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Abstract

The aging process has been shown to impair cognitive functions subsumed by the frontal lobes, but this region is heterogeneous and functions can be subdivided into different categories. Previous research focuses on aging within functions associated with dorsolateral and orbital prefrontal regions. This study investigates functions associated with another region – the medial prefrontal cortex. Tasks which tap abilities associated with dorsolateral and orbital prefrontal regions were administered to older and younger adults to replicate previous observations. Additionally, tasks which tap medial prefrontal abilities were administered, and age effects examined. Age-related differences were found on dorsolateral but not orbital prefrontal abilities. Significant age effects were also observed on both medial prefrontal tasks. These preliminary results support a region-specific theory of cognitive aging whereby dorsolateral and medial functions are most susceptible to decline, with orbital prefrontal functions remaining relatively preserved.

Keywords: medial prefrontal functions, frontal lobes, aging, AX-Continuous Performance Task, Simon Task

Introduction

The prefrontal cortex (PFC) is particularly vulnerable to the effects of aging (e.g., Dennis & Cabeza, 2008), with age-related changes manifesting in the PFC before changes in most other cortical areas (Raz, 2000). The aging process affects various cognitive functions associated with the PFC (e.g., MacPherson & Cox, 2017); consequently, theories of 'frontal aging' arose to explain the pattern of such deficits (e.g., Moscovitch & Winocur, 1992; West, 1996). However, the frontal lobes are heterogeneous and both anatomical maps – such as Brodmann's Areas (BA; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012) – and studies of cortico-cortical connections (e.g., Catani et al., 2012) have identified three distinct frontal subregions. In particular, the dorsolateral prefrontal cortex (DLPFC) can be defined as BAs 9 and 46, the orbital prefrontal cortex (OFC) can be defined as BAs 10, 11, 12, 13, 14 and parts of 47, and the medial prefrontal cortex (MPFC; which includes the anterior cingulate regions) can be defined as BAs 6, 24, 25 and 32. Crucially, each PFC region has been associated with distinct cognitive functions – the DLPFC with working memory manipulation and executive control (Braver & West, 2008); the OFC with emotional processing and social decision-making (Berthoz, Armony, Blair, & Dolan, 2002; Manes et al., 2002); and the MPFC with performance monitoring and conflict resolution (Botvinick, Cohen, & Carter, 2004; Kerns, 2006).

The resulting subdivision of frontal functions has highlighted the inadequacy of 'frontal' theories that purport there is a general frontal decline with age, and encourages further refinement to account for differential aging within the frontal lobes (MacPherson & Cox, 2017). For example, MacPherson, Phillips, and Della Sala (2002) found evidence for age-related differences in particular tasks chosen to represent functions associated with the DLPFC regions of the brain (i.e., Delayed Response Task; the Self-Ordered Pointing Task, SOPT; and the Wisconsin Card Sorting Task, WCST). In contrast, they found little evidence

for age differences on the majority of tasks subsumed by the OFC (which the authors refer to as the ventromedial PFC, VMPFC; as indicated by the Faux Pas Task and Iowa Gambling Task, IGT). MacPherson et al. (2002) proposed an account of cognitive aging in which declines in DLPFC function are responsible for the pattern of impairments noted in older adults (see also Phillips & Della Sala, 1998; for a review of age effects on frontal lobe tasks, see MacPherson, & Della Sala, 2015).

The functional heterogeneity of the frontal lobes is an important consideration when examining age-related cognitive decline. Yet, neuropsychological studies have not considered MPFC functions when examining the influence of age on the frontal lobes; only making a distinction between tasks assessing DLPFC and OFC functions (MacPherson et al., 2002; Lamar & Resnick, 2004; Baena, Allen, Kaut, & Hall, 2010). Yet, there exist a number of tasks thought to specifically assess MPFC functions including self-referential encoding (Gutchess, Kensinger, & Schacter, 2010), judgment of social scenes (Bradley, Keil, & Lang, 2012), and controlled processing of emotional faces (see Samanez-Larkin & Carstensen, 2011). Crucially, recent studies have highlighted the key role that medial prefrontal regions play in cognitive control functions, such as performance monitoring (Laubach, Caetano, & Narayanan, 2015) and adaption of behavior with changing reward contingencies (Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012; Dalton, Wang, Phillips, & Floresco, 2016). The main aims of the present study are to investigate whether cognitive functions associated with the MPFC change with age and whether there are differential effects of age compared to DLPFC and OFC functions in the same groups of younger and older adults.

Medial PFC Age-Related Changes

Medial regions of the PFC have more recently been shown to be susceptible to age-related decline. Studies have shown that healthy adults exhibit grey- and white-matter loss

within the MPFC (Farokhian, Yang, Beheshti, Matsuda, & Wu, 2017), and there is some suggestion that such changes are observable even before volumetric changes in more lateral prefrontal regions (Sowell et al., 2003). Furthermore, fMRI studies have revealed a greater degree of activation and recruitment of MPFC areas by older participants during the performance of various tasks (e.g., Grady et al., 2006). At the same time, other studies have suggested that MPFC regions show a marked susceptibility to age-related decline in activity during the performance of verbal memory tasks (particularly

within BAs 24 and 32; Hazlett et al., 2010; see also Paxton et al., 2008, Experiment 2). Damoiseaux and colleagues (2016) have also reported decreased functional connectivity of MPFC regions with age.

Tests for Assessing Medial PFC-Specific Function

The AX-Continuous Performance Task. The AX-Continuous Performance task (AX-CPT) involves participants monitoring a series of briefly presented letters and responding to a certain pattern (e.g., MacDonald et al., 2005). In the task, target trials (consisting of an A cue and an X probe) must be responded to with a different computer key than that of non-target trials (AY, BX, and BY). Furthermore, the three non-target trials produce different levels of response conflict, generated by the expectancy of a target trial (with AY trials producing the most conflict, and BY the least).

MPFC involvement during the AX-CPT appears to be higher in specific trials that require competition resolution and monitoring for errors (e.g., MacDonald et al., 2005). While DLPFC involvement is also associated with CPT performance, the involvement of the DLPFC represents the maintenance of contextual information across all trials, and changes in activation appear alongside manipulations of delay (MacDonald et al., 2003; 2005; Edwards, Barch, & Braver, 2010).

Braver et al. (2001) observed that aging was associated with longer reaction times in the AX-CPT with the largest differences appearing on high-conflict trials (e.g., AY trials). Indeed, no reaction time differences were noted in a later study when examining low-conflict trial performance (i.e., BY and AX trials; Paxton et al., 2008). Furthermore, Paxton and colleagues (2008) report age effects in sensitivity generally, and in accuracy on specific trial types. Older individuals committed significantly more errors than younger individuals on the BX trials of the task, and this was accompanied by age-related slowing of reaction times on these trials. Accuracy on AY trials, meanwhile, was not significantly different for older and younger individuals.

The Simon Task. During the Simon task (Simon, 1969), participants generate manual responses that are either ipsilateral (congruent) or contralateral (incongruent) to a presented color-square. The Simon effect - the cost in accuracy and reaction times for incongruent trials - reflects the increasing involvement of conflict monitoring in such trials (see Botvinick et al., 2004).

In a lesion study, di Pellegrino and colleagues (2007) noted that patients with MPFC damage involving the anterior cingulate took significantly longer to respond to incongruent stimuli than non-frontal lesion patients and healthy controls. Furthermore, medial activation during the Simon effect is stronger than in other cognitive phenomena such as the Stroop effect (Liu, Banich, Jacobson, & Tanabe, 2004), with particularly strong activation during incongruent trials (Kerns, 2006).

Older individuals exhibit both longer reaction times overall, and a larger Simon effect - in terms of reaction time - than younger individuals suggesting inhibitory control deficits with age (van der Lubbe & Verleger, 2002; Kawai, Kubo-Kawai, Kubo, Terazawa, & Masataka, 2012).

Dorsolateral PFC Age-Related Decline

DLPFC regions in particular appear to be susceptible to age-related decline, with neuronal shrinkage and tissue loss most prevalent in such areas (Dennis & Cabeza, 2008). Similarly, older individuals show significantly lower DLPFC activation and poorer performance compared to younger individuals on various working memory tasks (MacPherson & Cox, 2017).

Test for Assessing Dorsolateral PFC-Specific Function

The Self-Ordered Pointing Task. The Self-Ordered Pointing task (SOPT; Petrides & Milner, 1982) examines the ability to select items in an array one by one, avoiding perseverative responses. DLPFC lesion patients commit more perseverative responses than patients with non-DLPFC damage or healthy controls (Manes et al., 2002). The self-ordered element of the task has also been associated with right mid-DLPFC (BA 46) activation (Chase, Clark, Sahakian, Bullmore, & Robbins, 2008).

Healthy older individuals commit more perseverative errors than younger controls, suggesting working memory and executive impairments with age (Lamar & Resnick, 2004; MacPherson & Cox, 2017).

Orbital PFC Age-Related Decline

Age-related shrinkage in OFC neurons occurs later and less rapidly than in DLPFC neurons (Raz, 2000). Similarly, OFC white matter volume (Dennis & Cabeza, 2008), task-related activity (Beason-Held, Kraut, & Resnick, 2008) and chemical concentration (Grachev & Apkarian, 2001) appear to be relatively preserved when compared to other PFC regions. Older individuals have shown higher OFC activation despite similar performance compared to younger individuals in various emotional and social tasks (e.g., Grady et al., 2006).

Test for Assessing Orbital PFC-Specific Function

The Faux Pas Task. The Faux Pas task is a commonly used Theory of Mind task in which participants identify whether the protagonists in stories have unintentionally upset other characters in the stories (Stone et al., 1998). Patients with OFC damage, compared to DLPFC patients and healthy controls, commit more faux-pas identification errors despite understanding the non-social aspects of the story (Stone et al., 1998). Although direct neuroimaging evidence for the specificity of the Faux Pas task is lacking, significant activation of OFC regions in healthy individuals has been noted during social violation story tasks (e.g., Berthoz et al., 2002).

Performance on the Faux Pas task appears to be relatively preserved with age, as older individuals perform as well (MacPherson et al., 2002; Li, Wang, Wang, Tao, Xie, & Cheng, 2013).

The Present Study

The present study aimed to assess age-related performance on tasks thought to assess MPFC functions. Two such tests – the Simon task and the AX-CPT – were administered to both younger and older adults, and their performance contrasted to that on tests tapping DLPFC (the SOPT) and OFC (the Faux Pas task) functioning, which have been administered to older adults in previous studies (e.g., Cox et al., 2014; MacPherson et al., 2002; Lamar & Resnick, 2004). Notably, some studies have investigated age effects on medial functions (e.g., Braver et al., 2001; van der Lubbe & Verleger, 2002); however, these have not considered differential age effects within functions associated with other prefrontal regions. Crucially, such studies of MPFC functioning have relied on reaction time measures to support their hypotheses, but these are somewhat biased by their dependence on processing speed which is known to be affected by age (Salthouse, 1996). The main aim of the present study is

to investigate whether age effects in terms of MPFC-related functions exist independently from the contribution of processing speed.

Methods

Participants

Sixty-four participants were recruited for the study: 31 aged between 18 to 30 years (M = 20.16, SD = 2.61) and 33 aged between 61 and 81 years (M = 71.42, SD = 5.06). Younger participants were recruited through the undergraduate participant pool at the Psychology Department, University of Edinburgh and were rewarded for taking part with course credit. Older participants were recruited through a volunteer panel at the Psychology Department, University of Edinburgh and were reimbursed for their time. None of the participants had any history of the neurological or psychiatric disorders listed in the exclusion criteria for the Wechsler Adult Intelligence Scale-III UK and the Wechsler Memory Scale-III (WAIS-III UK and WMS-III UK respectively; Wechsler, 1997a, 1997b). Demographic information is summarized in Table 1. Older adults reported having spent significantly more years in full-time education than younger adults. The younger and older groups did not significantly differ in terms of handedness as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Informed consent was obtained for all volunteers according to the Declaration of Helsinki and the study was approved by the Philosophy, Psychology and Language Sciences Ethics Committee.

- Insert Table 1 around here -

All participants performed the Addenbrooke's Cognitive Assessment-Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) to assess overall cognitive ability,

the two-subtest Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) to assess IQ, the digit span forwards subtest from the WAIS-III (DF; Wechsler, 1997b) to assess memory span, and the digit symbol coding subtest from the WAIS-III (DSC; Wechsler, 1997b) to assess speed of processing. Administration and scoring of the tasks were according to the standard manual guidelines. The two age groups did not significantly differ in terms of ACE-R or DF performance (see Table 1). However, the older group exhibited a significantly higher full-scale IQ and slower speed of processing than the younger group.

Test of Dorsolateral PFC Dysfunction

The Self-Ordered Pointing Task. Participants were presented with a computerized version of the SOPT (Petrides & Milner, 1982; taken from MacPherson et al., 2002) in which a 4 x 3 array of black and white abstract designs appeared on a 20" touch-screen monitor. The task was created in Visual Basic. Participants were instructed to choose the items one at a time by touching the screen until they had selected all of the pictures in the set. Participants could select stimuli in any order but were encouraged not to choose any picture more than once. After each choice, some of the items within the array changed position to prevent reliance on a spatial strategy. Participants performed a 4-item 2 x 2 practice trial before performing 3 trials with 12 pictures. Participants were encouraged to carefully examine each item and focus on accuracy rather than speed. Responses were recorded by the computer, and errors were classified as items chosen more than once.

Test of Orbital PFC Dysfunction

The Faux Pas Task. Participants were read a series of 20 stories that related to social situations. Half of the stories contained a social faux pas in which one of the characters said something inappropriate or offensive, while the remaining 10 stories contained no such faux

pas. Stories were read aloud by the experimenter and after each one, participants were asked several questions to assess the participant's ability to identify the faux pas and who committed it, why it should not have been said, and the reason why it was likely to have occurred. Furthermore, a 'control' question represented the understanding of the narrative in general, and an 'empathy' question assessed the participant's ability to understand how the characters felt. Participants gave spoken answers to the questions. They were given paper copies of each story to read and refer to during the task, and could take as long as they wished to read the stories and answer the questions that followed. Correct answers included a reference to an unintentional faux pas and the naivety of the protagonist. Responses were incorrect if they implied that the utterance was deliberate or if they included facts that were not presented.

Tests of Medial PFC Dysfunction

AX-Continuous Performance Task. Participants were presented with a variant of a computerized expectancy AX-CPT taken from MacDonald, Pogue-Geile, Johnson and Carter (2003). The task was created in E-Prime (Version 2.0; Schneider, Eschman, & Zuccolotto, 2002). In this task, sequences of two letters were presented one-at-a-time on a computer monitor, followed by a fixation cross (for an example of the time-course of the AX-CPT see Braver et al., 2001, Figure 2). Participants were told that they should respond to each letter by pressing the right-hand key, unless they see an X that was preceded by an A within a letter pair (an AX trial), in which case they were to respond with the left key. Participants always responded with the right key to the first letter in each pair, and were required to use that letter as a cue to select the appropriate response to the probe letter (pressing either the right or left key). Participants were told to respond to the stimuli as quickly but as accurately as possible. No delay was present between cue-probe letters in the pairing; however, there was a delay of

7000ms between trials. The cue in the present task appeared on-screen for 1000ms and the probe for 500ms. Four blocks of 38 trials were presented. In this task, 79% of trials consisted of AX letter pairs. Furthermore, 8% of trials consisted of non-A letters followed by an X (i.e., BX trials), 8% consisted of an A followed by non-X letters (i.e., AY trials), and 5% consisted of non-A letters followed by non-X letters (i.e., BY trials; MacDonald et al., 2003). Non-A and non-X letters were chosen randomly from an array of 11 letters (Non-A: B, C, F, H, I, M, Q, R, T, V, Z; Non-X: D, E, G, J, L, N, O, P, S, U, W). Participants were given four practice trials, one of each type, before the task proper began. The experimenter prompted any necessary corrections in responses during the practice session. Reaction times and accuracy scores were recorded for both target- and cue-responses.

Simon Task. A classic computerized Simon spatial-incompatibility task was administered (taken from Tagliabue et al., 2007, Experiment 1). The task was created in E-Prime (Version 2.0; Schneider et al., 2002). Participants were briefly presented with a series of red or green squares one-at-a-time, on either the left- or right-hand side of the computer screen. Participants were required to respond by pressing either a red or a green key marked on a keyboard when they saw the appropriate colored square. Congruent (e.g., where a red square would appear on the left of the screen with the red response key also on the left of the keyboard), and incongruent (e.g., where a red square would appear on the right of the screen with the red response key on the left of the keyboard) stimulus-response trials were presented. The position of each response key, pressed by either the right or left hand, was counterbalanced across participants. Before each colored square appeared, a fixation cross was presented to refocus attention on the center of the screen. If a participant responded incorrectly, or failed to respond in time, a row of six exclamation marks appeared in the middle of the screen to indicate an error had been made. The task consisted of 240 randomly-ordered trials, half were congruent trials and half were incongruent trials. Eight practice trials

were administered before the experimental trials. Reaction times and accuracy scores were recorded for both trial types. A relative increase in errors committed and slower reaction times on incongruent trials when compared to congruent trials were indicative of a Simon effect (Tagliabue et al., 2007).

The test order was counterbalanced between participants, and participants were given opportunities to take short breaks between tests and in the middle of the study.

Analysis

For each prefrontal task, age effects were assessed using analysis of covariance (ANCOVA) to compare younger and older adult performance. In order to avoid the confounding effect of age on reaction times and cognitive abilities, the analysis focused on accuracy measures and scores. However, for both MPFC tasks (the AX-CPT and the Simon Task), reaction time data were also analyzed in line with previous studies (AX-CPT: Braver et al., 2001; Simon Task: van der Lubbe & Verleger, 2002). For each ANCOVA and MANCOVA, WASI full-scale IQ and the Digit-Symbol Coding scores were entered as covariates to examine whether the age effect survived controlling for IQ and processing speed differences between groups. Although the majority of the outcome variables were not normally distributed they were not transformed to ensure interpretability, and because ANCOVA and MANCOVAs are relatively robust to violations of normality assumptions (e.g., Levy, 1980). Bonferroni adjustments for multiple comparisons were used where appropriate. All analyses were conducted in SPSS (Version 22, IBM Corp., 2013).

Results

Replication

As expected, age effects were observed on the SOPT but not on the Faux Pas task. For the SOPT, a 2 (age: younger, older) x 3 (trial number: 1, 2, 3) mixed ANCOVA, including WASI full-scale IQ and Digit-Symbol Coding scores as covariates, was conducted. The analysis revealed that older adults (M = 7.67, SD = 2.06) committed significantly more errors than younger adults (M = 4.03, SD = 2.63), $F(1, 61) = 26.47$, MSE = 1.76, $p < .001$, $\eta^2_p = .30$, showing that neither IQ nor processing speed could account for all of the effects of age on the task. There was no significant main effect of trial number, $F(2, 122) = 1.18$, MSE = 1.16, $p = .31$, $\eta^2_p = .02$, or interaction between age and trial number, $F(2, 122) = .87$, MSE = 1.16, $p = .42$, $\eta^2_p = .01$, after accounting for the covariates.

On the Faux Pas task, a MANCOVA revealed no significant age effect when examining the number of errors committed on empathy (Younger M = 1.87, SD = 1.47; Older M = 1.15, SD = 1.35; $p = .30$), faux pas (Younger M = 10.06, SD = 5.87; Older M = 10.15, SD = 4.93; $p = .09$) or control (Younger M = .06, SD = .25; Older M = .00, SD = .00; $p = .23$) questions, Wilks's $\Lambda = .89$, $F(3, 58) = 2.48$, $p = .07$, $\eta^2_p = .11$. For the stories not containing a faux pas, a one-way ANCOVA revealed that the two age groups did not significantly differ in the number of errors committed (Younger M = .16, SD = .37; Older M = .15, SD = .44), $F(1, 60) = .48$, MSE = .17, $p = .49$, $\eta^2_p = .01$, and none of the participants made any errors on the control questions associated with these stories.

Tests of Medial PFC Dysfunction

AX-Continuous Performance Task Reaction Times. For the reaction time data, target (AX) trials and non-target (AY, BX, and BY) trials were analyzed separately, and only correct responses were considered (see Braver et al., 2001). A univariate ANCOVA, covarying for IQ and processing speed, demonstrated that older participants responded significantly more slowly than younger participants on target trials, $F(1, 60) = 6.99$, MSE =

12774.49, $p < .05$, $\eta^2_p = .10$ (see Figure 1A). Non-target trials were analyzed using a mixed ANCOVA with trial type included as a within-subjects factor, age group included as a between-subjects factor and IQ and processing speed included as covariates. Again, a significant age effect was found, with older adults responding significantly slower than younger adults, $F(1, 58) = 12.25$, MSE = 40702.17, $p < .01$, $\eta^2_p = .17$. However, there was no significant main effect of trial type, $F(2, 116) = 1.07$, MSE = 14207.12, $p = .35$, $\eta^2_p = .02$. Finally, the interaction between age and trial type was significant, $F(2, 116) = 3.29$, MSE = 14207.12, $p < .05$, $\eta^2_p = .05$, with older adults exhibiting slowing of BX trials relative to younger adults (Bonferroni-corrected $p < .001$).

AX-Continuous Performance Task Accuracy. Accuracy measures were converted to percentage error scores in order to account for the unequal number of trial types presented. The mean percentage of errors committed in response to the probe letter on each trial type (AX, AY, BX, BY) is shown in Figure 1B. As with the reaction time data, target (AX) and non-target (AY, BX, BY) trials were analyzed separately. A univariate ANCOVA conducted on AX errors showed no significant effect of age, $F(1, 60) = .45$, MSE = 151.79, $p = .51$, $\eta^2_p = .01$. A mixed ANCOVA was then performed on non-target trial percentage error scores with trial type (AY, BX, BY) entered as a within-subjects factor, age entered as a between-subjects factor, and IQ and processing speed entered as covariates. There was no significant main effect of age, $F(1, 60) = .42$, MSE = 1069.05, $p = .52$, $\eta^2_p = .01$. In contrast, the main effect of trial type was significant, $F(2, 120) = 9.12$, MSE = 396.61, $p < .001$, $\eta^2_p = .13$, with more errors committed on AY trials than BY trials ($p < .01$). Importantly, the interaction between trial type and age was significant, $F(2, 120) = 3.38$, MSE = 396.61, $p < .05$, $\eta^2_p = .05$. In particular, younger adults committed significantly more errors on AY trials than older adults (Bonferroni-corrected $p < .025$). Performance on BX and BY trials did not significantly differ between the age groups. Younger and older adults did not differ in terms

of sensitivity (*d'*; AX hit rate versus BX false-alarm rate: M = 0.24, SD = 1.68; M = -0.23, SD = 1.54 respectively), $t(62) = 1.17$, $p = .25$.

- Insert Figures 1A and 1B around here -

Simon Task Reaction Times. For the reaction time data, only correct responses were included in the analysis (see van der Lubbe & Verleger, 2002). To establish that a Simon effect was observed, separate paired-samples t-tests were performed on the RTs on the congruent trials compared to the RTs on the incongruent trials for the two age groups. Both younger and older adults' performance on the two types of trial did significantly differ, with slower RTs on incongruent trials than congruent trials, $t(31) = 3.98$, $p < .001$ and $t(33) = 9.67$, $p < .001$ respectively.

A mixed ANCOVA, including IQ and processing speed as covariates, with congruency as a within-subjects factor and age group as a between-subjects factor was conducted (see Figure 2A). There was no significant main effect of age with younger and older adults performing similarly in terms of reaction times, $F(1, 60) = 3.25$, MSE = 8390.98, $p = .08$, $\eta^2_p = .05$. There was no significant main effect of congruency, $F(1, 60) = 2.59$, MSE = 442.71, $p = .11$, $\eta^2_p = .04$. However, the interaction between age and congruency was significant, $F(1, 60) = 10.25$, MSE = 442.71, $p < .005$, $\eta^2_p = .15$. Age differences in reaction times were largest in the incongruent condition, with older adults responding particularly slower than younger adults (Bonferroni-adjusted $p < .001$. There was a significantly larger Simon effect in older adults than younger adults, $t(62) = 3.51$, $p < .01$.

Simon Task Accuracy. Firstly, separate paired-samples t-tests were performed on the number of errors on the congruent trials compared to the number of errors on the incongruent trials for the two age groups. Both age groups' performance on the two types of trial did

significantly differ, with more errors committed on incongruent trials than congruent trials, $t(30) = 2.26$, $p < .05$ and $t(32) = 5.67$, $p < .001$ respectively.

As there were equal numbers of congruent and incongruent trials, total number of errors were used as a measure of Simon Task accuracy (rather than percentage errors; see Figure 2B). A mixed ANCOVA, with IQ and processing speed entered as covariates, was performed on the total number of errors on the 'congruent trials' and the 'incongruent trials', with congruency as a within-subjects factor and age as a between-subjects factor. With covariates included, younger and older adults committed similar numbers of errors, $F(1, 60) = 2.40$, MSE = 17.04, $p = .13$, $\eta^2_p = .04$. Similarly, the number of errors committed did not differ between congruent and incongruent trials, $F(1, 60) = 5.72$, MSE = 8.43, $p = .41$, $\eta^2_p = .01$. The interaction between age and congruency was also not significant, $F(1, 60) = 1.81$, MSE = 8.43, $p = .18$, $\eta^2_p = .03$. The Simon effect, in terms of errors committed, did not significantly differ between younger and older adults, $t(62) = .98$, $p = .33$.

- Insert Figures 2A and 2B around here -

Discussion

The present study examined the age-related effects on several tasks thought to be sensitive to dorsolateral (DLPFC), orbital (OFC), and medial (MPFC) prefrontal cortex dysfunction across the same group of younger and older adults. Replicating the findings of MacPherson et al. (2002), age effects were observed on the test of DLPFC function (i.e., Self-Ordered Pointing task) but not the test of OPFC function (i.e., the Faux Pas task). As such, executive control and working memory functions appear most susceptible to age-related decline, whereas social or empathic functions appear relatively preserved.

The novelty of the current study resides in the assessment of MPFC functions within the same group of participants also tested on DLPFC and OFC functions. The results show that performance in terms of corrected accuracy on both of the tasks designed to tax MPFC functions was preserved in older individuals. In particular, older individuals performed well across all trial types within the AX-CPT (MacDonald et al., 2005) and committed fewer errors than younger adults on the Simon task (di Pellegrino, Ciaramelli, & Làdavas, 2007). Preserved accuracy in older adults across trial types has previously been observed on both the AX-CPT (Braver et al., 2001) and the Simon task (van der Lubbe & Verleger, 2002).

However, the analysis of reaction time data does point to age-related MPFC dysfunction. In the Simon Task, older adults exhibited a larger Simon effect than younger adults, primarily driven by much slower responses on incongruent trials (see van der Lubbe & Verleger, 2002; Kawai et al., 2012). Meanwhile, in the AX-CPT, older adults show slower responses on both AX and BX trials than their younger counterparts, a pattern consistent with previous observations (Braver et al., 2001; Bialystok, Craik, Klein, & Viswanathan, 2004). However, unlike Braver and colleagues (2001), we did not note a corresponding improvement in AY reaction times for older adults; instead, improvement was evident in accuracy where our older adults committed fewer AY trial errors than younger adults. Furthermore, unlike Chen et al. (1998) or Braver et al. (2001), we did not observe a reduction in sensitivity with age. Therefore, analysis of accuracy alone may be insufficient to detect age-related impairment, and future studies should consider both reaction times and accuracy measures to assess age-related changes in behavior.

The results of the AX-CPT are also in line with the idea of a shift towards a more reflexive approach with age. In particular, older adults appear to wait until the probe appears in order to retrieve the cue when appropriate; hence the slower reaction times on AX and BX trials. In contrast, younger adults appear to maintain the cue actively, affording faster reaction

times when the cue is required for the response. Importantly, this reflexive tendency in older adults may be driven by a working memory deficit, resulting in an inability to hold information in an active, online state. As such, it may be that the age-related impairments noted on the AX-CPT may simply be a result of DLPFC dysfunction, rather than MPFC dysfunction. However, given that age-related deficits were noted on the Simon Task as well, which places fewer demands on the working memory system, it seems wiser to conclude a concurrent impairment of functions related to the DLPFC and MPFC.

It may be that differences in levels of intelligence between samples might explain the age-related discrepancies in AX-CPT accuracy. Considering their high intelligence scores, it could be the case that our older group assessed in the present study were somewhat high functioning and perhaps atypical of the general older population. However, the two-subscale WASI relies heavily upon verbal abilities that are known improve with age (e.g., Cornelius & Caspi, 1987). Furthermore, IQ differences were controlled on a statistical level. Differences in the speed of information processing, too, seems an unlikely explanation for the discrepancy in accuracy findings, as processing speed was also controlled for. The accuracy impairments in previous studies may have been caused by underlying variation in intelligence and information processing abilities, whereas here, once these are controlled for, more subtle age differences are detected in reaction time data only.

In contrast, the age-related impairments in reaction times observed here on tasks associated with MPFC functioning remain after variation in both intelligence and processing speed has been accounted for. Similar attempts have been made to control for processing speed in the Simon Task (van der Lubbe & Verleger, 2002), but not in the AX-CPT. Furthermore, the present study is the only one to have considered both factors when analyzing reaction time data.

A Dorsolateral and Medial Theory of Aging

The dorsolateral theory of aging (MacPherson et al., 2002; Phillips & Della Sala, 1998) links age-related behavioral impairments on tasks that tap abilities associated with activation and volumetric changes in the DLPFC. In particular, the poorer performance of older adults on tasks such as the SOPT is similar to that of patients with damage to the DLPFC. Likewise, the performance of older adults in the present study on tasks associated with the MPFC, such as the Simon Task, is similar to that of patients with MPFC lesions (Baird et al., 2006; di Pellegrino et al., 2007). In particular, both groups exhibit slow reaction times on incongruent trials and trials that require context to be maintained. The pattern of age effects observed here is consistent with reports of longitudinal age-related blood flow decreases (Beason-Held et al., 2007; 2008), volumetric declines (Farokhian et al., 2017), and metabolic impairment (Garraux et al., 1999; Hazlett et al., 2010) within the DLPFC and the MPFC. This suggests that dysfunction associated with the MPFC should be added to our conception of cognitive aging, so that the theory encompasses dorsolateral and medial prefrontal functions.

Of course, this suggested modification to our theory of cognitive aging is preliminary, given our small sample size, and more research into the MPFC and its functional overlap with other prefrontal regions is required. However, the differential effects of age across tests in the same groups of individuals speak against a general age-related frontal lobe decline. PFC regions are heavily interconnected and declining DLPFC integrity and function can have implications for other PFC regions. For example, white matter integrity within the DLPFC predicts decreases in ACC activity during a working memory task (Nordahl et al., 2006), and both regions are increasingly recruited with rising levels of difficulty in executive tasks – such as self-ordered working memory tasks (Chase et al., 2008).

On a similar note, the regional specificity of the tasks involved here must be interpreted with caution. Firstly, the tasks used here as measures of MPFC have also been

associated with DLPFC functioning. For example, in a modified Simon Task involving faces, King and colleagues (2010) observed lateral prefrontal activation. Incongruent trials on a modified Simon Task provokes activation in DLPFC (BA 9), OFC (BA 10), and MPFC (BA 32), when contrasted to congruent trial activation (Fan et al., 2003; see also Kawai et al., 2012). Similarly, Ringholz observed that TBI patients with damage including either the DLPFC or OFC regions exhibited significantly poorer performance than healthy controls (Ringholz, 1989, unpublished doctoral dissertation, as cited in Riccio et al., 2002). Both DLPFC and more medial activation have been noted during the AX-CPT (Paxton et al., 2008; Yoon et al., 2008). However, lateral activation has been particular associated with the cue-probe delay (e.g., MacDonald, 2003; 2005), and given that the AX-CPT used in the present study incorporated no delay, it might be thought to have reduced the possibility of DLPFC involvement.

In regards to the OFC tasks used here, imaging studies suggest that various theory of mind tasks additionally and reliably recruit the frontal pole (Kobayashi, Glover, & Temple, 2007; Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Bzdok et al., 2012). However, differences in task-related activation could explain some of these findings, with story-based tasks activating a relatively circumscribed set of regions compared to cartoon-based tasks (Kobayashi et al., 2007) and scene-based tasks (Wakusawa, Sugiura, Sassa, Jeong, et al., 2007) which are all associated with additional activation of more anterior regions (e.g., medial BA9). While neuroimaging evidence for orbital prefrontal involvement in the Faux Pas task is somewhat lacking, lesion studies point to OFC regions being necessary for success. This may be in part due to the requirement to judge social rule violations (Berthoz et al., 2002) rather than take another person's perspective.

Research has also provided evidence of further prefrontal subdivisions, particularly within MPFC (e.g., Devinsky, Morrell, & Vogt, 1995; Margulies, Kelly, Uddin, Biswal, et

al., 2007). The further distinction between MPFC subregions could help to explain its involvement in seemingly different categories of tasks. For example, evidence suggests that dorsal regions of the ACC may be involved in the more cognitive tasks which rely on performance monitoring and rapid behavioral adaptation (e.g., Bush, Vogt, Holmes, Dale, et al., 2002; Swick & Turken, 2002), whereas rostral regions of the ACC have been implicated in socioemotional tasks often involving self-referential judgements or negative affective stimuli (e.g., Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Phan, Liberzon, Welsh, Britton, & Taylor, 2003). The two tasks chosen in the present study to tap MPFC regions may specifically involve dorsal MPFC regions. Therefore, future studies should include rostral MPFC-tapping tasks such as antisaccades (Polli, Barton, Cain, Thakkar, et al., 2005), viewing negative images (Phan et al., 2003), or emotional Stroop tasks (Etkin et al., 2006) in order to achieve a fuller assessment of MPFC function. However, to date there are no tasks that sufficiently discriminate rostral ACC functions from OFC functions, and all studies implicating MPFC regions in such socioemotional tasks have also implicated OFC regions. Further investigations into age-related functional changes in MPFC would benefit from tasks with specific discriminatory value.

Rubin (1999) has highlighted the importance of subcortical networks in the aging of cognitive functions. This coincides with a wider trend in cognitive neuroscience to identify functional networks within the brain. Rubin associated age-related functional declines with frontal-striatal circuits, and highlighted the role of the caudate in these networks. Many of the functions commonly reported as being the subject of age-related decrements (e.g., speed of information processing, inhibition, executive control) rely on these circuits, and so impairments at any stage in the circuit – not only the cortex – may explain the pattern of age effects (Rubin, 1999). Though none of the regions in the PFC act in isolation, the importance of specific cortical regions to their associated functions must also be considered. Indeed, in

the present study, evidence from both neuroimaging and lesion studies were used to identify areas of the PFC necessary and important for particular functions.

One of the biggest challenges for function-specific theories of aging is the observed decline of more domain-general abilities such as processing speed (Salthouse, 1996) and fluid intelligence (Gong et al., 2005; Phillips & Della Sala, 1998). However, it should be noted that in the present study, as well as in previous studies (Lamar & Resnick, 2004; MacPherson et al., 2002), age effects persisted over-and-above such measures. Furthermore, studies suggest that these abilities may themselves be localized within systems which include particular PFC regions (e.g., Duncan et al., 2000). Although both executive and intelligence tasks appear to share a reliance on particular prefrontal regions (e.g., left DLPFC), executive tasks have been shown to additionally (and uniquely) rely on other prefrontal regions (e.g., right DLPFC; Cox et al., 2014).

In the older age group sampled here, there is evidence to suggest deficits in conflict monitoring and response inhibition; two MPFC functions assessed by the AX-CPT and the Simon task, once the contributions of intelligence and processing speed are removed. In line with suggestions of anatomical shrinking (e.g., Farokhian et al., 2017), performance on tasks which tax the MPFC suggests that the associated functions are impaired with age alongside those associated with the DLPFC. Indeed, this study is the first that allows comparison between performance on tasks associated with dorsolateral, orbital, and medial PFC, within the same individuals. The results of the present study lend support to the idea that different PFC functions show different age-related trajectories – with OFC functions declining later and to a lesser degree than DL and MPFC functions. This suggests a modification to the DLPFC-specific theory of cognitive aging (MacPherson et al., 2002; Phillips & Della Sala, 1998) to include age-related decline in MPFC functions.

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Table 1

Demographic variables for the younger and older age groups.

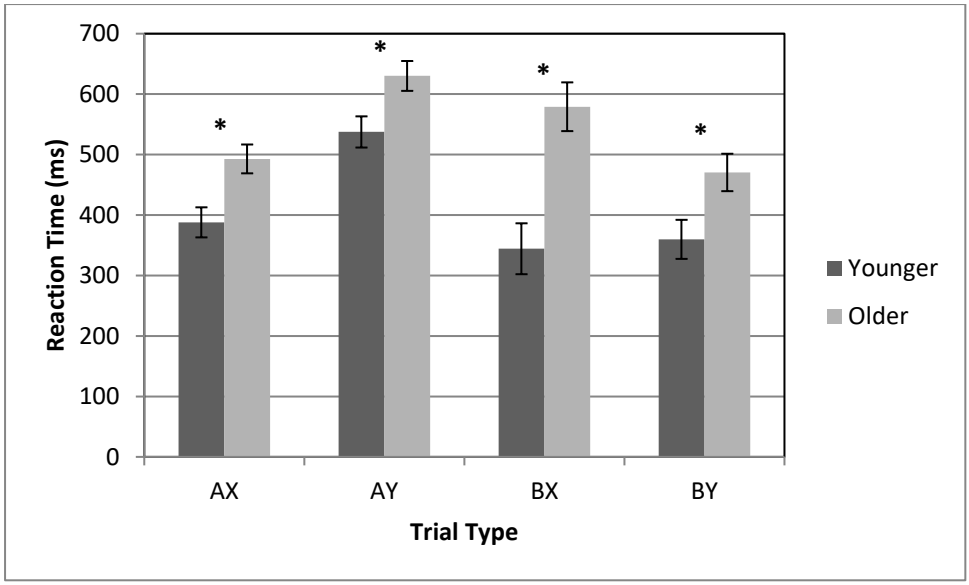
	Younger Mean (SD)	Older Mean (SD)	*t*(62)	*p*	*d*
Education (years)	14.42 (1.52)	16.12 (2.62)	3.20	<.01	0.79
EHI score (range = -100 to 100)	70.82 (42.35)	79.48 (25.64)	1.00	=.32	0.25
ACE-R Score (max = 100)	95.19 (4.81)	95.79 (3.36)	.58	=.57	0.14
WASI FSIQ	118.68 (10.79)	129.15 (7.78)	4.43	<.01	1.11
DF Score (max = 16)	12.29 (2.33)	11.88 (2.00)	.76	=.45	0.19
DSC Score (max = 100)	90.00 (13.37)	72.30 (12.11)	5.56	<.01	1.39

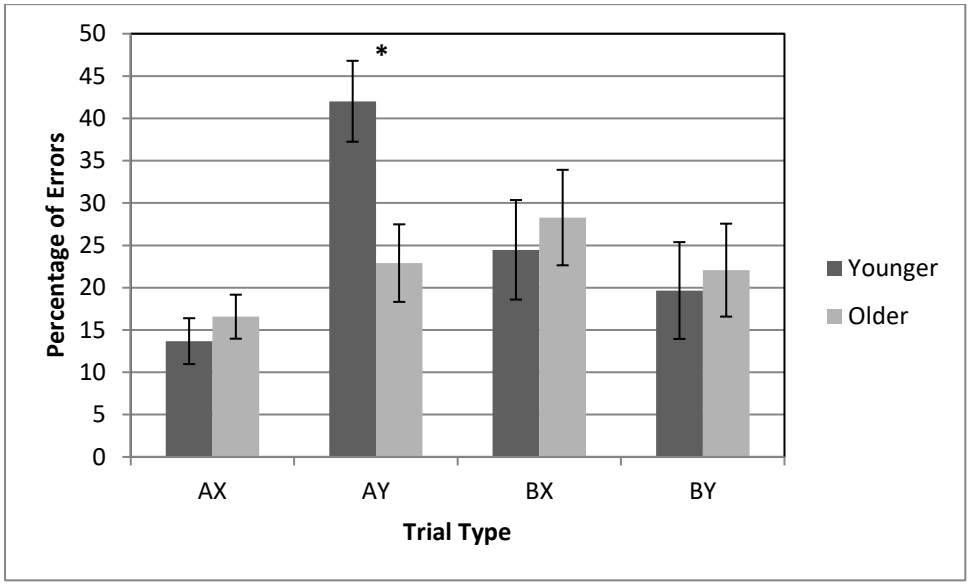
EHI = Edinburgh Handedness Inventory; ACE-R = Addenbrooke's Cognitive Examination – Revised; WASI FSIQ = Wechsler Abbreviated Scale of Intelligence Full-Scale IQ; DF = Digit Span Forwards; DSC = Digit Symbol Coding (WAIS-III).

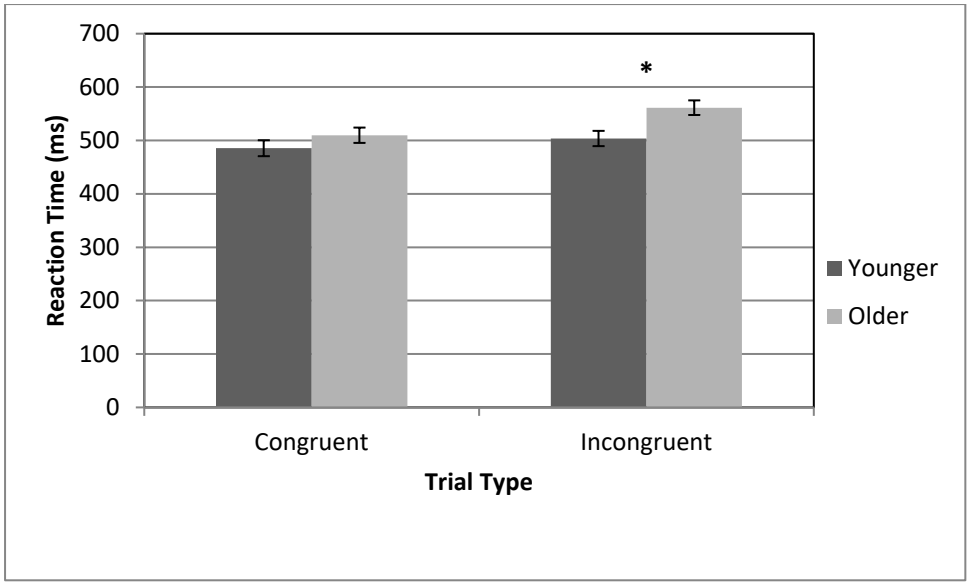
Figure Captions

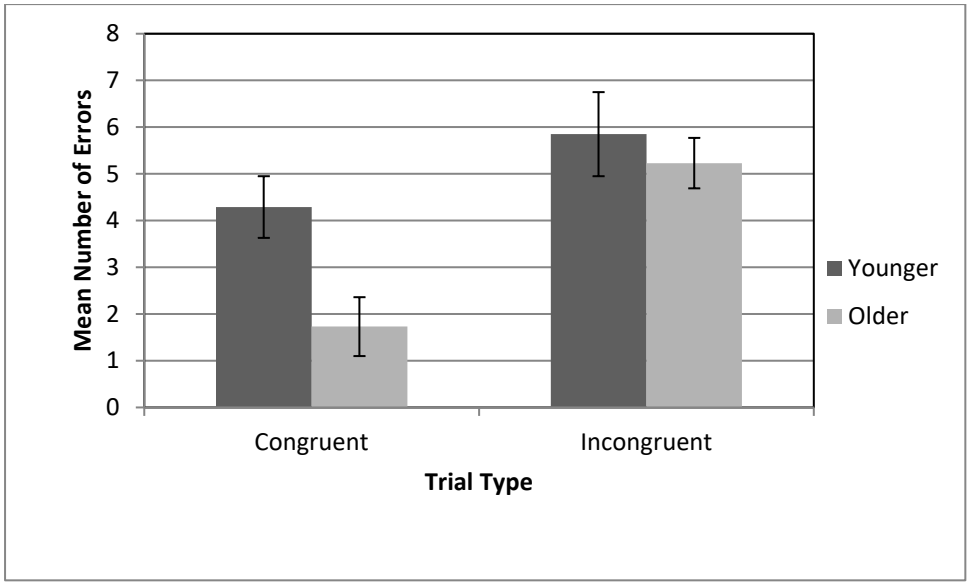
Figure 1: Means and standard errors of (A) reaction times and (B) the percentage error rates on the AX-Continuous Performance task (adjusted for IQ and processing speed), for each of the trial types and split by age group. Significant age differences ($p < 0.05$) identified in the ANCOVA and MANCOVA analyses are highlighted (*).

Figure 2: Means and standard errors of (A) the reaction times and (B) the error rates on the Simon Task (adjusted for IQ and processing speed), for each of the trial types and split by age. Significant age differences ($p < 0.05$) identified in the MANCOVA analyses are highlighted (*).


700
600
500
400
300
200
100
0
Reaction Time (ms)
*
*
*
*
AX
AY
BX
BY
Trial Type
Younger
Older


50
45
40
35
30
25
20
15
10
5
0
Percentage of Errors
*
AX
AY
BX
BY
Trial Type
Younger
Older


700
600
500
400
300
200
100
0
Reaction Time (ms)
*
Younger
Older
Congruent
Incongruent
Trial Type


8
7
6
5
4
3
2
1
0
Mean Number of Errors
Younger
Older
Congruent
Incongruent
Trial Type