et al., 2011; Deiber et al., 2015; Keeser et al., 2011; Wild-Wall et al., 2011). Among these ERP studies using n-back, the highest order of the task used when older adults and persons with MCI were involved was two-back task (Daffner et al., 2011; Deiber et al., 2015; Wild-Wall et al., 2011) which was the case in this study.

2.3 SUMMARY FOR WORKING MEMORY AND N-BACK TASK

To summarize the discussion so far and linking the neuro-mechanism (Figure 2.1), working memory involves DLPFC which likely reflects attentional selection or allocation in the process of manipulating and/or maintaining the information (Rowe & Passingham, 2001; Sakai et al., 2002) whereas the neighbouring VLPFC processes currently-relevant information (Badre et al., 2005; Hampshire et al., 2007; Toepper et al., 2010). Together, both DLPFC and VLPFC provides top-down modulation (Burgess et al., 2007; Rowe & Passingham, 2001; Sakai et al., 2002; Stuss & Alexander, 2007) to posterior parietal cortex which is associated with inhibition such as suppressing distractor (Bunge et al., 2003; Toepper et al., 2010), as well as to other primary and associative cortices (Fuster, 2000; Gazzaley et al., 2005; Miller & D'Esposito, 2005; Postle, 2005; Ranganath et al., 2004), and the inferior temporal cortex (Bunge et al., 2003; Eriksson et al., 2015; Ranganath, 2006; Ruchkin et al., 2003), to sustain or reactivate the relevant sensory information or representation when the external stimuli are absent. The match-mismatch processing indexed by N200 process might be linked to the VLPFC that is associated with processing currently-relevant information (Badre et al., 2005; Hampshire et al., 2007; Toepper et al., 2010) and the modulation

from DLPFC/VLPFC on PPC, an area associated with inhibition such as suppressing distractor (Bunge et al., 2003; Toepper et al., 2010). Attentional allocation to process relevant information indexed by the frontal P300 would likely linked to DLPFC (Rowe & Passingham, 2001; Sakai et al., 2002). Next, how aging might influence working memory is discussed.

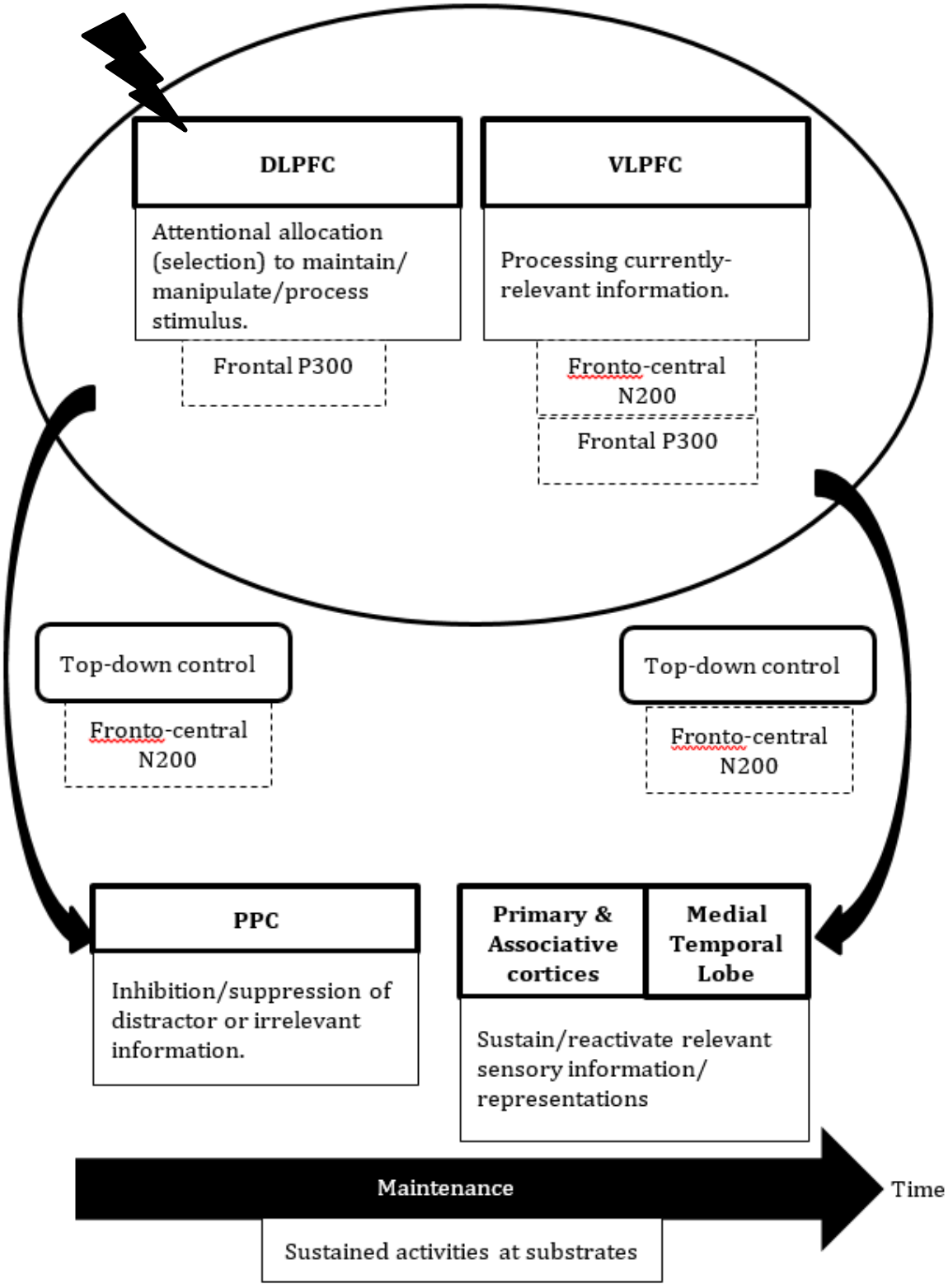

Figure 2.1. Overview of working memory neuro-mechanism in the context of the study with electrical stimulation at the frontal cortex.
DLPFC: dorsolateral prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; PPC: posterior parietal cortex (including intraparietal sulcus); Dotted squares denote those neural markers that are likely to be associated with the substrates based on functions.

2.4 AGING

2.4.1 Altered neural activation in aging

Cognitive decline such as memory due to aging is well documented (Craik & Rose, 2012; Daselaar & Cabeza, 2013; Hasher & Zacks, 1988). Altered age-related patterns of neural activation for working memory were observed in the PFC and MTL regions. Increased PFC activity (Craik & Rose, 2012; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Sala-Llonch et al., 2012) and a more bilateral distribution (Cabeza et al., 2004; Park et al., 2003; Reuter-Lorenz et al., 2000; Sala-Llonch et al., 2012) in healthy older adults performing simple maintenance tasks were observed. When the working memory tasks involved manipulation of memory load, both reduction and increase of PFC activity were observed such that the older adults would over-recruit PFC during low loads and under-recruit PFC at higher load (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Schneider-Garces et al., 2010). Hence, age-related changes in frontal activations manifested in both reduction and increase, and a shift in lateralization of the activation. For MTL, WM studies found reductions in hippocampal activity in healthy older adults when the tasks involved non-verbal stimuli (Grady et al., 1998; Mitchell, Johnson, Raye, & D'Esposito, 2000; Park et al., 2003) whereas neuroimaging studies using verbal materials to investigate age-related activity change were scarce.

There are different aging models attempting to describe the age-related neural change underlying memory decline. One age-related change in neural activity is a reduction in occipito-temporal activity coupled with increased frontal activity in cognitive aging (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Grady et al., 1994; Reuter-Lorenz et al., 2000), termed as the posterior-anterior shift in aging, in short, PASA (Davis et al., 2008). The phenomenon was first reported by Grady et al. (1994) where older adults showed reduced activation in the posterior region but increased activation in the anterior region relative to the young in both visual-perception tasks of faces and locations. Controlling for task difficulty by eliminating differences in accuracy, Davis et al. (2008) observed that older adults showed reduced activity in occipital and medial temporal regions but increased PFC activity (BA 45) in both the word recognition retrieval task and visual-perceptual task, confirming the PASA phenomenon. The PFC activity in older adults was negatively correlated with the occipital activity indicating the coupling between anterior activation and posterior

deactivation (Davis et al., 2008). The PFC activity in older adults was also positively correlation with both task performance, suggesting that the increased frontal activity was compensatory in nature (Davis et al., 2008).

Another observation of age-related changes in neural activity is that under similar circumstances, prefrontal activity during cognitive tasks tends to be less lateralized in older adults relative to the younger adults (Cabeza et al., 2004; Park et al., 2003; Reuter-Lorenz et al., 2000; Sala-Llonch et al., 2012); and it was conceptualized as Hemispheric Asymmetry Reduction in Old Adults or in short HAROLD (Cabeza, 2002). Blood-oxygen-level dependent (BOLD) contrast imaging from younger and older participants were compared as they performed three tasks: working memory, visual attention, and episodic retrieval; and the results showed that older adults had weaker activity in occipital regions (BA 18, 19, 31) and stronger activity in PFC regions (BA 6 and 44/45) in all 3 tasks (Cabeza et al., 2004). More importantly, the authors observed that older adults showed a more bilateral PFC activity in working memory and visual attention tasks relative to the younger adults (Cabeza et al., 2004).

Surveying the evidences from neuroimaging studies on aging and testing the compensatory explanation, Reuter-Lorenz and Cappell (2008) suggested that the sites of over-activation displayed by older adults are also activated by younger adults, the difference lies in that older adults would recruit these sites sooner at a lower cognitive task load relative to the younger adults as a response to task difficulty or demand; and at lower level of demand, such over-activation in older adults is associated with good performance (i.e. compensation); but at higher task demand, this additional activation by the older adults would fall short and task performance would fail to match up with the younger adults (Cappell et al., 2010; Mattay et al., 2006; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2010). This phenomenon is referred to as the compensation-related utilization of neural circuit hypothesis or in short, CRUNCH (Reuter-Lorenz & Cappell, 2008). Cappell et al. (2010) investigated the activity in DLPFC in younger and older adults at 3 levels of verbal WM load (4, 5, 7 items), and analysed the data according to the 3 phases of the WM task: target phase where 4, 5, or 7 consonants appeared simultaneously surrounding the central fixation, unfilled delay phase, and a probe phase where a single consonant was presented and the participants had to indicate whether the probe item was previously presented. Behaviourally, the

older adults only performed poorer than the younger adults at 7 items but performed equivalently at 4 and 5 items (Cappell et al., 2010). The authors observed robust age-related over-activation of BA 46 in right DLPFC at 5 items but not at 4 items; and conversely, this same area was under-activated at 7 items; and similar pattern was also evident in right BA 9 and 45, providing evidence towards the CRUNCH (Cappell et al., 2010).

2.4.2 Aging effect on N200 and P300

Gleaning from the neuro-mechanism of working memory, sustained activity at DLPFC likely reflected attentional selection or allocation in the process of manipulating and/or maintaining the information in working memory whereas the neighbouring VLPFC processes currently-relevant information. Together, both DLPFC and VLPFC provided top-down modulation to posterior parietal cortex which is associated with inhibition such as suppressing distractor, as well as to other primary and associative cortices associated with the representations. Given that cognitive-aging is accompanied by altered frontal activation, frontal ERP P300 during n-back which is associated with attentional allocation would be implicated in aging-related changes, as well as N200 which reflects a mismatch process that served to distinguish targets from non-target, a process likely to involve DLPFC, VLPFC, PPC and their interaction.

2.4.2.1 *Amplitude*

Older adults, similar to the young adults, were found to exhibit a more negative-going N200 for non-target than target (Daffner et al., 2011; Gajewski & Falkenstein, 2014) during n-back task. Gajewski and Falkenstein (2014) did not find any age-related difference in N200 amplitude but Daffner et al. (2011) found that N200 in the older adults was generally less negative-going relative to the young. The different results from the two studies were attributed to the lower educated elderly cohort in the later study (Gajewski & Falkenstein, 2014), rendering them less able to activate sufficient frontal activity to cope with the task.

A more positive-going frontal P300 in older adults than the younger adults was often reported in n-back tasks (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013). Albeit not differentiating between target and non-target trials, Saliasi et al. (2013) found that P300 in young participants was higher at parietal sites as expected and correlated with better task performance, but the older adults exhibited

a high-frontal-low-parietal P300. Among the two studies that examine target and non-target trials, Gajewski and Falkenstein (2014) observed that the frontal P300 amplitude in older adults was only higher than the younger participants for non-target but attenuated for target trials; with a concurrent lower parietal P300 in older adults relative to younger participants generally. Conversely, Daffner et al. (2011) found that P300 for target trials was higher in older adults than younger participants particularly at the frontocentral region. Both studies found older adults performing poorer and slower than younger adults but no correlation between the ERP components and behavioural measures were reported (Daffner et al., 2011; Gajewski & Falkenstein, 2014). Daffner et al. (2011) divided each group into high- and low-performers by a median split on the d-prime measure in two-back task, compared high-performing older adults with low-performing younger adults, and found that the older group had a more anteriorly distributed P300 coupled with a less negative-going N200 relative to the younger group despite having similar overall P300 amplitude. Given that the high-performing older adults performed similarly as the low-performing younger adults, the results hinted the frontal P300 activity in older adults as a compensatory mechanism, and also the possibility that preceding age-related less-negative N200 might cascade a greater demand on the subsequent P300 activity (Daffner et al., 2011). This interpretation corroborated with a study using auditory oddball paradigm to compare parietal and frontal P300 in 1572 participants from various age groups ranging from 6 years old to 87 years old (van Dinteren, Arns, Jongsma, & Kessels, 2014), where the authors found that as parietal P300 declined with age, the frontal P300 was still preserved and older adults recruited this frontal neural resources to compensate and hence preserved the task performance (van Dinteren et al., 2014), demonstrating cognitive reserve hypothesis (Stern, 2009) in the context of CRUNCH (Cappell et al., 2010; Mattay et al., 2006; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2010).

Put together, the findings on the P300 amplitude elicited during n-back task were consistent with the age-related frontal hyperactivity in the PASA model on aging (Davis et al., 2008) and there might be a possibility that when the preceding N200 is less negative-going due to aging, there is a greater demand on the subsequent P300 activity (Daffner et al., 2011).

2.4.2.2 *Latency*

In the two studies that examined aging effect in N200 during n-back task, Gajewski and Falkenstein (2014) observed that N200 generally was delayed in the older adults, although they did not find any age-difference in the amplitude as mentioned previously. On the other hand, Daffner et al. (2011) did not find any age-related difference in N200 latency among the younger and older participants in their study.

The latency of frontal P300 in older adults was consistently found to be delayed relative to the young adults (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013), with a larger group difference for target (Gajewski & Falkenstein, 2014) and accounting for the higher error rate in target trials in the older adults.

In essence, N200 in older adults is still more negative-going for non-target than for target trials as in the younger adults, but the general N200 amplitude in the older adults might be attenuated relative to the young. The frontal P300 was consistently found to be larger and delayed in the older adults relative to the young.

2.4.3 Summary of aging effect on working memory

Age-related neural changes in working memory (summarized in Figure 2.2) were manifested as frontal over-activation (Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Sala-Llonch et al., 2012), frontal under-activation at higher load (Cappell et al., 2010; Schneider-Garces et al., 2010), and possibly a reduction in hippocampal activity (Grady et al., 1998; Mitchell et al., 2000; Park et al., 2003). Akin to the altered neural activity at DLPFC/VLPFC, the frontocentral N200 was diminished in older adults (Daffner et al., 2011; Gajewski & Falkenstein, 2014) suggesting a declining ability to distinguish target and non-target. The frontal P300 was heightened in older adults (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013), indicating that the older adult engaged more attentional allocation to maintain and/or manipulate stimulus.

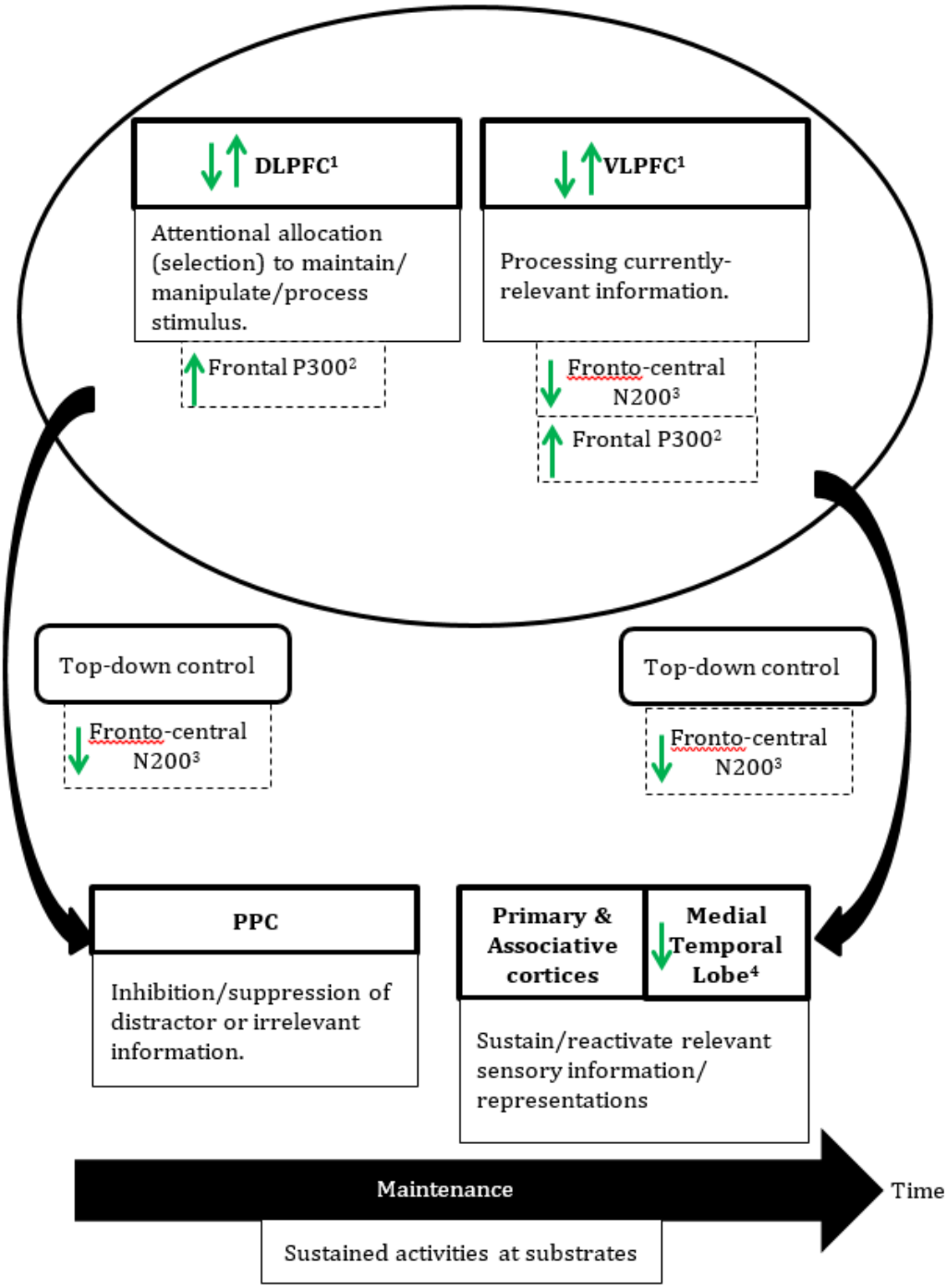

Figure 2.2. Summary of age-related changes in neuro-mechanism of working memory. Dotted squares denote those neural markers that are likely to be associated with the substrates based on functions. Green arrows denote the increase or decline of activity related to aging.

[1] Frontal over-activation (Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Sala-Llonch et al., 2012) and under-activation (Cappell et al., 2010; Schneider-Garces et al., 2010)
[2] Increased frontal P300 (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013)
[3] Reduced fronto-central N200 (Daffner et al., 2011; Gajewski & Falkenstein, 2014)
[4] Reduction in hippocampal activity (Grady et al., 1998; Mitchell et al., 2000; Park et al., 2003)

Pathological cognitive-aging, such as mild cognitive impairment, has been suggested to be a transitional phase for those older adults who eventually developed dementia, specifically Alzheimer's disease (Gauthier et al., 2006; Jack et al., 2010; Jicha et al., 2004) with proposed trajectory of disease development in the various biomarkers. The extent to which MCI-related neural alteration is different from age-related ones would help in understanding the MCI influence on working memory.

2.5 MILD COGNITIVE IMPAIRMENT (MCI)

2.5.1 Definition and diagnostic criteria

Mild Cognitive Impairment is defined as a syndrome with cognitive decline larger than that expected for an individual's age and education level but does not significantly interfere with activities of daily life or ADLs (Gauthier et al., 2006). The diagnostic algorithm proposed by Petersen (2004) classified MCI into two subtypes: amnestic and non-amnestic MCI (Figure 2.3). Amnestic MCI is clinically significant memory impairment yet to meet the criteria for dementia, with other cognitive abilities such as language, executive function, visuospatial skills, as well as functional activities intact, along with mild inefficiencies (Petersen, 2004, 2011). The recommendations for general criteria of MCI from the International Working Group on MCI (Winblad et al., 2004), as listed in Table 2.1, were similar to the criteria proposed by Petersen (2004, 2011).

A more quantifiable research diagnostic criteria for MCI was developed for a national study in Germany (Perneczky et al., 2006) which included a cut-off score from Clinical Dementia Rating for questionable dementia, and included performances in seven cognitive domains as illustrated in Table 2.1. Perneczky et al. (2006) compared the MCI group with healthy controls and found that MCI group had limitation on daily tasks that require either memory or complex reasoning; and that most MCI were impaired in three or more cognitive domains. These domains set out in the German study largely overlap with the criteria set out for Mild Neurocognitive Disorders in the recent edition of Diagnostic and Statistical Manual of Mental Disorders: DSM-TR (American Psychiatric Association, 2013). Mild neurocognitive Disorder (mNCD) falls under a subsection entitled "Neurocognitive Disorders (NCDs) which replaces the category of delirium, dementia, and amnestic and other cognitive disorders category in the DSM-IV (American Psychiatric Association, 2000), and is defined as a less severe

cognitive impairment subsumed under "cognitive disorder not otherwise specified" in DSM-V. Among the domains, learning and memory in DSM-V was delineated into verbal and non-verbal in Perneczky et al. (2006) and verbal fluency and naming in the German study were grouped under Language in DSM-5; executive functions and visuo-motor/perceptual motor were similarly covered in both criterion. Perneczky et al. (2006) included the domain of information processing speed which was not stated in DSM-V. Conversely, complex attention and social cognition indicated in DSM-V was not included in the German study.

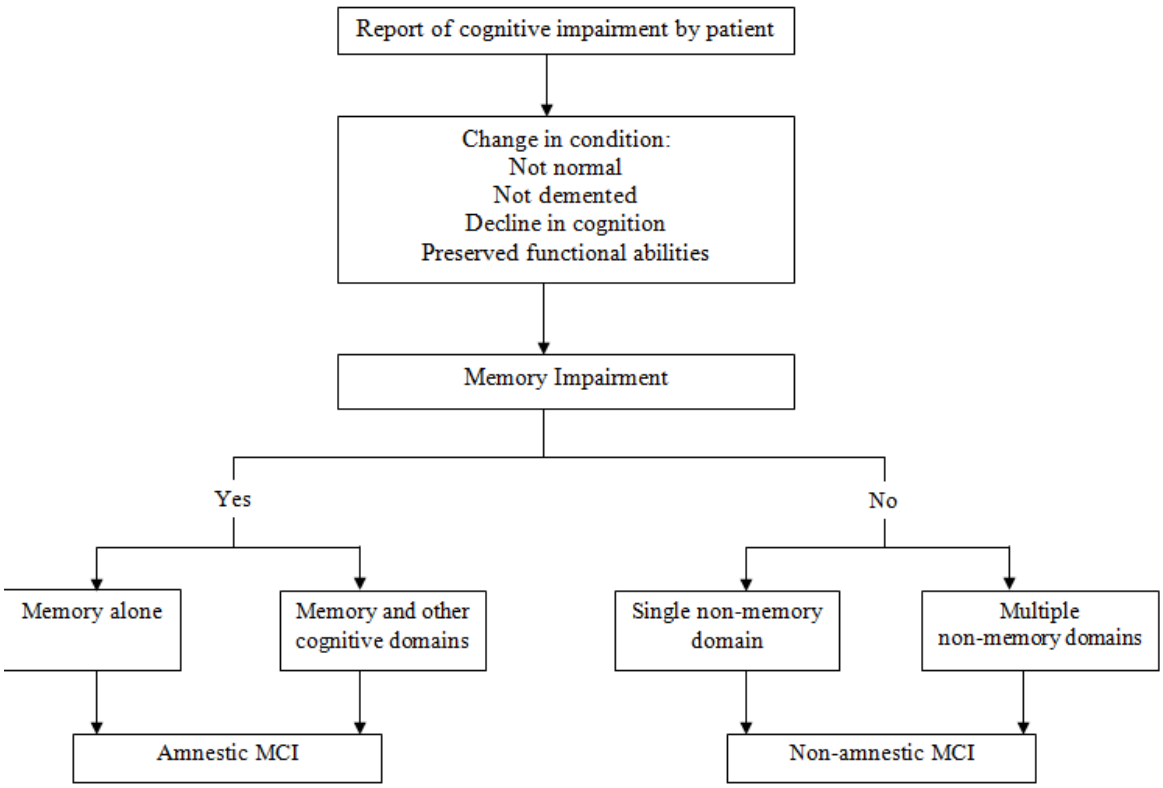

Figure 2.3. Diagnostic algorithm for amnestic and non-amnestic Mild Cognitive Impairment (Petersen, 2004).

Table 2.1. Comparison of diagnostic criteria for Mild Cognitive Impairment.

	National study in Germany Perneczky et al. (2006)	International Working Group on MCI Winblad et al. (2004)	DSM-5 "Mild Neurocognitive Disorders" American Psychiatric Association (2013)
Functional daily activities	Intact basic ADLs; complex ADL slightly impaired	Intact functional daily activities, or at least impairment is minimal	Cognitive deficits do not interfere with capacity for independence in everyday activity (i.e. complex instrumental ADLs are preserved, but greater effort, compensatory strategies, or adaptation may be needed)
Diagnosis of dementia	Clinical Dementia Rating of 0.5	Judged as not normal apart from not fulfilling diagnostic criteria for dementia	Do not occur exclusively in the context of delirium, and not better explained by another mental disorder
Subjective report of cognitive decline	Cognitive deterioration from previously higher level of ability		
			• Learning and memory • Language • Perceptual motor • Executive function • Complex attention • Social cognition

The guideline set out in DSM-V highlighted the importance of standardized or at least quantified assessment (American Psychiatric Association, 2013) and there is a need for sensitive and user-friendly cognitive tests for clinicians to sift out MCI from healthy older adults (Gauthier et al., 2006). This is just as important for researchers investigating the electrophysiological markers of cognitive processes in this population, ensuring that the sample is pre-clinical dementia and not early dementia as the mental processes would have already differed in these two groups. A systematic review of cognitive screening instruments for MCI revealed that the Montreal Cognitive Assessment or MoCA in short (Nasreddine et al., 2005) was among the four comprehensive (i.e. covering each of the primary domains of cognition) screening tests to achieve high sensitivity (> 80%) for detecting MCI among the healthy older adults with high specificity (Lonie, Kalu, & Ebmeier, 2010). MoCA was described as sensitive and user-friendly for clinicians by two working groups for MCI and AD (Gauthier et al., 2006; Massoud et al., 2007). Nasreddine et al. (2005) validated the MoCA with three groups of older adults: healthy control, those with MCI and those with Alzheimer's disease (AD), and the MoCA scores differed significantly between the three groups, with healthy control scoring better than MCI group who in turn scored better than AD group. The cut-off score of 26 in the original English MoCA (i.e. scores of 25 or below indicate impairment) was found to yield the best balance between sensitivity and specificity for the MCI and AD groups (Nasreddine et al., 2005).

2.5.2 Influence of MCI on neuroanatomy of working memory

To reiterate, working memory entails sustained activity at DLPFC that reflected attentional selection or allocation in the process of manipulating and/or maintaining the information in working memory whereas the neighbouring VLPFC processes currently-relevant information. In addition, DLPFC and VLPFC provided top-down modulation to posterior parietal cortex which is associated with inhibition such as suppressing distractor, as well as to other primary and associative cortices and medial temporal lobe (MTL) for sensory information and/ long-term memory representations.

With regards to persons with MCI, evidences on the neural underpinning of the memory impairment characteristic of MCI appears to spotlight on medial temporal lobe with involvement of prefrontal and parietal lobes. The structural MRI findings from the longitudinal, multi-centre study, the Alzheimer's Disease Neuroimaging Initiative, in

short, ADNI (Weiner et al., 2012) showed that the first indications of neurodegeneration happened within the medial temporal lobe (MTL) particularly the hippocampus and entorhinal cortex (Fennema-Notestine et al., 2009) and the atrophy eventually becomes more widespread as the condition progresses to Alzheimer's disease (Fennema-Notestine et al., 2009; McDonald et al., 2009) when the data from three groups of participants (healthy older adults, MCI group, AD group) were compared in a cross-sectional manner.

The picture is less clear when it comes to task-related brain activation. On one hand, studies had demonstrated an over-recruitment of MTL in MCI relative to healthy older adults (Bookheimer et al., 2000; Dickerson et al., 2005; Grady, 2012; Kircher et al., 2007). Both healthy elderly participants and MCI patients in the study by Kircher and his colleagues (2007) intentionally encoded list of words in the scanner followed by a recognition task; comparison of successful encoding fMRI signal revealed that the MCI group had greater activation at left hippocampus and MTL during successful encoding, leading the authors to suggest that increased MTL activation was necessary for association of new information into existing knowledge and was recruited more as a compensatory mechanism to keep up the memory performance. Conversely, there are findings that showed a lower MTL activity in MCI relative to healthy older adults (Clément, Belleville, & Mellah, 2010; Johnson et al., 2006; Machulda et al., 2003; Trivedi et al., 2006). Machulda et al. (2003) had normal elderly participants, AD and MCI patients memorized photographs of people engaging in daily activities with pixilated images as control stimuli in the scanner, and found that MCI and AD patients had less MTL activation than normal elderly and this depressed activation was not due to global impaired BOLD response as evidenced in similar activation for the control sensory task between the groups. In another study, healthy elderly and MCI patients encoded lists of concrete word followed by a recognition test in the scanner, and the fMRI results revealed reduced activation in the occipital regions and the MTL in MCI relative to the healthy older adults, together with a relatively heightened activation in left VLPFC which the authors attributed as a compensatory mechanism for the reduced activation at MTL (Clément et al., 2010). In addition, interpretation of increased or decreased MTL activity might not be straightforward given that MTL activity was observed to be modulated by cognitive load such that MTL over-recruitment only occurred at lower

memory load but at higher load, the MTL activity in MCI became lower relative to their healthy counterparts (Kochan et al., 2011).

Peripheral to the much highlighted temporal lobe specifically MTL and hippocampus, there were suggestions that the neural underpinning of memory impairment in MCI could have involved the frontal area. This is plausible since the brain atrophy observed eventually involved prefrontal region as MCI progresses in the disease (Fennema-Notestine et al., 2009; McDonald et al., 2009). The suggestion that the frontal region was involved came from reports of reduced frontal activation in MCI relative to healthy older adults such as during verbal episodic memory encoding task (Dannhauser et al., 2008) and visuospatial working memory task (Alichniewicz et al., 2012; Lou et al., 2015) but there were also reports of increased frontal activations during memory tasks of picture stimuli (Bondi, Houston, Eyler, & Brown, 2005; Jin, Pelak, Curran, Nandy, & Cordes, 2012) and words (Bookheimer et al., 2000). Hence, the evidence of neurodegeneration in MCI involving MTL and the frontal lobe is consistent albeit the interpretation still needs elucidation. One speculation based on the evidences of the progressive neural changes, it is likely that persons with MCI would still capable of recruiting additional neural resources like their healthy counterpart at the PFC, particularly to support the declining MTL; however, it is unknown how far the ability of frontal over-recruitment in persons with MCI would differ from healthy older adults; just as older adults were observed to plateau their neural resources earlier than the younger adults (Cappell et al., 2010), it remains a possibility that persons with MCI would likewise plateau their neural resources earlier than their healthy counterparts for the frontal recruitment. This in turn would implicate the functions associated with

2.5.3 Influence of MCI on working memory ERP

Studies investigating the changes of brain electrical activity in MCI were largely using oddball paradigm and few were using working memory tasks (Deiber et al., 2015; Missonnier et al., 2007; Missonnier et al., 2005).

As far as studies investigating the influence of MCI using n-back task and analysed N200 and/or P300, Deiber et al. (2015) found that P300 amplitude recorded at parietal sites during letter two-back task were lower in MCI than healthy controls, indicating a compromised higher-level discrimination processes in MCI. Similarly using letter two-back task, Missonnier et al. (2007) found that N200 latency was delayed in

those MCI participants who had deteriorated at 1-year follow-up relative to healthy older adults but there was no difference between stable MCI and healthy participants. The authors interpreted N200, together with P200, as reflecting early storage and retrieval phases of working memory (Missonnier et al., 2007). To reiterate, N200 in n-back task is frequently suggested to reflect match-mismatch processing (Daffner et al., 2011; Patel & Azzam, 2005; Riis et al., 2008) and P300 is associated attentional allocation to select information in working memory based on the presented stimulus (Daffner et al., 2011).

The majority of MCI studies using oddball paradigm demonstrated mixed results. Some studies found no group difference between healthy older adults and MCI participants in N200 (Golob, Johnson, & Starr, 2002; Lai et al., 2010; Li et al., 2010) and P300 (Gironell, García-Sánchez, Estévez-González, Boltes, & Kulisevsky, 2005; Golob et al., 2002; van Deursen, Vuurman, Smits, Verhey, & Riedel, 2009) components. However, MCI was observed to have a delayed N200 relative to healthy older adults (Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011). P300 was observed to less positive-going (Lai et al., 2010; Li et al., 2010; Papaliagkas et al., 2011) and delayed (Golob, Irimajiri, & Starr, 2007; van Deursen et al., 2009) in MCI than their healthy counterparts.

Hence, the evidence from ERP studies on MCI was not clear-cut: the observation of reduced P300 was largely distributed at parietal region which was associated to subsequent memory storage and processing and intimately related to temporal-parietal region (Polich, 2007). This corresponded well with the atrophy (Fennema-Notestine et al., 2009; McDonald et al., 2009) and reduced activity observed at MTL and hippocampus (Clément et al., 2010; Johnson et al., 2006). However, reports on N200 and frontal P300 related to working memory were inconclusive.

Putting together as illustrated in Figure 2.4, the influence of MCI on the neuro-mechanism of working memory mainly implicated the MTL with either increased MTL activity (Bookheimer et al., 2000; Dickerson et al., 2005; Grady, 2012; Kircher et al., 2007) or reduced MTL activity (Clément et al., 2010; Johnson et al., 2006; Machulda et al., 2003; Trivedi et al., 2006) or load-dependent activity (Kochan et al., 2011). However, there were also evidences that PFC is also implicated, albeit the direction was inconsistent as in the case for MTL (Alichniewicz et al., 2012; Dannhauser et al., 2008; Lou et al., 2015) (Bondi et al., 2005; Jin et al., 2012). Correspondingly, the parietally-

maximal P300 associated with subsequent memory storage and processing was reduced in persons with MCI (Lai et al., 2010; Li et al., 2010; Papaliagkas et al., 2011) and delayed (Golob et al., 2007; van Deursen et al., 2009) but no reports on frontal P300. This is coupled with a delayed N200 (Missonnier et al., 2007), which might implicate a slower match-mismatch processing (Daffner et al., 2011; Patel & Azzam, 2005; Riis et al., 2008).

Apparently, the age-related and the MCI-related neural changes in working memory differ. One question that stimulates both research and clinical interests on aging memory would be whether there is a chance that its activity can be changed by external means and how far the aging brain would respond to the alteration. Furthering the question would be to ask if the pathological brain would respond in similar manner as the aging brain.

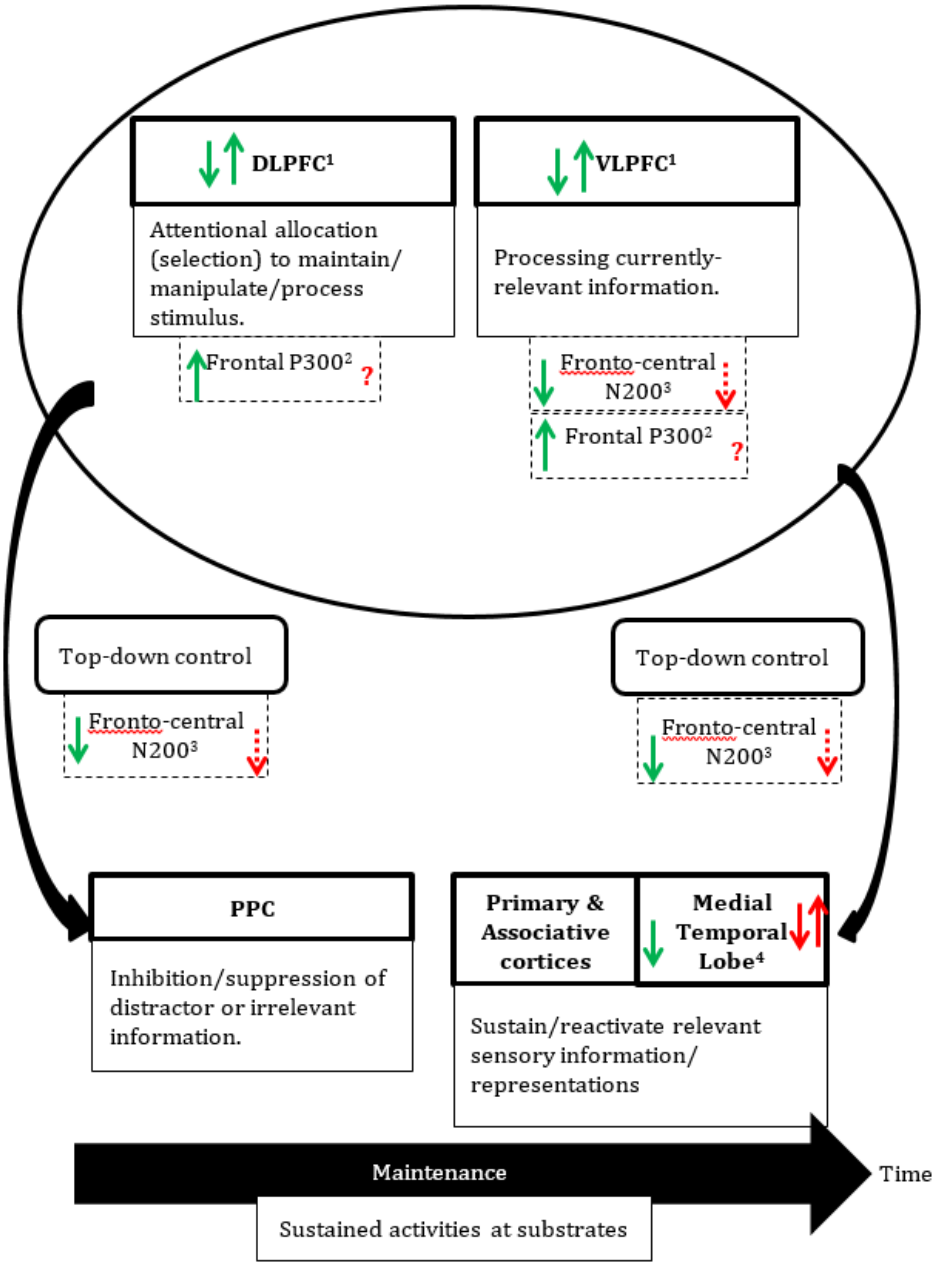

Figure 2.4. Summary of age- (green arrows) and MCI-related (red arrows) changes in the neuro-mechanism of working memory.
Dotted squares denote neural markers that are likely to be associated with the substrates based on functions. Dotted arrow denotes delayed activity.

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[1] Frontal over-activation (Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Sala-Llonch et al., 2012) and under-activation (Cappell et al., 2010; Schneider-Garces et al., 2010) in older adults.

[2] Increased frontal P300 (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013). Difficult to speculate on MCI-related changes to P300.

[3] Reduced fronto-central N200 (Daffner et al., 2011; Gajewski & Falkenstein, 2014) in older adults. Delayed N200 in persons with MCI.

[4] Age-related reduction in hippocampal activity (Grady et al., 1998; Mitchell et al., 2000; Park et al., 2003). Either increased MTL activity (Bookheimer et al., 2000; Dickerson et al., 2005; Grady, 2012; Kircher et al., 2007) or reduced MTL activity (Clément et al., 2010; Johnson et al., 2006; Machulda et al., 2003; Trivedi et al., 2006) or load-dependent activity (Kochan et al., 2011) in persons with MCI.

2.6 HIGH-DEFINITION TRANSCRANIAL DIRECT CURRENT STIMULATION (HD-TDCS)

Non-invasive neuromodulatory techniques including transcranial direct current stimulation (tDCS) have been shown to modulate performance on a variety of cognitive domains. tDCS alters cortical excitability and neural plasticity by delivering weak electric current to the scalp to enhance or inhibit excitability of underlying cortical regions (Nitsche et al., 2005; Priori, 2003; Wassermann & Grafman, 2005). However, conventional tDCS was limited by the poor spatial specificity of the stimulation site as it uses two large rectangular pad (usually each of the size 35 cm^2) with one as the anodal and the other as the cathodal electrode. High-definition tDCS (HD-tDCS) is a recent modification of the conventional tDCS, replacing the two pad electrodes with 5 small ring electrodes in 4x1 configuration, has greatly improved the spatial focality of the electric field induced (Borckardt et al., 2012; Datta et al., 2009; Dmochowski et al., 2011; Edwards et al., 2013; Garnett & den Ouden, 2015; Kuo et al., 2013; Villamar, Volz, et al., 2013).

2.6.1 Effects during and after stimulation

Anodal tDCS (positively-charge active electrode) generally elicits excitatory effect whereas cathodal stimulation (negatively-charged active electrode) produces inhibitory effect, termed as the Anodal excitatory Cathodal inhibitory (AeCi) effect (Jacobson, Koslowsky, & Lavidor, 2012; Wassermann & Grafman, 2005). During stimulation, in the case of anodal tDCS, the excitability of neurons are enhanced via membrane depolarization (Nitsche et al., 2003; Stagg & Nitsche, 2011).

Nitsche et al. (2003) tested the cortical excitability modulation elicited during conventional tDCS on the human primary motor cortex via sodium and calcium channel conductivity, by applying the sodium channel blocker carbamazepine (CBZ) and the calcium channel blocker flunarizine (FLU) before the stimulation. The authors observed that the tDCS effect during stimulation arose from membrane polarisation as blocking the sodium channels eliminated the excitability enhancement observed during anodal stimulation, and blocking the calcium channels reduced the enhanced excitability, indicating that the anodal tDCS caused neuronal depolarization (Nitsche et al., 2003). In addition, no synaptic modification was found to be effecting during stimulation as

dextromethorphane (DMO), a N-methyl-D-aspartic (NMDA) receptor antagonist, had no modulatory effect on the response during stimulation (Nitsche et al., 2003).

In contrast, the after-effect (post-stimulation effect) appeared to involve synaptic modification as well as membrane depolarization/hyperpolarization (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003). Liebetanz et al. (2002) applied conventional tDCS on 11 participants with age ranged from 25 to 48 years old who underwent two different pharmacological intervention and a placebo control session combined with both cathodal and anodal tDCS. The two pharmacological interventions were carbamazepine (CBZ) and dextromethorphan (DMO): CBZ is sodium channel blocker and DMO is N-methyl-D-aspartate (NMDA) receptor antagonist; they were used to test the plastic excitability changes after stimulation (Liebetanz et al., 2002). The authors observed that DMO suppressed the post-stimulation effect of both anodal and cathodal stimulation, suggesting that NMDA receptor, in turn, synaptic modification, was involved in the aftereffect. On the other hand, CBZ selectively suppressed the cortical excitability increase by anodal stimulation, implying that after-effect from anodal tDCS involved a depolarization of membrane potentials since the sodium-channel blocker CBZ prevented sodium opening which is essential for depolarization. The reason why CBZ did not have an effect on the after-effect from cathodal stimulation as the membrane had been hyperpolarized by the cathodal stimulation and CBZ acts in a voltage-dependent manner such that CBZ would take effect when the the cell is depolarized and remains absent when the cell is hyperpolarized. In rat studies using single-session stimulation, it was found that tDCS induced cortical response that augment synaptic plasticity dependent on NMDA-receptor (Monai et al., 2016) and brain-derived neurotrophic factor (BDNF) (Fritsch et al., 2010). In essence, short-term tDCS can induce cortical response that is associated with neuroplasticity.

2.6.2 Duration of after-effect

The after-effect from the conventional tDCS outlasts the stimulation period arising from the mechanism of synaptic modification (Brunoni et al., 2012; Liebetanz et al., 2002; Nitsche et al., 2003; Paulus, 2004). In the two pharmacological studies examining the after-effect of tDCS via channel blockers in young participants, Liebetanz et al. (2002) used 5-minute of 1-mA conventional tDCS in both the anodal and cathodal

conditions whereas Nitsche et al. (2003) applied anodal tDCS at 1 mA for 11 or 13 minutes. Prior to these two studies, the pivotal study by Nitsche and Paulus (2000) systematically tested the after-effect duration of tDCS on motor cortex in young participants. By varying intensity from 0.2 - 1.0 mA applied for 5 minutes, the authors found that at least 0.6 mA applied for 5 minutes would be needed to induce an motor-evoked potential (MEP) above baseline, that is, after-effect (Nitsche & Paulus, 2000). When the authors varied stimulation between 1 - 5 minutes with 1 mA, they found that the stimulation needed to be applied for at least 3 minutes in order to induce an after-effect (Nitsche & Paulus, 2000). In another study, the two authors applied 1 mA of tDCS on the motor cortex of young participants for 5, 7, 9, 11 or 13 minutes to map out how long the after-effect measured by MEP (Nitsche & Paulus, 2001) would last. They found that the 1-mA anodal stimulation for 5 and 7 minutes induced a significant increased MEP above baseline (after-effect) for less than 10 minutes after stimulation but a 9-minute stimulation produced an after-effect that lasted 30 minutes post-stimulation, a 11-minute stimulation induced an after-effect that lasted 50 minutes and the 13-minute stimulation induced an after-effect that lasted 90 minute after stimulation (Nitsche & Paulus, 2001). Hence, as far as conventional tDCS and motor-related cortical activity are concerned, a 1-mA anodal stimulation for 10 minutes would induce an after-effect apparent immediately after stimulation and would at least last for 50 minutes after stimulation.

The after-effect from the newly developed HD-tDCS, however, was reported to peak at 30 minutes post-stimulation rather than immediate rise in excitability when applied on motor function (Kuo et al., 2013; Villamar, Wivatvongvana, et al., 2013). Kuo et al. (2013) compared the after-effect between the conventional tDCS and the HD-tDCS using 2-mA anodal stimulation that was applied for 10 minutes on the motor cortex. The authors found that the after-effect from the HD-tDCS only peaked at 30 minutes post-stimulation and the MEP measuring the cortical excitability returned to baseline at 120 minutes after stimulation (Kuo et al., 2013). In contrast, the after-effect from the conventional tDCS peaked immediately after stimulation and declined progressively (Kuo et al., 2013). Similarly, a delayed after-effect measured behaviourally was observed by Villamar and his colleagues (2013) when they applied 20 minutes of 2-mA anodal HD-tDCS on patients with fibromyalgia at the motor cortex. Based on past

evidences that neuromodulatory techniques are able to modify sensory aspect of pain via the modulation of M1-thalamic inhibitory networks as well as other projections involved in pain processing pathway and result in analgesic effect, the authors hypothesized and found that the stimulation reduced the pain rating by the patients after stimulation but the rating was lowest at 30 minutes after stimulation relative to immediately after stimulation (Villamar, Wivatvongvana, et al., 2013). Put together, the time-course of the effect after stimulation from HD-tDCS appeared to be different from that of conventional tDCS. One caveat is that these evidences were obtained from stimulation at motor cortex and more evidence is needed for the after-effect duration from stimulation applied on non-motor brain regions; this is the motivation for the pilot study described in Chapter 3.

2.6.3 Adverse symptoms/sensations and contraindications

Adapting the safe protocol of 0.5 – 2 mA of current applied for durations up to 20 min via electrode size of 25 - 35 cm^2 in conventional tDCS studies (Bikson, Datta, & Elwassif, 2009; Brunoni et al., 2011), adverse symptom or sensation commonly reported were: transient and mild tingling sensation, itchiness, warmth and headache (Brunoni et al., 2011; Tadini et al., 2011); which were similar to HD-tDCS studies (Borckardt et al., 2012; Kuo et al., 2013; Villamar, Volz, et al., 2013). In a systematic review of possible adverse symptoms and sensations associated with conventional tDCS, Brunoni et al. (2011) recommended active monitoring and proposed a comprehensive questionnaire "Adverse Effects Questionnaire" for surveying the effects which was adopted in current study.

Similar to other neuromodulatory techniques, it was also advised that persons with unstable medical conditions or conditions that may increase the risk of stimulation and those with metallic implants, non-intact skin, skull defects and brain lesions be excluded from receiving tDCS; and medication taken by participants that might change baseline cortical excitability would also need to be considered as pharmacotherapy and tDCS interact (Brunoni et al., 2011; Villamar, Volz, et al., 2013).

2.6.4 Modulation of working memory

Numerous studies had evidenced the efficacy of anodal tDCS on enhancing memory function (Bennabi et al., 2014; Manenti et al., 2013) particularly working memory in healthy young adults (Carvalho et al., 2015; Fregni et al., 2005; Keeser et al.,

2011; Lally, Nord, Walsh, & Roiser, 2013; Ohn et al., 2008; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011) and healthy older adults (Berryhill & Jones, 2012). Proof-of –concept studies using tDCS for cognitive deficits in MCI specifically were scarce and to our best knowledge, only one study systematically examined the behavioural and neural effects of tDCS on MCI (Meinzer et al., 2015). With the aim to assess the efficacy of anodal tDCS in counteracting pathological alteration of task-related activation in persons with MCI, Meinzer et al. (2015) administered 20 minutes of 1-mA anodal tDCS or 30-s sham on left ventral inferior frontal gyrus in MCI and healthy control when they were performing a semantic-word-retrieval task in the MRI scanner using double-blind, sham-controlled, cross-over design. They found that MCI had more error and higher frontal neural activity relative to control with sham-tDCS but both measures were reduced after anodal-tDCS condition such that MCI performed similarly as the control (Meinzer et al., 2015). The authors suggested that the anodal stimulation reduced the frontal over-recruitment in persons with MCI which was originally employed to compensate for the structural impairment of left medial temporal lobe needed for the semantic retrieval task; in turn this resulted in efficient processing that was corresponded with improved task performance (Meinzer et al., 2015). This finding seemingly suggested that the neural processing in persons with MCI could be enhanced in the presence of structural impairment and the need for compensatory mechanism could be minimized by tDCS. Thus, there is a possibility that stimulation at DLPFC might lessen the need for compensatory mechanism to be employed in the older adults. However, there remains the question on why an anodal tDCS would result in reduction of the frontal recruitment, against the commonly known anodal-excitatory-cathodal-inhibitory effect mentioned previously.

There are also relatively few studies examining the underlying neuroplasticity induced by tDCS that is associated with working memory. Among these few studies that employed EEG/ERP techniques on working memory, the investigations were only conducted in the young samples (Keeser et al., 2011; Zaehle et al., 2011). Both Keeser et al. (2011) and Zaehle et al. (2011) applied anodal conventional tDCS over the left dorsolateral PFC (DLPFC) on healthy young participants and had them performed two-back task after that while recording their EEG. Accuracy improved after stimulation in both studies with either no change (Zaehle et al., 2011) or faster response time (Keeser

et al., 2011). A larger P300 at the frontal and midline site Fz was found by Keeser et al. (2011) whereas Zaehle et al. (2011) did not find any change in the amplitude of P300 with respect to anodal stimulation. The different foci of P300 analysis in the two studies might have contributed to the inconsistency: Keeser et al. (2011) analysed the midline sites at frontal, central and parietal whereas Zaehle et al. (2011) focused on the posterior aspects (occipito-parietal and Pz). Keeser et al. (2011) accounted for the increased P300 amplitude after anodal stimulation relative to the sham stimulation as indicating that the stimulation directly increased the component as the generators involved DLPFC among others. The authors also interpreted the increased P300 after stimulation in light of the higher activation of left parahippocampal gyrus after stimulation in the same time-window found in their sLORETA analysis, suggesting that the DLPFC stimulation influences the frontal cortex via the fronto-hippocampal and fronto-parietal connections by making it easier to get the network activated during task (Keeser et al., 2011). This seems to point out that the neural processes in working memory could be modulated by the electrical stimulation via neural networks, thus not limiting the modulation to processes that are associated with the stimulation site. Hence, there is a possibility of stimulating DLPFC and in turn modulate connected regions involved in the working memory neuromechanism (Figure 2.4). In contrast, the neural response towards electrical stimulation as well as age-related changes or compensation reflected in N200 were relatively unexplored.

Given that this study adopted stimulation to be applied on left DLPFC during the task taking process, it would be of interest to examine the electrophysiological changes proximal to the stimulation sites e.g. F7 apart from Fz. In view of the evidenced age-related frontal hyperactivity (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013), frontal region would additionally be important if the question on how healthy older adults might respond to the stimulation electrophysiologically is to be investigated as frontal over-recruitment is one of the key age-related neural changes.

Pertaining to the use of the newly-developed HD-tDCS to modulate cognitive function, there were two studies to date albeit not on working memory. One study applied anodal HD-tDCS on either left DLPFC, planum temporale (PT), or medial temporal lobe (MTL) in healthy young adults to investigate the stimulation effect on declarative verbal learning and memory (Nikolin, Loo, Bai, Dokos, & Martin, 2015). The

anodal HD-tDCS improved the accuracy rate of verbal learning and quickened the speed for the working memory task that was included as one of the secondary outcome measures (Nikolin et al., 2015). The other study attempted to compare the effect from conventional and HD-tDCS on response inhibition in healthy young adults receiving response inhibition training concurrently with anodal stimulation (1 mA for 20 minutes) at inferior frontal cortex (Hogeveen et al., 2016). The authors randomly assigned the participants into three groups: 1) conventional tDCS, 2) HD-tDCS, and 3) conventional tDCS at control site (mid-occipital); and had them attended two sessions of experiment: one session to test and train response inhibition (stop-signal task), another session for choice response task (Hogeveen et al., 2016). The gain score of the participants in stop-signal task indicated that response inhibition was improved after conventional and HD-tDCS at inferior frontal cortex relative to the control site (Hogeveen et al., 2016). However, the underpinning neural changes from HD-tDCS were unknown from the two behavioural studies.

In summary, there is potential for HD-tDCS to be used as a tool to modulate working memory behaviourally and neutrally within a relatively short duration of stimulation: anodal tDCS (conventional or HD-tDCS) to DLPFC was found to improve working memory performance in the young adults on accuracy (Keeser, Zaehle) and response time (Keeser et al., 2011; Nikolin et al., 2015), and in healthy older adults (Berryhill & Jones, 2012); as well as semantic memory in persons with MCI (Meinzer et al., 2015). Neurally, anodal tDCS was found to increase frontal P300 in young adults performing n-back task (Keeser et al., 2011) and reduced the compensatory frontal activity in MCI who engaged in word-generation task (Meinzer et al., 2015). Based on evidences from conventional tDCS, 1 mA of anodal stimulation for 10 minutes would be more than sufficient to induce an after-effect that would at least last for 50 minutes (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001) and that the after-effect involves synaptic modification (Liebetanz et al., 2002; Nitsche et al., 2003). The only caveat is that the time-course of the after-effect induced by HD-tDCS might differ such that the peak after-effect surfaced not immediately but approximately 30 minute after the stimulation ended when a 2-mA stimulation was applied for 10 minutes (Kuo et al., 2013). As such, this study intended to use HD-tDCS to stimulate the brain and examine

the response of the aging brain as reflecting its extent of neuroplasticity and how the MCI condition would further influence this neuroplasticity.

2.7 STUDY RATIONALE

2.7.1 Objectives and significance

The summary of evidences on age- and MCI-related changes in working memory (Figure 2.4) demonstrated that the underlying match-mismatch processing to distinguish target and non-target indexed by ERP signature N200 is impaired in healthy older adults and delayed in MCI group.

The stimulus-driven attentional processes needed to perform working memory task as reflected by the frontal P300 was over-recruited and delayed in healthy older adults and was likely also heightened in persons with MCI.

The evidences on transcranial direct current stimulation showed that there is potential for HD-tDCS to be used as a tool to modulate working memory behaviourally and neurally. The electrical stimulation to the brain would allow investigation on how the aging brain responds to it, thus reflecting its extent of neuroplasticity. This would also allow a comparison with persons with MCI to examine how the MCI condition would further influence this neuroplasticity.

Hence, this study aimed to test how MCI would influence augmentation of neural processes associated with working memory for reflecting the neuroplasticity of older adults. The augmentation of the neural processes was by means of applying short-lifting external electrical stimulation to the brain using HD-tDCS. The whole study consisted of one pilot study and a main study: the pilot study aimed to verify the time-course of HD-tDCS after-effect in order to temporally position the experimental task optimally, and the main study compared the neuromodulation of working memory processes and performances by HD-tDCS in younger adults, healthy older adults and persons with MCI.

The findings from the current study would shed light on the extent and how tDCS could initiate modulation of the neural processes associated with working memory function. By comparing the results of healthy older and younger adults, the aging-effects on the augmentation processes can be ascertained. By comparing the results of participants with MCI and their healthy counterpart, the additional limitations of the neuroplasticity due to MCI can be further explored. These offer new insights into

neurodegeneration on working memory, and hence better understanding of how MCI impacts on cognitive functions of older adults.

2.7.2 Operationalization

In the current study, we applied anodal HD-tDCS on the left DLPFC (F3 according to the 10/20 International system for electrode placement) to alter the cortical activity so as to modulate the working memory performance of younger participants (YG), healthy older participants (OG) and participants with MCI (MG). A digit two-back task was used to reflect the participants' performance on working memory before and after the stimulation. The participants' neurophysiological responses were captured using electroencephalogram (EEG) measurements.

2.7.3 Hypotheses

Based on the available behavioural evidences from tDCS/HD-tDCS studies, it was hypothesized that:

1. the stimulation would improve the response time and accuracy rate in the three groups: YG, OG and MG.

The compensatory mechanism and the neural response towards electrical stimulation in N200 were relatively unexplored. However, the compensatory frontal hyperactivity in MCI was observed to be reduced and induced an efficient process that led to improved task performance (Meinzer et al., 2015) in the presence of structural deficits that created the need for compensation initially, therefore,

2. the frontal N200 that is related to the match-mismatch discriminative process was hypothesized to become more negative-going (particularly for non-target) and earlier in the three groups of participants.

A more positive-going frontal P300 in older adults than the younger adults was often reported as a compensatory mechanism to match up the task performance, demonstrating the cognitive reserve hypothesis (Stern, 2009) that the brain tries to cope with deficits activity by using existing cognitive processes or by recruiting compensatory processes. Based on the view that degraded N200 would cascade greater demand on the subsequent P300 processes due to aging (Daffner et al., 2011), we would expect the stimulation-enhanced N200 to lower the need for the adaptive, compensatory frontal P300 in the healthy older adults. Hence, it was hypothesized that:

3. the frontal P300 in the OG would be elicited earlier (earlier latency) and be attenuated (less positive-going waveform).

Due to limited evidence on the frontal P300 in MCI, we would explore the modulation of this ERP marker with stimulation in MCI but expect:

4. P300 in MG to respond in the same manner as the healthy counterparts. The electrophysiological changes were expected to associate with the behavioural improvement.

CHAPTER 3 PILOT STUDY

This chapter describes the behavioural pilot study that was conducted with young adults to verify the time-course for the maximal after-effect from HD-tDCS so as to guide the timing for tasks after stimulation in the main study.

3.1. BACKGROUND

The mechanism and the after-effect of tDCS were mainly understood by studying how motor functions were modulated after stimulating the motor cortex using conventional tDCS as seen in the previous chapter. There is evidence that the time-course of the after-effect from HD-tDCS on motor cortex apparently differed from that from conventional tDCS. Kuo et al. (2013) compared the after-effect of 2 mA anodal stimulation that was applied for 10 minutes on the motor cortex between the conventional tDCS and the HD-tDCS. The authors found that the after-effect from the HD-tDCS only peaked at 30 minutes post-stimulation and the motor-evoked potential (MEP) measuring the cortical excitability returned to baseline at 120 minutes after stimulation (Kuo et al., 2013). In contrast, the after-effect from the conventional tDCS peaked immediately after stimulation and declined progressively (Kuo et al., 2013). Similarly, a delayed after-effect was observed by Villamar and his colleagues (2013) when they applied anodal HD-tDCS on patients with fibromyalgia at the motor cortex. As hypothesized, the stimulation reduced the pain rating by the patients after stimulation but the rating was lowest at 30 minutes after stimulation relative to immediately after stimulation (Villamar, Wivatvongvana, et al., 2013). Put together, the time-course of the effect after stimulation from HD-tDCS appeared to be different from that of conventional tDCS. However, such evidence was obtained from stimulation at motor cortex. There is a need to verify the time-course of HD-tDCS effect preliminarily on non-motor brain regions. Hence, a pilot study preceding the main study was conducted to examine the effects of HD-tDCS on working memory and the time-course of after-effect. The pilot study was designed to investigate the after-effect of HD-tDCS on frontal lobe at different time points post-stimulation. The result would inform the next stage of the study in terms of the timing to position the experimental task after stimulation.

The stimulation site was at F7 on scalp according to the 10/20 international system of electrode placement, which covered parts of left lateral PFC (Nozari,

Woodard, & Thompson-Schill, 2014). As mentioned in the previous chapter, the lateral PFC plays a role in monitoring and manipulating working memory content (Barbey, Koenigs, & Grafman, 2013; Miller & Cohen, 2001; Petrides, 2000, 2005). Working memory would be measured using the n-back task (Dobbs & Rule, 1989) in which one has to identify if the currently-presented stimulus is the same as the one presented n trials ago. The study adopted a within-group design by comparing the after-effect of the stimulation across different time-points. A sham group was included to serve as a control to the real stimulation group.

Based on existing evidence (Kuo et al., 2013; Villamar, Wivatvongvana, et al., 2013) that the stimulation after-effect peaked at 30 minutes after stimulation, it was hypothesized that a larger change in the task performance index relative to that at baseline would be at 30 minutes after stimulation as compared to other post-stimulation time-points.

3.2. METHODS

3.2.1. Participants

A total of thirty-one healthy young adults were recruited. Two male participants were excluded in the data analysis as their response latencies were consistently low (below 1.5 to 3.0 of the inter-quartile range in the Box-and-Whisker plot). The final sample size was 29 (16 male; 55.2%) with a mean age of 24.0 years (SD = 2.6). The participants were all right-handed and received university education or above. They were randomly assigned to either the group receiving real stimulation (Real, n = 14) or sham stimulation (Sham, n = 15).

The selection criteria for healthy young participants were: a) aged 18 to 28, b) a native Chinese speaker, c) having normal or corrected-to-normal vision, d) without history of memory impairment, and e) without history of neurological or psychiatric conditions.

Any person recruited with following contraindications to transcranial direct current stimulation was excluded from participating in the study as recommended (Brunoni et al., 2011; Villamar, Volz, et al., 2013): 1) unstable medical conditions or conditions that may increase the risk of stimulation, e.g. epilepsy; 2) metallic implants; 3) non-intact skin at scalp; 4) skull defects; 5) brain lesions. Information on contraindications was obtained through self-report and a screening questionnaire

adapted from Transcranial Magnetic Stimulation Adult Safety Screen (TASS) as shown in Appendix 1A and 1B (Keel, Smith, & Wassermann, 2001).

Ethics approval was obtained from Department of Rehabilitation Sciences, The Hong Kong Polytechnic University (Appendix 2). Informed consent (Appendix 3A and 3B) was obtained from each participant before the session started. Information sheets stating the purposes, procedure of HD-tDCS and details of the two-back task (Appendix 4A and 4B) were provided to each participant with verbal explanation. Both consent form and information sheet were available in English and Chinese. In addition, opportunity was provided for any concerns and questions from participant to be voiced and addressed before the commencement of stimulation to minimize any possible anxiety (Norris, Degabriele, & Lagopoulos, 2010). All participants received HK$200 as compensation for the transportation and meal costs.

3.1.1. Task stimuli

Single digit stimulus (0 to 9) was used in the visual two-back task. The stimulus was prepared in white, positioned centrally against a black background using the font Arial bolded at size 150. The stimuli were presented visually using the Presentation of the stimuli used E-prime software (Psychology Software Tools, Pennsylvania, USA) on a 15-inch liquid-crystal display (LCD) monitor with a black background, subtending maximum visual angles of 2.6˚ (vertical) and 1.8˚ (horizontal).

3.1.2. Task design

Sequence of single digit (0-9) was presented in pseudo-randomized order and the participants were required to respond to each stimulus by indicating whether the digit presented on screen was the same digit presented two trials ago before it (Figure 3.1). A digit was presented for 1000 ms followed by a blank screen that lasted for 1000 ms before the next digit appeared. The participants were required to respond once the stimulus appeared. The participants responded by pressing the key on computer keyboard labeled "✓" if the currently presented digit was the same digit presented 2 trials ago, or the key labeled "✗" if otherwise. The keys "1" and "2" were used as response keys and the allocation was counterbalanced between participants; they were instructed to use right index finger and middle finger for the two response keys.

All participants completed one or more practice block of 20 trials with 7 target trials before the experimental session started to familiarize them to the task and they

had to reach a minimum correct rate of 80% to proceed to the test block. This was meant to minimize the within-group heterogeneity in performing on the two-back task which might weaken the power of detecting potential differences across the 60-minute repeated measures. The test block consisted of 100 trials with approximately 30 targets trials.

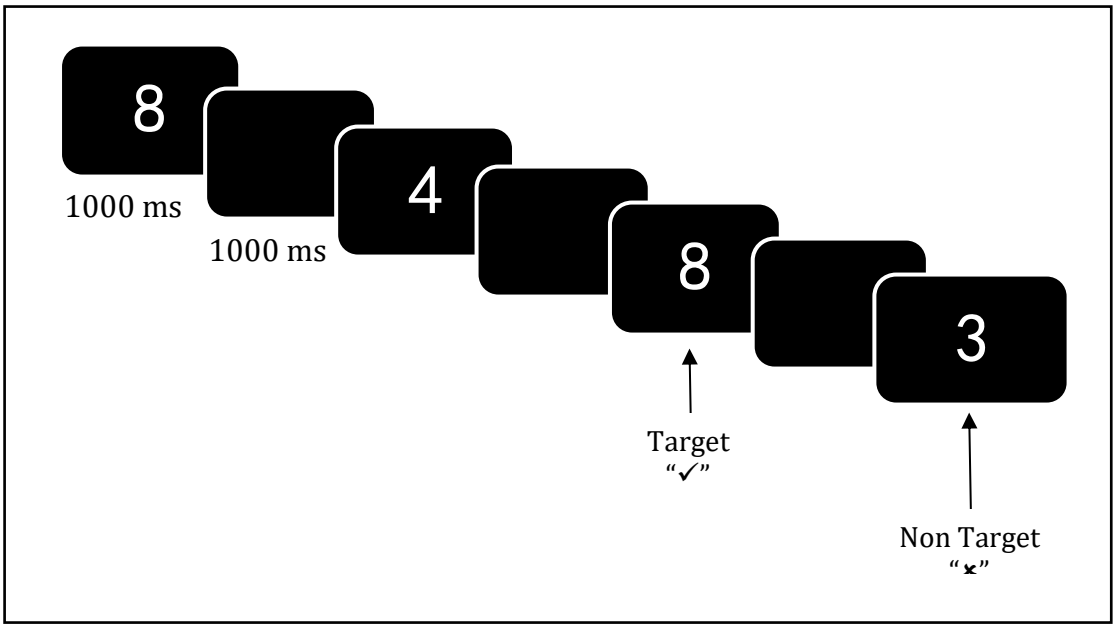


Figure 3.1. Illustration of the two-back task.

3.1.3. Experimental procedure

The participants completed the TASS and informed consent after the details of experiment were explained at the beginning of the session. The participants sat comfortably in a radio frequency-shielded room at a table with a computer monitor and a keyboard. The participants were required to complete practice blocks of the two-back task with at least 80% correct rate to ensure that they were familiar with the task. After offsetting up the HD-tDCS electrodes, the participants performed one block of the two-back task. Stimulation from the HD-tDCS (real or sham) was next administered for 10 minutes. After the stimulation, the participants performed the two-back task at four time-points: 15, 30, and 60 minutes. Upon completing the session, the participants were asked to guess whether they received real or sham stimulation as well as to rate how confidence they were with their guess. This was done using a Blinding measure (Appendix 6) administered orally by the researcher. The participants were asked to respond to: 1) whether the stimulation received was "real" or "fake"; and 2) rate on the

confidence level of the real/fake response against a three-point scale: with "1" indicating least confident and "3" indicating most confident. Each experimental session lasted approximately 2.5 hours.

During the stimulation, the participants was asked to report and rate any sensations or adverse effects by completing the Adverse Effects Questionnaire (AEQ) as presented in Appendix 5A and 5B at stimulation onset, 5 minute into stimulation and at the last 30 seconds of stimulation as recommended by Brunoni et al. (2011). The most frequently reported sensations in tDCS studies were tingling, itching and burning (Brunoni et al., 2011; Kessler, Turkeltaub, Benson, & Hamilton, 2012). The participant completed follow-up AEQ at 1-day and 1-week post experiment.

3.1.4. HD-tDCS set-up

The participants were fitted with the HD-tDCS cap with electrodes according to their head circumference. Proper fitting and alignment were ensured by locating vertex electrode (Cz) at junction of mid-distance between left and right periauricular points and that between nasion and inion. The 10-minute tDCS schedule began with a preset 30-s tickle delivered before the actual stimulation for participants of both Real and Sham stimulation groups. This procedure was to acclimatize the participants to the stimulation. Stimulation was delivered for 10 minutes at 1 mA (current density at skin = 1.179 mA/cm^2) with preset ramp-up and ramp-down in the first and last 30 seconds of the 10-minute duration in the Real condition. In the Sham condition, stimulation was delivered via the preset mode that consisted one minute of ramp-up and ramp-down to 1 mA at the beginning and end of the duration.

The HD-tDCS cap is an elastic cap (Easycap, Bavaria, Germany) with slits arranged according to the 10/20 international system for electrode placement. Sintered Ag-AgCl electrodes were placed in the HD-tDCS electrode plastic holders (SMI) filled with conductive Signa Gel (Parker Laboratories, New Jersey, USA) embedded in the slits on the cap (Figure 3.2a).

The electrodes were arranged in a 4 x 1 configuration with the active electrode mounted on the F7 location and the four surrounding electrodes at F3, AF7, F9 and FT7 (Figure 3.2b). F7 was chosen as the stimulation site as it covers parts of both ventrolateral and dorsolateral PFC (Nozari et al., 2014) and at pilot study phase, it was intended to keep to the broader lateral PFC than to be specifically on dorsolateral PFC.

HD-tDCS was delivered through a battery-driven constant current stimulator (Soterix Medical Inc, SMI, New York, USA) connected to a HD-tDCS adaptor device (SMI) as shown in Figure 3.2c.

a **b** **c**

Figure 3.2. Set-up of HD-tDCS
(a) Elastic cap with holders for HD-tDCS electrodes and slits for EEG electrodes according to 10-20 international electrode placement system. (b) The 4x1 configuration shown has the active electrode at F7 and four surrounding electrodes at F3, AF7, F9 and FT7. (c) Battery-operated HD-tDCS devices.

3.2. DATA ANALYSIS

3.2.1. Behavioural data

Correct trials with response time falling beyond 1.5 interquartile range in the box-and-whisker plot were excluded from analysis. Mean response times for correct trials (Correct RT) and the percentage of correct trials (Accuracy) were computed to derive the inverse efficiency score (IES). IES is a composite score to minimize any speed-accuracy trade-off and the formula is $\frac{Correct\ RT}{Accuracy}$ (Bruyer & Brysbaert, 2011), expressed in ms and lower IES reflects a better performance. In order to analyse the pattern of task performance changes after the real and sham stimulations respectively, ratio change in IES (Chen et al., 2017; Yang, Yang, & Kang, 2014) with the formula $\%\Delta IES = [(IE_{baseline} - IE_t)/IE_{baseline}]*100$ at each of the three post-stimulation time-points (15-, 30-, and 60-minute) were compared using paired-samples t-test to examine the difference in task performance change between time-point within each group separately. Critical p-value was hence set at 0.017.

3.2.2. AEQ data

Frequency of reports for each sensation was tabulated. Ratings of the three most frequently reported sensations were analysed using Mann-Whitney test for between-group comparisons and Wilcoxon signed-rank test for within-group comparisons.

3.2.3. Blinding data

The proportion of participants in each group perceiving the two stimulations were computed. Rating of confidence was tabulated.

In all the analyses of variance, Greenhouse-Geisser correction was applied whenever the sphericity assumption was violated. In such case, the original degree of freedom was reported. Pairwise comparisons were conducted for significant interaction effects with Bonferroni adjustment for the p-values. The statistical analysis was conducted using IBM SPSS Statistics 22.

3.1. RESULTS

3.1.1. Two-back task

The mean accuracy rate, response time (correct RT), inverse efficiency score (IES) and the percentage change in IES (%ΔIES) of correct trials for the two-back task at the different time-points are presented in Table 3.1.

Repeated-measure ANOVA on the percentage change in IE (%Δ IE) for the Real stimulation group revealed a trend of a difference in performance change across time-points ($F(2,26) = 3.09$, $p = .062$). Driven by the a-priori hypotheses to examine the changes in task performance by the stimulation with greatest change predicted at 30-minute after stimulation, paired samples t-tests on the %Δ IE was performed.

The %Δ IE at 15-minute after real stimulation was significantly smaller than the %Δ IE at 30-minute ($t(13) = -2.83$, $p = .014$) whereas there was no significant difference in %Δ IE between 15-minute and 60-minute ($t(13) = -1.29$, $p = .221$) as well as between the %Δ IE at 30-minute and 60-minute ($t(13) = 1.03$, $p = .322$) as shown in Figure 3.3, indicating a peak improvement in task performance between 15 to 30 minutes after real stimulation.

Table 3.1. Performance of 2-Back task in Real and Sham groups across time-points.

	Group	Baseline	15 minutes	30 minutes	90 minutes
		M[a] (SD)[a]	*M* (SD)	*M* (SD)	*M* (SD)
	Real (*n*=14)	94.94 (3.36)	94.60 (4.59)	94.62 (4.30)	95.19 (4.46)
	Sham (*n*=15)	89.64 (5.65)	90.92 (5.33)	90.69 (4.24)	91.51 (4.18)
	Real (*n*=14)	513.01 (46.96)	502.12 (49.63)	473.78 (34.94)	483.03 (54.48)
	Sham (*n*=15)	495.14 (40.55)	469.75 (41.03)	460.81 (41.31)	463.05 (34.15)
	Real (*n*=14)	5.41 (0.54)	5.32 (0.61)	5.02 (0.41)	5.15 (0.63)
	Sham (*n*=15)	5.56 (0.72)	5.19 (0.65)	5.10 (0.59)	5.07 (0.52)
	Real (*n*=14)	N.A.	1.60 (6.32)	6.97 (6.17)	4.89 (6.33)
	Sham (*n*=15)	N.A.	6.30 (7.11)	7.66 (10.31)	8.26 (7.56)

[a] M = mean, SD = standard deviation.

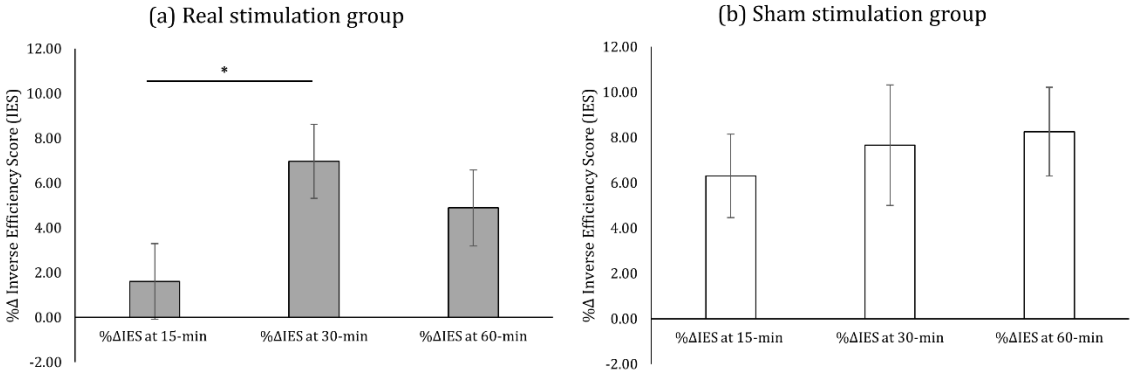


Figure 3.3. Percentage change in Inverse Efficiency Score (%ΔIES) at the three post-stimulation time-points for (a) Real group and (b) Sham group.
%ΔIES at 30-minute post-stimulation was larger than that at 15-minute for Real group but no significant differences among the time-points for Sham group.

3.1.2. AEQ

Among the items in AEQ, the sensations that were reported by more than 50% of the 29 participants were tingling (76%) and itching (59%). Burning sensation was reported by 21% of the participants. Further analysis was performed on these 3 sensations.

Table 3.3 showed the proportion of participants reporting the three sensations as well as the distribution of participants across the rating levels. As shown in Figure 3.4, the Real group had more reports of tingling (86%) than itching (43%) and burning (29%) at onset whereas the Sham group had more reports of itching (73%) and tingling (67%) than burning (13%). At 5 minutes into stimulation, similar number of reports of the three sensations felt was made by the Real group (14% to 79%) whereas a much lesser number of reports were made by the Sham group (7% to 25%). The number of reporting of the sensation felt was observed to regress to the means in both groups (Real group: 29% to 50%, nil for burning; Sham group: 13% to 47%) at the last 30 seconds of stimulation.

Table 3.2. Proportion of participants (%) with ratings of tingling, itching and burning at three occasions during stimulation in Real (n =14) and Sham (n = 15) groups.

		Collated ratings		Rating distribution when sensation is present		
		Absent (Score 1)	Present (score ≥ *2*)	Mild Score = 2	Moderate Score = 3	Severe Score = 4
	Real	14	86	50	21	15
	Sham	33	67	40	20	7
	Real	21	79	57	21	0
	Sham	93	7	7	0	0
	Real	50	50	43	7	0
	Sham	87	13	0	13	0
	Real	57	43	29	14	0
	Sham	27	73	67	7	0
	Real	57	43	36	7	0
	Sham	73	27	27	0	0
	Real	71	29	21	7	0
	Sham	53	47	40	7	0
	Real	71	29	29	0	0
	Sham	87	13	7	7	0
	Real	86	14	14	0	0
	Sham	93	7	7	0	0
	Real	100	0	0	0	0
	Sham	87	13	13	0	0

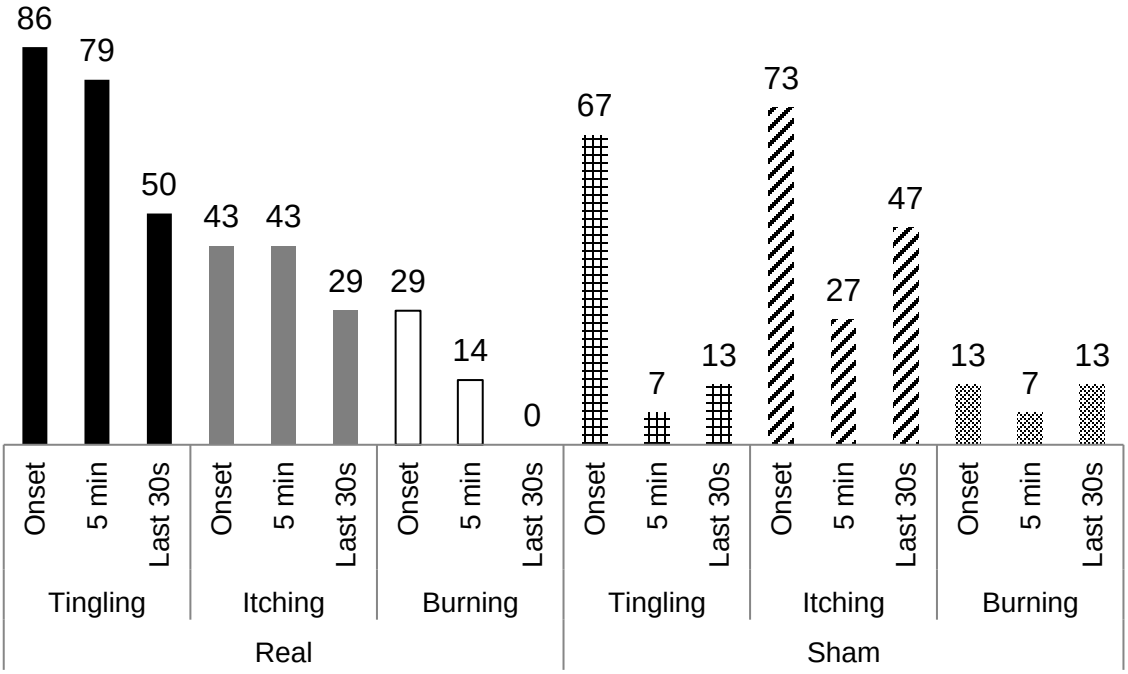


Figure 3.4. Proportion of participants (%) reported presence of tingling, itching and burning (ratings ≥ 2) at three occasions during stimulation in Real (n =14) and Sham (n = 15) groups.

The mean rating of the three sensations by the two groups of participants during stimulation is presented in Table 3.3. Further analysis of the differences in rating (Figure 3.5) revealed that the only between-group difference was found in tingling sensation at 5-min into stimulation (U = 28.00, p < .001) where Real group rated higher than the Sham group (2.0 ± 0.7 vs. 1.1 ± 0.3). Within the Real group, tingling sensation was rated lower at the last 30-sec of stimulation relative to onset (Z = -2.65, p = .008) and to 5-min into stimulation (Z = -2.45, p = .014), suggesting a declining tingling sensation as stimulation progressed in the Real group (Figure 3.4). In contrast, the Sham group rated lower tingling (Z = -2.72, p = .006) and itching (Z = -2.53, p = .011) sensation only at 5-min into stimulation relative to the onset, indicating that the Sham group did not experience progressively lower sensation throughout the stimulation duration (Figure 3.5). No further report of adverse effects was made at the end of session, one day and one week post-experiment.

Table 3.3. Descriptive statistics of rating of tingling, itching and burning.

Rating (1-5 scale)		Real (n=14)		Sham (n=15)	
		Mean	SD	Mean	SD
	Onset	2.4	0.9	2.0	0.9
	5-min	2.0	0.7	1.1	0.3
	Last 30s	1.6	0.7	1.3	0.7
	Onset	1.6	0.8	1.8	0.6
	5-min	1.5	0.7	1.3	0.5
	Last 30s	1.3	0.5	1.2	0.6
	Onset	1.1	0.4	1.1	0.3
	5-min	1.4	0.6	1.5	0.6
	Last 30s	1.0	0.0	1.1	0.4

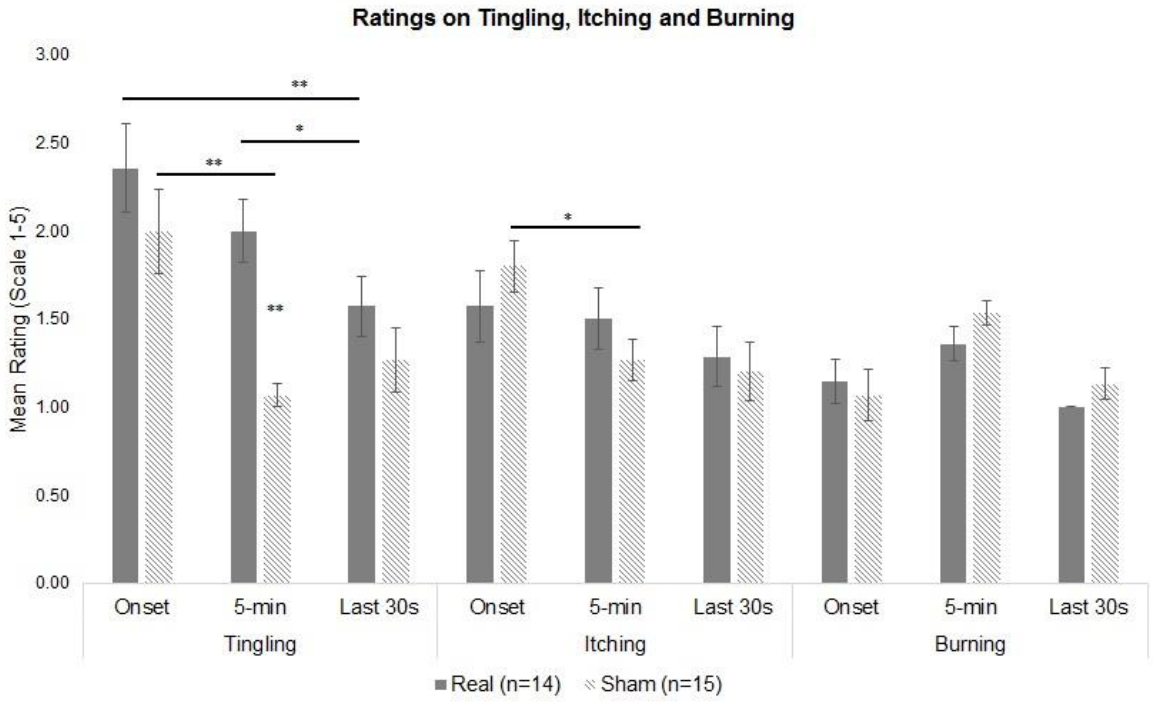


Figure 3.5. Differences in mean rating of tingling, itching and burning.

3.1.3. Blinding measure

In both the Real and Sham groups, majority of the participants perceived the stimulation received as real (93% from Real group, 87% from Sham group). Out of those who perceived the stimulation as real, 43% from Real group rated their perception as with the "most confident". In contrast, only 20% from sham-stimulation group made

the same rating. Instead, 53% of those in Sham group who perceived the stimulation as real rated their perception as with "moderately confident" (Table 3.4).

Table 3.4. Blinding measure. Number of participants and proportion (%) of confidence ratings and perception of stimulation in blinding measure.

Group	Collated across confidence level		Perceived as Real			Perceived as Fake		
	Real	**Fake**	**3**[a]	**2**[a]	**1**[a]	**3**	**2**	**1**
Real (*n* =14)	13 (93%)	1 (7%)	6 (43%)	5 (36%)	2 (14%)	0 (0%)	1 (7%)	0 (0%)
Sham (*n* =15)	13 (87%)	2 (13%)	3 (20%)	8 (53%)	2 (13%)	1 (7%)	1 (7%)	0 (0%)

[a]1 = Least confident. 2 = Moderately confident. 3 = Most confident.

3.2. DISCUSSION

The main finding was that the largest improvement in working memory task performance due to 10 minutes of anodal HD-tDCS applied to the lateral PFC was apparent at 30-minute after stimulation. In contrast, participants in the sham-stimulation group showed a general improvement in task performance.

This time-course of the enhancements observed with real stimulation was comparable to those reported in previous studies that stimulated the motor cortex (Kuo et al., 2013; Villamar, Wivatvongvana, et al., 2013). Tingling, itching, and burning sensations were most frequently reported by the participants regardless of group membership, although the groups differed in their ratings of tingling sensation midway through the stimulation. In the real-stimulation group, the rating of tingling declined progressively over time, which was not observed in the sham counterpart.

3.2.1. Delayed maximal aftereffect

The delayed maximal aftereffect of HD-tDCS over the left lateral PFC in enhancing cognitive function found in this study further contribute to the evidence reported on HD-tDCS applied over the motor cortex (Kuo et al., 2013). The largest change in the task performance index occurred at 30 minutes after stimulation, a finding that concurs with the peak MEP observed at 30-minute post-stimulation reported in other HD-tDCS studies (Baxter, Edelman, Zhang, Roy, & He, 2014; Kuo et al., 2013; Villamar, Wivatvongvana, et al., 2013). The current study is among the first studies to examine the time-course of HD-tDCS aftereffect in brain regions apart from

the motor cortex. The present finding suggests that the HD-tDCS aftereffect manifests a similar temporal time-course in the frontal cortex as it does in the motor cortex, and in cognition as well as in motor-related activity, indicating that there may be a similar neural mechanism underlying its enhancement effects. This calls for future study to verify the temporal time-course proposition on the neural mechanism underlying the HD-tDCS aftereffect.

3.2.2. Peak enhancement with real stimulation

The larger enhanced working memory performance found on the the two-back task among participants who received real HD-tDCS stimulation observed in the present study are consistent with the findings on response time reported in two other HD-tDCS studies involving non-motor brain regions (Nikolin et al., 2015; Richardson, Datta, Dmochowski, Parra, & Fridriksson, 2015) in a naming task and three-back task. Unlike the present study, these two studies applied HD-tDCS concurrently as part of a treatment for post-stroke patients (Richardson et al., 2015) or during a task in a study on healthy subjects (Nikolin et al., 2015), and therefore they did not address the time-course issue of the HD-tDCS aftereffect. In comparison to the current study, Nikolin and his colleagues (Nikolin et al., 2015) applied 4x1 channel HD-tDCS to the left medial temporal lobe, left DLPFC and left planum temporale of healthy young adults and found improved RT in the three-back task, which was performed between 25 and 30 minutes after stimulating the left DLPFC only. Restricted to working memory, the current study together with the findings from Nikolin et al. (2015) suggest that HD-tDCS applied to the left lateral frontal region improves the response time of working memory measured by the n-back task.

3.2.3. General enhancement with sham stimulation

The current study observed that the task performance of the sham stimulation group improved albeit in a general manner with no specific peak change. There is also the possibility that the preset sham protocol produced some stimulation effect although this phenomenon has not been systematically tested. For example, Keeser et al. (2011) observed that the reaction time in the two-back task was faster after anodal tDCS when compared with baseline measure but not when compared to the sham stimulation measure. More evidence is needed to account for the difference and intensity of the effect from sham stimulation.

3.2.4. Adverse effect and sensation

In the present study, the frequency of reports as well as the rating of the adverse effects and sensations experienced was systematically analyzed. Tingling, itching, and burning sensations were most frequently reported, in accordance with previous reports (Brunoni et al., 2011; Kessler et al., 2012). The two groups in the present study differed in the rating for tingling sensation midway through the stimulation, when the real-stimulation group rated tingling higher than the sham group; however, this rating by the former group declined as the stimulation progressed. In addition, the sensations experienced were transient, as there was no report of sensations felt after the stimulation. The underlying mechanism of common sensations and symptoms from the stimulation has not been systematically studied, but it has been commented that the tingling, itching, skin redness, and burning were likely due to vasomotion or increased skin temperature as well as excitation of the cutaneous receptors from the electrical current (Fertonani, Ferrari, & Miniussi, 2015)

3.2.5. Limitation and future study

The findings would have been more robust if a controlled group without stimulation was included in view of the possible general enhancement from sham stimulation. Future studies could use a more challenging task for reflecting the potential after-effects. The use of modelling software in a future study to provide information on the intra-cranial EF induced would provide insight on the time lag in the after-effect.

3.3. CONCLUSION

The current study found that 10 minutes of 1 mA HD-tDCS at the left lateral PFC produced a greater enhancement in the working memory performance at about 30 minutes after stimulation. The time-course of the after-effect is delayed relative to that of conventional tDCS reported in literature, which might be attributable to the distinctive nature of the current direction and EF distribution between the two different electrode configurations that affected the neural response. However, this needs further investigation to systematically clarify. The improved task performance from the stimulation added to the previous evidence on the use of HD-tDCS (Nikolin et al., 2015).

CHAPTER 4 METHODS

This study aimed to test how MCI would influence augmentation of neural processes associated with working memory for reflecting the neuroplasticity of older adults. The augmentation of the neural processes was by means of applying short-lifting external electrical stimulation to the left DLPFC (F3) with HD-tDCS. A digit two-back task was used to reflect the participants' performance on working memory before and after the stimulation. The participants' neurophysiological responses were captured using ERP and EEG measures.

This chapter covers the method of the study. It describes the participants with the inclusion and exclusion criteria, the neuropsychological measures, the experimental design, procedure, stimulation protocol, data acquisition and analyses, and statistical analyses.

4.1. PARTICIPANTS

4.1.1. Younger participant group (YG)

The selection criteria for the younger participants were: a) aged 18 to 28, b) a native Chinese speaker, c) having normal or corrected-to-normal vision, d) without history of memory impairment, and e) without history of neurological or psychiatric conditions. Participants were recruited via notices posted within the university premise or friend referral. A remuneration of HK$200 was given to each participant who completed the experimental session.

Twenty-four younger adults were recruited and out of which two were excluded from the analysis because one participant had the pre-stimulation data missing, whereas the other younger adult had correct rate that fall below 1.5 to 3.0 of the inter-quartile range in the Box and Whisker plot. Hence, the total sample size for Young group submitted for analysis was 22.

All the 22 younger participants aged 18 to 28 years (mean age = 19.7 ± 1.6, 9 males, 13 females) were receiving tertiary education (mean years of education = 14.3 ± 1.6). All except one participant were right-handed.

4.1.1. Healthy older participant group (OG)

The selection criteria for participants who formed the healthy older adult group (OG) were: a) aged 60 and above, b) a native Chinese speaker, c) having normal or corrected-to-normal vision, d) received at least 2 years of formal education, e) without

a history of neurological or psychiatric conditions, and f) scored above 24 in the screening test using the Montreal Cognitive Assessment Hong Kong version (HK-MoCA). Participants were recruited via notices posted within the university premise or friend referral. Participants who completed the experimental session were remunerated with HK$300 to compensate for the transportation and meal costs.

A total of forty-nine older adults were recruited and assigned to either healthy older adult group (OG) or Mild Cognitive Impairment group (MG) based on their scores in HK-MoCA which is described in later section. Twenty-nine of them who scored 24 and above in the HK-MoCA were assigned to the Old group. Eleven of them were excluded from the analysis due to poor behavioural performance in accuracies and/or response time that fall below 1.5 to 3.0 of the inter-quartile range in the Box and Whisker plot. Hence, the total sample size for OG submitted for analysis was 18.

The 18 older participants aged 60 years or above (mean age = 63.1 ± 2.6, ; 10 males, 8 females) had an average of 9.1 ± 3.7 years of education. All participants in the OG were right-handed.

4.1.2. Participant with MCI group (MG)

The selection criteria for participant with MCI group (MG) were identical to the OG except the former scored within the 19 - 24 cut-off points in the HK-MoCA. Additional selection criteria for this group were: a) having not met the diagnostic criteria for dementia, b) having intact or minimally impaired functions in activities of daily living (ADL), and c) self-reported and/or informant report of cognitive decline. Participants were recruited through cognitive screening exercise at elderly activity centers. Those who completed the experimental session were remunerated with HK$300 to compensate for the transportation and meal costs.

Based on the MoCA score, 20 older adults were classified as participants with MCI. Two of them were excluded from the analysis due to poor accuracies and/or slow response time falling fall below 1.5 to 3.0 of the inter-quartile range in the Box and Whisker plot. Hence, a total of 18 participants with MCI were included in the analysis. The 18 MG participants (5 males, 13 females) had a mean age of 68.3 years (SD = 7.1) with 7.4 ± 3.3 years of education and all of them were right-handed.

4.1.3. Contraindications to tDCS

The following contraindications to transcranial direct current stimulation were used to exclude participants in this study (Brunoni et al., 2011):

1. Unstable medical conditions or conditions that may increase the risk of stimulation, e.g. epilepsy;
2. Metallic implants;
3. Non-intact skin at scalp;
4. Skull defects;
5. Brain lesions.

Information on the contraindications was obtained through self-report and a screening questionnaire (Appendix 1A and 1B) adapted from Transcranial Magnetic Stimulation Adult Safety Screen (Keel et al., 2001).

Ethic approval was obtained from Department of Rehabilitation Sciences, The Hong Kong Polytechnic University (Appendix 7). Informed consent (Appendix 8A and 8B) was obtained from each participant before the session started. Information sheets stating the purposes and detailed content of the HD-tDCS and EEG recording (Appendix 9A and 9B,) as well as the two-back task (Appendix 10A and 10B) were provided to each participant with verbal explanation. Both consent form and information sheet were available in English and Chinese. In addition, opportunity was provided for any concerns and questions from participant to be voiced and addressed before the commencement of stimulation to minimize any possible anxiety (Norris et al., 2010).

4.2. NEUROPSYCHOLOGICAL TESTS (PRE-STIMULATION)

4.2.1. Montreal Cognitive Assessment Hong Kong version (HK-MoCA)

Montreal Cognitive Assessment (MoCA) is a short test that can be administered in 10 - 15 minutes covering 8 cognitive domains, namely short-term memory recall task, visuospatial abilities, executive functions, attention, concentration, working memory, language and orientation to time and place (Nasreddine et al., 2005). The maximum possible score is 30 points with a cut-off score set at < 26 (additional 1 point for education ≤ 12 years) to screen for persons with MCI.

HK-MoCA was validated to be sensitive and specific at a cut-off score of 21/22 (additional 1 point for education ≤ 6 years) to differentiate persons with MCI from healthy control and the cut-off score was lower than the original MoCA due to difference

in general educational level of the population in the two regions (Yeung, Wong, Chan, Leung, & Yung, 2014). Indeed, the cut-off tended to be lower in other Asian countries similar to Hong Kong, e.g. optimal cut-off score of 23/24 achieved sensitivity of 92% and specificity of 78% for MCI using MoCA-Taiwan (Tsai et al., 2012) and in Singapore optimal cut-off point of 19/20 achieved sensitivity of 80% and specificity of 92% (Dong et al., 2013). In an attempt to establish population-based norm for MoCA in Texas, Rossetti, Lacritz, Cullum, and Weiner (2011) found that more than half of the sample scored below the expected optimal cut-off score of 26 and advocated utilizing normative data and interpret MoCA scores based on mean and SD in each age or educational group. Indeed, in the validation study by the original MoCA authors (Nasreddine et al., 2005), the cut-off for MCI was based on a reported score range (19.0 - 25.2). Drawing reference from the cut-off scores found in Hong Kong, Taiwan, Singapore and the original MoCA, a cut-off range of 19 - 24 (additional 1 point for education ≤ 12 years) was adopted for the present study.

4.2.2. Consortium to Establish a Registry for the Alzheimer's disease – Neuropsychological Assessment Battery (CERAD-NAB) Chinese-Cantonese version

The CERAD-NAB consists 8 subtests to assess the specific cognitive deficits that appear in persons with AD such as memory impairment, loss of expressive and receptive language (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988). One of the subtests is the mini mental state examination or MMSE in short (Folstein, Folstein, & McHugh, 1975). The total score of CERAD-NAB using either 6 or 7 subtests was found to be more accurate in discriminating persons with MCI from healthy older adults than using MMSE alone (Chandler et al., 2005; Paajanen et al., 2010; Seo et al., 2010) with sensitivity above 79% and specificity ranging from 64 – 75% (Chandler et al., 2005; Seo et al., 2010). The Chinese-Cantonese version of CERAD-NAB was developed and validated in 187 healthy older adults in Hong Kong and found to have good content validity and excellent inter-rater reliability (Liu et al., 2011); scores of the subtests from these Chinese older adults in Hong Kong sorted according to age, gender and education were available. The present study used the Chinese-Cantonese version of CERAD-NAB as one of the neuropsychological tests and analysed the subtest scores.

4.2.3. Profile of participants in OG and MG on MoCA and CERAD-NAB

The total score on HK-MoCA and the sub-scores of CERAD-NAB by the OG and MG are presented in Table 4.1. Independent sample t-tests were conducted on the scores to examine the group differences. The OG scored significantly higher than the MG in HK-MoCA total score as well as subscales in CERAD-NAB that are related to memory: Mini-mental State Exam, word list memory, and word list recall (Figure 4.1).

Table 4.1. Scores of HK-MoCA and CERAD-NAB by the OG and MG.

Screening	**OG (n=18)**		**MG (n=13)**		***t*-test**
measures	Mean	SD	Mean	SD	*p*-value
MoCA	28.33	1.46	24.44	1.25	**<.001**
J1	21.11	6.17	19.28	3.20	.274
J2	14.67	0.69	14.50	3.73	.853
J3 (MMSE)	29.72	0.57	28.11	1.78	**.002**
J4	23.44	3.93	21.00	3.71	**.063***
J5	10.56	0.86	10.22	1.26	.360
J6	9.22	1.00	8.06	1.39	**.007**
J7	20.00	0.00	19.89	0.32	.163
J8	11.44	3.17	9.06	2.86	**.023**

Note. * OG scored marginally higher than MG in word list memory. J1: verbal fluency; J2: Boston naming test; J3: Mini-mental State Exam; J4: word list memory; J5: constructional praxis; J6: word list recall; J7: word list recognition; J8: recall of constructional praxis. OG = older participant group; MG = participant with MCI group.

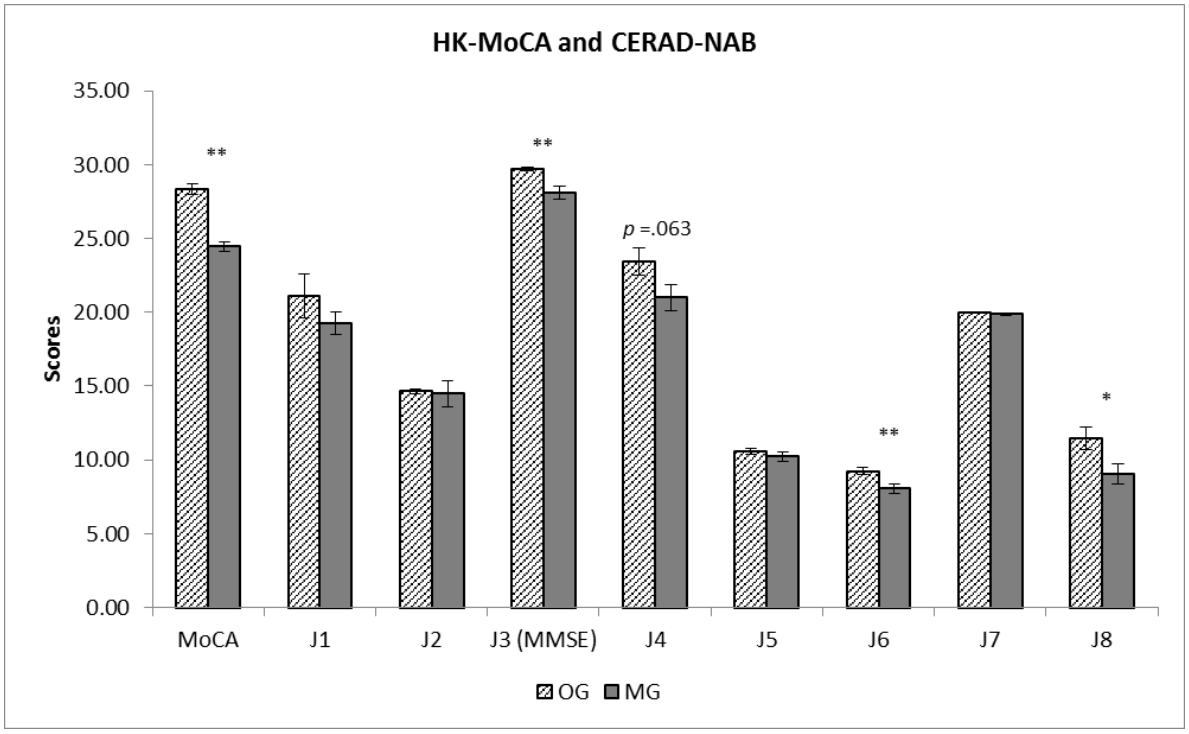


Figure 4.1. The performance on HK-MoCA and CERAD-NAB by the older participant group (OG) and participant with MCI group (MG).
The OG scored higher than the MG in HK-MoCA total scores and subscales in CERAD-NAB that are related to memory (J4 marginally, J6, J8).
Note. J1: verbal fluency; J2: Boston naming test; J3: Mini-mental State Exam; J4: word list memory; J5: constructional praxis; J6: word list recall; J7: word list recognition; J8: recall of constructional praxis. ** $p < .01$, *$p < .05$, two-tailed. Error bar denotes ± 1 standard error.

4.3. STIMULI

Single digit stimulus (0 to 9) was used in the visual two-back task. The stimulus was prepared in white positioned centrally against a black background using the font Arial bolded at size 150 (see Figure 4.2 for an example). The stimuli were presented visually using the STIM2 software (Compumedics Neuroscan, Charlotte, North Carolina, USA) on a 15-inch liquid-crystal display (LCD) monitor with a black background, subtending maximum visual angles of 2.6˚ (vertical) and 1.8˚ (horizontal).

4.4. TASK DESIGN: DIGIT TWO-BACK TASK

Sequence of single digits (0-9) was presented in random order and participants were to respond to each stimulus by indicating whether the digit presented was identical to the digit presented two trials back in the sequence (Figure 4.2). Participants responded by pressing the key on computer keyboard labeled "✓" if the presented digit

was identical to the digit presented 2 trials back in the sequence, or the key labeled "✗" if otherwise. A target trial is one where the currently-presented stimulus and the stimulus presented 2 trials ago matches; a non-target trial is one where the two stimuli mismatches. The keys "A" and "L" were used as response keys and the allocation was counterbalanced between participants; they were instructed to use left and right index fingers for the two response keys.

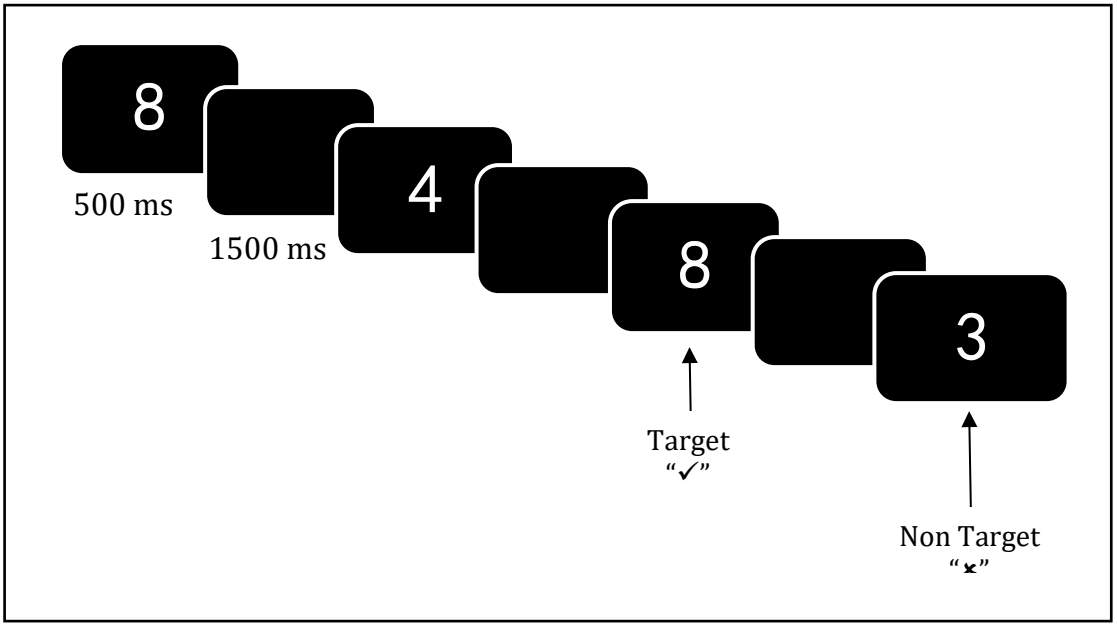


Figure 4.2. Illustration of the two-back task.
The blank screen lasted 1500 ms for the younger adult group and 2500 ms for the two groups of older adults.

In a typical trial, the digit was presented for 500 ms followed by a blank screen that lasted for 1500 ms (for YG) or 2500 ms (for OG and MG) before the next digit appeared. The blank screen for the OG was longer in order to minimize any confound due to slower response (Daffner et al., 2011). Participants were required to respond once the stimulus appeared. Participants completed one or more practice block of 25 trials with 8 target trials before the experimental session started to familiarize them to the task. Participants had to reach a minimum correct rate of 80% to proceed to the test block. The test block consisted of 100 trials with approximately 30 targets trials.

4.5. EXPERIMENTAL PROCEDURE

The participants performed one block of the two-back task before receiving the HD-tDCS. Next, they received 10 minutes of anodal HD-tDCS. Participants rested for

approximately 25 minutes after the stimulation. Next, they performed a block of two-back task. Simultaneous EEG recording was carried out during the two-back task.

The 10-minute HD-tDCS stimulation schedule began with a preset 30-s tickle delivered before the actual stimulation for all three groups. This procedure was to pre-condition the scalp skin and to acclimatize the participants to the stimulation. The stimulation was delivered for 10 minutes at 1 mA (current density at skin = 1.179 mA/cm^2) with pre-set ramp-up and ramp-down each lasting 30 seconds.

During the stimulation, the participant was asked to report and rate any sensations or adverse effects by completing the Adverse Effects Questionnaire (Appendix 5A and 5B) at stimulation onset, 5 minute into stimulation and at the last 30 seconds of stimulation as recommended (Brunoni et al., 2011). The most frequently reported sensations were tingling, itching and burning (Brunoni et al., 2011; Kessler et al., 2012). The participant completed follow-up AEQ at 1-day and 1-week post experiment.

4.6. HIGH-DEFINITION TRANSCRANIAL DIRECT CURRENT STIMULATION

Each participant was fitted with the HD-tDCS cap according to their head circumference. Sintered Ag-AgCl electrodes were placed in the HD-tDCS electrode plastic holders (SMI) filled with conductive Signa Gel (Parker Laboratories, New Jersey, USA) embedded in an elastic cap (Easycap, Bavaria, Germany) with slits arranged according to the 10/20 international system for electrode placement. The electrodes were arranged in a 4 x 1 configuration with the active electrode mounted on the F3 location (approximating left DLPFC) and the four surrounding electrodes at F1, F5, FC3 and AF3 (Figure 4.3a). Proper fitting and alignment were ensured by locating vertex electrode (Cz) at junction of mid-distance between left and right periauricular points and that between nasion and inion. HD-tDCS was delivered through a battery-driven constant current stimulator (Soterix Medical Inc, SMI, New York, USA) connected to a HD-tDCS adaptor device (SMI) as shown in Figure 4.3b.

(a) (b)

Figure 4.3. Set-up of HD-tDCS
(a) Elastic cap with holders for HD-tDCS electrodes and slits for EEG electrodes according to 10-20 international electrode placement system. The 4x1 configuration shown has the active electrode at F3 and four surrounding electrodes at F1, F5, FC3 and AF3 (b) Battery-operated HD-tDCS devices.

4.7. ELECTROENCEPHALOGRAM DATA ACQUISITION

Electroencephalograms (EEGs) were recorded from 21 channels (Ag/AgCl sintered electrodes) using the SynAmps2 amplifier and Acquire 4.3 software (Compumedics Neuroscan, Charlotte, North Carolina, USA) together with the EEG-compatible HD-tDCS electrode cap (Easycap, Bavaria, Germany). Impedance was maintained at below 10 kΩ at all electrode sites. All channels were referenced to the left mastoid. The ground electrode was positioned on the forehead between AFz and Fpz. Vertical electrooculograms (EOGs) were recorded using electrodes located above and below the left eye and horizontal EOGs were recorded from electrodes located at the outer canthus of each eye. The EEGs and EOGs were sampled at 1000 Hz with a 200 Hz low pass filter.

Offline data pre-processing was performed using Edit 4.3 software (Compumedics Neuroscan, Charlotte, North Carolina, USA). EEG signals were merged with behavioural response data files. Signals were re-referenced offline to link the left and right mastoids. Digital band-pass filtering with zero phase-shift from 0.1 to 30 Hz (48dB/oct) was applied and ocular artefacts in EEGs were corrected. Continuous EEG signals were then segmented into epochs from -200 ms to 1000 ms after stimulus onset and baseline-corrected by the pre-stimulus interval. Epochs with amplitude of ±70 mV

in any of the 21 channels were excluded. The remaining epochs were then averaged and separated into correctly identified non-target trials and target trials.

4.8. DATA ANALYSIS

4.8.1. Behavioral data

Mean response time (RT) and accuracy rate (%) on correct trials, target trials and non-target trials were computed. Three-way repeated-measure ANOVAs using the within-subject factors Stimulation (Pre vs. Post) and Type (Target vs. Non-target), and the between-subject factor Age (YG vs. OG in Study One, OG vs. MG in Study Two) were conducted on the RT and accurate rate respectively.

4.8.2. ERP waveform

The ERPs amplitude was measured relative to 200 ms pre-stimulus baseline. Amplitude of N200 component of individual participant was averaged within the time-window of 200-300 ms (YG) or 250 - 350 ms (OG and MG) after stimulus onset. P300 amplitude was averaged within the time-window of 300 - 450 ms (YG) or 350 - 500 ms (OG and MG) after stimulus onset. The time-window was determined based on visual inspection, literature review and verified with independent component analysis. Contrast between non-target and target for N200 amplitude was computed as the difference would highlight the relatively higher activation in processing non-target stimulus than target stimulus (Daffner et al., 2011; Gajewski & Falkenstein, 2014). Comparison between P300 for target and that for non-target (Wild-Wall et al., 2011) would highlight the difference in attention towards the two types of stimuli and the contrast between them (target minus non-target P300) would isolate the target effect in attention (Vierheilig, Mühlberger, Polak, & Herrmann, 2016). The ERPs latencies were determined by detecting the peak within the corresponding time-window and extracting the latency at which the peak occurred. The component N200 from Fz was analysed as this negative component associated with match-mismatch processing is frontally distributed (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Patel & Azzam, 2005). The component P300 (between 300 – 400 ms after stimulus onset) was analysed at Fz, which is a positive frontal component that is related to the attentional allocation to process task-relevant stimulus, inclusive of maintenance and manipulation of information in working memory (Gajewski & Falkenstein, 2014; Keeser et al., 2011; Polich, 2007; Saliasi et al., 2013). Given that the stimulation was applied on left DLPFC

to investigate working memory as elicited by two-back task, it would be of interest to examine the electrophysiological changes proximal to the stimulation sites e.g. F7 apart from Fz. In view of the evidenced age-related frontal hyperactivity (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Saliasi et al., 2013), frontal region would additionally be important if the question on how healthy older adults might respond to the stimulation electrophysiologically is to be investigated.

The same three-way repeated-measure ANOVA model: Age × Stimulation × Type was conducted on testing the amplitudes and latencies of the N200 and P300. Any significant interactions were analysed with pairwise comparisons with Bonferroni adjustment for the p-values. Correlations between ERPs and behavioural data were conducted using Pearson's correlation method for any significant difference to further the interpretation. The statistical analysis was conducted using IBM SPSS Statistics 22.

4.8.3. Independent component analysis (ICA)

ICA refers to a signal processing technique for blind source separation of a linear mixture of evoked electrophysiological data into temporarily independent and spatially stationary sources (Delorme, Sejnowski, & Makeig, 2007; Makeig, Bell, Jung, & Sejnowski, 1996; Onton & Makeig, 2006). ICA from CURRY 7 (Compumedics Neuroscan, Charlotte, North Carolina, USA) was applied to all channels except the EOGs and reference channels. ICA-components with signal-to-noise ratio (SNR) more than 1.0 in target and non-target trials before stimulation were surveyed to verify the components of interest and their corresponding time-windows.

4.9. AEQ DATA

Frequency of reports for each symptom was tabulated. Ratings of the three most frequently reported symptoms as well as the perceived relatedness to HD-tDCS were also tabulated and examined. The ratings of the three most frequently reported symptoms during stimulation were next further analysed using Kruskal-Willis test for three-group comparison. Post hoc group comparison of the symptoms with statistical significant group difference revealed by the Kruskal-Willis test was carried out with Mann-Whitney test. Next, the differences in rating on the three symptoms across the occasions during the stimulation duration (onset, 5-minute into stimulation, last 30s of stimulation) within each group were examined using Wilcoxon signed-rank test.

The frequency of report and rating of each symptom on AEQ by all the participants is presented in Appendix 11. The symptoms that were reported by more than 25% of the participants on any one occasion during stimulation were tingling and itching. Sleepiness was reported by 17.2% of the participants at stimulation onset, 20.7% at 5-minute into stimulation and 24.1% at the last 30s of the stimulation duration. Burning sensation, unlike in the pilot study, was only reported by at most 20.7% of the participants in any one occasion. Hence, tingling, itching and sleepiness were further analysed.

4.9.1. Frequency of reports: Tingling, itching and sleepiness

The proportion of participants reporting the three sensations as well as the distribution of participants across the rating level in the three groups are presented in Table 4.2. At stimulation onset and 5-minute into stimulation, all three groups reported tingling more than other two symptoms (Figure 4.4). During the last 30s of stimulation, the YG had similar reports of the three symptoms (41%) hinting that at least reports of tingling and itching had progressively decreased and the number of reports for sleepiness had increased. The OG still reported more of tingling (56%), followed by itching (44%) and sleepiness (11%) during the last 30s of stimulation: tingling and itching had progressively decreased from onset and 5-minute into stimulation but reports of sleepiness had increased from 6% at preceding occasions to 11%. In the MG, the reports of tingling and itching had decreased from the previous two time-points whereas the reports of sleepiness at the three occasions was constant (23%).

In essence, the number of reports for tingling and itching generally decreased progressively from onset, 5-minute into stimulation to the last 30s in the three groups. Reports of sleepiness increased over the three occasion in the younger participants, remained the same in the older participants at onset and 5-minute into stimulation but increased towards the end of stimulation, and remained constant in the MG.

Table 4.2. Proportion (%) of participants reported tingling, itching and sleepiness. Distribution of the rating when symptom was present by the YG (n=22), OG (n=18) and MG (n=18).

Symptoms	Percentage (%)	Collated of ratings		Rating distribution when symptom was present		
		Absent (Rate = 1)	Present (Rate ≥ 2)	Mild Rate = 2	Moderate Rate = 3	Severe Rate = 4
	YG	23	77	50	27	0
	OG	22	78	50	22	6
	MG	50	50	44	6	0
	YG	32	68	68	0	0
	OG	28	72	61	11	0
	MG	50	50	50	0	0
	YG	59	41	41	0	0
	OG	44	56	44	11	0
	MG	72	28	28	0	0
	YG	36	64	41	14	9
	OG	39	61	44	11	6
	MG	78	22	17	0	6
	YG	45	68	45	22	0
	OG	44	33	33	0	0
	MG	72	28	28	0	0
	YG	59	41	41	0	0
	OG	56	44	39	6	0
	MG	89	11	11	0	0
	YG	73	27	27	0	0
	OG	94	6	6	0	0
	MG	83	17	11	0	6
	YG	64	36	36	0	0
	OG	94	6	6	0	0
	MG	83	17	11	6	0
	YG	59	41	41	0	0
	OG	89	11	11	0	0
	MG	83	17	11	6	0

Note. Percentages rounded up to whole number. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

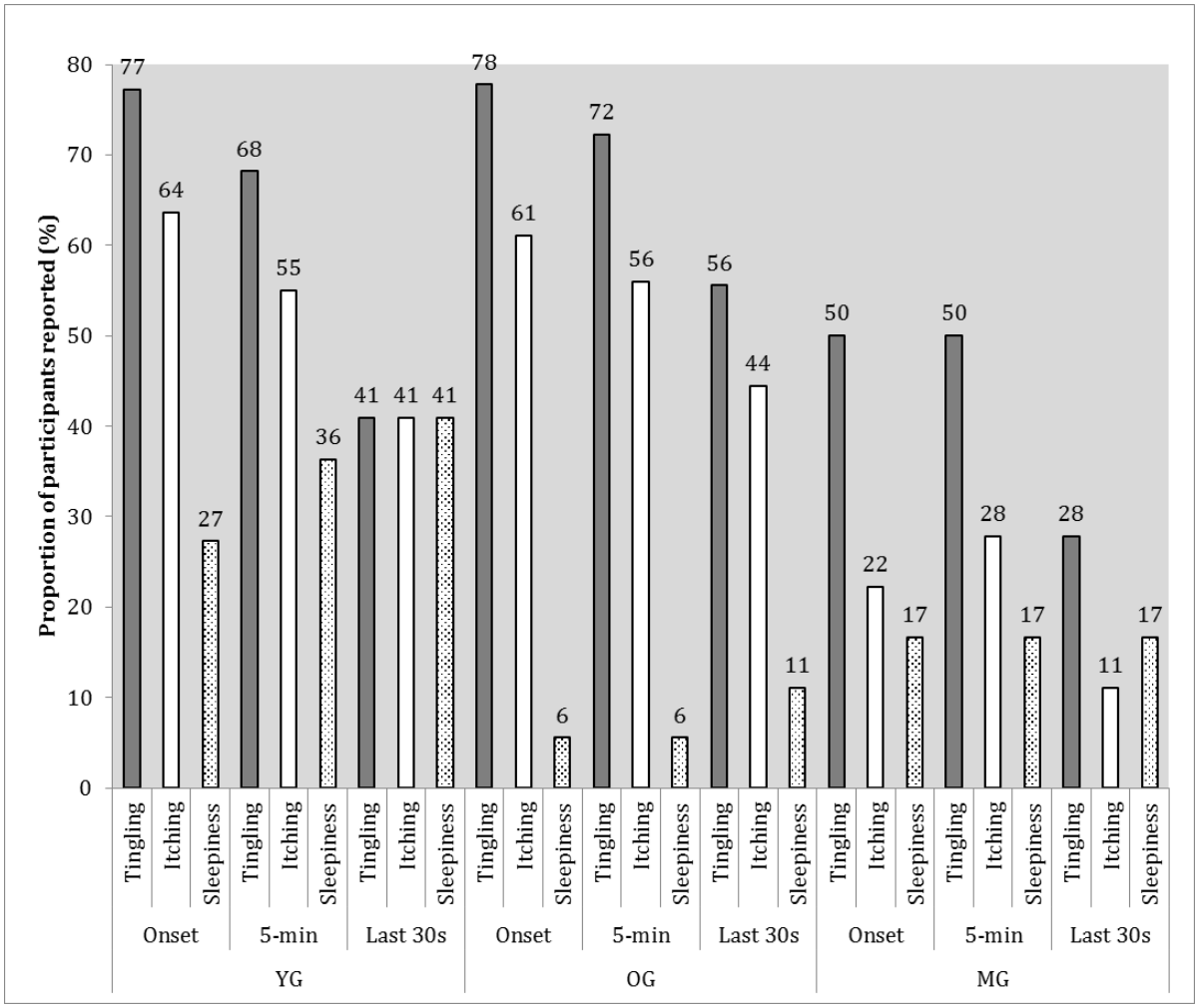


Figure 4.4. Trends on proportion of reports (%) for tingling, itching and sleepiness. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

4.9.2. Perceived relatedness of symptoms to HD-tDCS: Tingling, itching and sleepiness

To further examine the three symptoms, the subjective rating from participants on how far they perceived the symptoms to be related to HD-tDCS, the relatedness rating was tabulated and presented in Figure 4.5 – 4.7.

Tingling and itching were generally perceived as probably or definitely related to the stimulation by the three groups (Figure 4.5 and 4.6). There were two younger participants who reported itching at baseline, they explained it was the electrode conductance gel causing the itch and rated either “remotely” or “not related” (Figure 4.6).

Sleepiness were reported substantially in YG and MG but were largely perceived as "not related" or "remotely" (Figure 4.7). Those who perceived the sleepiness experienced as not related to the stimulation all attributed to insufficient sleep during recent days or perpetual fatigue; those who perceived it as remotely related to the stimulation attributed to the prolonged sitting during the experimental session.

There was 1 participant (#02) from OG who reported sleepiness at baseline and perceived it as remotely related due to prolonged sitting. At onset and 5-minute into stimulation, one OG participant (#25) reported sleepiness and attributed it as definitely related to the HD-tDCS applied. During the last 30s of stimulation, two OG participants (#03 and #25) reported sleepiness and one perceived it to be definitely related to the stimulation (#25) whereas the other perceived it as only remotely related (#03) due to prolonged sitting.

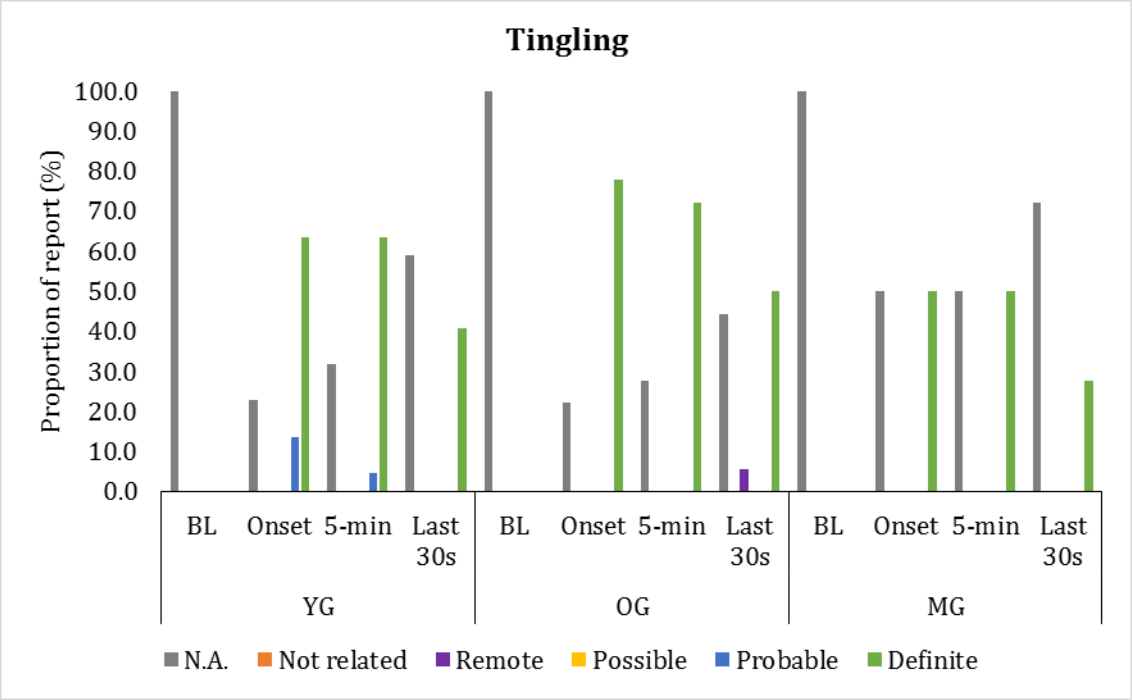


Figure 4.5. Subjective perception of the extent that the experienced tingling were related to HD-tDCS.
Note. N.A. denotes the proportion of participants not reporting the specified symptoms. BL denotes the perception of the specified symptom before stimulation. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

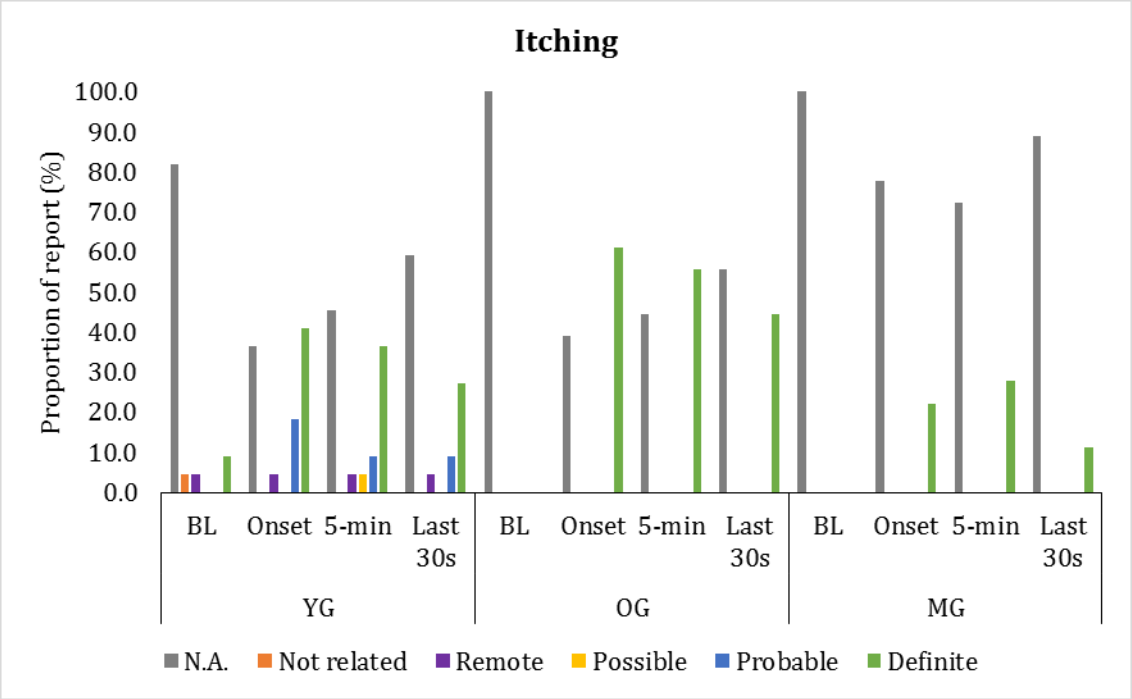


Figure 4.6. Subjective perception of the extent that the experienced itching were related to HD-tDCS.

Note. N.A. denotes the proportion of participants not reporting the specified symptoms. BL denotes the perception of the specified symptom before stimulation. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

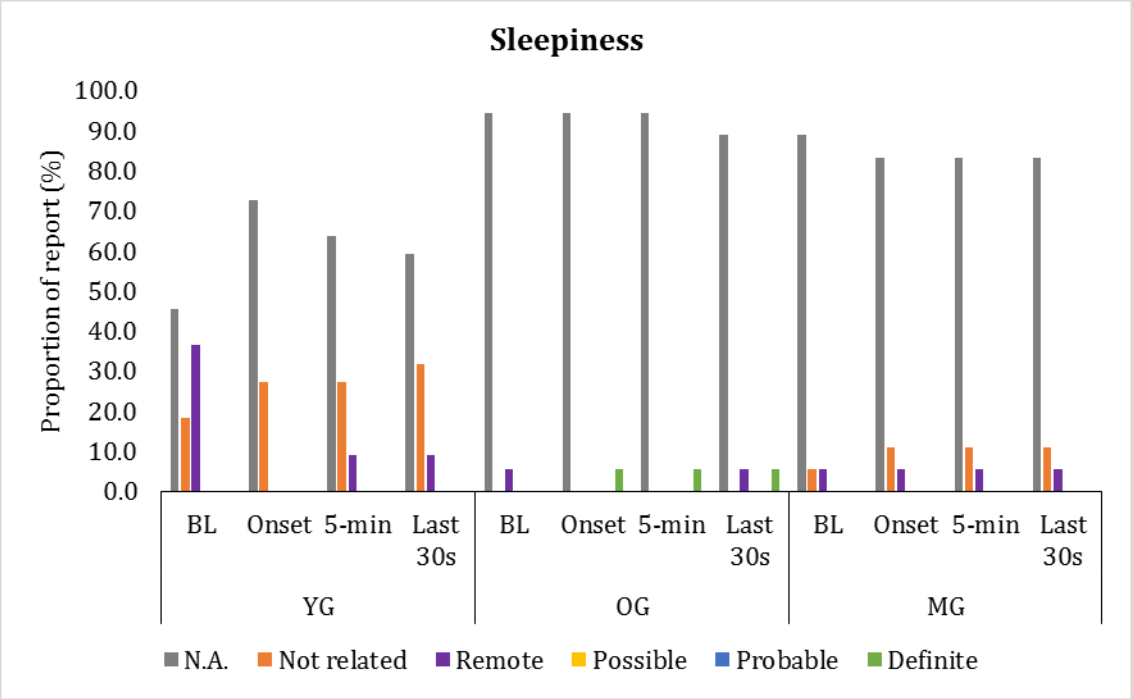


Figure 4.7. Subjective perception of the extent that the experienced sleepiness were related to HD-tDCS.
Note. N.A. denotes the proportion of participants not reporting the specified symptoms. BL denotes the perception of the specified symptom before stimulation. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

4.9.3. Differences in intensity rating of symptoms: Tingling, itching and sleepiness

The intensitiy rating of tingling, itching and sleepiness, being the three most frequently reported symptoms during stimulation, were next further compared among the groups using Kruskal-Willis test.

The mean rating of tingling, itching and sleepiness by the three groups of participants during stimulation is presented in Table 4.3.

Table 4.3. Ratings of tingling, itching and sleepiness during stimulation.

Rating of symptoms		YG		OG		MG	
Symptoms	**Occasions**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	Onset	2.05	0.72	2.11	0.83	1.56	0.62
	5-min	1.68	0.48	1.83	0.62	1.50	0.51
	Last 30s	1.41	0.50	1.67	0.69	1.28	0.46
	Onset	1.95	0.95	1.83	0.86	1.33	0.77
	5-min	1.64	0.66	1.78	0.81	1.28	0.46
	Last 30s	1.41	0.50	1.50	0.62	1.11	0.32
	Onset	1.27	0.46	1.06	0.24	1.28	0.75
	5-min	1.36	0.49	1.06	0.24	1.22	0.55
	Last 30s	1.41	0.50	1.11	0.32	1.22	0.55

Note. Rating on a 4-point scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe. YG = younger participant group; OG = older participant group; MG = participant with MCI group.

4.9.4. Between-group differences

The Kruskal-Wallis test revealed group difference in itching at stimulation onset (H = 7.32, p = .026) and a trend of group difference at last 30s of stimulation (H = 5.63, p = .060). Post hoc comparisons were performed using Mann-Whitney test to examine the difference in itching experience between YG and OG, and between OG and MG groups respectively at stimulation onset and last 30s of stimulation. There was no significant group difference in the itching experience between YG and OG (all ps > .05). There was significant difference in itching experience at stimulation onset between OG and MG groups (U = 99.50, p = .047; 1.83 ± 0.86 vs. 1.33 ± 0.77) where the OG rated the itching higher than the MG (Figure 4.8), but there was no significant group difference in the experience of itching at last 30s of stimulation (U = 107.00, p = .085; 1.50 ± 0.62 vs. 1.11 ± 0.32).

The Kruskal-Wallis test also revealed a marginally significant group difference in tingling at stimulation onset (H = 5.93, p = .052). Post hoc comparisons using Mann-Whitney test to examine the group difference in tingling experienced revealed no group difference between YG and OG (all ps > .05) but there was a marginal group difference between OG and MG in the tingling experience at stimulation onset (U = 101.00, p = .055; 1.67 ± 0.69 vs. 1.28 ± 0.46) such that OG rated higher tingling sensation than MG as illustrated in Figure 4.8.

4.9.5. Within-group differences

Next, the differences in the rating of each of the three symptoms at the three occasions within each group were examined respectively using Wilcoxon Signed Ranks test with Bonferroni-adjusted critical p-value set at 0.017. The YG rated tingling lower during the last 30s of stimulation than at onset (Z = -3.50, p < .001; 2.05 ± 0.72 vs. 1.41 ± 0.50) and at 5-minutes into stimulation (Z = -2.45, p = .014, 1.68 ± 0.48 vs. 1.41 ± 0.50); they rated itching lower during the last 30s of stimulation than at onset (Z = -2.76, p = .006; 1.95 ± 0.95 vs. 1.41 ± 0.50). The OG only rated itching lower during the last 30s than at onset (Z = -2.45, p = .014; 1.83 ± 0.86 vs. 1.50 ± 0.62) as illustrated in Figure 4.8. The MG did not differ significantly in their rating on any of the three symptoms across the occasions (all ps > .017).

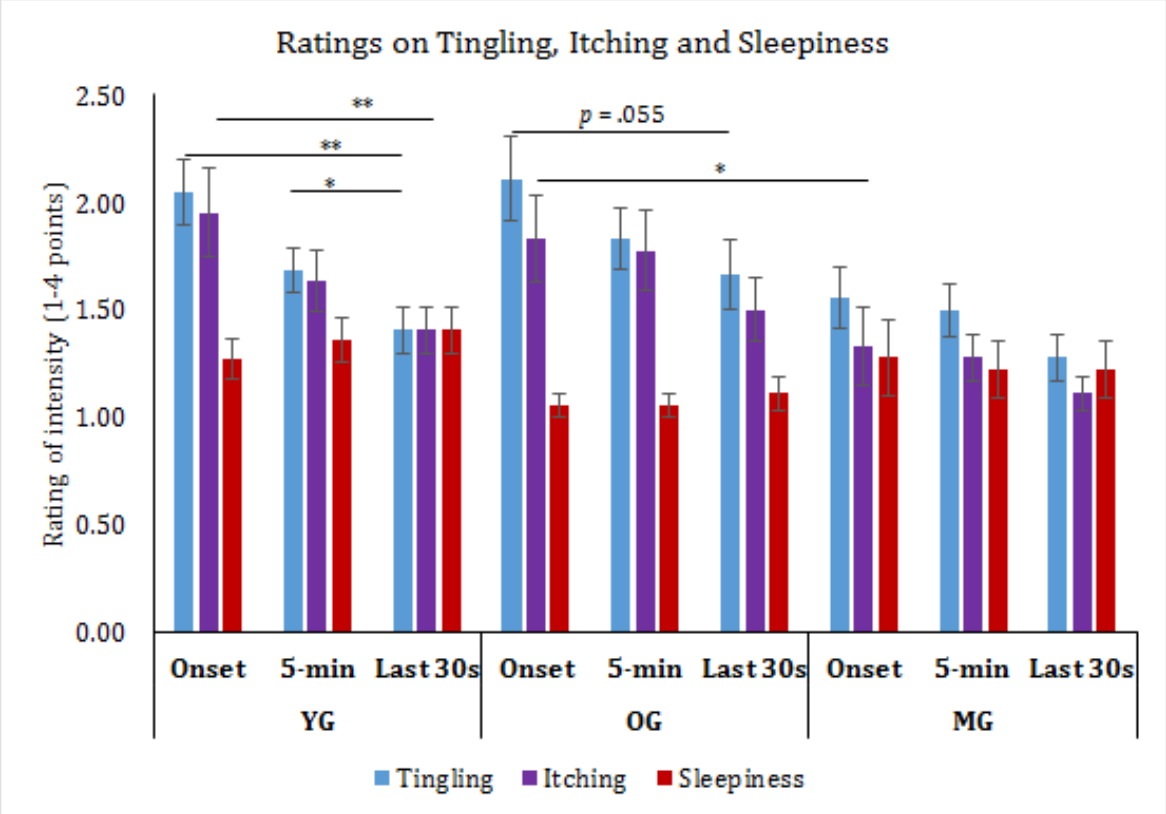


Figure 4.8. Differences in ratings on tingling, itching and sleepiness.
Note. YG = younger participant group; OG = older participant group; MG = participant with MCI group. ** p < .01, *p < .05, two-tailed. Error bar denotes ± 1 standard error.

CHAPTER 5 RESULTS

This chapter reports the results of the two studies in separate sections: Study One is comparing between the younger participants (YG) and the healthy older participants (OG); Study Two compares between the healthy older participants (OG) and the MCI participants (MG).

Each section is structured to report the following sequence: demographic information, behavioural results, ERP results, and time-frequency analysis. In the section for Study Two, results from the Montreal Cognitive Assessment Hong Kong version and CERAD-NAB Chinese-Cantonese version are reported together with demographic information. The outcome of the adverse effects questionnaire is reported at the end of the chapter.

5.1. STUDY ONE: YG VERSUS OG

5.1.1. Behavioural results

The behavioural performance in the two-back task of the YG (n = 22) and the OG (n = 18) is presented in Table 5.1. A three-way ANOVA was performed to investigate the effects of the within-subject factors of Stimulation (Pre vs. Post) and Type (Target vs. Non-target), and the between-subject factor of Age (YG vs. OG) on the accuracy rate and response time (RT) respectively. A target trial is one where the currently-presented stimulus matches the stimulus presented two trials ago whereas a non-target trial is one where the two stimuli mismatch.

5.1.1.1. *Accuracy*

The Stimulation effect was significant ($F(1,38) = 10.13$, $p = .003$, 88.63% vs. 90.70%), indicating general increases in the accuracy rate of identifying targets and non-targets across all groups. The Type effect was also significant ($F(1,38) = 5.65$, $p = .023$; 91.34% vs. 88.00%) whereby the accuracy rate was higher in the non-target than the target trials. The Age effect was marginally significant ($F(1,38) = 3.08$, $p = .087$; YG = 91.19% vs. OG = 88.14%), showing a trend of higher accuracy rate in the YG than OG.

The Stimulation x Type effect ($F(1,38) = 3.23$, $p = .080$) was marginally significant. Post-hoc analysis showed that the accuracy rate on non-target trials improved after the stimulation (89.60% vs. 93.08%, $p < .001$), but no difference in the

accuracy rates on the target trials was revealed after the stimulation (87.66% vs. 88.31%, p = .590) (Figure 5.1).

Type x Age effect was found significant (F(1,38) = 7.39, p = .010). The YG had significantly higher accuracy rate in the non-target than the target trials (94.79% vs. 87.59%, p = .001), which was not the case in the OG (87.90% vs. 88.38%, p = .819). The Stimulation x Age (F(1,38) = 1.34, p = .254) and Age x Stimulation x Type effects (F(1,38) = 0.52, p = .475) were not significant.

In summary, the accuracy for the two-back task generally improved in both the YG and OG after the HD-tDCS stimulation.

Table 5.1. Behavioural performance of the two-back task by YG and OG.

		Accuracy rate (%)				Response time (ms)			
Behavioural measures		**Pre-stimulation**		**Post-Stimulation**		**Pre-stimulation**		**Post-stimulation**	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	YG (n=22)	91.87	5.56	93.48	4.55	606.97	155.61	543.90	156.38
	OG (n=18)	86.31	8.20	89.96	6.43	878.86	191.60	792.11	163.82
	YG (n=22)	93.71	6.51	95.87	3.93	613.60	162.13	540.32	153.18
	OG (n=18)	85.50	11.02	90.30	8.41	907.57	205.36	807.92	177.91
	YG (n=22)	87.36	7.38	87.83	8.42	588.76	152.45	552.72	174.91
	OG (n=18)	87.96	8.37	88.80	6.90	815.76	191.41	757.95	168.40

Note. YG = Younger participant group; OG = Older participant group. SD = standard deviation.

5.1.1.2. *Response Time*

Next, the same ANOVA model was applied to analyse the response time data. The Stimulation effect (F(1,38) = 16.62, p < .001) was found significant whereby RT generally was faster after the stimulation (731.42 ms vs. 664.73 ms) (Figure 5.2). The Type effect was also found significant (F(1,38) = 7.22, p = .011), indicating that the RTs

for the non-target trials were slower than those for the target trials (717.35 ms vs. 678.80 ms). The Age effect was also significant ($F(1,38) = 24.87$, $p < .001$) such that the YG generally performed faster than the OG (573.85 ms vs. 822.30 ms).

The Type x Age effect was found significant ($F(1,38) = 5.08$, $p = .030$). Post-hoc analysis showed that the RT on the non-target trials was slower than that on the target trials in the OG (857.74 ms vs. 786.86 ms, $p = .002$) which was not the case for the YG (576.96 ms vs. 570.74 ms, $p = .748$).

The Stimulation x Type effect was significant ($F(1,38) = 6.75$, $p = .013$). Post-hoc analysis showed that, before the stimulation, the RT on the non-target trials was slower than that of the target trials (760.58 ms vs. 702.26 ms, $p = .001$). But the RTs on the non-target and target trials were not significantly differed after stimulation (674.12 ms vs. 655.33 ms, $p = .253$). The Stimulation x Age ($F(1,38) = 0.54$, $p = .466$) and the Age x Stimulation x Type effects ($F(1,38) = 0.02$, $p = .881$) were not statistically significant.

Overall, the YG showed a trend of higher accuracy than the OG and a significantly faster response time than the OG. The accuracy was improved and the response time was faster in both YG and OG after the HD-tDCS stimulation.

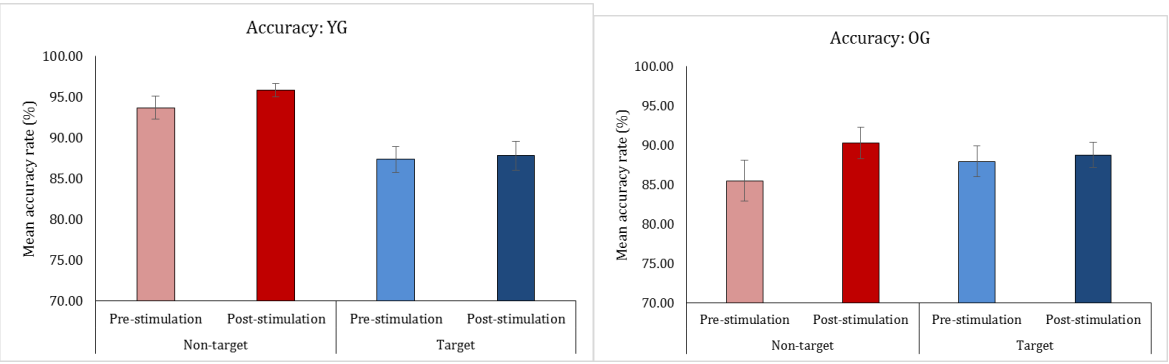


Figure 5.1. Measures of accuracy rate in the YG (left) and OG (right).
YG = Younger participant group; OG = Older participant group. Error bar = ±1 standard error of mean.

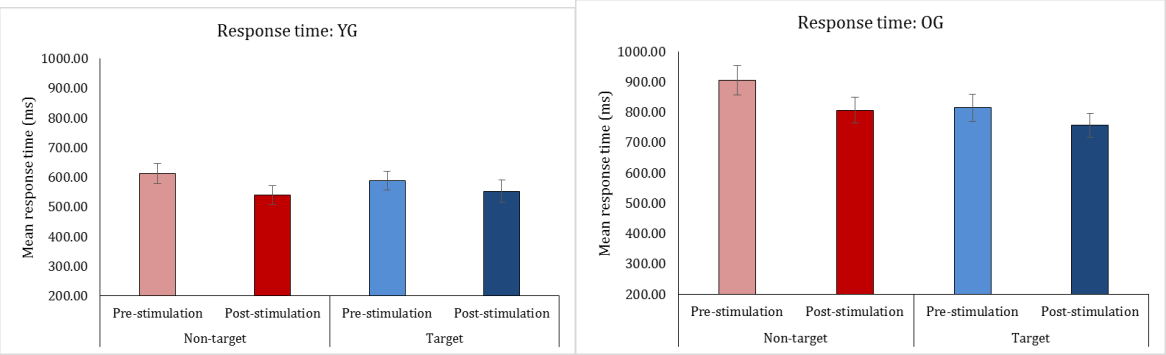


Figure 5.2. Measures of response time in the YG (left) and OG (right).
YG = younger participant group; OG = older participant group. Error bar = ±1 standard error of mean.

5.1.2. ERP components verification

Independent Component Analysis (ICA) was performed to verify the components of interest (N200, P300) and the corresponding time-windows. The ICA-components with corresponding scalp topography that had signal-to-noise ratio (SNR) more than 1.0 in the target and non-target trials before and after the participants receiving HD-tDCS stimulation in the YG and OG are shown in Figure 5.3 and 5.4 respectively. The epoch of signals extracted were within the -200 ms to 1000 ms time-window relative to stimulus onset.

The ICA-component identified as N200 in the YG was characterized by the anterior negativity that peaked around 250 ms, which accounted for 11.1% (target trials) and 10.1% (non-target trials) of the total variance. The ICA-component identified as P300 was characterized by the posterior positivity with maximal peak occurred approximately at 350 ms after stimulus onset, which accounted for 19.9% (target trials) and 13.6% (non-target trials) of the total variance (Figure 5.3).

In the OG, the ICA-component identified as N200 was characterized by the fronto-central negativity that peaked at around 240 ms, which accounted for 8.4% (target trials) and 12.1% (non-target trials) of the total variance (Figure 5.4). The P300 was characterized by the posterior positivity that peaked around 430 - 450 ms, which explained 10.0% and 8.5% of the total variance for the target and non-target trials respectively.

Considering the time-windows of the two ERP components of interest from the visual inspection of grand-average ERP of both groups (Figure 5.5) as well as the ICA results, the N200 amplitude can be obtained from the area under the curve within the

200 - 300 ms time-window after the stimulus onset in YG. In contrast, the N200 amplitudes were obtained within the 250 - 350 ms time-window in OG. Similarly, the amplitudes of the P300 were obtained from the area under the curve within the 300 - 450 ms time-window in YG and within the 350 - 500 ms time-window in OG.

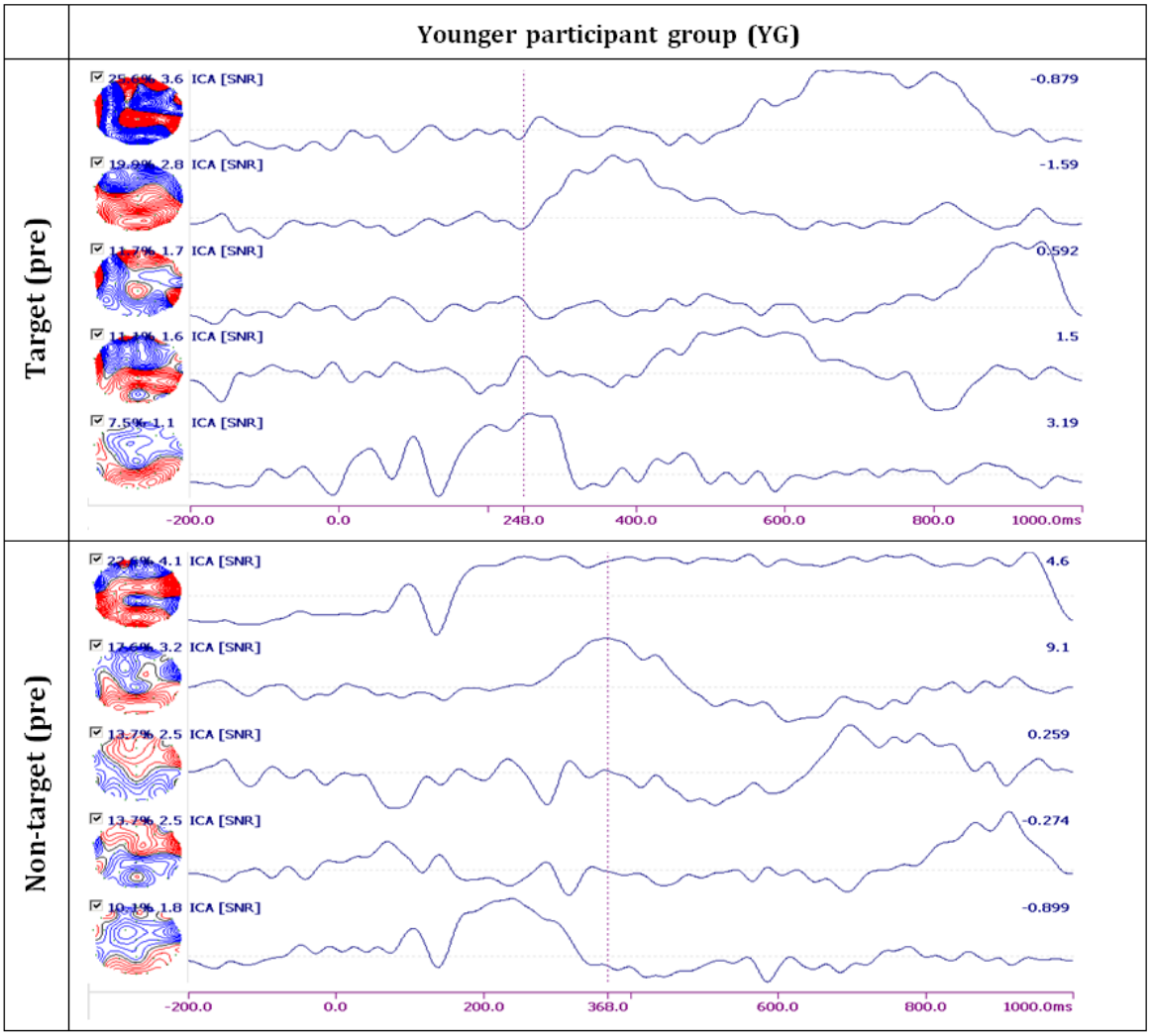


Figure 5.3. Independent component analysis (ICA) in younger participant group (YG). ICA-components for target (top) and non-target trials (bottom) before stimulation. In both target (top) and non-target (bottom) trials, ICA-component #2 was identified as P300, characterized by posterior positivity that peaked around 350 ms; component #5 was identified as N200, characterized by anterior negativity peaking at 250 ms.

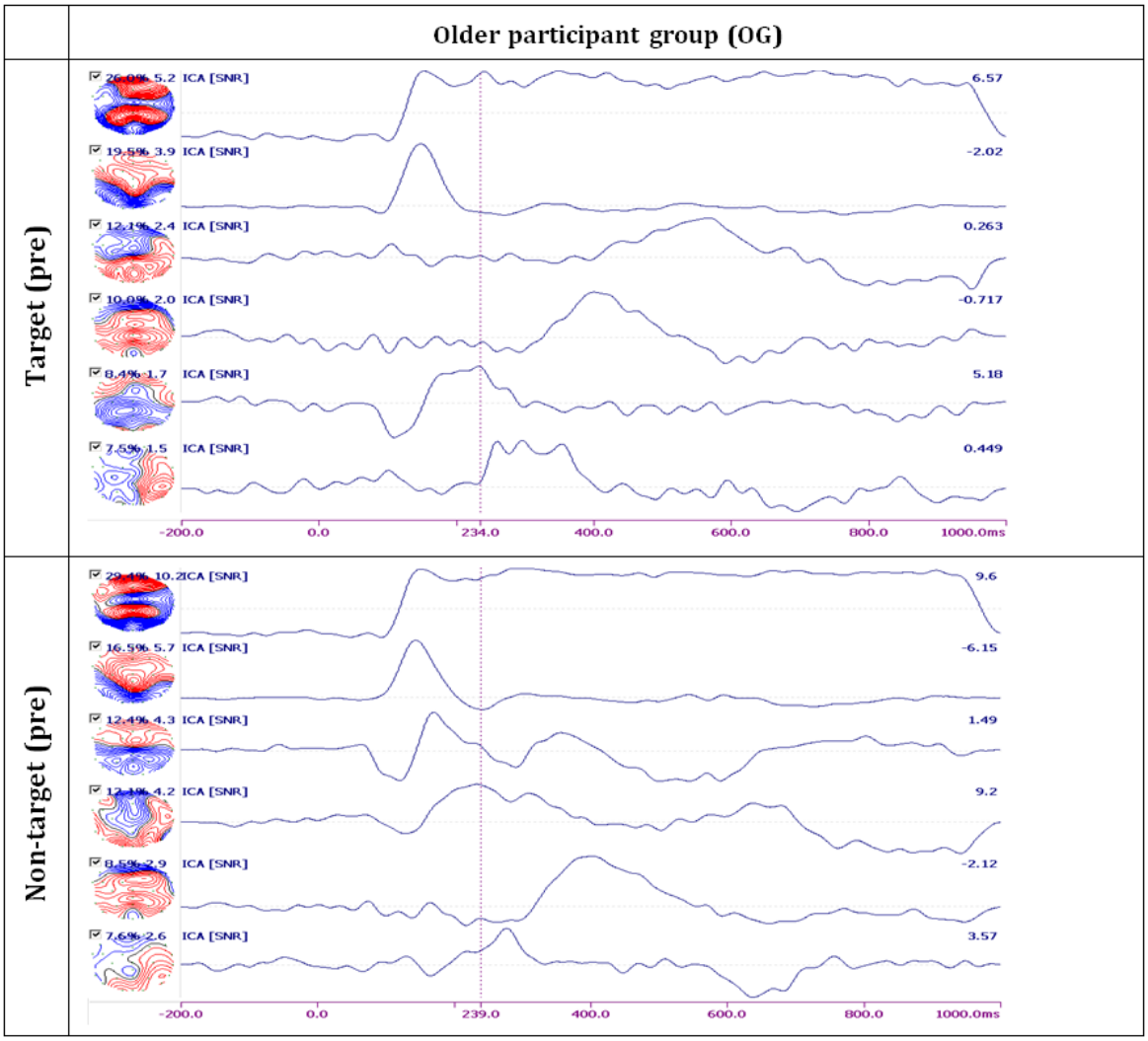


Figure 5.4. Independent component analysis (ICA) in older participant group (OG). ICA-components for target (top) and non-target trials (bottom) before stimulation. Top panel: ICA-component #4 was identified as P300 with posterior positivity that peaked around 430 ms; ICA-component #5 identified as N200 with anterior negativity that peaked around 200 - 230 ms. Bottom panel: ICA-component #4 was identified as N200 with anterior negativity that peaked around 240 ms whereas ICA-component #5 was identified as P300 that peaked around 400 ms after stimulus onset, characterized by posterior positivity.

5.1.3. ERP results

The amplitude and latency of the ERP data were analyzed to examine the electrophysiological changes during the task taking processes before and after the HD-tDCS. The ERP grand averaged waveforms for YG and OG on non-target and target trials recorded at Fz and F7 are presented in Figure 5.5. The N200 (250 – 300 ms after stimulus onset) elicited from Fz was analysed as it was previously found to associate with the match-mismatch process (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Patel & Azzam, 2005). It was also of interest to analyse the ERP signals elicited from F7 as it was proximal to the stimulation site. The component analysed at F7 was P300 (300 – 400 ms after stimulus onset) which was reported to relate to the attentional allocation process, inclusive of maintaining the content in the working memory (Gajewski & Falkenstein, 2014; Keeser et al., 2011; Polich, 2007; Saliasi et al., 2013). The three-way repeated-measure ANOVA model for analysing N200 at Fz and P300 at F7 had a between-subject factor of Age (YG vs. OG), and two within-subject factors of Stimulation (Pre vs. Post) and Type (Non-target vs. Target).

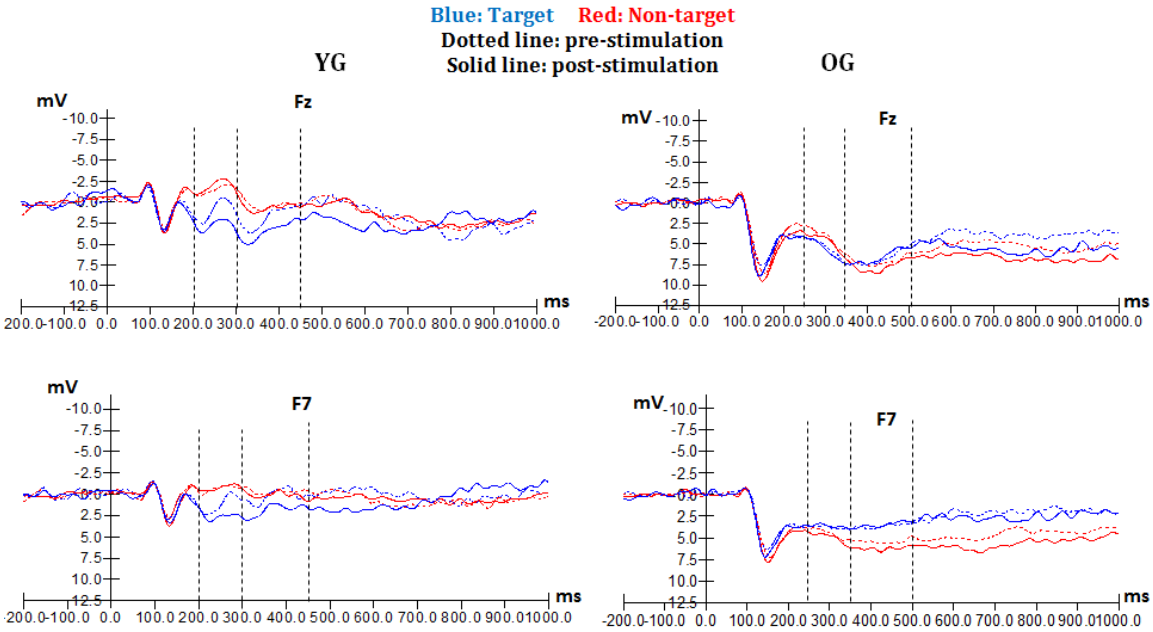


Figure 5.5. Grand averaged waveforms recorded at Fz and F7 in YG and OG.
YG = younger participant group; OG = older participant group. Time-windows for N200 and P300 in each group were indicated (YG: N200 = 200 - 300 ms, P300 = 300 - 450 ms; OG: N200 = 250 - 350 ms, P300 = 350 - 500 ms).

5.1.3.1. *N200 amplitude*

The Type effect was significant on the N200 amplitudes elicited at Fz ($F(1,38) = 21.27$, $p < .001$; 3.77 mV vs. 1.44 mV), whereby the amplitudes for the target trials were less negative-going than those for the non-target trials (Figure 5.6, top). The Age effect on the N200 amplitudes at Fz was also significant ($F(1,38) = 17.42$, $p < .001$; 5.10 mV vs. 0.11 mV), indicating that the amplitudes for the OG were less negative-going than those for the YG. The Stimulation effect however was not significant ($F(1,38) = 2.75$, $p = .105$). Notably, the Type x Stimulation x Age effect was marginally significant ($F(1,38) = 3.27$, $p = .079$). Comparisons between the N200 amplitudes elicited at Fz before and after the tDCS stimulation were conducted at different levels of Age and Type. In the YG, the N200 amplitude for the target trials became significantly less negative-going after the stimulation (1.00 mV vs. 2.80 mV, $p = .032$; Figure 5.6, top). However, the N200 amplitudes for the non-target trials showed no significant change after the stimulation (-1.44 mV vs. -1.90 mV, $p = .263$). In the OG , no post-stimulation significant change in the N200 amplitudes was found for both the non-target (4.28 mV vs. 4.81 mV, $p = .241$) and target (5.54 mV vs. 5.76 mV, $p = .808$) trials. These results suggested that the amplitudes of N200 elicited at Fz for the target trials were modulated by the electrical stimulation only among the younger participants whereas the amplitudes of N200 in the older participants did not show the responses as among their younger counterpart.

No other interaction effects were found significant except the Type x Age effect ($F(1,38) = 5.94$, $p = .020$). In the YG, the amplitudes of N200 at Fz were more negative-going for the non-target than target trials (-1.67 mV vs. 1.90 mV, $p < .001$); and such difference was not observed in the OG (4.55 mV vs. 5.65 mV, $p = .151$).

The less negative N200 for target in YG after stimulation resulted in a smaller value for non-target-minus-target N200 amplitude. When correlated with the behavioural results, smaller differences in the non-target-minus-target N200 amplitude at Fz were significantly related to faster correct RTs ($r = .445$, $p = .038$), non-target RT ($r = .434$, $p = .044$), and target RT ($r = .439$, $p = .041$) in the YG after the stimulation. In other words, targets which originally elicited smaller N200 relative to non-targets had now elicited an even smaller N200 and faster response time in YG. The significant relationships were not observed in the OG after the stimulation ($r = -.093$, $p = .715$) (Figure 5.6, bottom).

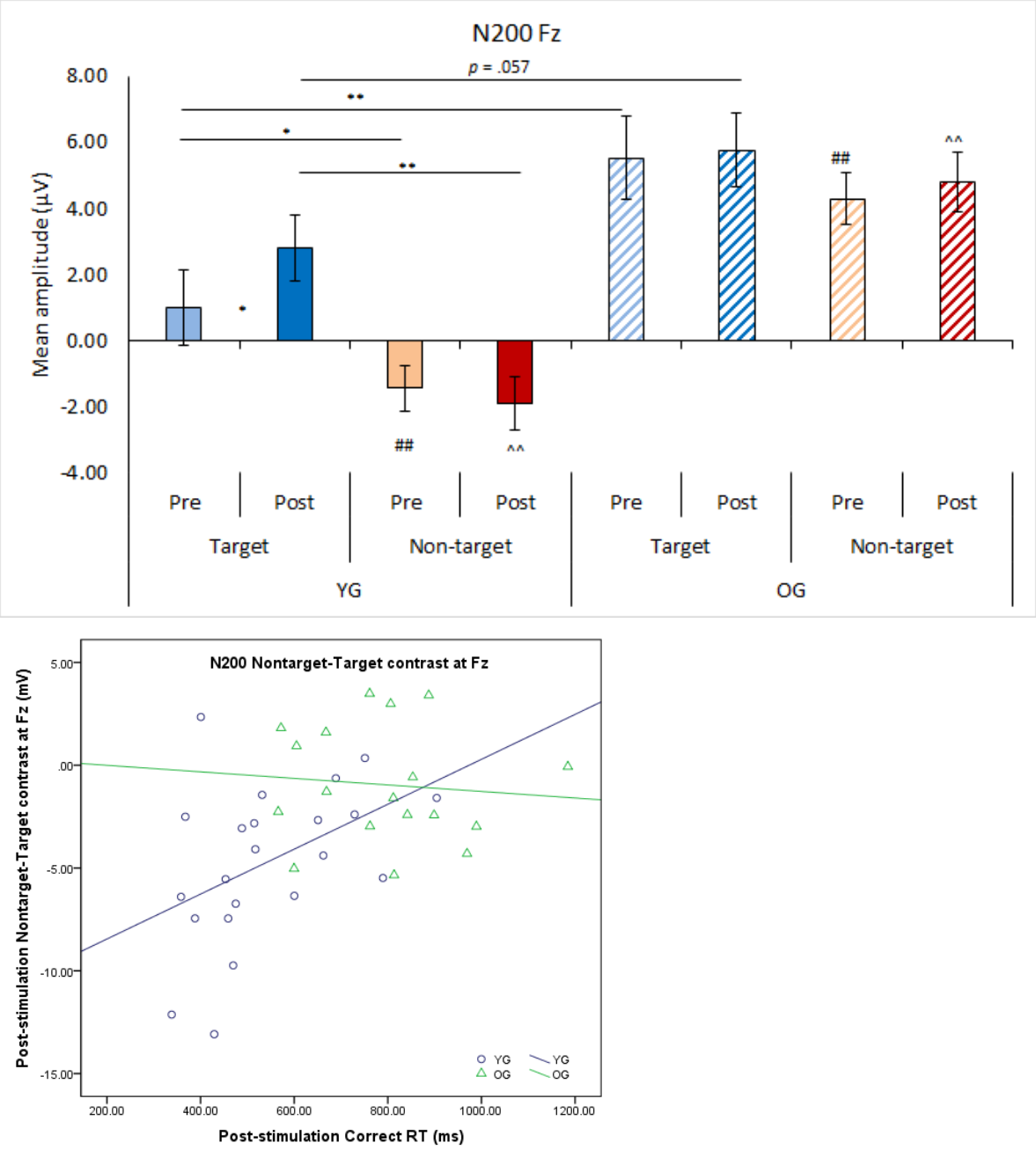


Figure 5.6. N200 amplitude at Fz in YG and OG.
Top: Post-hoc comparisons for the N200 amplitudes recorded at Fz showed that the amplitudes of N200 for the target trials in younger participant group (YG) became less negative-going after stimulation and widened the nontarget-target contrast. Bottom: The N200 non-target-target contrasts at Fz correlated positively with the response times in YG after stimulation (r = .445, p = .038) whereas no significant correlations were revealed in the older participant group (OG) (r = -.093, p = .715). ** p-value < .01; * p-value < .05, two-tailed. Error bar = ±1 standard error of mean. ## and ^^ = pairs of comparison that were significantly different.

The same ANOVA models applied to the N200 amplitude recorded at F7. The results revealed were rather similar to those for the Fz. The Type effect on the

amplitudes of N200 elicited at F7 was marginally significant (F(1,38) = 3.81, p = .058; 2.86 mV vs. 2.06 mV), such that the amplitudes elicited by the target trials was less negative-going than those elicited by the non-target trials. The Age effect was significant (F(1,38) = 14.01, p = .001; 0.61 mV vs. 4.30 mV), that the amplitudes at F7 in OG was less negative-going than those in YG. The Stimulation effect however was not significant (F(1,38) = 2.42, p = .128). Similar to the N200 elicited at Fz, the Age x Stimulation x Type effect was found to be marginally significant (F(1,38) = 3.40, p = .073). In the YG, the N200 amplitude elicited at F7 for the target trials became significantly less negative-going after the stimulation (1.23 mV vs. 2.62 mV, p = .031) whereas those for the non-target trials showed no significant change (-0.66 mV vs. -0.77 mV, p =.792). In the OG, no significant change after the stimulation in the N200 amplitude at F7 was found in both the non-target (4.58 mV vs. 5.06 mV, p = .276) and target (3.85 mV vs. 3.72 mV, p = .687) trials.

Putting together, the amplitudes of the N200 elicited by the target trials recorded at Fz and F7 became less negative-going after the stimulation in the YG, of which the differences were not observed in the OG. Consequently, the larger post-stimulation non-target-minus-target N200 amplitudes at Fz was significantly associated with faster correct response in the YG.

5.1.1.1. *P300 amplitude*

The same ANOVA model was applied to test the significance of the Age, Stimulation and Type effects on the amplitudes of P300 elicited at Fz and F7. At Fz, the Age effect was significant and the , the OG had more positive-going P300 amplitudes than the YG (F(1,38) = 23.55, p < .001; 1.58 mV vs. 7.16 mV). Both the Stimulation (F(1,38) = 1.46, p = .235) and Type (F(1,38) = 1.94, p = .172) effects were not significant. The Age x Type effect was found significant (F(1,38) = 7.38, p = .010) and that the amplitudes of P300 elicited at Fz in the target trials were more positive-going than in the non-target trials for the YG (2.70 mV vs. 0.46 mV, p = .004). The differences in the YG were not observed in the OG (6.80 mV vs. 7.52 mV, p = .378). Other interaction effects did not reach statistical significance (ps > .05).

The Stimulation effect on the amplitudes of P300 elicited at F7 yielded a marginal significance (F(1,38) = 3.70, p = .062), and a trend of more positive-going P300 was observed after the stimulation (2.29 mV vs. 2.97 mV). The Age effect was also found

significant ($F(1,38) = 21.20$, $p < .001$) in that the amplitudes of P300 were more positive-going for the OG than YG (0.49 mV vs. 4.77 mV). The Type effect was not significant ($F(1,38) = 1.54$, $p = .222$).

Importantly, similar to N200 at Fz, a marginally significant Stimulation x Type x Age effect on the amplitudes of P300 at F7 were revealed ($F(1,38) = 3.03$, $p = .090$). In the YG, no significant changes in the amplitudes of P300 at F7 were observed after the stimulation for the non-target ($t(21) = 0.94$, $p = .356$) and target trials ($t(21) = 1.64$, $p = .116$) (Figure 5.7, top). In contrast, in the OG, it showed a trend of more positive-going P300 elicited at F7 after the stimulation for the non-target ($t(17) = 1.97$, $p = .066$; 5.51 mV vs. 6.29 mV) but not for the target trials ($t(17) = 0.32$, $p = .750$; 3.70 ± 3.32 mV vs. 3.58 ± 3.65 mV). Correlational analysis also indicated that after the stimulation, smaller differences in the target-minus-nontarget P300 amplitude at F7 were significantly correlated with faster correct RT ($r = .522$, $p = .026$, Figure 5.7, bottom) and target RT ($r = .554$, $p = .017$) among the OG. The post-stimulation significant relationships revealed in the OG were not observed in the YG ($r = -.179$, $p = .426$).

The Type x Age effect was found significant ($F(1,38) = 15.28$, $p < .001$). For the OG, the amplitude of P300 elicited at F7 was more positive-going in the non-target than target trials (3.64 mV vs. 5.90 mV, $p = .001$). For the YG, an opposite trend to that of the OG was observed despite it reached marginal significance, that the P300 amplitude at F7 was less positive-going for the non-target than target trials (-0.09 mV vs. 1.07 mV, $p = .054$). Other interaction effects of Age x Stimulation ($F(1,38) = 1.01$, $p = .322$) and Stimulation x Type ($F(1,38) = 0.06$, $p = .804$) did not reach statistical significance.

In summary, the P300 amplitude elicited at F7 in the non-target trials became more positive-going after stimulation in the OG but not in the YG. The smaller post-stimulation target-minus-non-target P300 amplitudes at F7 was associated with faster correct responses in the OG.

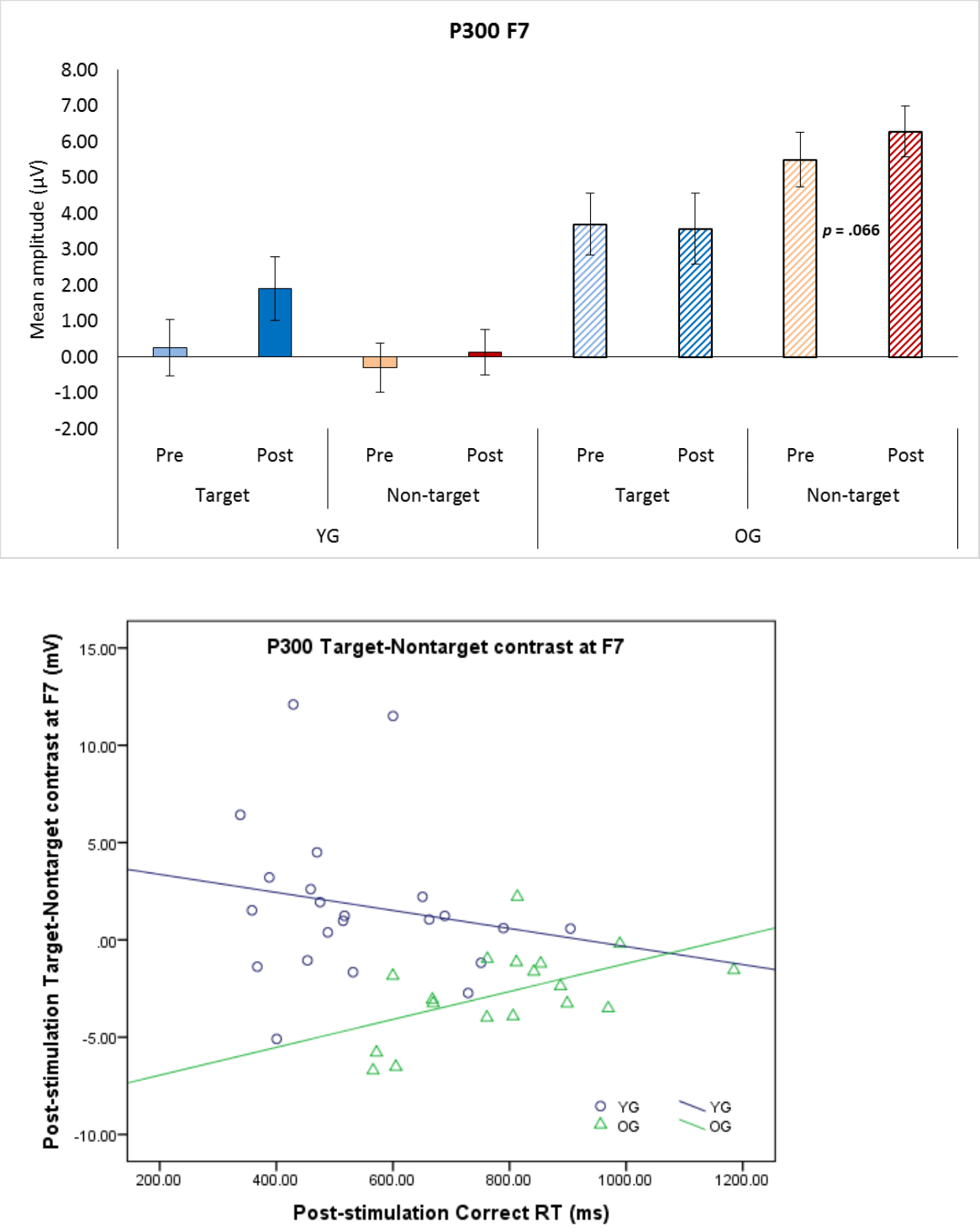


Figure 5.7. P300 amplitude at F7 in younger participant group (YG) and older participant group (OG).
Top: Mean amplitude of P300 recorded at F7 for non-target trials in OG showed a trend of increase after stimulation, thus making the target-nontarget contrasts smaller values. No change from stimulation was observed in the YG. Bottom: P300 amplitude target-nontarget contrasts at F7 correlated positively with correct RT in OG after stimulation *(r* = .522, *p* = .026) whereas no significant correlations were observed in the YG *(r* = -.179, *p* = .426). Error bar = ±1 standard error of mean.

5.1.2. ERP latency results

The latencies of the peak amplitudes of N200 and P300 were analysed using the same repeated-measure ANOVA model applied on the amplitude. Again, the peak latencies recorded at Fz and F7 were analysed respectively.

5.1.1.1. *N200 latency*

The Type effect was significant on the peak latency of N200 recorded at Fz ($F(1,38) = 5.61$, $p = .023$; 258.97 ms vs. 266.00 ms), whereby the latency in the target trials was significantly earlier than that in the non-target trials. The Age effect was also found significant ($F(1,38) = 7.29$, $p = .010$; 251.22 ms vs. 273.75 ms), where the N200 latency in OG was more delayed than the YG. The Stimulation effect did not reach statistical significance ($F(1,38) = 0.96$, $p = .333$). The Stimulation x Type effect on the N200 latency at Fz was found significant ($F(1,38) = 5.51$, $p = .024$), and the latency in the target trials was earlier after the stimulation (264.56 ms vs. 253.37 ms, $p = .034$), which was not the case for the non-target trials (264.05 ms vs. 267.94 ms, $p = .417$). Other Type x Age ($F(1,38) = 0.76$, $p = .389$) and Stimulation x Age ($F(1,38) = 1.24$, $p = .272$), as well as Age x Stimulation x Type effects ($F(1,38) = 0.47$, $p = .496$) were not statistically significant.

The Age effect on the N200 latency recorded at F7 was significant ($F(1,38) = 20.59$, $p < .001$; 248.46 ms vs. 283.14 ms), and the OG had significant delays in the latency than the YG. The Type ($F(1,38) = 0.01$, $p = .918$) and Stimulation ($F(1,38) = 2.35$, $p = .134$) effects were not significant. The Stimulation x Age effect in contrast was significant ($F(1,38) = 4.95$, $p = .032$), and that the N200 latency at F7 in YG became earlier after stimulation (255.98 ms vs. 240.93 ms, $p = .008$), which was not the case in the OG (281.75 ms vs. 284.53 ms, $p = .643$). The Stimulation x Type was also significant ($F(1,38) = 9.65$, $p = .004$), that the N200 latency at F7 in the target trials became earlier after stimulation (274.85 ms vs. 256.26 ms, $p = .007$), which was not the case for the non-target trials (262.88 ms vs. 269.21 ms, $p = .179$). The Type x Age ($F(1,38) = 1.82$, $p = .186$) and the Age x Stimulation x Type interactions ($F(1,38) = 0.17$, $p = .687$) were not significant. Earlier N200 latency at F7 in the target trials was marginally correlated with faster RT on both the correct trials ($r = .268$, $p = .094$) on non-target trials ($r = .293$, $p = .066$) and after the stimulation.

In sum, the post-stimulation N200 latencies elicited in the target trials at both Fz and F7 were found to in general earlier than those before the stimulation in both YG and OG. No significant changes in the N200 latencies due to the stimulation were observed in both YG and OG for the non-target trials.

5.1.1.2. *P300 latency*

The Age effect on the P300 latency at Fz was significant ($F(1,38) = 20.00$, $p < .001$; 367.58 ms vs. 414.92 ms), and that the latency in the OG was significantly delayed relative to that of the YG. The Type effect on the latency was marginally significant ($F(1,38) = 3.54$, $p = .068$; 384.94 ms vs. 397.55 ms) whereby the P300 latency at Fz for the target trials was significantly earlier than that for the non-target trials. The Stimulation ($F(1,38) = 1.45$, $p = .237$) and all other interaction effects did not reach statistical significance (all ps > .05).

The Age effect was significant ($F(1,38) = 24.72$, $p < .001$; 364.10 ms vs. 418.25 ms) whereby the latency at F7 in the OG was significantly delayed than that of the YG The Type effect was marginally significant ($F(1,38) = 3.22$, $p = .081$; 384.00 ms vs. 398.36 ms), and the P300 peak latency at F7 for the target trials was significantly earlier than that for he non-target trials. No other significant main or interaction effects were found (all ps > .05).

5.2. STUDY TWO: OG VERSUS MG

5.2.1. Behavioural results

The behavioural performances of the two-back task by OG (n = 18) and MG (n = 18) are presented in Table 5.3. A three-way repeated-measure ANOVA was performed to investigate the effects of the within-subject factors of Stimulation (Pre vs. Post) and Type (Target vs. Non-target trial), and the between-subject factor of Group (OG vs. MG) on the accuracy rate and response time (RT) respectively.

5.2.1.1. *Accuracy*

A significant Stimulation x Group interaction ($F(1,34) = 4.54$, $p = .040$) was found where the OG improved their accuracies generally after stimulation (86.73% vs. 89.55%, $p = .012$) but there was no change in MG (84.87% vs. 84.46%, $p = .709$). The Stimulation x Type interaction was found to be marginally significant ($F(1,34) = 3.80$, $p = .060$) where the accuracy for non-target trials improved after stimulation (85.62% vs. 88.06%, $p = .004$) but not for target trials (85.97% vs. 85.95%, $p = .986$). No other significant main effect or interaction effect was found (all ps > .05).

Table 5.2. Behavioural performance of the two-back task by OG and MG.

Behavioural measures	Accuracy rate (%)				Response time (ms)			
	Pre-stimulation		Post-stimulation		Pre-stimulation		Post-stimulation	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OG (n=18)	86.31	8.20	89.96	6.43	878.86	191.60	792.11	163.82
MG (n=18)	85.21	11.57	85.04	9.99	913.06	174.29	905.57	187.98
OG (n=18)	85.50	11.02	90.30	8.41	907.57	205.36	807.92	177.91
MG (n=18)	85.75	14.34	85.82	12.63	950.33	203.30	939.19	201.77
OG (n=18)	87.96	8.37	88.80	6.90	815.76	191.41	757.95	168.40
MG (n=18)	83.98	10.19	83.11	11.51	826.83	144.90	823.29	188.43

Note. OG = older participant group; MG = participant with MCI group.

5.2.1.2. *Response time*

A significant main effect of Stimulation ($F(1,34) = 7.73$, $p = .009$; 875.12 ms vs. 832.09 ms) was found and the response time was generally faster after stimulation, and the main effect of Type was significant where the response time on non-target trials was slower than on target trials ($F(1,34) = 19.01$, $p < .001$; 901.25 ms vs. 805.96 ms). The Stimulation x Group interaction was significant ($F(1,34) = 5.32$, $p = .027$), indicating that OG improved their response time generally after stimulation (861.67 ms vs. 782.93

ms, p = .001) whereas MG had no change in their response time (888.58 ms vs. 881.24 ms, p = .739). No other significant main effect or interaction effect was found (all ps > .05).

In sum, it was observed that the OG had faster RT and were more accurate after stimulation but there was no change observed in MG behaviourally.

5.2.2. ERP components verification

Independent component analysis (ICA) was similarly performed to verify the components of interest (N200, P300) and the corresponding time-windows. The ICA-components with corresponding scalp topography that had signal-to-noise ratio (SNR) more than 1.0 in target and non-target trials before stimulation were shown in Figure 5.14 (MG) and Figure 5.15 (OG) before and after stimulation within the epoch from -200 ms to 1000 ms relative to stimulus onset.

The ICA-component identified as N200 in the MG was characterized by frontocentral negativity that peaked within a range of approximately 245 – 330 ms and accounting for 10.2% (target trials) and 18.7% (non-target trials) of the variance; whereas the ICA-component identified as P300 was characterized by posterior positivity with maximal peak occurring approximately at 450 ms after stimulus onset and accounting for 13.0% (target trials) and 12.0% (non-target trials) of the variance (Figure 5.14).

Reiterating the components identified in the OG, the ICA-component characterized by fronto-central negativity that peaked around 240 ms and accounting for 8.4% (target trials) and 12.1% (non-target trials) of the variance was identified as N200. P300 was characterized by posterior positivity that peaked around 430 - 450 ms and explained 10.0% and 8.5% of the variance in target and non-target trials respectively (Figure 5.15).

Considering the time-windows of the two ERP components of interest from the visual inspection of grand-average ERP of both groups as well as the ICA outcome together, N200 amplitude was obtained by area under the curve from 250 - 350 ms and P300 amplitude was area under the curve from 350 - 500 ms in both OG and MG.

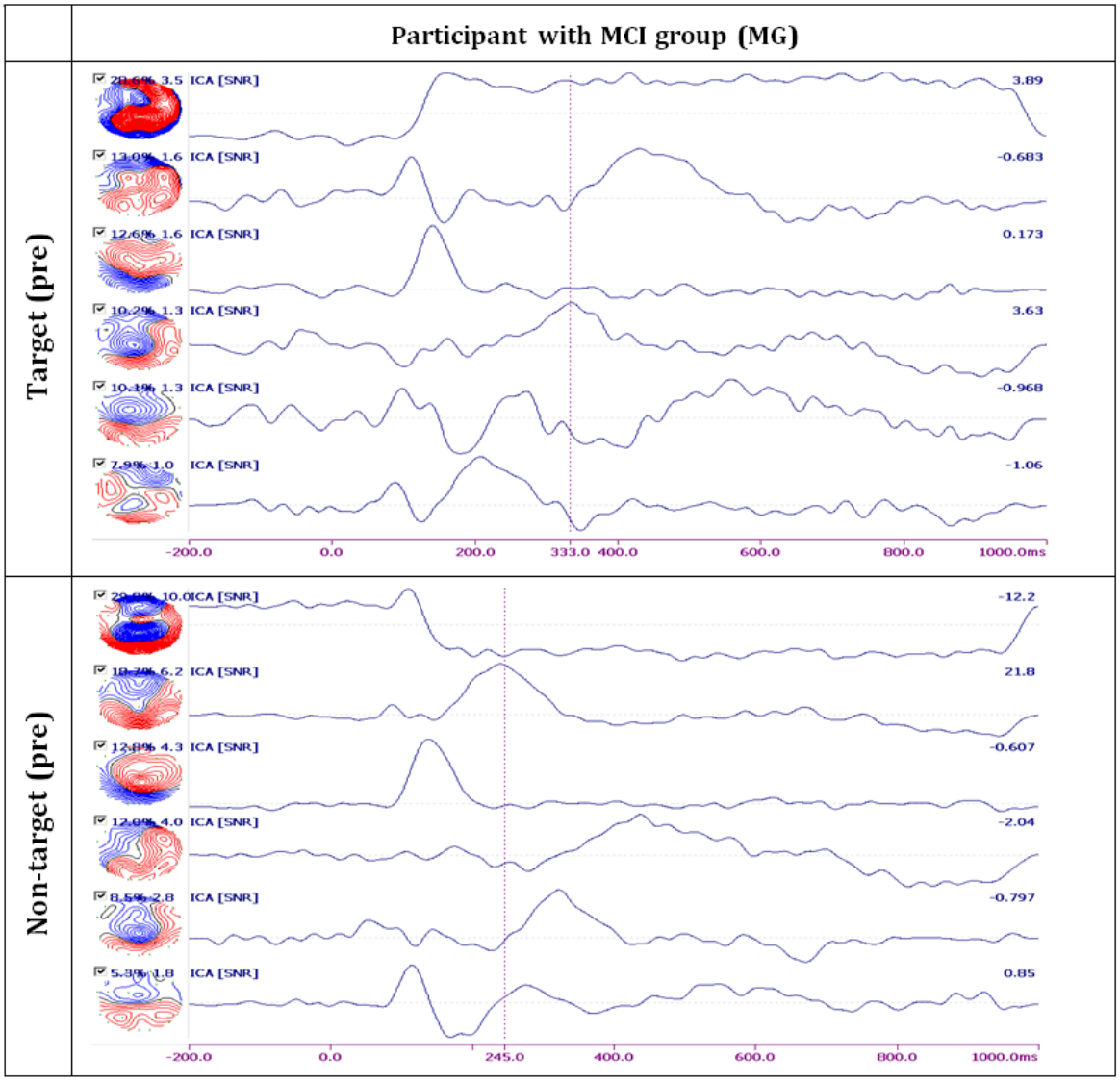


Figure 5.8. Independent component analysis (ICA) in participant with MCI group (MG). ICA-components of MG for target (top) and non-target trials (bottom) before stimulation. Top panel: In target trials, ICA-component #2 was identified as P300, characterized by posterior positivity that peaked around 450 ms; component #4 was identified as N200, characterized by anterior negativity peaking at 330 ms. In non-target trials (bottom), ICA-component #4 and #2 were identified as P300 and N200 respectively.

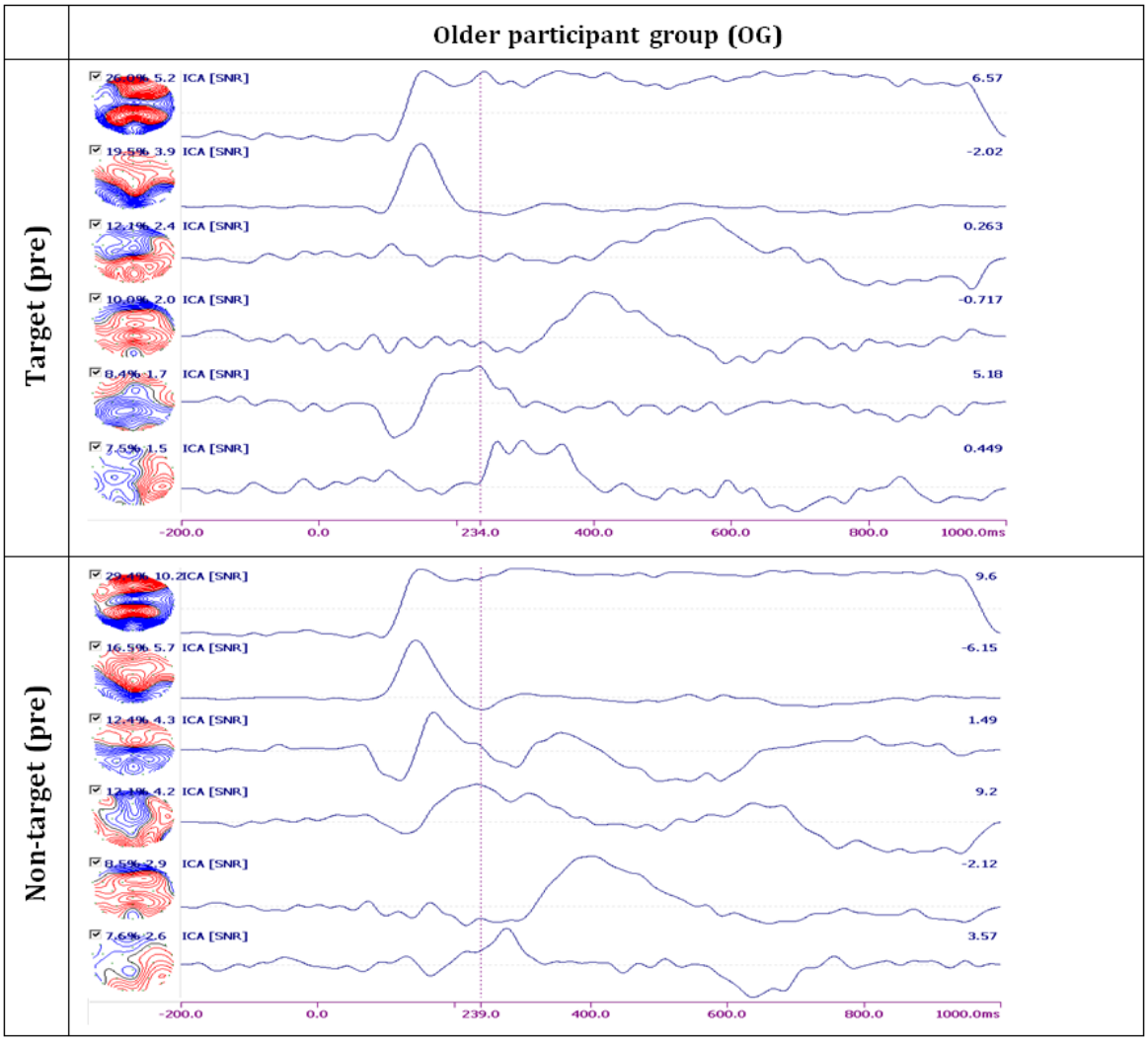


Figure 5.9. Independent component analysis (ICA) in older participant group (OG). ICA-components of OG for target (top) and non-target trials (bottom) before stimulation. Top panel: In target trials (top), ICA-component #4 and #5 were identified as P300 and N200 respectively. In non-target trials (bottom), ICA-component #4 and #5 was identified as N200 and P300 respectively.

5.2.3. ERP amplitude results

The ERP grand averaged waveforms for OG and MG participants on non-target and target trials recorded at channels Fz and F7 are presented in Figure 5.16. The amplitudes and latencies of N200 and P300 recorded at Fz and F7 were analysed with three-way repeated-measure ANOVA using the between-subject factor of Group (OG vs. MG), and the within-subject factors of Stimulation (Pre vs. Post) and Type (Non-target vs. Target).

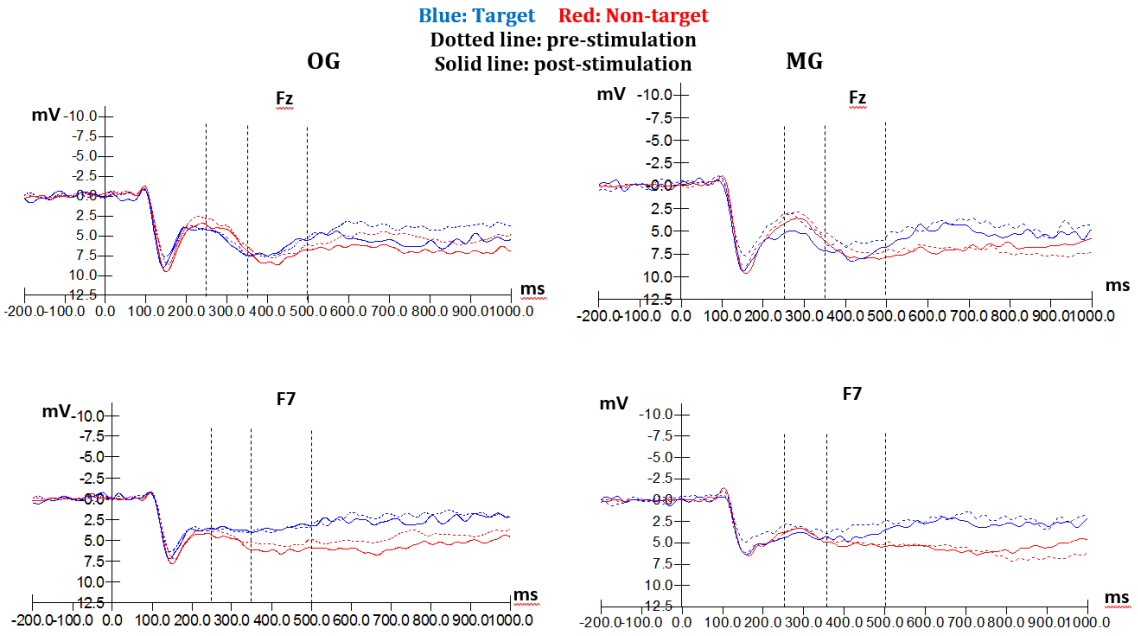


Figure 5.10. Grand averaged waveforms recorded at Fz and F7 in OG and MG. Time-windows for N200 (250 - 350 ms) and P300 (350 - 500 ms) were indicated. OG = older participant group; MG = participant with MCI group.

5.2.3.1. *N200 amplitude*

The main effect of Stimulation was significant on N200 amplitude elicited at Fz ($F(1,34) = 7.98$, $p = .008$; 4.45 mV vs. 5.19 mV) whereby N200 became less negative-going generally after stimulation. The main effect of Type was also significant ($F(1, 34) = 5.77$, $p = .022$; 5.32 mV vs. 4.31 mV) such that N200 for non-target trials was more negative than for target trials. No other significant main effect or interaction effect was found (all *p*s > .05).

The three-way interaction of Stimulation x Type x Group on N200 amplitude recorded at F7 was marginally significant ($F(1,34) = 2.96$, $p = .094$) indicating that N200 for non-target was less negative-going than target trials after stimulation in OG (5.06

mV vs. 3.72 mV, p = .021) but there was no such difference before stimulation in OG (4.58 mV vs. 3.85 mV, p = .268) and in MG (all ps > .05). No other significant main effect or interaction effect was found (all ps > .05).

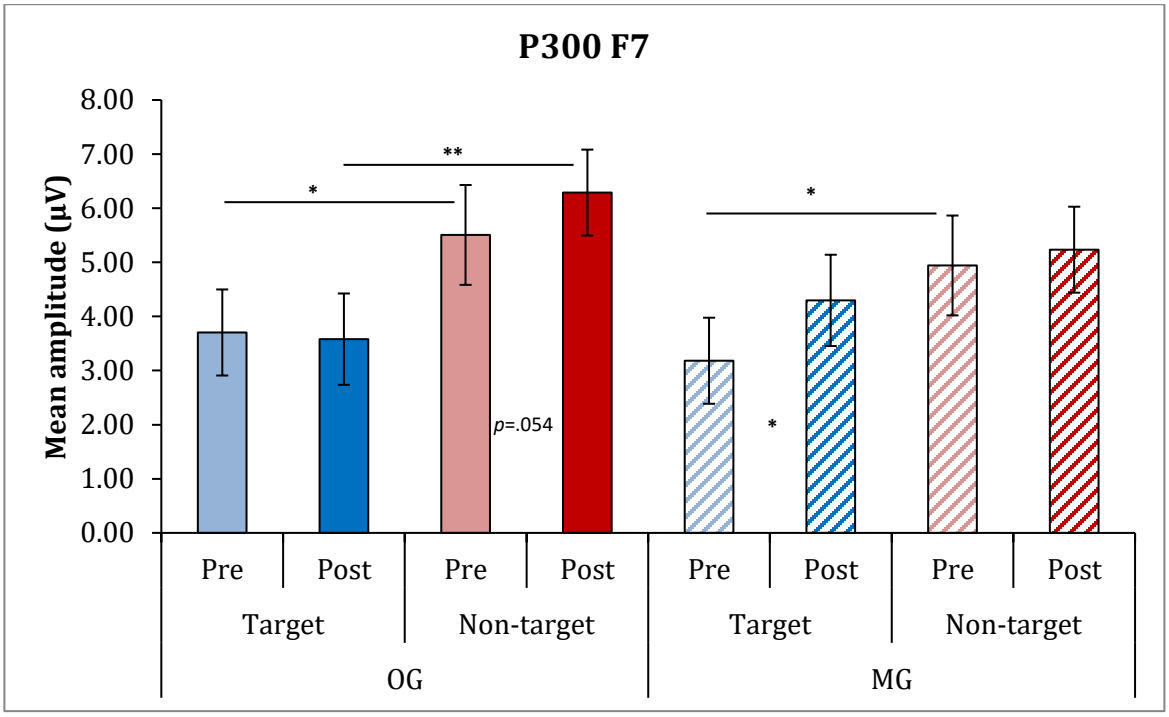
5.2.3.2. *P300 amplitude*

The main effect of Stimulation on P300 amplitude recorded at Fz was marginally significant (F(1,34) = 3.80, p = .060; 6.81 mV vs. 7.43 mV) such that the P300 amplitude was generally higher after stimulation. No other significant main effects or interaction effect was found (all ps > .05).

The main effect of Stimulation on P300 amplitude recorded at F7 was marginally significant (F (1,34) = 4.08, p = .051; 4.33 mV vs. 4.85 mV), indicating a trend of higher P300 amplitude after stimulation; and the main effect of Type was significant (F(1,34) = 18.42, p < .001; 3.69 mV vs. 5.49 mV) where P300 was lower on target trials than on non-target trials. Importantly, the Stimulation x Type x Group interaction was found to be significant (F(1,34) = 4.68, p = .038) such that P300 for target increased after stimulation in MG (3.18 mV vs. 4.30 mV, p = .038) but it was P300 for non-target that showed a trend of increase after stimulation in OG (5.51 mV vs. 6.29 mV, p = .054), as illustrated in Figure 5.17a. There was no such change in the target trials in OG (p = .813) and the non-target trials in MG (p = .461) respectively after stimulation and no other significant main effect or interaction effect was found (all ps > .05).

Further analysis to determine if the difference in P300 on target and non-target trials (Target-Nontarget contrast) was related to behavioural performance revealed that a smaller value of P300 Target-Nontarget contrast arising from the increased P300 for non-target in OG was correlated with faster correct RT after stimulation (r = .52, p = .026) as shown in Figure 5.18b. In contrast, a larger Target-Nontarget contrast arising from increased P300 for target in MG was associated with poorer correct rate after stimulation (r = -.62, p = .006) as depicted in Figure 5.18c.

In sum, the analysis revealed that P300 recorded at F7 for non-target in OG was modulated after the stimulation but it was P300 for target recorded at F7 that was modulated in MG. The increased P300 for non-target in OG resulted in smaller target-nontarget contrast that was associated with faster response time after stimulation, whereas the increased P300 for target in MG resulted in a larger target-nontarget contrast that was associated with poorer accuracy.



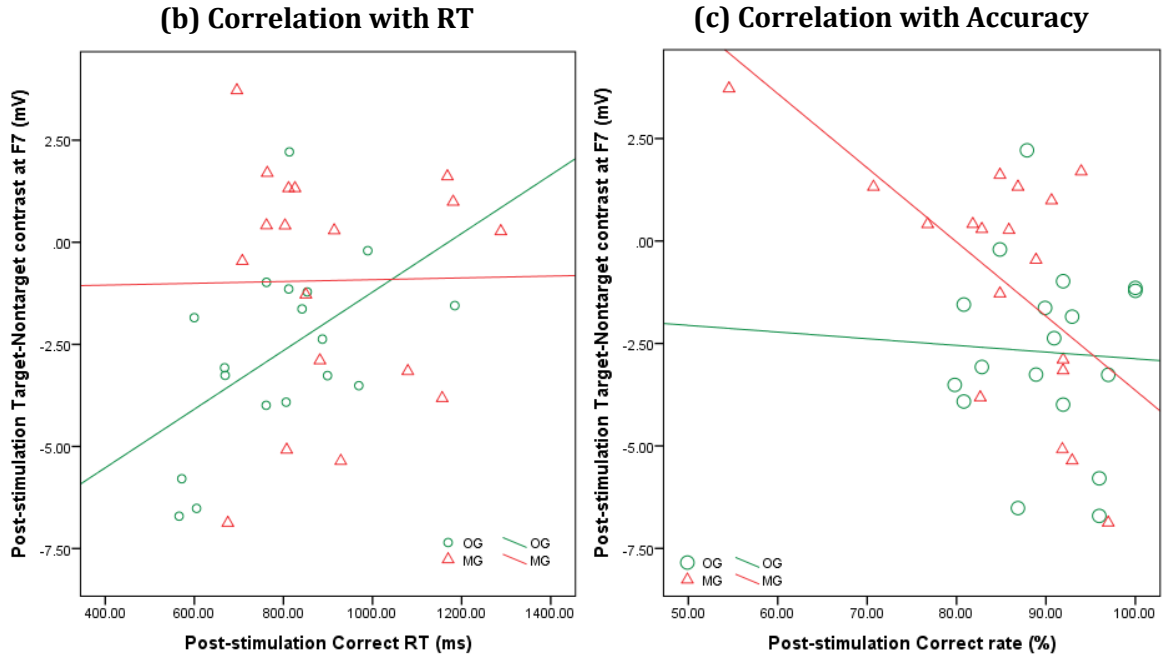


Figure 5.11. Amplitude of P300 recorded at F7 in older participant group (OG) and participant with MCI group (MG).
(a) Post hoc comparison of 3-way interaction in P300 recorded at F7 showed a trend of increased P300 for non-target trials after stimulation in OG whereas it was P300 for target that increased after stimulation in MG. (b) P300 Target-Nontarget contrast at F7 correlated positively with correct response time in OG after stimulation. (c) P300 Target-Nontarget contrast at F7 correlated negatively with correct rate in MG after stimulation. * *p*-value < .05, two-tailed. Error bar = ±1 standard error of mean.

5.2.4. ERP latency results

The latency of each component with its highest amplitude in its respective time-window was analysed using the same repeated-measure ANOVA model applied on the amplitude. Similarly, the peak latencies recorded at Fz and F7 were analyzed respectively.

5.2.4.1. *N200 latency*

No significant main effect or interaction was found (all *p*s > .05) in the analyses on N200 latency recorded at Fz and F7 respectively.

5.2.4.2. *P300 latency*

The main effect of Stimulation on P300 at Fz was marginally significant ($F(1,34) = 3.48$, $p = .071$; 421.60 ms vs. 428.82 ms) whereby P300 latency had the trend of being delayed after stimulation. The main effect of Type was significant ($F(1,34) = 9.95$, $p = .003$; 417.24 ms vs. 433.18 ms) such that the latency for target trials was earlier than non-target trials. The Group effect was marginally significant ($F(1,34) = 3.23$, $p = .081$), indicating a trend that P300 latency in general was delayed in MG relative to OG. No interaction effect was found significant (all *p*s > .05).

The main effect of Type on P300 peak latency at F7 was significant ($F(1,34) = 4.21$, $p = .048$; 413.53 ms vs. 429.43 ms) whereby the latency for target trials was earlier than non-target trials. No other main or interaction effects were significant (all *p*s > .05).

In essence, the P300 peak latencies recorded at Fz and F7 were found to be earlier in target trials than in non-target trials.

CHAPTER 6 DISCUSSION

The aim of this study was to examine the augmentation of neural processes associated with working memory for reflecting the neuroplasticity of older adults with the use of external electrical stimulation, and how MCI condition would influence this augmentation. This chapter discusses the main findings obtained in Study One and Study Two.

6.1 STUDY ONE: YOUNGER AND HEALTHY OLDER PARTICIPANTS

The comparison between the younger adult group (YG) and the older adult group (OG) in Study One revealed differential age-related post-stimulation effects on modulating the working memory processes despite similar behavioural improvement after 1 mA of HD-tDCS was applied at left dorsolateral prefrontal cortex for 10 minutes. The N200 amplitude for target trials in the YG was modulated after stimulation, which reflected enhanced match-mismatch processing such that the targets were less perceived as non-targets. On the other hand, it was P300 amplitude for non-target trials in the OG that was modulated after stimulation, suggesting enhanced stimulus-driven allocation of attentional resource specifically on the non-targets involved in the 2-back task. In both cases, the neurophysiological changes were associated with faster response. This suggested that the discriminative processing between target and non-target had turned more efficient in the YG such that the target was less perceived as a non-target after stimulation. The neural augmentation from the stimulation in the OG was not on this discriminative processing but in the adaptive frontal attentional allocation to process stimulus such as manipulation and maintenance. The findings further support the functional plasticity of normal aging brain at the frontal region, suggesting that it can be responsive to a brief excitatory stimulation. However, the excitatory responses appear to be differed from their younger counterpart by compensating attention rather than enhancing task-relevant process. This differential neural response to the stimulation in older participants relative to the younger group echoed the age-related neural mechanism described by the cognitive models of neuro-degeneration such as the posterior to the anterior shift as stipulated in the PASA model and also the dedifferentiation hypothesis (Li, Lindenberger, & Sikstrom, 2001) which posits that neural representations of different cognitive states become less distinctive in aging brain.

6.1.1 Modulation of P300

The present study found that the frontal P300 amplitude, which indexes attentional allocation to process stimuli, on non-target trials in the OG increased after the anodal HD-tDCS applied at left DLPFC. This resulted in a larger P300 contrast between target and non-target and associated with faster response in the OG after stimulation. Albeit observed in younger participants, Keeser et al. (2011) found a higher P300 that was related to the enhancement of attentional allocation in two-back task after anodal stimulation relative to sham stimulation but not with the baseline. This study did not differentiate the ERP signals related to target and non-target and did not have an older adult group for comparison, hence it could not explain the increased frontal P300 for non-target trials observed here in the OG of the current study. We do know from ERP studies on aging that the frontal P300 was higher towards target than non-target in the younger, middle-aged and older participants and additionally, the P300 related to target was relatively higher in the younger participants than in older participants (Gajewski & Falkenstein, 2014; Wild-Wall et al., 2011). These indicated that P300 for target might be declining during aging but P300 for non-target remains relatively intact. Hence, it might be possible that after HD-tDCS, the OG utilized the relatively intact non-target P300 more to perform the task. The current finding showed that the stimulation modulated the relatively intact attentional process on perceiving non-target and subsequently enhanced the task performance as reflected in the significant correlation between the P300 amplitude target-nontarget contrast and the correct RT. Being among the first HD-tDCS study on older adults using ERP, limited reference can be drawn from other studies.

In contrast, the present study did not find any significant change in frontal P300 in response to the stimulation in the younger participants. Similarly applying stimulation at left DLPFC in healthy young adults albeit using conventional tDCS at 2 mA for 20 minutes, Keeser et al. (2011) found a trend of increased P300 at Fz after anodal stimulation when compared with baseline, but the P300 amplitude was significantly higher relative to sham stimulation. One speculation to explain the difference in findings between current study and Keeser et al. (2011) was that the latter study applied the stimulation with higher intensity and longer duration which modulated beyond the task-specific processes in the young participants and influenced the stimulus-driven allocation of attentional resource indexed by the

frontal P300 via the neural network. This speculation was gathered from the observation of a higher activation at left parahippocampal gyrus after stimulation which the authors interpreted as the prefrontal tDCS influencing via the frontohippocampal connections (Keeser et al., 2011).

The current study did not find any change in P300 latency in response to the stimulation in both groups. Albeit not a tDCS study, Daffner et al. (2011) observed that the P300 latency generally increased with task load (n-back from 0 to 2) in the older participants whereas the latency remained stable in the younger participants across task load. Based on this observation, as far as the older participants are concerned and given no change in the working memory load in this study, one hint might be that the stimulation modulated the neural response not in the manner that the task was processed as easier (thus no change in the latency) but the adaptively-increased attentional allocation was further increased (thus change in the amplitude). With regards to the younger participants, no change in P300 latency after stimulation was also observed by Keeser et al. (2011) where significant change in latency was only observed when comparing between real stimulation with sham but not with baseline. The explanation for the unchanged latency remains to be investigated.

6.1.2 Modulation of N200

The frontal N200 amplitude is related to match-mismatch discriminative process; t is common to observe a larger N200 when a non-target happens than when a target happens (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Patel & Azzam, 2005), reflecting mismatch processing that served to distinguish targets from non-targets (Du et al., 2008; Folstein & Van Petten, 2008; Yi & Friedman, 2011). The modulation of N200 recorded at frontal region among the older participants was found not significant and did not support the hypothesis set out in this study. However, the modulation on N200 was statistically significant on the target condition in the younger participants. These findings suggested that single-session excitatory stimulation at DLPFC resulted in the less negative-going N200 at Fz, reflecting enhanced match-mismatch processing of targets presented in the 2-back task. This was supported by the larger differences in the post-stimulation N200 negativity between the targets and non-targets significantly associated with faster response time in the younger group. The ERP component N200 reflects a mismatch between a presented stimulus and a representation being held in memory, hence

targets would elicit less negative-going N200 than non-targets (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Patel & Azzam, 2005). The less negative-going N200 on target trials suggested modulations were likely to be on perceiving the targets more differently from the non-targets, and hence benefited the performance on the 2-back task among the younger participants. It is noteworthy that the post-stimulation modulation in the N200 was on the task-relevant process which was not observed in the older adult participants. This finding corroborates with those revealed in other age-related studies that augmentation of cognitive function with non-invasive brain stimulation exert less effect on the task-relevant process among older participants (Meinzer et al., 2013; Vidal-Piñeiro et al., 2014). For instance, Meinzer et al. (2013) revealed that single-session anodal tDCS at left ventral inferior frontal gyrus (vIFG), which is associated with semantic word generation or retrieval, largely reduced the activities at bilateral vIFG and middle frontal gyrus (MFG), as well as ACC and precuneus. Activities at bilateral vIFG and MFG were higher in the older participants than in the younger group during sham stimulation (Meinzer et al., 2013). However, the same stimulation protocol on the younger participants only reduced activity specifically at left vIFG and not in other brain regions (Meinzer et al., 2012). This hinted that the modulation was on task-relevant process in the younger participants whereas the modulation tended to be generic in older participants. This is possible in the light of dedifferentiation hypothesis (Li et al., 2001). Besides neural representation becoming less distinctive and specific in aging brain, the hypothesis concurs with observation of bilateral activation in older adults against unilateral brain activation found in young adults (Cabeza, 2002; Reuter-Lorenz et al., 2000) as well as the age-related decreases in modularity whereby decreases in intramodule connectivity coupled with increases in intermodule connectivity was observed in older adults, essentially suggesting a pattern of dedifferentiation (Chen, He, Rosa-Neto, Gong, & Evans, 2011). In essence, dedifferentiation of aging brain was observed in neural representation, processing and connectivity. Hence, one possible explanation on why the electrical stimulation augmented task-specific process in the young adults but task-general in the older adults could be a dedifferentiation of neuromodulation in the aging brain.

The current study found that the N200 latency for target generally became earlier after stimulation. Daffner and his colleagues (2011) found that N200 latency of high performers in two-back task earlier relative to low performers, albeit theirs

is not a tDCS study. The earlier N200 latency for the target trials modulated by HD-tDCS is likely to attribute to the improved performance generally on the two-back task.

6.1.3 Modulation of behavioural performance

The present study observed that the accuracy and response time for the two-back task were improved generally in both the OG and YG after the stimulation. Our results concur with those reported in Keeser et al. (2011), where both response time and accuracy in their young participants improved after anodal stimulation.

However, there were studies applying electrical stimulation at DLPFC and using n-back task but yielding diverse behavioural results. There were studies where the response time but not the accuracy was improved after receiving HD-tDCS (Nikolin et al., 2015) and conventional tDCS (Hoy et al., 2013) in young participants, or conversely, only the accuracy was improved (Seo, Park, Seo, Kim, & Ko, 2011; Zaehle et al., 2011). Mylius et al. (2012) applied tDCS at DLPFC and did not observe any modulation of response time or accuracy from the tDCS stimulation.

Similarly using HD-tDCS on DLPFC and performing n-back after stimulation, Nikolin et al. (2015) only observed faster response time after the stimulation despite using a higher intensity (2 mA) over a longer duration (20 minutes) than the current study. It might be tempting to attribute the difference between findings revealed in this study and those in others to task difficulty: three-back in Nikolin et al. (2015) in contrast to two-back in the current study. However, the accuracies of the participants in Nikolin et al. (2015) did not reflect task difficulty (accuracies being 90% and above), and in any case the probability of two-back task exhibiting ceiling effect and resulting in no change in accuracy is higher than that with three-back task.

Hoy et al. (2013) used 1 mA of tDCS for 20 minutes and found only the response time in the two-back task improved after the stimulation, with which the parameters employed was similar to the ones used by Kim et al. (2014) who found improved response time and accuracy in three-back task after stimulation. Although Kim et al. (2014) found nine participants who improved in response time and/or accuracy after stimulation, the authors did not specify if these participants improved in both or one of the measures. Hence, the comparison among these studies is further limited apart from differences in parameters and task.

It was also interesting to note that Seo et al. (2011) and Zaehle et al. (2011) both found improved accuracies (and not response time) in two-back task after

anodal stimulation at left DLPFC yet the former used 2 mA for 30 minutes whereas the latter used 1 mA for 15 minutes. Notably, Mylius et al. (2012) used the same tDCS parameters as Keeser et al. (2011) and in contrary, found no change in both response time and accuracy. Evidently, the behavioural findings from tDCS studies were mixed given the same task.

Among the older participants, there was suggestion that only the accuracy improved selectively in those who were highly-educated after tDCS applied at DLPFC (Berryhill and Jones (2012). Another tDCS study employing n-back in older adults also found improved accuracy (Meinzer et al., 2013) and both cohorts (Berryhill & Jones, 2012; Meinzer et al., 2013) had comparable years of education (16.9 years and 15.9 years). However, the older participants in the present study had 9.1 years of education on average which was comparably low but in contrary, there was a general improvement of response time and accuracy after stimulation. Proponent of cognitive reserve suggested that the brain actively tries to cope with brain deficits by using pre-existing cognitive processes or by recruiting compensatory processes (Stern, 2009). Although education is evidenced to be one of the factors influencing cognitive reserve in terms of neural reserves and neural compensation (Arenaza-Urquijo et al., 2013; Springer, McIntosh, Winocur, & Grady, 2005; Stern, 2009), other factors such as lifestyle (Bennett, Arnold, Valenzuela, Brayne, & Schneider, 2014; Scarmeas, Zarahn, Anderson, Habeck, et al., 2003) also contributed to it. The older participants in the present study might have other factors enhancing their cognitive reserve such as active lifestyle, which render them possessing substantial cognitive reserve despite the low educational level. Hence, they could probably be recruiting compensatory processes such that adaptive mechanism was further boost by the stimulation and resulted in a general improvement of response time and accuracy after stimulation.

6.2 STUDY TWO: HEALTHY OLDER PARTICIPANTS AND PERSONS WITH MCI

In Study Two, it was observed that after stimulation, the frontal P300 amplitude for target trials was increased in persons with Mild Cognitive Impairment or MCI group (MG) in contrast to the same component for non-target that was increased in the OG. The increased P300 in MG, however, was associated with poorer task performance. The finding suggested that while the adaptive attentional allocation was augmented in the two groups, the MG might have already exhausted their resources to render this compensatory mechanism effective.

6.2.1 Modulation of P300 amplitude for target in persons with MCI

It was found that the frontal P300 amplitude for target in MG became more positive-going after the stimulation whereas it was the frontal P300 amplitude for non-target in OG that was increased by the stimulation, indicating a differential modulation of attentional allocation to process stimuli indexed by the frontal positivity. Interestingly, this increased attentional allocation to process target was associated with poorer accuracy rate in MG whereas the increased P300 for non-target in OG was related to faster correct response. This phenomenon reflects possible decline in the plasticity of the brain of the participants with MCI, when compared with their healthy counterpart.

To reiterate, it was mentioned in previous section that the healthy older participants in the current study would have an augmented non-target frontal P300 in response to the stimulation, an adaptive, compensatory mechanism. Such adaptive mechanism appears to have been compromised among the participants in the MCI group.

Based on the few ERP studies investigating the influence of MCI on working memory using n-back tasks (Deiber et al., 2015; Missonnier et al., 2007; Missonnier et al., 2005), Deiber et al. (2015) found that P300 amplitude recorded at parietal sites during letter two-back task were lower in persons with MCI than in healthy controls, indicating a compromised higher-level discrimination processes in MCI group but no report on the frontal P300 was made. Missonnier and his colleagues (2007; 2005) did not report on P300 and hence the reason was unclear for the heightened frontal P300 observed in MCI group when no manipulation or intervention was imposed on them. However, referring to evidences on aging memory, the frontal P300 is likely an adaptive mechanism of top-down modulation to support the declining posterior regions and their connectivities (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Davis et al., 2008; Grady et al., 1994; Reuter-Lorenz et al., 2000).

Referring to the scarce evidence of the response towards tDCS in persons with MCI, Meinzer et al. (2015) used semantic word generation task and measured task-related and resting-state fMRI in healthy older adults and the MCI group; they found that the MCI group already had bilateral frontal hyperactivity relative to the healthy controls to begin with when only sham stimulation was administered and this was associated with lower accuracy rate. The anodal tDCS applied on left

inferior frontal cortex improved the accuracy and reduced the hyperactivity at left lateral PFC in the MG to a level comparable with the healthy controls, leading the author to suggest that there was neural facilitation in response to the anodal stimulation, resulting in more efficient or less effortful processing (Meinzer et al., 2015). In the present study, we found increased frontal P300 amplitude for target trials after the electrical stimulation in the MCI participants that was associated with poorer accuracy rate. The current finding seemed to mirror the situation of the sham condition in the study by Meinzer et al. (2015) where the MG showed a frontal hyperactivity associated with poorer accuracy.

It is intuitively to assume that a further increased attentional allocation to target after stimulation would correspond to an improved task performance, just like the older participants responded with an adaptive top-down modulation resulted in increased attentional allocation to non-target. However, the post-stimulation increased frontal P300 amplitude in MG was associated with a poorer task accuracy.

One explanation for the different outcome in response to the electrical stimulation by OG and MG could be explained with the Compensation-related Utilization of Neural Circuits Hypothesis, in short CRUNCH (Schneider-Garces et al., 2010). The CRUNCH asserts that older adults engage more neural circuits to meet task demands due to their declining neural efficiency and manifest in over-activation or recruitment of other areas, and at a lower level of cognitive demand relative to the younger adults. As the task load increases, the young adults would engage such additional neural resources too but by then, the older adults would exhibit under-activation as they have exhausted their resources (Cappell et al., 2010; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2010; Schneider-Garces et al., 2010). Given that MCI condition marks a further deterioration from normal aging, it would imply that the MCI participants would have recruited additional neural resources but to a point exhausted the compensatory mechanism earlier than the healthy older participants. This offers a plausible explanation on the finding that increased in the frontal P300 amplitude did not benefit the task performance.

In comparison to Meinzer et al. (2015), the current study similarly used anodal stimulation at 1 mA on proximal sites (left ventral inferior frontal vs. left DLPFC) but differed in the task (semantic generation task vs. n-back), the stimulation duration (20 vs. 10 minutes) and the electrode montage (conventional

tDCS vs. HD-tDCS). Both cohorts of MCI participants were comparable in age (67.4 ± 7.3 vs. 68.3 ± 7.1 years) and the MMSE scores (27.17 ± 1.34 vs. 28.11 ± 1.78) although the MCI participants in the current study had relatively fewer years of education (14.3 ± 2.2 vs. 7.4 ± 3.3 years). The difference in the results between the present study and Meinzer et al. (2015) could be accounted for by the different tasks, stimulation durations and electrode montages employed by the two studies but the educational level of participants might be the more likely contributing factor in the light of CRUNCH (Cappell et al., 2010; Mattay et al., 2006; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2010) and cognitive reserve (Arenaza-Urquijo et al., 2013; Springer et al., 2005; Stern, 2009). Correlational analysis showed that the post-stimulation changes in the frontal P300 amplitudes for non-target at Fz albeit not F7 among the MCI participants showed rather strong correlation with the years of education (r = .69, p = .009), indicating that higher education was associated with stronger responses to the electrical stimulation.

The cognitive reserve hypothesis asserted that the brain actively tries to cope with brain deficits by using pre-existing cognitive processes or by recruiting compensatory processes (Stern, 2009), and that education (Arenaza-Urquijo et al., 2013; Springer et al., 2005; Stern, 2009) and lifestyle (Bennett et al., 2014; Scarmeas, Zarahn, Anderson, Habeck, et al., 2003) contributed to it.. The relatively lower level of education of the MCI participants in the current study, relative to Meinzer et al. (2015), suggests that the former would have had a lower cognitive reserve and hence the potential of further augmenting the attentional allocation process in response to the electrical stimulation, which did not benefit the task performance anymore. The educational level of the MCI participants did not differ significantly from that of the older participants in the present study, it is reasonable to speculate that the cognitive reserves of the MCI participants would have been lower than the older participants due to other factors apart from education such as lifestyle, which explains the difference in the post-stimulation augmentative frontal P300 amplitudes and the corresponding functional responses.

6.2.2 No modulation in behavioural performance in persons with MCI

The participants in MG did not exhibit significant behavioural change despite the neurophysiological changes. In addition, it was known from the correlational analysis that the increased frontal P300 amplitude after the stimulation observed in

the MG was associated with poorer accuracy. A neurophysiological change with no corresponding behavioural change did occur in the study by Zaehle et al. (2011) where they found a significantly larger accuracy rate after anodal stimulation relative to sham but observed no effect on P300 amplitude during the n-back task performance, although they found modulation of the theta and alpha oscillations. To our best knowledge, the only tDCS study investigating MCI group with neurophysiological measure did find reduced frontal hyperactivity coupled with improved accuracy rate (Meinzer et al., 2015). The explanation for differential neurophysiological and behavioural observations after tDCS thus remained unknown, particularly for the MCI group.

6.3 CLINICAL IMPLICATION

The present study observed that the adaptive, compensatory frontal process of attentional allocation for non-target in the healthy older participants was enhanced by the electrical stimulation and related to an improved response time in the task. This points towards the potential for external stimulation such as tDCS to augment cognitive reserves in the older adults.

Proof-of-concept studies are still needed to examine the outcome and the underlying mechanism particularly as the technical aspect of tDCS modified (e.g. HD-tDCS). Studies using conventional tDCS to examine the behavioural effects (Berryhill & Jones, 2012; Manenti et al., 2013) as well as mechanism (Meinzer et al., 2013; Meinzer et al., 2015) in older adults are good examples to follow to further the clinical potential of external stimulation to augment cognitive reserves. Studies investigating the dosage of the electrical stimulation to produce lasting neural changes (e.g. Boggio et al., 2011 on Alzheimer's disease) would also be crucial in extending this clinical potential of electrical stimulation.

The present findings would inform the development and design of interventions for the MCI condition which marks a transitional stage between normal aging and dementia. Apart from clarifying the extent of neuro-enhancement from stimulation as a therapeutic tool in persons with MCI, more importantly is the arm of research in designing interventions to delay MCI via strengthening the cognitive reserve in normal older adults and those at risk of MCI. The present finding appeared to concur with the evidence that cognitive reserve was associated with the ability to recruit brain networks more effectively in older adults (Scarmeas, Zarahn, Anderson, Hilton, et al., 2003; Stern, 2002) and that cognitive reserve also

modulated task-related brain activity in those persons with aMCI who scored higher in cognitive reserve proxies such as IQ, education, occupation, social lifestyle, physical activity, cognitively-stimulating leisure activity (Bosch et al., 2010). These suggested that one would have to factor cognitive reserve when designing interventions for the MCI population.

CHAPTER 7 CONCLUSION

7.1 MAIN FINDINGS

Study One of the present study found that the match-mismatch processing of target indexed by N200 amplitude in the young adult group (YG) was modulated by the 1-mA HD-tDCS applied at left dorsolateral prefrontal cortex for 10 minutes, indicating that target stimuli elicited less activation in the YG after stimulation whenever the presented stimulus was processed against the representation held in working memory and resulted in faster response to the two-back task. In essence, the processing of target relative to non-target became more efficient in the younger participants after the stimulation.

Concurrently, the same electrical stimulation modulated the P300 amplitude for non-target trials in the healthy older group (OG), indicating that the stimulation might have enhanced the adaptive, compensatory frontal process of attentional allocation for non-target stimuli, thus improving the response time of the OG in the task. This seems to reflect a plausible adaptive mechanism of focusing attention on non-target stimuli developed in response to the external stimulation. The augmented attentional allocation on the processing of non-target stimuli in response to the external stimulation resulted in enhanced performance on the two-back target.

The mild cognitive impairment participants (MG) in Study Two responded to the external stimulation in a similar way, which was increased in the amplitude of the frontal P300. But different from those in the OG, participants in the MG showed modulation in the target rather than non-target trials. The modulated process did not seem to result in changes in the task performance. This may be explained by the notion that the MCI participants may have relatively lower level of plasticity in their brain than their healthy counterpart which would have limited the post-stimulation compensatory attentional allocation process. Another plausible explanation is the limited cognitive reserve relative to the healthy older participants which would have constrained the augmentation of the attentional allocation process for benefitting task performance after the external stimulation.

7.2 LIMITATIONS

The present study is limited in a number of aspects, namely, the experimental design and the stimuli distribution. The experimental design might have been more robust by implementing another session with sham stimulation and/or no stimulation, which would improve the intensity of the external stimulation

particularly for the MCI participants; and by standardizing the activity during the 25-minute interval after stimulation before the post-stimulation experimental task, which would improve the internal validity of the results. In addition, the number of target trials was low relative to the non-target trials which would improve the power of the statistical analyses.

7.2.1 Lack of a session with sham or no stimulation

The findings might have been more robust if there was a sham and/or no stimulation session to contrast with the anodal stimulation. This would enable us to ascertain the augmentation effect of the electrical stimulation emitted by the HD-tDCS for modulating the anticipated neural processes among the three groups of participants. A caveat to one additional session was the risk of attrition particularly in the older and MCI groups. In addition, a second session might aggravate any learning effect as the participants perform the task for multiple times. Despite the limitation, the pilot study implemented sham stimulation to contrast with the anodal stimulation which formed a basis for the two main studies. The pre-stimulation baseline did serve the purpose as a contrast to the anodal stimulation albeit it was not the most ideal scenario.

7.2.2 Non-standardized activity during post-stimulation interval

The activity during the 25-minute interval after stimulation and before the post-stimulation experimental task was not standardized which was not ideal as the basal neural activity of the latter might have influenced the neuromodulatory aftereffect from HD-tDCS (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Carvalho et al., 2015; Jantz, Katz, & Reuter-Lorenz, 2016). This would have threatened the internal validity of the results gathered from the experiment. The participants were instructed to rest either in standing or sitting as they preferred with minimal conversation. One way to standardize the activity during this interval could be watching a documentary video-clip. Despite the shortcoming, all participants in the present study were instructed to close their eyes for approximately 2 minutes before they commenced the experimental task, which was likely sufficient to put them in comparable state.

7.2.3 Number of target trials

It is common in n-back task to have relatively lower proportion of target than non-target trials (Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missonnier et al., 2007; Wild-Wall et al., 2011). In the present study, there were approximately 30

target trials embedded in each experimental block of 100 trials; implying that the maximum possible number of correct target trials from any participant is 30. The low number of target trials might create noisy ERP data and also lowered the power in statistical analysis. However, the caveat to increase the absolute number of target trials would be to lengthen the experimental block due to the nature of the n-back task, which might create attentional fatigue in the participants particularly the older adults and affect the task performance.

7.3 FUTURE RESEARCH

The various findings from the present study triggered gaps in a few aspects that could be explored in future investigation, namely, the mechanistic variation related to stimulation parameters, the time-course of HD-tDCS aftereffect, the modulation of the adaptive mechanism in healthy older adults, the neuromodulation that would benefit pathological cognitive aging such as MCI condition, and the aging effect in working memory in more fine-grained manner.

7.3.1 Investigation into mechanistic variation

In light of the issues with tDCS effect, the findings from current study would be enriched with the modelling of the electric field strength and spread to explore how it might correlate with the task performance and the neurophysiological responses; and the extent of difference in the electric field induced in the older adults relative to the young.

Another question to further investigate is whether or not 1 mA of anodal stimulation for 10 minutes used in the present study is considered too low a dose to generate an effect. Future study could answer this question by manipulating different combination of intensity and duration particularly for non-motor brain regions and cognitive tasks.

7.3.2 Neurophysiological measure for the time-course of aftereffect

The pilot study in the present study was a preliminary step to investigate the possible different time-course of HD-tDCS from the conventional tDCS. The weak but apparent quickening of response time between 15 minutes and 30 minutes after stimulation with active anodal stimulation relative to the sham stimulation renders the need to explore the time-course of HD-tDCS aftereffect with neurophysiological measure.

7.3.3 Modulation of aging process in working memory

The current finding of an enhanced frontal adaptive mechanism in older adults with stimulation generates the question on whether or not stimulation at the posterior brain regions, e.g. parietal, would enhance the posterior processes and thus minimize the need for the anterior-posterior-shift phenomenon observed in aging, and strengthen recollection-based rather than familiarity-based retrieval.

7.3.4 Neuromodulation that would benefit pathological cognitive aging

The HD-tDCS was found to increase the adaptive stimulus-driven attentional allocation in the persons with MCI group but this increase was associated with poorer task performance, triggering the doubt that what works for the healthy aging might not work for this group with pathological cognitive aging. Future research could investigate what might be uniquely beneficial for the MCI group. This is reasonable when we do know that the pathology underlying the cognitive impairment in MCI is clearly different from normal aging.

7.3.5 Task that allows fine-grain analysis of sub-processes

In this study, we employed the classical n-back task so that the results can be easily comparable to other working memory studies using a similar task. The use of EEG measurements is also advantageous as it allows sensitive detection of the multiple underlying neurocognitive sub-processes related to the performance of the n-back task. While it is possible that the dissociable neurophysiological changes between the old and young were related to the improvements of different sub-processes, it was difficult to manifest these improvements by using the gross behavioural measurements in the n-back task. Future studies that involve the development of a behavioural task that allows fine-grained investigations of these sub-processes will be useful for a better understanding of the age-specific behavioural improvements associated with tDCS.

7.4 CONCLUDING STATEMENTS

High-definition transcranial direct current stimulation (HD-tDCS) was applied at left dorsolateral prefrontal cortex with an intensity of 1 mA for 10 minutes in three groups of participants: the young, healthy older and mild cognitive impairment. The stimulation enhanced the match-mismatch processing of target in the younger adults, but it was the adaptive, compensatory attentional allocation to non-target involving discrimination between the incoming and stored stimuli in the healthy older participants that responded to the stimulation. The stimulation also

increased the adaptive mechanism among the MCI participants, which augmented the attentional allocation process. Nevertheless, the noticeable modulation did not seem to result in enhanced performance.

The findings provide further information on how the processes of working memory in the healthy brain might respond to the external, electrical stimulation, how the cognitive reserve reflected in the adaptive mechanism adopted by the aging brain could be further augmented, and that the cognitive reserve might be too stretched to benefit from further enhancement in those with pathological cognitive aging. Clinically, the findings point out the potential of using external stimulation to induce more lasting enhancement of cognitive reserve. The findings also trigger future investigation on the effect of HD-tDCS, the effect of stimulation on the aging process apart from the adaptive process in healthy older adults, and what would benefit the MCI group.

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APPENDIX 1A: TRANSCRANIAL MAGNETIC STIMULATION ADULT SAFETY SCREEN (TASS) ADAPTED FOR USE WITH TRANSCRANIAL DIRECT CURRENT STIMULATION (ENGLISH VERSION)

Participant No: _____

SN	Yes	No	Questions
1	☐	☐	Have you ever had an adverse reaction to tDCS?
2	☐	☐	Have you ever had an EEG?
3	☐	☐	Have you ever had a seizure?
4	☐	☐	Have you ever had a stroke?
5	☐	☐	Have you ever had a head injury (including neurosurgery)?
6	☐	☐	Do you have any metal in your head (outside of the mouth) such as shrapnel, surgical clips, or fragments of welding or metalwork?
7	☐	☐	Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?
8	☐	☐	Do you suffer from frequent or severe headaches?
9	☐	☐	Have you ever had any other brain-related condition?
10	☐	☐	Have you ever had any illness that caused brain injury?
11	☐	☐	Are you taking any medications?
12	☐	☐	If you are woman of childbearing age, are you sexually active, and if so, are you not using a reliable method of birth control? [possibility of pregnancy]
13	☐	☐	Does anyone in your family have epilepsy?
14	☐	☐	Do you need further explanation of tDCS and its associated risks?
If any item was marked as "yes", please provide a comment here:			

Adapted from Keel, Smith, & Wassermann (2000)

_____ _____

Name and Signature Date

APPENDIX 1B: TRANSCRANIAL MAGNETIC STIMULATION ADULT SAFETY SCREEN (TASS) ADAPTED FOR USE WITH TRANSCRANIAL DIRECT CURRENT STIMULATION (CHINESE VERSION)

經顱磁刺激安全篩選（成年版）(TASS)

改編作為高清經顱電刺激之用途

被試者編號 ：_____

	是	否	Questions
1	☐	☐	你對高清經顱電刺激是否曾經有不良反應?
2	☐	☐	你是否曾經接受過腦電圖?
3	☐	☐	你是否有過癲癇發作?
4	☐	☐	你是否有過中風?
5	☐	☐	你是否有過頭部外傷（包括神經外科）?
6	☐	☐	你的頭部是否有任何金屬（口腔以外），如彈片，外科夾閉，焊接或金屬碎片?
7	☐	☐	你是否有任何植入設備，如心臟起搏器，醫用泵，或腔內線?
8	☐	☐	你是否經常頻繁頭痛或有劇烈頭痛?
9	☐	☐	你是否有過其他任何有關腦部的病況?
10	☐	☐	你是否有過任何疾病，造成腦損傷?
11	☐	☐	你目前是否服用任何藥物?
12	☐	☐	你是否證實懷孕或有可能正在懷孕?
13	☐	☐	你是否有任何家屬患有癲癇?
14	☐	☐	你是否需要有關高清經顱電刺激和其相關風險的進一步解釋?

如果以上任何項目答案為“是”，請在此空欄提供詳情:

改編自 Keel, Smith, & Wassermann (2000)

_____ _____

姓名和簽名 日期

APPENDIX 2: ETHIC APPROVAL FROM DEPARTMENTAL RESEARCH COMMITTEE: PILOT STUDY

To	CHAN Che Hin (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	29-Jun-2012

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 02-Jul-2012 to 31-Dec-2012:

Project Title:	Investigating aging effect on encoding: Using ERP and HD-tDCS (Pilot Study)
Department:	Department of Rehabilitation Sciences
Principal Investigator:	CHAN Che Hin

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

APPENDIX 3A: INFORMED CONSENT: PILOT STUDY (ENGLISH VERSION)

Code: _____
Gender: _____
Age: _____
Hand: _____

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences
Research Project Informed Consent Form

Project title: Investigating aging effect on encoding: Using ERP and HD-tDCS (Pilot Study)
Investigators: Prof. Chetwyn C H Chan, Tan Gim Hoon, Davynn (1090)

Project information:

The aim of this pilot study is to investigate any difference in the after-effect of High-Definition Transcranial Direct Current Stimulation (HD-tDCS) during the early and late phase of the post-stimulation period. Memory task performance will be used to reflect the after-effect. The result will inform the next stage of project which will investigate the aging effect on memory encoding processes.

The whole session will last 1 – 1.5 hours. In the session, you will be stimulated by HD-tDCS technique for 10 minutes and will need to perform one memory task. HD-tDCS is a safe and non-invasive technique using low-intensity direct current (1mA) to stimulate the brain activity. You will be monitored closely for any discomfort throughout the stimulation. The memory task is computer-generated and involves single number. The task requires you to detect if the number shown on screen has appeared two trials before. You respond by pressing relevant key on keyboard. Details of the procedure are provided during the session. The task is designed to capture the mental processes in memory encoding.

The findings of this pilot study together with subsequent stage of the project would enable us to understand the processes underlying memory encoding and how aging and pathological memory decline (e.g. dementia) affects these processes, in turn, inform the designing of clinical intervention to enhance memory of these populations.

You may approach the investigator for any clarification. Your participation in this study is entirely on a voluntary basis.

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Ms Davynn Tan at telephone 2766-4675 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mr Leung Ka Yan, secretary of Departmental Research Committee, at 2766-5398. I know I will be given a signed copy of this consent form.

Signature (subject): _____ Date: _____

Signature (witness): _____ Date: _____

APPENDIX 3B: INFORMED CONSENT: PILOT STUDY (CHINESE VERSION)

编号: _____
性别: _____
年龄: _____
慣用手: _____

香港理工大學康復治療科學系科研同意書

科研題目：研究老年退化對於記憶編碼的影響 – 使用“事件誘發電位 ”和“高清經顱電刺激”（初步試驗階段）

科研人員：陳智軒教授，陳錦芬小姐(1090)

科研內容：

這項初步試驗階段研究主要探討經過“高清經顱電刺激”之後的前期效應和後期效應是否有差別。效應將透過記憶測試表現來評估。現階段研究的結果將有助於我們設計下個階段研究老年退化對於記憶編碼之影響的试验。

此項研究為時大約 1-1.5 個小時，當中包括接受 10 分鐘“高清經顱電刺激”和進行一項有關記憶的試驗活動。“高清经颅电刺激”使用微弱電流（1mA）調節大腦皮層神經元興奮性，是一個安全和無痛無創的技巧。接受電刺激的過程中，您會受到密切的觀察，檢測是否有任何不適的現象。所使用的記憶試驗活動都屬電腦操作，你需要偵測屏幕顯示的數字是否曾經在兩個數字前出現過，並按鍵作答。活動詳情將在試驗進行前詳細解說和提供練習。這個記憶試驗活動是專為引發記憶編碼之過程而設。

對項目參與人仕和社會的益處：

這項初步試驗階段研究的結果和之後階段的研究將有助於了解記憶編碼之過程和老年退化如何影響這個過程，從而有效地設計有關的臨床治療方法。

潛在危險性：沒有

同意書：

本人_____已瞭解此次研究的具體情況。本人願意參加此次研究，本人有權在任何時候、無任何原因放棄參與此次研究，而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27664675 來聯繫此次研究課題負責人，陳錦芬小姐。若本人對此研究人員有任何投訴，可以聯繫梁先生（部門科研委員會秘書），電話：27665398。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）：_____ 日期：_____

簽名（證人）：_____ 日期：_____

APPENDIX 4A: INFORMATION SHEET FOR PILOT STUDY (ENGLISH VERSION)

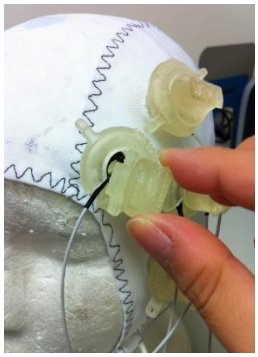
Project title: Investigating aging effect on encoding: Using ERP and HD-tDCS (Pilot Study)

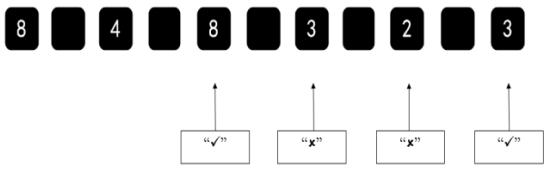
Project information:

This pilot study aims to investigate any difference in the after-effect of HD-tDCS during the early and late phase of the post-stimulation period. The result will inform the next stage of project which will investigate the aging effect on memory encoding processes. The session will start off with a memory task (with practice before actual task), followed by 10 min HD-tDCS stimulation, and lastly by performing the memory task again.

HD-tDCS Stimulation

1. You will be comfortably seated in a chair.
2. A cap with electrode holders will be fitted onto your scalp as shown in the photos.
3. Conductive gel will be injected into the holder followed by electrodes being placed in the holders.
4. The electrodes will be connected to a battery-driven stimulator and an adaptor device.
5. The stimulation will last for 10 min with direct current of 1 mA.
6. Just sit back and relax during the stimulation. You may close your eyes but do not fall asleep.
7. Throughout the stimulation, you will be asked to describe sensations felt on a scale of 1-4 based on a questionnaire.
8. After 10 minutes, the electric current will be switch off, and you will proceed to perform the memory task for the second time as instructed at the allocated time.





Memory Task: Two-Back Task

1. A sequence of single digits will be presented. No response is required for the first 2 digits.
2. Subsequently, when the digit presented is the digit that has appeared 2 digits before, you respond by pressing the key "□" with your right index finger.
3. If the digit presented is not the digit that has appeared 2 digits before, you respond by pressing the key "□" with your right middle finger.

Try your best to respond as fast AND as accurately as possible.

You can withdraw from this study at any time without giving reasons, and it will not lead to any punishment or prejudice against you. Your personal information will not be disclosed to people who are not related to this study and your name or photograph will not appear on any publications resulted from this study.

Thank you very much for participating in this study.

APPENDIX 4B: INFORMATION SHEET FOR PILOT STUDY (CHINESE VERSION)

香港理工大学康复治疗科学系科研内容說明書

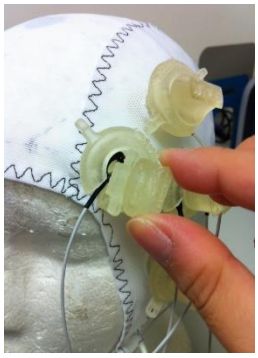
研究題目： 研究老年退化對於記憶編碼的影響 – 使用“事件誘發電位 ”和“高清經顱電刺激”（初步試驗階段）

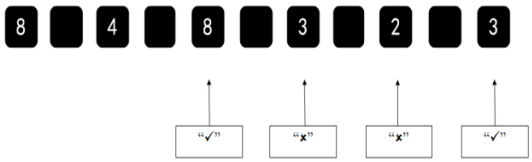
研究内容

這項初步試驗階段研究主要探討經過“高清經顱電刺激”之後的前期效應和後期效應是否有差別。現階段研究的結果將有助於我們設計下個階段研究老年退化對於記憶編碼之影響的试验。實驗過程從練習和實際進行第一輪的記憶試驗活動開始，接著接受“高清經顱電刺激”,最後再進行第二輪的記憶試驗活動。

高清经颅电刺激

1. 您會舒適地坐在椅子上接受“高清經顱電刺激”。
2. 如照片所示，你會戴上附有電極裝具的頭帽。
3. 電極裝具將會注入導電膠，之後才裝入電導。
4. 電導將會被連接到電流發動機和適配器。
5. 您將接受 10 分鐘，以 1 個 mA 的微弱電流進行的“高清經顱電刺激”。
6. 接受電刺激時，請盡量放鬆。您也可閉上雙眼，但請不要進入睡眠狀態。
7. 電刺激進行過程中，研究人員將間接詢問您是否有任何感覺，并且按照评估表评估程度。
8. 10 分鐘過後，電流將停止；您將按照指示，在指定的時間開始進行第二輪的記憶試驗活動。





記憶試驗活動

1. 電腦屏幕將顯示一系列的數字。首先出現的兩個數字，無須作答。
2. 你需要偵測屏幕顯示的數字是否曾經在兩個數字前出現過。
3. 之後，如果顯示的數字曾經在兩個數字前出現過，請用右食指按“✓”鍵。
4. 如果顯示的數字沒有在兩個數字前出現過，請用右食指按“×”鍵。

請盡量回答得**快而準**。

您可以隨時在不需作出解釋之情況下退出此項研究，而將不會受到處罰或歧視。您的個人資料將不會向本研究以外之人仕公開，並且您的姓名或照片將不會出現於任何研究之報告內。

謝謝您參與這項研究。

APPENDIX 5A: ADVERSE EFFECT QUESTIONNAIRE – AEQ (ENGLISH VERSION)

Adverse Effects Questionnaire

Participant No: _____

Experience the following symptoms or side-effects?	Rate 1-4 1: Absent 2. Mild 3. Moderate 4. Severe							If present, is this related to HD-tDCS? 1. None 2. Remote 3. Possible 4. Probable 5. Definite					Notes
	BL	Onset	5 min	Last 30s	Exit	1 day	1 wk	Onset	5 min	Last 30s	Exit	1 day	1 wk	
Headache														
Neck pain														
Scalp pain														
Tingling														
Itching														
Burning sensation														
Skin redness														
Sleepiness														
Trouble concentrating														
Acute mood change														
Others (specify):														

Brunoni, Amadera, et al. (2011)

APPENDIX 5B: ADVERSE EFFECT QUESTIONNAIRE – AEQ (CHINESE VERSION)

不良效果問卷

被試者編號: _____

感受下列症狀或副作用?	評估 1-4 1: 無 2. 輕微 3. 中等 4. 嚴重								若有症狀或副作用，是否與“高清经颅电刺激”有關? 1. 無關 2. 細微有關 3. 可能有關 4. 很可能有關 5. 肯定有關						備註
	就醫前	開始	5 分鐘	後 30 秒	離開時	1 天后	1 週後		開始	5 分鐘	後 30 秒	離開時	1 天后	1 週後	
頭痛															
頸痛															
頭皮痛															
刺痛															
痕癢															
燒灼															
皮膚發紅															
困倦															
注意力無法集中															
急性情緒變化															
其他（註明）：															

APPENDIX 6: BLINDING MEASURE

Subjective Questionnaire on Stimulation

1. In your opinion, you think you have received a *real / fake** stimulation in this session.
2. How confident are you of your answer?

0 — 1 — 2 — 3

Not confident — Very confident

Code	Name	Session 1			Session 2		
		Real / Fake	Rating	Actual Condition	Real / Fake	Rating	Actual Condition

APPENDIX 7: ETHIC APPROVAL FROM DEPARTMENTAL RESEARCH COMMITTEE: MAIN STUDY

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Chan Che Hin (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	24-Jun-2013

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 01-Jul-2013 to 31-Dec-2014:

Project Title:	Electrical Stimulation on Modulating Encoding Process among Normal Elderly and People with Mild Cognitive Impairment (MCI)
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Chan Che Hin

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

APPENDIX 8A: INFORMED CONSENT FOR MAIN STUDY (ENGLISH VERSION)

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project title: Investigating aging effect on encoding: Using ERP and HD-tDCS
Investigators: Prof. Chetwyn C H Chan, Tan Gim Hoon, Davynn (1090)
Project information:

The aim of the study is to investigate aging effect on memory encoding through using event-related potential (ERP, a technique of capturing brain electrical activity). In addition, the study will be using a safe and non-invasive technique using low-intensity direct current (1 mA) to stimulate the brain, called high-definition transcranial direct current stimulation (HD-tDCS), as a way to study the change in encoding process. tDCS has been widely used to study and enhance mood, attention and motor movement.

The whole session will last 2.5 hours. In the session, you will be stimulated by HD-tDCS technique for 10 minutes and will need to perform one memory task with ERP signal being recorded. Low-intensity direct current (1 mA) will be used to stimulate the brain activity through the HD-tDCS technique. You will be monitored closely for any discomfort throughout the stimulation. The memory task is computer-generated using Chinese character. The task requires you to identify stipulated features of the Chinese character shown, followed by a recognition test. You only respond by pressing relevant key on keypad. Details of the procedure are provided during the session. These tasks are designed to capture the mental processes in memory encoding.

The findings of this study would enable us to understand the processes underlying memory encoding and how aging and pathological memory decline (e.g. dementia) affects these processes, in turn, inform the designing of clinical intervention to enhance memory of these populations.

You may approach the investigator for any clarification. Your participation in this study is entirely on a voluntary basis.

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Ms Davynn Tan at telephone 2766-4675 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mr Leung Ka Yan, secretary of Departmental Research Committee, at 2766-5398.

I know I will be given a signed copy of this consent form.

Signature (participant): _____ Date: _____

Signature (witness): _____ Date: _____

APPENDIX 8B: INFORMED CONSENT FOR MAIN STUDY (CHINESE VERSION)

香港理工大學康復治療科學系科研同意書

科研題目：研究老年退化對於記憶編碼的影響 – 使用“事件誘發電位 ”和“高清經顱電刺激”

科研人員：陳智軒教授，陳錦芬小姐(1090)

科研內容：

這項研究的目的是通過使用“事件誘發電位”（Event-related Potential or ERP，一種收錄大腦電活動的技術）來研究老年退化對於記憶編碼之影響。此外，這項研究也將使用一種安全和無痛無創的技巧“高清經顱電刺激”（1 mA 微弱電流）來調節大腦皮層神經元興奮性,以研究大腦在編碼處理過程中的變化和老年退化對此變化的效應。“高清經顱電刺激” 已被廣泛用於研究和提高情緒，注意力和電機的運動。

此項研究為時大約 2.5 個小時，當中包括接受 10 分鐘“高清經顱電刺激”和進行一項有關記憶的試驗活動。接受電刺激的過程中，您會受到密切的觀察，檢測是否有任何不適的現象。記憶試驗活動都屬電腦操作：活動中，你需要偵測屏幕現實的中文字之特徵，之後進行記憶測試。整個活動只需要您按鍵作答。當您在進行記憶測試時，我們會用“事件誘發電位”技術收錄您的大腦電活動。活動詳情將在試驗進行前詳細解說和提供練習。這些活動是專為引發記憶編碼之過程而設。

對項目參與人仕和社會的益處：

這項研究的結果將有助於了解記憶編碼之過程和老年退化如何影響這個過程，從而有效地設計有關的臨床治療方法。

潛在危險性：沒有

同意書：

本人_____已瞭解此次研究的具體情況。本人願意參加此次研究，本人有權在任何時候、無任何原因放棄參與此次研究， 而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27664675 來聯繫此次研究課題負責人，陳錦芬小姐。若本人對此研究人員有任何投訴，可以聯繫梁先生（部門科研委員會秘書），電話：27665398。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）：_____日期：_____

簽名（證人）：_____日期：_____

APPENDIX 9A: INFORMATION SHEET: STUDY AIM AND HD-TDCS AND EEG RECORDING DETAILS (ENGLISH VERSION)

Project title: Investigating aging effect on encoding: Using ERP and HD-tDCS

Project information:

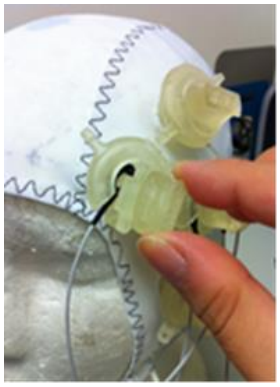
The study aims to investigate the aging effect on memory encoding through using event-related potential (ERP, a technique of capturing brain electrical activity). HD-tDCS, a safe and non-invasive technique using low-intensity direct current (1 mA) will be used to stimulate the brain so as to study the change in encoding process. The findings of this study would enable us to understand the processes underlying memory encoding and how aging and pathological memory decline (e.g. dementia) affects these processes, in turn, inform the designing of clinical intervention to enhance memory of these populations.

The session will start off with practice of the memory tasks, followed by 10 min of HD-tDCS stimulation, and lastly by the actual performance of the memory tasks while ERP signal is being recorded.

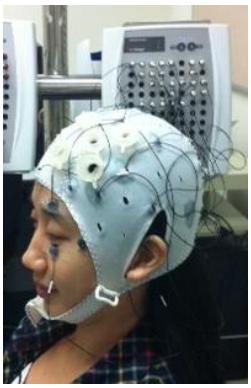
HD-tDCS Stimulation

1. You will be seated in a chair in the sound-proof chamber.
2. A cap with electrodes will be fitted onto your scalp.
3. Conductive gel will be injected into the electrodes.
4. The electrodes will be connected to two battery-driven devices.
5. The stimulation will last for 10 minutes with direct current of 1 mA.
6. Just sit back and relax during the stimulation. You may close your eyes but do not fall asleep.
7. During the stimulation, you will be asked to describe sensations felt on a scale of 1-4 based on a questionnaire.

Cap with HD-tDCS electrode in holder



Electrode gel injected into holder and electrode secure in place



Add on EEG electrodes for brain-wave recording

ERP recording

1. The electrode-cap will be connected to a computer outside the chamber to record your brain signal when you are performing the memory task.
2. During the memory task, doors of the room will be closed and the lightings dimmed.

You can withdraw from this study at any time without giving reasons, and your withdrawal will not lead to any punishment or prejudice against you. Your personal information will not be disclosed to people who are not related to this study and your name or photograph will not appear on any publications resulted from this study. Thank you very much for participating in this study.

APPENDIX 9B: INFORMATION SHEET: STUDY AIM AND HD-TDCS AND EEG RECORDING DETAILS (CHINESE VERSION)

香港理工大学康复治疗科学系科研内容說明書

研究題目： 研究老年退化對於記憶編碼的影響 – 使用“事件誘發電位 ”和“高清经颅电刺激”

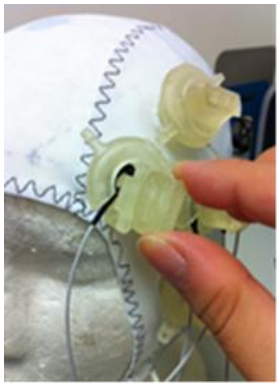
研究内容

這項研究的目的是通過使用“事件誘發電位”（ERP，一種捕捉大腦電活動的技術）來研究老年退化對於記憶編碼之影響。同時也使用安全和無痛無創的“高清經顱電刺激”（1 mA 微弱電流）來調節大腦皮層神經元興奮性，以研究大腦在編碼處理過程中的變化和老年退化對此變化的效應。這項研究的結果將有助於了解記憶編碼過程的老年退化影響，從而有效地設計臨床治療方法。

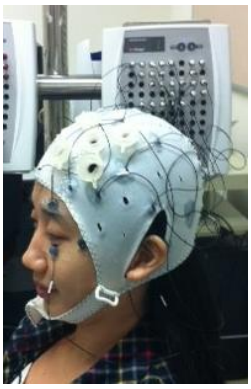
高清经颅电刺激

9. 您會舒適地坐在在隔音室內接受“高清经颅电刺激”。
10. 記錄您在進行記憶活動時的腦電波活動。
11. 電極將會注入導電膠。
12. 電導將會被連接到電流發動機和適配器你會戴上附有電極的頭帽。
13. “高清经颅电刺激”將以 1 mA 的微弱電流進行 10 分鐘。
14. 接受電刺激時，請盡量放鬆。您也可閉上雙眼，但請不要進入睡眠狀態。
15. 電刺激進行過程中，研究人員將間接詢問您是否有任何感覺，并且按照评估表评估程度。

你會戴上附有電極的頭帽



電極將會注入導電膠，並 確保不脫落



記錄腦電波活動

事件誘發電位

1. 電導頭帽將會被連接到隔音室外的電腦以記錄您在進行記憶活動時的腦電波活動。
2. 當您在進行記憶活動時，隔音室的門將會被關上，室內的燈光也會被調暗。

您可以隨時在不需作出解釋之情況下退出此項研究，而將不會受到處罰或歧視。您的個人資料將不會向本研究以外之人仕公開，並且您的姓名或照片將不會出現於任何研究之報告內。

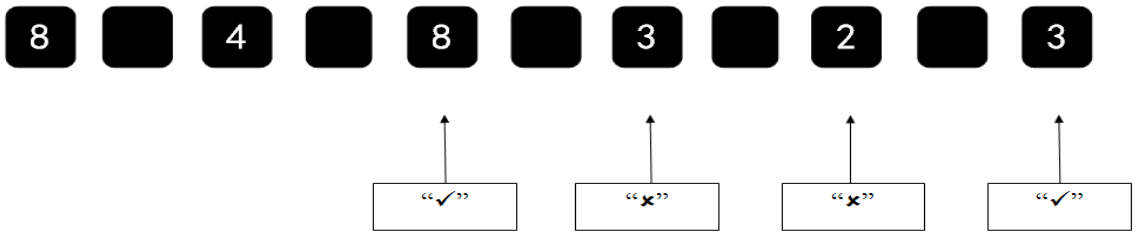
謝謝您參與這項研究。

APPENDIX 10A: INFORMATION SHEET: DETAILS OF TASK (ENGLISH VERSION)

Two-Back Task

1. A sequence of single digits will be presented. No response is required for the first 2 digits.
2. Subsequently, when the digit presented is the digit that has appeared 2 digits before, you respond by pressing the key "✓" .
3. If the digit presented is **not** the digit that has appeared 2 digits before, you respond by pressing the key "×".

Try your best to respond as ***fast*** AND as ***accurately*** as possible.

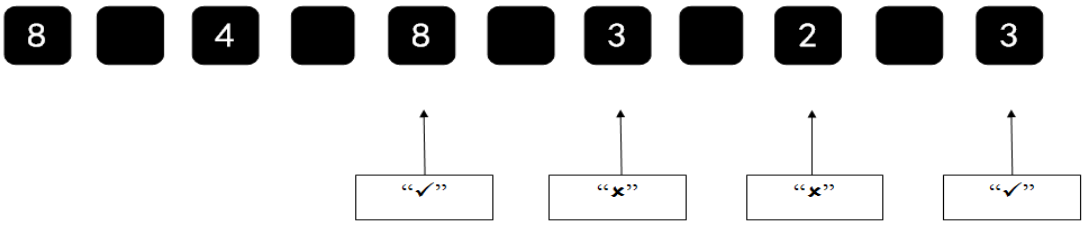


APPENDIX 10B: INFORMATION SHEET: DETAILS OF TASK (CHINESE VERSION)

倒數 2 項測驗

5. 電腦屏幕將顯示一系列的數字。首先出現的兩個數字，無須作答。
6. 你需要偵測屏幕顯示的數字是否曾經在兩個數字前出現過。
7. 之後，如果顯示的數字曾經在兩個數字前出現過，請按“✓”鍵。
8. 如果顯示的數字沒有在兩個數字前出現過，請按“×”鍵。

請盡量回答得**快而準**。



APPENDIX 11: AEQ SYMPTOMS: FREQUENCY OF REPORT AND RATING

Symptoms	Rating	Group	Baseline		Onset		5-min		Last 30s		Exit		1 day		1 week	
			Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Tingling	None	YG	22.0	100.0	5.0	22.7	7.0	31.8	13.0	59.1	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	4.0	22.2	5.0	27.8	8.0	44.4	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	9.0	50.0	9.0	50.0	13.0	72.2	18.0	100.0	18.0	100.0	18.0	100.0
	Mild	YG			11.0	50.0	15.0	68.2	9.0	40.9						
		OG			9.0	50.0	11.0	61.1	8.0	44.4						
		MG			8.0	44.4	9.0	50.0	5.0	27.8						
	Moderate	YG			6.0	27.3										
		OG			4.0	22.2	2.0	11.1	2.0	11.1						
		MG			1.0	5.6										
	Severe	YG														
		OG			1.0	5.6										
		MG														
	Total (≥ mild)		*0.0*	*0.0*	*40.0*	*69.0*	*37.0*	*63.8*	*24.0*	*41.4*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Itching	None	YG	18.0	81.8	8.0	36.4	10.0	45.5	13.0	59.1	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	7.0	38.9	8.0	44.4	10.0	55.6	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	14.0	77.8	13.0	72.2	16.0	88.9	18.0	100.0	18.0	100.0	18.0	100.0
	Mild	YG	4.0	18.2	9.0	40.9	10.0	45.5	9.0	40.9						
		OG			8.0	44.4	6.0	33.3	7.0	38.9						
		MG			3.0	16.7	5.0	27.8	2.0	11.1						
	Moderate	YG			3.0	13.6	4.0	22.2								
		OG			2.0	11.1			1.0	5.6						
		MG														
	Severe	YG			2.0	9.1										
		OG			1.0	5.6										
		MG			1.0	5.6										
	Total (≥ mild)		*4.0*	*6.9*	*29.0*	*50.0*	*25.0*	*43.1*	*19.0*	*32.8*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Sleepiness	None	YG	10.0	45.5	16.0	72.7	14.0	63.6	13.0	59.1	21.0	95.5	22.0	100.0	22.0	100.0
		OG	17.0	94.4	17.0	94.4	17.0	94.4	16.0	88.9	18.0	100.0	18.0	100.0	18.0	100.0
		MG	16.0	88.9	15.0	83.3	15.0	83.3	15.0	83.3	18.0	100.0	18.0	100.0	18.0	100.0
	Mild	YG	12.0	54.5	6.0	27.3	8.0	36.4	9.0	40.9	1.0	4.5				
		OG	1.0	5.6	1.0	5.6	1.0	5.6	2.0	11.1						
		MG	2.0	11.1	2.0	11.1	2.0	11.1	2.0	11.1						
	Moderate	YG														
		OG														
		MG					1.0	5.6	1.0	5.6						
	Severe	YG														
		OG														
		MG			1.0	5.6										
	Total (≥ mild)		*15.0*	*25.9*	*10.0*	*17.2*	*12.0*	*20.7*	*14.0*	*24.1*	*1.0*	*1.7*	*0.0*	*0.0*	*0.0*	*0.0*
Burning	None	YG	22.0	100.0	17.0	77.3	21.0	95.5	21.0	95.5	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	14.0	77.8	15.0	83.3	15.0	83.3	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	15.0	83.3	13.0	72.2	15.0	83.3	18.0	100.0	18.0	100.0	18.0	100.0
	Mild	YG			4.0	18.2	1.0	4.5	1.0	4.5						
		OG			3.0	16.7	2.0	11.1	3.0	16.7						
		MG			2.0	11.1	4.0	22.2	3.0	16.7						
	Moderate	YG			1.0	4.5										
		OG			1.0	5.6	1.0	5.6								
		MG					1.0	5.6								
	Severe	YG														
		OG														
		MG			1	5.6										
	Total (≥ mild)		*0.0*	*0.0*	*12.0*	*20.7*	*9.0*	*15.5*	*7.0*	*12.1*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Headache	None	YG	21.0	95.5	21.0	95.5	21.0	95.5	21.0	95.5	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	17.0	94.4	17.0	94.4
		MG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	16.0	88.9	18.0	100.0
	Mild	YG	1.0	4.5	1.0	4.5	1.0	4.5	1	4.5						
		OG											1	5.6	1	5.6
		MG											2	11.1		
	Total (≥ mild)		*1.0*	*1.7*	*1.0*	*1.7*	*1.0*	*1.7*	*1.0*	*1.7*	*0.0*	*0.0*	*3.0*	*5.2*	*1.0*	*1.7*
Neck pain	None	YG	22.0	100.0	22.0	100.0	22.0	100.0	21.0	95.5	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
	Mild	YG							1.0	4.5						
		OG														
		MG														
	Total (≥ mild)		*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*1.0*	*1.7*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Concentration	None	YG	20.0	90.9	19.0	86.4	20.0	90.9	20.0	90.9	18.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
		MG	17.0	94.4	17.0	94.4	17.0	94.4	17.0	94.4			18.0	100.0	18.0	100.0
	Mild	YG	2.0	9.1	3.0	13.6	2.0	9.1	2.0	9.1						
		OG	1.0	5.6												
		MG	1.0	5.6	1.0	5.6	1.0	5.6	1.0	5.6						
	Total (≥ mild)		*4.0*	*6.9*	*4.0*	*6.9*	*3.0*	*5.2*	*3.0*	*5.2*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Scalp pain	None	YG	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
Redness	None	YG	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
Mood	None	YG	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0	22.0	100.0
		OG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0
		MG	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0	18.0	100.0