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Journal

Psychology and Aging, 30(2)

ISSN

0882-7974

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Publication Date

2015-06-01

DOI

10.1037/pag0000027

Peer reviewed

Published in final edited form as:

Psychol Aging. 2015 June ; 30(2): 475–485. doi:10.1037/pag0000027.

The Double Burden of Age and Major Depressive Disorder on the Cognitive Control Network

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Abstract

Poor cognitive control (CC) is common among older individuals with major depressive disorder (OMDD). At the same time, studies of CC in OMDD with fMRI are relatively limited and often have small samples. The present study was conducted to further examine poor CC in OMDD with early-onset depression, as well as to investigate the interactive effects of MDD and aging on cognitive control. Twenty OMDD, 17 older never-depressed comparisons (ONDC), 16 younger adults with MDD (YMDD), and 18 younger never-depressed comparisons (YNDC) participated. All participants completed the Go level of the Parametric Go/No-Go Test, which requires sustained attention and inhibitory control while undergoing functional MRI. YNDC were faster in reaction times to go targets relative to the other three groups, and the YMDD group was faster than the OMDD group. fMRI effects of both age and diagnosis were present, with greater activation in MDD, and in aging. Additionally, the interaction of age and MDD was also significant, such that OMDD exhibited greater recruitment of fronto-subcortical regions relative to older comparisons. These results are consistent with prior research reporting that OMDD recruit more fronto-striatal regions in order to perform at the same level as their never-depressed peers, here on a task of sustained attention and inhibitory control. There may be an interaction of cognitive aging and depression to create a double burden on the CC network in OMDD, including possible fronto-striatal compensation during CC that is unique to OMDD, as younger MDD individuals do not show this pattern.

Keywords

depression; cognitive control; fMRI; aging

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Conflicts of Interests

INTRODUCTION

The literature in normal aging indicates that multiple cognitive processes, such as working memory, episodic memory, inhibition, processing speed, attention, and executive function, show declines with age (Schaie, 1996). Interestingly, the majority of these processes are ones considered to be within the domain of the cognitive control (CC) network, which mediates top-down, attention-dependent executive tasks such as working memory, decision-making, and task switching (Miller, 2000). Studies investigating the CC network often cite the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, dorsomedial thalamus, and the inferior parietal cortex as key regions in this network (Seeley et al., 2007; Smith et al., 2009). The caudate also likely plays an important role, particularly with regard to regulating cognitive activities through inhibition and initiation (Crosson, Benjamin, & Levy, 2007; Langenecker, Briceno, Hamid, & Nielson, 2007). Consistent with this, literature on the neuroanatomy of normal aging indicates that the prefrontal and parietal cortices, or regions involved in the CC network, are the most strongly affected in the aging brain. Functional MRI studies of healthy older adults commonly observe hyperactivation, relative to younger adults, in the context of equivalent task performance. For example, hyperactivation in prefrontal regions, especially lateral and inferior prefrontal areas, has been found in older adults relative to younger adults during successful trials of tasks requiring response inhibition (Langenecker & Nielson, 2003; Langenecker, Nielson, & Rao, 2004). Less frequently, poorer performance is observed in the context of hypoactivation (Schendan, Tinaz, Maher, & Stern, 2013).

One explanation for this phenomenon of increased activation has been referred to as the Scaffolding Theory of Aging and Cognition (STAC; Park & Reuter-Lorenz, 2009), and it is one of compensation, in which older adults must rely on greater brain resources, or the involvement of additional brain regions, in order to perform at the same level as a younger adult, due to neural and functional deterioration with age (Langenecker & Nielson, 2003). Alternatively, there is evidence that the pattern of hyperactivation may be more diffuse, with some activation nodes supporting compensation, and other nodes potentially the result of dedifferentiation in the specificity of brain regions in relation to given network functions (Cabeza, 2001; Park, Polk, Mikels, Taylor, & Marshuetz, 2001).

The current study asked whether a disease process in late life (i.e., depression) interacts with aging to result in additive or compounded (e.g., interactive) effects of hyperactivation in the aging brain. Both additive and compounded effects describe a pattern of “double burden” from both age and disease processes; however, the amount of burden varies between the two trajectories (Weisenbach et al., 2014b). In an additive model trajectory, age effects are linear, in that the same level of disease-related brain changes are observed in both young and aging cohorts. The slope of decline is not defined differently by age, yet the absolute level of impairment is greater with age and depression. Depression caused a decline, and the additional age decline lowers functional capacity and performance. More dramatically, in a compounded model, disease-related effects are accelerated with aging, demonstrating a significantly greater vulnerability in the aging brain. Major Depressive Disorder (MDD) in late life, or over the age of 65 (hereafter described as older-adult MDD (OMDD), is not a normal part of aging, yet at least 15% of the geriatric population has significant depressive

symptoms (Beekman, Copeland, & Prince, 1999). Studies investigating cognitive functioning in OMDD have discovered striking deficits in functions supported by the CC network on neuropsychological testing (see Tadayonnejad & Ajilore, 2014 for review). Therefore, research has suggested that the underlying neural dysfunction in a common phenotype of OMDD resides in frontal and striatal CC circuits.

FMRI studies comparing OMDD to their older, non-depressed peers are conflicted in observations of hypoactivation versus hyperactivation in regions of the CC network, and there are relatively few published to date. Using a sequence learning task, Aizenstein and colleagues (2006), found patterns of decreased activation in OMDD, relative to never depressed comparisons (NDC) in prefrontal and anterior cingulate regions, including reduced dorsolateral prefrontal cortex and striatal activity. Similarly, a recent study of 11 OMDD demonstrated decreased activation in lateral parietal and frontal regions during an n-back task of working memory, relative to 12 NDC (Dumas & Newhouse, 2014). Additionally, decreased metabolic activity at rest has been observed in the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, as well as diminished functional connectivity between these two regions, during episodes of depression (Aizenstein et al., 2009; Alexopoulos et al., 2012; Alexopoulos et al., 2013). One Positron Emission Tomography (PET) study found bilateral hypoactivation in the dorsal anterior cingulate and hippocampus during both resting state and during a paced word generation task in OMDD compared to controls (de Asis et al., 2001). Another study also found decreased resting cerebral blood flow and glucose metabolism in prefrontal and anterior cingulate regions (Nobler, Pelton, & Sackeim, 1999). In contrast, however, a recent study found that fifteen unmedicated participants with OMDD showed increased activation and additional activated areas within frontostriatal-limbic circuitry when performing a stop signal task compared to healthy nondepressed comparisons (Bobb et al., 2012). The authors interpreted this finding as a compensatory mechanism for increased processing demands and/or increased depression-related limbic activity due to fronto-striatal dysfunction. Disparate findings reported (i.e., hypoactivation versus hyperactivation), may be due to the type of challenge employed (i.e., nature of the task), the difficulty of the challenge (e.g., ceiling effects can mask true behavioral differences in the context of activation differences), variations in how the on and off sampling timing is set up for contrasts, or sample characteristics.

CC network structures have also been shown to be altered in younger adults with MDD (YMDD), as they also demonstrate executive dysfunction (Austin, Mitchell, & Goodwin, 2001). Functional neuroimaging studies find hypoactivation in the dorsal anterior cingulate (Davidson, Pizzagalli, Nitschke, & Putnam, 2002), even in unmedicated adolescents with MDD (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Halari et al., 2009). However, there are also many functional neuroimaging studies that find over-recruitment of fronto-striatal circuits during executive function tasks in MDD; for example, the rostral anterior cingulate, dorsal anterior cingulate, and left dorsal lateral prefrontal cortex have shown increased activation in MDD when performing at the same level as healthy comparisons (Pizzagalli, 2011, for review).

Given the finding that YMDD demonstrate neuroimaging functional changes in the CC network when compared to never-depressed comparisons (NDCs; disease-related effects)

and that older NDCs (ONDC) demonstrate greater functional changes in the CC network compared to younger NDCs (YNDC; age-related effects), it can be proposed that OMDD may result in additive and/or compounded effects of disease in the context of aging, specifically in the CC network. In other words, the presence of MDD in late life increases neural network dysfunction, and possibly greater hyperactivation when performing at a high level; greater than what would be expected from age alone. Interactive effects of age and disease could manifest in behavioral disruptions in performance accuracy or speed, but may also be reflected in increased and more diffuse engagement during successful performance.

The purpose of this investigation was to examine the hypothesis of interactive effects of age and disease (i.e., MDD) on CC. In addition to a comparison of older NDCs to OMDD, both YNDCs and YMDD were included in this study to examine neural differences between OMDD and YMDD, and whether differences between the two young groups would be similar or different to what would be observed in the two older groups. To our knowledge, no studies have examined the specific neurofunctional changes between OMDD and YMDD when engaging the CC network in a 2*2 fMRI design such as this one. We can determine whether the cognitive changes and underlying brain abnormalities observed in OMDD are more closely related to the changes observed in normal aging, or are due to additive or compounded effects of experiencing the effects of MDD and of older age. Our hypotheses were that on performance measures of CC, we would observe an interaction between age and OMDD. That is, OMDD participants will show greater difficulty performing the task than their similarly aged NDCs as well as relative to the younger MDD cohort. In addition, when examining activation patterns during correct behavioral responses, we hypothesize both a main effect of age (increases in frontal regions, more diffuse activation) and MDD (increased activation in the CC network), as well as an interaction between age and MDD on neural activation.

METHODS

Participants

This study was approved by the Institutional Review Board at the University of Michigan, and all participants gave informed consent prior to participation. Forty-seven older adults over age 65 (24 OMDD, 23 ONDC) were recruited through geriatric psychiatry and primary care clinics, clinical research volunteer databases, and community advertisements. An additional two participants were initially recruited for the study but excluded from analyses - one had significant atrophy observed on the anatomical scan and the second had a significant dorsal section of the brain missing due to misalignment of the field of view. Thirty-four younger adults ranging in age from 18 to 33 (16 YMDD, 18 YNDC) were recruited through print advertisements in the community and through a university website designed to recruit local research volunteers. All participants were right-handed, with the exception of one OMDD and one YNDC who were left-handed, and one OMDD who was ambidextrous. All participants gave their written informed consent in order to participate in the study and were paid up to $60.

Exclusionary criteria for all participants included contraindications for MRI, Mini Mental Status Exam (MMSE; cognitive screening measure) score < 24 out of 30, uncontrolled

hypertension or diabetes, any neurological disorder, head injury with loss of consciousness of > 5 minutes, and major medical conditions that could affect the central nervous system. Participants were also excluded if psychotic symptoms, bipolar disorder or schizophrenia was present in the psychiatric interview or if there was current substance use disorder or history of substance dependence within the past five years. Individuals were not excluded on the basis of taking psychotropic medications, though those with "as necessary" anxiolytic usage were encouraged to avoid use the day of the scan. All OMDD participants had age of MDD onset before the age of 55, due to possible etiological differences between early and late onset MDD (Murata et al., 2001; Sachs-Ericsson et al., 2013) and to minimize the likelihood of the contribution of other medical processes (i.e., cardiovascular, metabolic processes) to disease pathogenesis. All MDD participants were actively experiencing a Major Depressive Episode and diagnosed according to the Structured Clinical Interview for the DSM-IV criteria (First, Spitzer, Gibbon, & Williams, 2002). Depression severity was measured with the Hamilton Rating Scale for Depression (HDRS)–17 item (Hamilton, 1967). Both ONDC and YNDC participants had no history of psychiatric illness.

Measures

The Parametric Go-No-Go Test (PGNG; Langenecker et al., 2005) based upon Garavan, Ross, & Stein, 1999; Langenecker & Nielson, 2003; Nielson, Langenecker, & Garavan, 2002) is a test that consists of three separate levels, but only the first level, which focuses on sustained attention and cognitive control, was used for this study. It is completed in 15 blocks each of 28 random letter stimuli. A random serial stream of all 26 letters is presented (black letter in 40-point Times font on a white background computer screen), each letter for 500ms intervals with a 0-ms inter-stimulus interval. The task requires the participant to respond to the target letters ("x," "y," and "z") every time they appear, regardless of order. Over the 15 blocks, the ratio of targets (go events) to non-targets (no-go events) averages to be around 1:8. Participants are told to respond as quickly as possible using the index finger of the preferred hand by key-press on a designated computer keyboard key (letter "n"). Due to the random order of the letters presented and the lack of an inter-stimulus interval, the same target could be presented twice in a row without the participant being able to discern two different targets were presented. In these instances, the second target with the corresponding behavioral data was removed from analyses. This task measures sustained attention, cognitive control, and visuomotor processing speed, and three dependent measures were used: Go accuracy, Go reaction time, and efficiency.

Go accuracy (measuring sustained attention and set maintenance) is computed by dividing the correct target responses by the total number of possible target responses. Go reaction time to hits (measuring processing speed in a multiple target search) is defined to be the average response time for correct targets. Efficiency is a measure that balances reaction time with accuracy, such that those who respond accurately and rapidly have the highest efficiency scores and those who are slower and less accurate have the lowest efficiency scores. The efficiency ratio is computed with the following formula: percentage correct/ reaction time*100 (Gur et al., 1992; Langenecker, et al., 2005).

Procedure

Prior to entering the scanner, participants performed a practice trial of the PGNG test once for familiarity on a laptop using Eprime display software (Schneider, Eschman, & Zuccolotto, 2001). For PGNG Level 1, they were told to make a button-press response each time they saw the letters “x,” “y,” or “z” presented in a visual stream. During scanning, the fMRI-PGNG, Level 1 only, was embedded in a verbal memory task, the Semantic List Learning Test (SLLT; (Langenecker, Caveney, Persad, & Giordani, 2004; Ryan et al., 2012; Weisenbach, et al., 2014) as a distraction between encoding and delayed recall phases. Memory results and analyses from the SLLT will not be discussed, as they are beyond the purview of this paper (see Weisenbach, et al., 2014a). The fMRI-PGNG occurred at 67.75 seconds into each of 15 SLLT blocks. Due to the random presentation of stimuli, there was variability in the number of go stimuli presented per block. However, there were no differences between the four groups for the total number of go stimuli presented.

fMRI procedures were similar in detail and followed the method used in our previous work (Langenecker et al., 2007; Langenecker et al., 2012; Weisenbach, et al., 2014a). Briefly, a GE Signa 3T scanner (release VH3) was used to conduct whole brain fMRI. Thirty-six contiguous oblique-axial slices, each captured in 3.75 × 3.75 × 4 mm voxels, composed the fMRI series. Data were acquired using a reverse-forward spiral sequence in a 24 cm field of view. Slices were acquired serially at 1750 msec temporal resolution for a total of 770 time points in five runs. The task was presented inside the scanner using E-Prime (Schneider, et al., 2001) via reverse projection with prism glasses, and visual acuity correction was used when necessary. Subjects lay supine, and responses for the distractor task were recorded via index finger using a five button key-press apparatus attached to the right hand. Participants wore earplugs inside the scanner in order to reduce the noise experienced from 95 dB to well below 75 dB. Head motion was minimized inside the scanner by using foam padding and a Velcro fixation strap, and movement was specifically evaluated to be certain that movement in the x, y, and z planes was well below 1/2 voxel width in any dimension. High resolution T_1 SPGR anatomical images were obtained after SLLT task administration.

Statistical Analyses

Accuracy (correct hits/total number of Go targets), Go reaction time for correct hits (ms), and efficiency (percentage correct/reaction time*100) comprised the behavioral data entered into SPSS for statistical analysis. Two-way ANOVAs (age group × diagnostic group) were conducted with follow-up Tukey post hoc tests to examine group differences for demographic and behavioral analyses, and chi-square analyses were used for dichotomous variables.

Functional imaging data were processed and analyzed using MATLAB (Lee et al., 2003), SPM8 (Kurth, Luders, & Gaser, 2010) and FSL software (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Functional images were normalized to fit a MNI canonical template, which included reslicing to 2*2*2 mm voxels and subsequently smoothed with a 5 mm FWHM. AlphaSim correction (1000 iterations) was used for all analyses, balancing height ($p < .003$) and extent (264 mm^3) thresholds to achieve a whole brain correction of $p < .05$. The fMRI-PGNG blocks were entered into first level models with the hemodynamic

response function of event-related activation during correct hits as the condition of interest. Group analyses were run in SPM8 and employed a two-way analysis of variance, with age group and diagnostic group as the independent variables, and the correct hits contrast as the dependent variable, followed by post-hoc t tests. In order to determine task-specific, or CC "network" activation, a mask was created from the activation pattern of the whole group. This mask was then applied to each of the other participant groups and contrasts to determine in-network vs. out-of-network activation regions by group. The MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) was used to extract mean signal change during correct hits in significant regions of interest (ROIs), followed by Tukey post-hoc tests for each ROI to examine specific activation differences between groups.

RESULTS

Demographics and Behavioral Analysis of PGNG

There were no significant differences in age between the two older age groups (OMDD *M* age = 66.8; ONDC *M* age = 67.9); however, the YMDD group (*M* age = 26.4) was significantly older than the YNDC group (*M* age = 21.8), $t(1,35) = -4.03$, $p < 0.001$. This age difference is not a likely confound, because PGNG functioning is stable up until the third decade (Votruba & Langenecker, 2013). There were no significant differences in education or sex between any of the groups. The MDD groups both had an average of 15 on the Hamilton Depression Rating Scale and the NDC groups both had an average between 0–1. Mean years of illness for the OMDD group was 39.8 (SD = 16.8) and for the YMDD was 9.7 (SD = 5.9). 78% of the OMDD group and 32% of the YMDD group were taking psychotropic medication.

Analysis of performance for Go accuracy on PGNG-level 1 revealed there was no main effect of age or diagnosis, and there was no significant interaction of age × diagnosis. Go reaction time analysis revealed a significant main effect of age, $F(1, 77) = 32.2$, $p < 0.001$, $d = 1.23$ (Figure 1), in that the older groups had significantly longer reaction times than the younger groups. There was also a significant main effect of diagnosis, $F(1,77) = 6.4$, $p = 0.01$, $d = 0.50$, indicating that the MDD groups had significantly longer Go reaction times than the comparison groups. The interaction of age × diagnosis on Go reaction time was not significant, $F(1,77) = 0.52$, $p = .47$. Post hoc analyses indicated that the effect of age was larger for normal controls (ONDC × YNDC; $p < .0001$, $d = 1.4$) than for MDD (OMDD × YMDD; $p < 0.01$, $d = 1.08$), and that the effect of diagnosis was larger in younger cohorts (YMDD × YNDC; $p = 0.15$, $d = 0.60$) than in older cohorts (OMDD × ONDC; $p = 0.51$, $d = 0.50$). For efficiency, no main effects of age or diagnosis, nor the interaction of age × group, were significant. See Figure 1 for summary of performance data.

fMRI Activation During Correct Hits for Each Group

Overlapping areas of activation were observed for all groups, as displayed within Figure 2, Panel A by group and reported in Supplemental Table 1 (for each group individually). Additionally, as depicted in Figure 3, the number of voxels within and outside the CC network was calculated for each group as a percentage of the entire number of activated voxels within network, using whole sample activation to define the network.

Areas of significant activation in the OMDD group included the right superior temporal, fusiform gyri, lateral globus pallidus, and bilateral middle frontal gyrus.

ONDC demonstrated significant activation in right precentral, medial frontal, superior temporal, fusiform gyri, superior parietal lobule, and claustrum. The left insula and culmen of the cerebellum, as well as bilateral middle frontal gyrus and thalamus were also activated.

YMDD demonstrated significant activation in a number of regions included in the CC network, including right precentral gyrus, cingulate gyrus, middle frontal gyrus, inferior parietal lobule and declive of the cerebellum. There was also activation in left inferior frontal gyrus, insula, precuneus, mammillary body, tonsil of the cerebellum and supramarginal gyrus, as well as bilateral inferior occipital gyrus.

YNDC also demonstrated significant activation in the CC network, including frontal regions (right inferior, medial, and middle frontal gyri, as well as bilateral anterior cingulate), in addition to left superior temporal, inferior occipital gyri, and tonsil and pyramis of the cerebellum. Significant activation was also observed in the right fusiform gyrus, inferior parietal lobule, and thalamus.

Main Effects of Age and Depression on fMRI Activation During Correct Hits

A two-way ANOVA (age group x diagnostic group) for BOLD signal during Correct Hits revealed both main effects of age and diagnosis (Figure 2, Panel B). Nineteen regions, both in and out of network, were significantly different for age (older groups demonstrating greater activation) in numerous frontal areas (right superior frontal and precentral gyri, and bilateral middle and inferior frontal gyri, and anterior cingulate), right precuneus, parahippocampal gyrus, and middle occipital gyrus, left transverse temporal and lingual gyri, and bilateral middle temporal gyrus. The right thalamus and left culmen of the cerebellum were also significantly more active in the older relative to the younger groups. There were no regions for which younger groups demonstrated greater activation than the older groups. Only one region (in-network) was significant for diagnosis (MDD demonstrating greater activation), in the right cuneus. There were no regions where control groups demonstrated greater activation than MDD groups (Table 1).

Interaction of Age and Depression on fMRI Activation During Correct Hits

The interaction between age group × diagnostic group revealed three areas of significant differences: left caudate head (out-of-network), right precentral gyrus (innetwork), and right inferior temporal gyrus (in-network). Extracted activation values demonstrated that all groups deactivated the left caudate, except for the OMDD group. Right precentral activation in OMDD was significantly greater than YMDD and ONDC. In the right inferior temporal gyrus, the OMDD and the YNDC groups demonstrated significantly greater activation than the ONDC (Table 1, Figure 2, Panel B).

Post-hoc analysis on fMRI Activation During Correct Hits

Follow-up post-hoc analyses were conducted to clarify group differences in activation (Table 2). Post-hoc tests revealed that the OMDD group demonstrated significantly greater

activation than the ONDC group in the right precentral gyrus, extending to the edges of the CC network and beyond. There were also many areas clearly outside the CC network more active in the OMDD group relative to the ONDC group, including in the right middle frontal gyrus, left middle occipital gyrus, amygdala, and globus pallidus, and bilateral fusiform gyrus and caudate. CC in-network regions were also significantly more activated in the OMDD compared to the ONDC, including regions within the right anterior cingulate, parahippocampal, supramarginal gyri, cuneus, and mammillary body. There were no regions where ONDC demonstrated greater activation than OMDD.

OMDD also demonstrated greater activation than the YMDD group in a number of regions outside of the in-network mask, including bilateral anterior cingulate, precuneus, and middle occipital gyri, the left middle frontal, superior frontal, middle temporal, and lingual gyri, the left claustrum, caudate, amygdala, and the right uncus, culmen and declive of the cerebellum. Greater in-network activation regions in the OMDD compared to the YMDD involved the bilateral fusiform gyrus, the left postcentral gyrus, and the right parahippocampal and superior temporal gyri, and thalamus. There were no regions where YMDD demonstrated greater activation than OMDD. See Figure 2, Panel C for OMDD activation in comparison to the other three groups.

ONDC demonstrated greater in-network activation than YNDC in the left middle frontal and transverse temporal gyri, the left precuneus, and in the right dentate gyrus. ONDC also demonstrated greater out-of-network activation than YNDC in the left medial frontal and middle temporal gyri, and the right cuneus. There were no regions where YNDC demonstrated greater activation than ONDC.

Finally, the YMDD group displayed greater activation than the YNDC in an out-of-network region in the left cuneus. There were no regions where YNDC demonstrated greater activation than YMDD.

DISCUSSION

In examining the neural functioning of individuals with OMDD (older adults with MDD) during a task involving CC, we determined that OMDD is associated with increased activation in the CC network (compensation) as well as multiple other regions (dedifferentiation) when compared to older never-depressed comparisons (ONDC). Specifically, compared to the ONDC group, OMDD participants demonstrated greater activation in the right precentral and anterior cingulate regions, bilateral middle frontal gyri, and basal ganglia (bilateral caudate and right globus pallidus), and right supramarginal gyrus, all of which are considered to be key regions in the CC network (Seeley et al., 2007). Additionally, the OMDD group showed greater activation in out-of-network regions when compared to their healthy peers, such as in limbic regions (right parahippocampal and mammillary body, and left amygdala), the right cuneus, and bilateral fusiform gyrus. Not surprisingly, the OMDD group demonstrated the most diffuse pattern of activation, with the greatest number of activation regions outside of the CC network, as illustrated in Figure 2, Panel C and in Figure 3. These findings were observed during correct hits on a go task

(PGNG) and within the context of equivalent behavioral performance (reaction time, accuracy, and efficiency ratings) between the two older groups.

This pattern of neural hyperactivation in CC regions was present in older compared to younger groups, and also in the OMDD group relative to ONDC. The within network hyperactivity is consistent with prior reports of neural compensation, as described in the literature (Langenecker et al., 2007; Langenecker & Nielson, 2003; Langenecker et al., 2004). That is, individuals with OMDD require greater neural reserve or activity in order to perform behaviorally at a similar level as their never-depressed peers. Additional regions of hyperactivation outside of CC regions might be indicative of dedifferentiation (Park, et al., 2001). It is striking that many of the regions active within the OMDD group extended well outside what would be considered in-network, as defined by the whole group, while most regions in the ONDC group were within network. This suggests a greater degree of de-differentiation in the OMDD relative to the ONDC group, with greater utilization of task-irrelevant structures. Such a pattern of dedifferentiation has been demonstrated in studies of various pathological states, measuring activation of the default-mode network during task (Hansen et al, 2014; Landin-Romero et al, 2014; Rodriguez-Cano et al., 2014).

This study's novel design of including a younger cohort (aged 18–33) of depressed and never depressed young adults allowed for a direct comparison of OMDD and YMDD (younger adults with MDD), as well as an examination of the interaction between age and depression. When comparing the two MDD groups, the OMDD group demonstrated greater activation than the YMDD group in fronto-striatal, CC areas, such as the bilateral anterior cingulate, right thalamus, and left caudate, as well as numerous other limbic (right parahippocampal gyrus and uncus, and left amygdala), frontal (left middle and superior frontal), temporal (right superior temporal, left middle temporal, bilateral fusiform), parietal (left postcentral, bilateral precuneus), and occipital (left lingual and bilateral middle occipital gyrus) regions. There were no regions of significantly greater activation in YMDD than OMDD. Although these findings may suggest an additive effect of age, the two older adult groups also demonstrated numerous significant differences in activation, as noted above. Therefore, these findings suggest that overactivation observed in OMDD subjects during CC is not related to MDD itself, but to the additional, or compounded burden of MDD combined with aging, to suggest accelerated aging in the context of MDD. This is also evident in Figure 2, where in Panel B, numerous black ROIs demonstrate activation related to age alone; however, far more regions were activated in the OMDD group, as compared to the other three groups (Panel C), both within and outside the CC network than from age alone. Finally, given largely comparable behavioral performances between all groups, this compounded effect of age and depression may be evident in neural activation patterns only, indicating that MDD results in diminished neural resources and efficiency, or advanced neural age in the context of equal physical age.

The sole region demonstrating an effect of diagnosis was in the cuneus. In the context of very large age effects, and of age by depression interaction effects, it suggests that effects of MDD are more modest in comparison to those of age. Specifically, age effects in executive functioning and CC are relatively large, yet more moderate for MDD. Study designs of this type will then be more likely to illustrate age effects, which may to some extent obscure

MDD related effects. The dorsal cuneus is at the interface between visual perception and attention networks, and hyperactivation in MDD could represent an aspect of hypervigilance, as observed in attention and emotion processing paradigms (Briceno et al., In Press; Chan, Norbury, Goodwin, & Harmer, 2009; Johnson, Nolen-Hoeksema, Mitchell, & Levin, 2009).

There were three significant regions of interest when examining the interaction between age and depression. Activation in the right inferior temporal gyrus was significantly greater in the OMDD and YNDC groups compared to the ONDC group. Right precentral gyrus activation, or the primary motor cortex, was significantly greater in OMDD than both the YMDD and ONDC groups. Additionally, the left caudate head was significant in the interaction model, and further analysis revealed that all groups deactivated the head of the caudate during the task, except for the OMDD group, which demonstrated increased activation. The caudate plays an integral role in CC network functioning, and the interaction leads to further questions and points of discussion. In addition to the basal ganglia's involvement in regulating movement, it is also involved in enhancing selected cognitive activities while simultaneously suppressing competing or irrelevant stimuli (Braaten, Moore, Cooley, & Stringer, 2010). The OMDD hyperactivation in the caudate and precentral gyrus, when other groups are showing deactivation, may be reflective of a failure in inhibitory feedback projections in motor and cognitive functions. It should be noted, however, that interaction effects, especially those in neuroimaging studies where cell sizes are often small, may be unreliable and more prone to type I error and should be interpreted with caution.

There are a few limitations that should be considered in interpreting results and before generalizing findings to the wider population of individuals with late-life depression. First, our OMDD sample was highly educated and was classified as having depression of early-onset (< age 55), which may not be representative of all individuals with OMDD. Second, because all MDD participants were actively depressed, it is not clear whether their functional patterns represent state, or trait effects of depression. Additionally, because this is not a longitudinal study, it is not clear the extent to which our functional findings might be indicative of incipient cognitive decline, or how the burden of illness over time may differ across the OMDD group. Finally, the majority of MDD patients were taking antidepressant medications, which may impact imaging findings, although the samples are underpowered to consider the impact of medication on activation.

The present study shows that age considerations are an important, and perhaps overpowering feature, for understanding MDD course; features of illness that may be present in the early stages of illness may be very different than what is observed in later life. Apart from the well-known heterogeneity in OMDD individuals, the findings from this carefully screened and selected MDD sample are consistent with an advanced, additive aging model of MDD. MDD may work to decrease efficiency and load tolerance in given cognitive control circuits over the course of chronic illness. Recruitment and dedifferentiation tend to be present in the context of equal performance and slowed processing. CC circuitry may be an important target in attaining and retaining wellness (Pizzagalli, 2011), as well as a target for remediation. This could potentially be targeted through adaptive therapies like problem

solving therapy or similar treatments, and may include cognitive remediation (Cicerone et al., 2005; Cuesta, 2003; Huckans et al., 2013).

Moving forward, future studies involving specific matching by age and sex, as well as investigation of tighter age windows might diminish the relatively greater influence of age on any other potential effects observed. In addition, longitudinal designs can more effectively disentangle these sorts of challenging interactions. They require large sample sizes and are expensive. An alternative is accelerated longitudinal designs, where some of the age specific effects can be modeled within the context of disease progression. In addition, it may also be interesting to investigate patterns of activation during rest, to understand whether default mode network is differentially active on- and off-task in the OMDD group. The challenges in studies of OMDD remain formidable, with possible interactive age and disease processes masked within large age effects, and thoughtful and careful designs are necessary to better test double burden models of age and MDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Faunding: This research was supported by funding from the University of Michigan Depression Center (SLW, SAL), University of Michigan fMRI Laboratory (SLW, SAL), the Michigan Alzheimer's Disease Research Center (SLW, SAL P50 AG008671), the National Alliance for Research on Schizophrenia and Depression (SAL). We also thank Ciaran Considine, Brennan Haase, Kathleen Hazlet, Nadia Huq, Lindsay Franti, Alison Kade, Rachel Kay, Kortni Meyers, E. Michelle McFadden for their contributions to this project in data collection and processing. This work was presented in part at the 2014 Annual Meeting of the International Neuropsychological Society.

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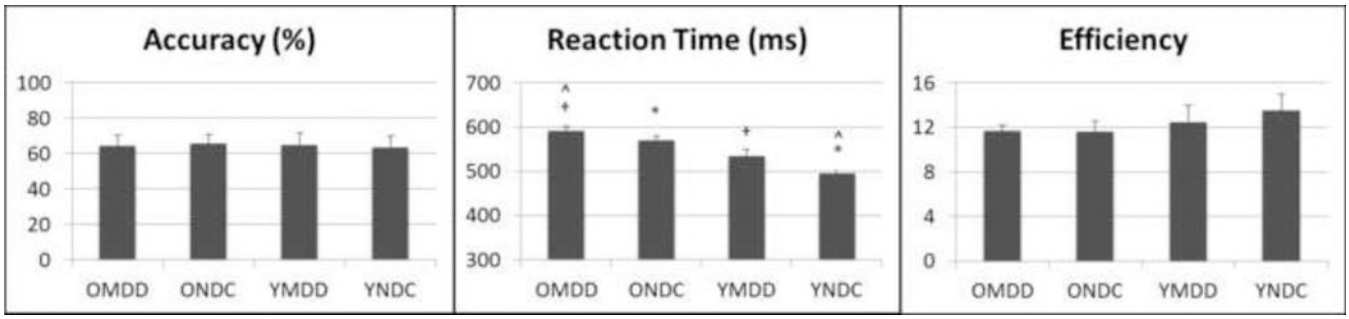

Figure 1. BEHAVIORAL PERFORMANCE DURING PGNG-LEVEL 1 (means and standard error bars).

Illustrates equivalent performance for accuracy and efficiency and significantly different reaction times between groups. ^. OMDD > YNDC, $p < 0.001$; $d = 1.7$, *. OMDD > YMDD, $p < 0.001$; $d = 1.4$, >+. ONDC > YNDC, $p = 0.005$; $d = 1.08$

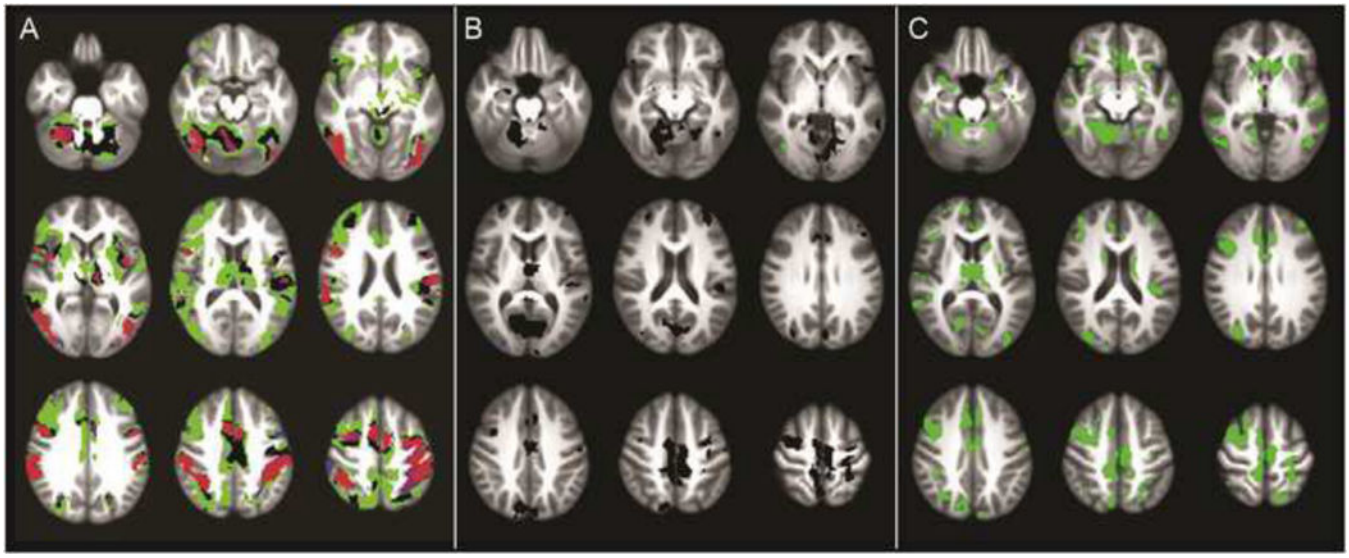

Figure 2. INDIVIDUAL GROUP SIGNIFICANCE MASKS AND BETWEEN GROUP DIFFERENCES IN COGNITIVE CONTROL NETWORKS BASED UPON AGE AND DEPRESSION.

Panel A illustrates areas of convergence in Go networks across all four groups (red), at least three groups (YMDD, ONDC, OMDD in purple), only in the older groups (black), only in the MDD groups (blue), and only in the older MDD group (green). Panel B illustrates the main effects of diagnosis (MDD > HC in blue), age (Older > Younger in black), and the interaction between diagnosis and age (green). Panel C illustrates the targeted contrast of OMDD > all other three groups in the posthoc analysis about double burden of age and disease (green).

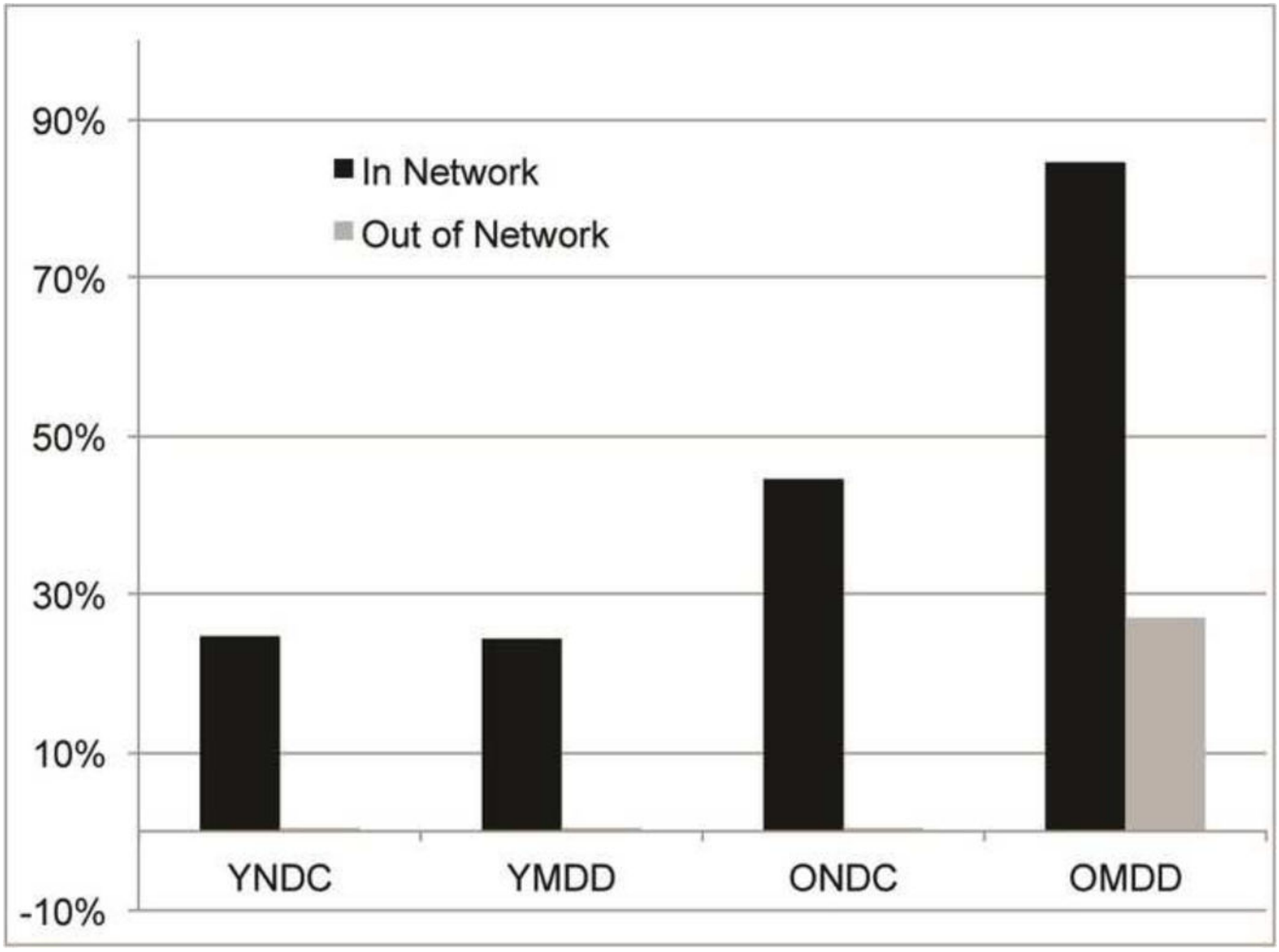

Figure 3. PERCENTAGE OF ACTIVATED VOXELS WITHIN AND OUTSIDE NETWORK BY GROUP.

Within-network is derived from suprathreshold voxels within the whole sample activation map by group. Outside-network network is calculated by the number of suprathreshold voxels outside the cognitive control network, expressed as a percentage of the total number of voxels within the entire sample cognitive control mask.

Table 1 A-C.

Main Effects of Age and Depression and their Interaction on fMRI Activation During Correct Hits

			MNI Coordinates				
Lobe	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
A. Main Effect of Age							
Older Groups > Younger Groups							
Frontal	***Middle Frontal**	**6**	**30**	**−6**	**64**	**4.2**	**3992**
		10	−34	46	18	4.7	1432
	Middle Frontal	9	−46	24	32	3.4	568
		10	−42	50	6	3.4	384
	Inferior Frontal	47	−50	16	−4	3.7	1144
	*Inferior Frontal	47	46	22	−12	3.3	632
	*Superior Frontal	10	30	46	22	3.5	1032
	Anterior Cingulate	32	−4	24	34	3.9	968
	*Anterior Cingulate	24	2	16	38	3.6	432
	*Precentral	6	38	6	36	3.5	392
Parietal	*Precuneus	7	4	−44	72	5.3	30848
Temporal	*Transverse Temporal	41	−46	−28	16	3.5	1464
	Middle Temporal	21	−62	−44	0	5.0	896
	*Middle Temporal	37	66	−42	2	3.7	664
	Parahippocampal	34	24	−8	−20	3.7	456
Occipital	Lingual	18	−4	−72	8	5.0	35528
	*Middle Occipital	19	34	−80	24	3.5	616
Subcortical	*Thalamus (MDN)	--	2	−10	10	3.6	1440
Cerebellum	*Culmen	--	−40	−50	−18	3.4	368
Younger Groups > Older Groups							
None							
B. Main Effect of Diagnosis							
MDD > Controls							
Occipital	*Cuneus	18	30	−90	4	3.4	288
Controls > MDD							
None							
C. Interaction of Age by Diagnosis							
Frontal	*Precentral	6	50	−2	46	3.1	264
Occipital	*Inferior Temporal	--	44	−62	2	3.4	448
Subcortical	Caudate Head	--	−14	20	−8	3.6	272

Notes. OMDD: Older major depressive disorder; ONDC: Older never depressed comparisons; YMDD: Younger major depressive disorder; YNDC: Younger never depressed comparisons. MDN: Medial Dorsal Nucleus.

*Denotes in-network regions (network derived from **whole group activation**).

Table 2.

Group Comparisons of fMRI Activation During Correct Hits

				MNI Coordinates				
Groups	**Lobe**	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**
OMDD > ONDC								
	Frontal	*Precentral	6	36	2	40	4.3	3256
		Middle Frontal	6	24	22	56	3.3	384
			11	28	36	−18	3.8	336
		*Anterior Cingulate	32	12	22	34	3.3	304
		Precentral	9	44	20	40	3.2	264
	Temporal	Fusiform	20	52	−22	−24	4.2	992
			20	−44	−16	−26	3.5	1312
		*Parahippocampal	19	48	−40	−2	3.7	496
	Parietal	*Supramarginal	40	42	−38	38	3.3	440
	Occipital	*Cuneus	18	30	−90	2	3.5	400
		Fusiform	19	42	−64	0	3.9	344
		Middle Occipital	18	−34	−84	6	3.7	336
	Subcortical	Caudate Head	--	−14	20	−8	4.5	2736
		Caudate Body	--	16	8	16	3.6	392
		*Mammillary Body	--	6	−10	−4	3.7	408
		Amygdala	--	−24	0	−16	3.3	304
		Lateral Globus Pallidus	--	−30	−12	4	3.3	280
ONDC > OMDD								
	None							
OMDD > YMDD								
	Frontal	Anterior Cingulate	32	−4	24	34	4.7	6344
			32	6	52	6	3.3	368
			25	8	22	−8	3.5	520
OMDD > YMDD								
	Frontal	Middle Frontal	9	−48	24	32	4.4	5848
		Superior Frontal	10	−22	60	−12	3.4	296
	Parietal	Precuneus	7	4	−44	72	4.7	46600
			7	−8	−60	48	3.2	376
		*Postcentral	3	−56	−12	44	4.4	496
	Temporal	*Parahippocampal	19	48	−40	0	3.8	1904
		*Fusiform	37	−50	−56	−14	4.1	1080
			37	50	−62	−6	3.4	808
		Middle Temporal	21	−62	−44	0	3.6	296
		*Superior Temporal	41	56	−30	16	3.4	288

Groups	Lobe	Region	BA	MNI Coordinates x	y	z	Z	mm³
		Uncus	28	34	4	−22	3.6	288
	Occipital	Lingual	18	−6	−74	8	4.0	8096
		*Middle Occipital	18	−36	−82	6	3.4	448
		Middle Occipital	19	34	−84	18	3.2	400
			18	−16	−98	22	3.6	320
		*Fusiform Gyrus	19	−48	−66	−2	3.3	424
	Subcortical	*Medial Dorsal Nucleus of Thalamus	--	4	−14	12	4.3	3768
		Claustrum/Insula	--	−30	30	−2	4.8	2536
		Caudate Head	--	−14	20	−8	4.1	2120
		Amygdala	--	−26	−2	−22	3.4	448
	Cerebellum	*Culmen	--	16	−56	−8	4.0	6992
		Culmen	--	12	−26	−34	3.5	456
		Declive		22	−78	−18	3.2	784
YMDD > OMDD								
	None							
ONDC > YNDC								
	Frontal	Medial Frontal	6	−8	−20	68	4.0	5440
		*Middle Frontal	6	−34	−10	50	3.8	792
	Temporal	*Transverse Temporal	41	−46	−24	14	3.2	528
		Middle Temporal	37	−62	−44	−2	4.3	496
	Parietal	*Precuneus	7	−32	−42	56	3.8	696
	Occipital	Cuneus	19	4	−80	40	4.1	11752
	Cerebellum	*Dentate	--	18	−56	−22	3.8	1248
YNDC > ONDC								
	None							
YMDD > YNDC								
	Occipital	Cuneus	18	−2	−88	24	3.4	416
YNDC > YMDD								
	None							

Notes. OMDD: Older major depressive disorder; ONDC: Older never depressed comparisons; YMDD: Younger major depressive disorder; YNDC: Younger never depressed comparisons.

*Denotes in-network regions (network derived from whole group activation).