Investigating the relationship between age of onset of depressive disorder and cognitive function

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Key Points

1) Using an online dataset of 7344 individuals over 50 years with depression, we investigated whether there are differences in cognitive function profiles between individuals who developed a depressive disorder before the age of 40 (early-onset), and those who developed a first episode of depression between the age of 40 to 60 (midlife-onset) and after the age of 60 (late-onset).
2) Participants with midlife-onset depression (40-60 years) or late-onset depression (> 60 years) performed significantly worse on the verbal reasoning task, compared to participants with early-onset depression (< 40 years). Furthermore, participants with midlife-onset depression (40-60 years) performed better on the paired-associates learning task than participants with early-onset depression.
3) Although this study found that executive function is more impaired in late onset compared to early onset depression the most significant factor in overall cognitive impairment in patients with depression was the current severity of depressive symptoms.

Keywords: age of onset, depression, cognitive impairment, early onset, late onset, mid-life onset, cognitive function.

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ABSTRACT

Objectives: Depressive disorder is commonly associated with impaired cognitive function; however, it is unclear whether the age of onset of the first episode of depression, current depression severity or historical severity of depressive episodes are associated with cognitive performance.

Methods: This study examined baseline cross-sectional data from the ongoing online PROTECT study. 7344 participants, 50 years or older, with a history of depression and no diagnosis of dementia were divided into 3 groups according to age of onset of their first depressive episode; early-onset, midlife-onset and late-onset. Performance on measures of visuospatial episodic memory, executive function, verbal working memory and visual working memory were evaluated. Demographic and clinical characteristics such as age, education, severity of depressive symptoms during their worst previous depressive episode and current depression severity were included in multivariate regression models.

Results: The late-onset depression group scored significantly lower on the verbal reasoning task than the early-onset group while there were no significant differences found on the other tasks. Participants with midlife-onset depression performed better in the visual episodic memory tasks, but worse on the verbal reasoning task, than participants with early-onset depression. Current depression severity was negatively correlated with all four cognitive domains, while historical severity score was found to be significantly associated with cognitive performance on the verbal reasoning and spatial working memory tasks.

Conclusions: The most important indicator of cognitive performance in depressive disorder appears to be current, rather than historic depression severity, however late onset depression may be associated with more executive impairment than an early age of onset of

the first depressive episode.

INTRODUCTION

Major depressive disorder is common in later life and associated with substantial disability and poor quality of life [1]. Moreover, depression leads to significant morbidity and mortality [2], with estimates of an annual prevalence of 6.6% and a lifetime prevalence of 16.2% [3]. If a first episode of depression occurs after the age of 65 years the term later-onset depression (LOD) is used. Cognitive impairment may occur in major depressive disorder at any age and different patterns of cognitive difficulties in LOD compared with early onset depression (EOD) have been reported [4–6]. However, results have been conflicting, with greater executive dysfunction demonstrated in patients with LOD than EOD in some studies[4,5,7–9] with others finding the reverse [10,11]. Similarly, a number of studies have shown that patients with LOD are more impaired in memory function [5,9,11–14], specifically in episodic memory [14,15], while others have had opposite results [4,8], or found similar patterns of cognitive impairment in LOD and EOD patients [4,16–18].

Depression in late life has been identified as a risk factor for cognitive decline and specifically for Alzheimer's disease and vascular dementia[19–21]. Mid-life depression has also been found to increase the risk of dementia by 20% [22]. However, it remains unclear as to whether depressive symptoms in late life are a prodromal symptom of dementia [23] or an independent risk factor for subsequent dementia [24–27] or both. To help disentangle this relationship an initial step is to clarify the pattern of cognitive impairment in depression, and whether this pattern is associated with the age of onset of depression in individuals without dementia. The mechanisms underlying cognitive impairment associated with depression may differ depending on age of depression onset. An early onset of depression may be associated with repeated episodes and a more severe and chronic course of illness

[28,29]. This may, in turn, be associated with hippocampal damage [30], potentially related to prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol release [30–32]. Additionally, EOD may be more associated with genetic factors [33], a family history of mood disorders [34,35], comorbid personality disorders and higher levels of neuroticism [36], than LOD.

It has been found that mid-life depressive symptoms in women may be related to menopausal transition and fluctuations of hormones may affect brain function[37]. Therefore, if triggered by different mechanisms, mid-life onset depression may have a different presentation of cognitive impairment than EOD and LOD. It has been suggested that cognitive impairment in LOD may be associated with frontostriatal dysfunction[11,38], cerebrovascular disease [38–42], subcortical white matter lesions [32,38,41], neurodegenerative processes [9,11,43–46], and structural brain abnormalities [4] including hippocampal atrophy [31,47–52], and decreased gray matter volume [20].

Some theorise that, rather than age of onset, depression severity could be the determinant of the nature of the cognitive impairment for some domains such as episodic memory [53], executive function [53–55], processing speed [53,54] and semantic memory [55]. This study aims to assess whether age of onset of depression, current depression severity or historical severity are associated with cognitive performance among mid- and late-life population with no diagnosis of dementia. We aimed to identify differences in cognitive function profiles between individuals who developed a depressive disorder before the age of 40 (early-onset), and those who developed a first episode of depression between the age of 40 to 60 (mid-life onset) and after the age of 60 (late-onset). On the basis of the potentially differing mechanisms behind early-onset and late-onset depression and

previous results reported in the literature we hypothesized that individuals with late-onset depression (>60) will have a different profile of cognitive impairment compared with individuals with midlife onset (40 to 60) and early-onset (<40) and specifically that memory impairments will be more impaired in late-onset individuals compared to early-onset individuals, while early-onset individuals will show more impairment in executive function[10,11].

METHODS

Study Design and Participants

This study uses baseline data from the PROTECT study. PROTECT is an ongoing study initiated by King's College London (www.protectstudy.org.uk), launched in November 2015 to understand how the functioning of the brain changes as we age. Inclusion criteria for the PROTECT study are adults over the age of 50 years, who live in the UK, have a good working understanding of English and are able to use a computer with Internet access. Participants who have an established diagnosis of dementia are excluded. Potential participants registered via the online website, downloaded the study information sheet and provided consent via an approved online platform. If participants had answered 'yes' to the question "Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?" they were subsequently asked questions regarding the onset and severity of depressive symptoms and were included in the current analyses.

Data Collection

Demographic, Lifestyle and Medical Data Collection

After enrolment in the study, participants completed online baseline questionnaires of demographic information (age gender, education, ethnicity), medical history and lifestyle information. For the current analyses variables including age, level of education, gender, history of stroke, current depression severity, historical depression severity which is the severity of depressive symptoms during their worst previous depressive episode and the age of onset of depression were included. These factors were hypothesised as being potentially relevant to cognitive function based on previous studies assessing cognitive function in this cohort [56].

Cognitive Assessment

In order to assess baseline cognitive function, the PROTECT study used a validated online cognitive test package containing four tasks [57]; 1) Verbal reasoning test (VR), which assesses a combination of grammatical and reasoning skills (executive function) [58]; 2) Digit span task (DS), which measures verbal working memory by assessing the ability to remember a sequence of numbers [56]; 3) Paired associate learning task (PAL), which assesses visuospatial episodic memory [59] and 4) Self-ordered search test (SOS), which assesses complex visual working memory [60]. Each task was performed online by participants on three occasions during one week to provide a baseline assessment. Please see the supplementary methods section for further description of the cognitive tasks.

Depression Assessment

Current Depression Severity

An online version of the Patient Health Questionnaire 9 (PHQ-9) was used in order to assess participants' current depression severity.

Historical Depression Severity

A historical depression severity score was created from 10 questions that asked participants about the frequency and severity of a range of depressive symptoms during a two-week period in their life when their depression was at its worst. Please see supplementary methods section for detailed descriptions of the PHQ-9 and historical severity measures.

Variables Included in the Analysis

Education, exercise, age, current depression severity, historical depression severity, stroke, gender and age of onset of depression independent variables were included in the

regression models.

Current depression severity score was assessed by the total score on the online version of the PHQ-9 questionnaire and used as a continuous variable in the analysis.

Historical depression severity score was assessed by total score on the historical severity questions as above and used as a continuous variable in the analysis.

Participants provided a response to “About how old were you the FIRST time you had a period of two weeks like this (episode of depression)?” and 3 categories were created according to their response. The three categories are in the following:

1) <40 years (early-onset)

2) 40-60 years (midlife-onset)

3) >60 years (late-onset)

The early-onset group (<40) were used as a reference group in the regression analysis.

Statistical Analysis

Multivariate regression analyses were conducted to see if age of onset of depression, current depression severity and historical depression severity predicted the four different cognitive measures. Separate analyses were conducted with the average performance across the three sessions for each of the four cognitive measures (DS, PAL, VR and SOS) as the dependent variable and independent variables (age of onset of depression, current depression severity, historical severity of depression as main variables of interest and age, education, exercise, stroke and gender as covariates) were included into the model using the enter method. Dummy variables were created for all variables with ordinal responses.

The dependent variables were summary scores on the four cognitive tasks. Normal

distribution of raw data and residuals were examined using histograms and Q-Q plots, and the data was winsorized (outliers replaced with mean score +/- 2.5 SD). Assumption of independence of observations was checked using the Durbin-Watson statistic and multicollinearity was excluded by inspecting correlation coefficients and Tolerance/VIF values. Heteroscedasticity was assessed by examining scatterplots of predicted residuals. As there was evidence of potential heteroscedasticity in the data, heteroscedasticity consistent standard errors were calculated [61]. All analyses were conducted using SPSS v 24 software.

RESULTS

Between November 2015 and April 2016, 7344 participants completed four baseline cognitive tasks and questionnaires and were included in the current analyses, according to their positive response to “Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?”, as these participants had provided data regarding onset of depression and historical severity of depressive symptoms. Demographic information of the 7344 included participants is shown in Table 1. Means scores in each cognitive task for early-onset (N=4562), midlife-onset (N=2402) and late-onset groups (N=380) are shown in Table 2.

Summary of The Model

The results of the multivariate regression with forced entry indicated that the overall model with all variables included was significant for each of the four cognitive tasks as shown in Table 3.

Analysis of Independent Variables

Age of Onset of Depression

Compared to the early-onset depression group (<40 years), the late onset depression group (>60 years) demonstrated lower performance on the verbal reasoning task (ß = -1.1147, SE=.4521, p=0.0137), however no significant differences between late and early onset depression groups were detected on any of the other cognitive tasks. Moreover, in the mid-life onset group (40-60 years) significant differences in the paired associates learning and verbal reasoning task, compared to the early-onset group, were detected. The midlife onset group demonstrated higher scores on the paired associates learning task (ß =.0620, SE=.0184, p<0.001), and a negative co-efficient on verbal reasoning (ß = -.4730, SE=

.2144, p=0.0274) compared to the early-onset group. Multiple linear regression models reporting coefficients for the four cognitive tasks are shown in Table 4.

Current Depression Severity

For all four cognitive tasks, a significant negative relationship with current depression severity was found (SOS ß = -.0230, SE=.0065, p=.0004; DS ß = -.0204, SE=.0045, p<.001; PAL ß = -.0081, SE=.0024, p=.0006; VR ß = -.0647 SE=.0278, p=.0201).

Historical Depression Severity

Historical depression had non-significant negative effects on paired associates task and digit span task. There was a positive association between historical severity and performance on the verbal reasoning task (ß =.0578, SE=.0248, p=.0201) and a negative association between historical severity and self-ordered search task (ß =-.0118, SE=.0056, p=.0348).

Education, Age, Exercise, Gender and Stroke

The results of the education, age, exercise, gender and stroke variables are shown in Table 4. Compared to lowest level of education (GCSE), all education groups showed significant positive associations with performance on the verbal reasoning tasks. All levels of education except vocational level of education were associated with higher scores on the digit span task; all levels of education except A level of education were associated with higher performances on the self-ordered search task and finally only undergraduate and postgraduate education were significantly associated with higher scores on the paired associates task.

Age had a significant negative effect on performance of all of the four tasks. Please see supplementary methods section figure 1 for the effect of age on cognitive tasks.

Female gender was negatively associated with performance on the self-ordered

search and digit span tasks.

Having a history of stroke was found to negatively associated with self-ordered search task and verbal reasoning task.

Exercise was associated with better performance on digit span task, paired associates learning task and verbal reasoning task.

DISCUSSION

In our study of more than 7,000 older adults with a history of depression, a late onset of depression was associated with impaired performance on the verbal reasoning task, compared with an early onset of depression. No significant differences were detected between those with late-onset depression (>60 years) and early-onset depression (18-40 years) for digit span task, paired-associates learning task and self-ordered search task. Participants with midlife-onset depression (40-60 years) performed better on the paired-associates learning, but worse on the verbal reasoning task than participants with early-onset depression. Higher severity of current depression was associated with lower performance on all four cognitive tasks, while historical depression severity was associated with lower scores on the self-ordered search task and higher scores on the verbal reasoning task. The significant effects of depression on cognitive task performance persisted when covariables known to be associated with cognitive performance (such as education, age, exercise, history of stroke) were included in the analyses.

Contrary to our initial hypotheses, although the analysis found a significant difference between late onset depression and early onset depression in verbal reasoning, this was more impaired in the late onset, rather than early onset group, as hypothesised. There were no significant differences between late onset depression and midlife or early onset depression for digit span, paired-associates learning task and self-ordered search task. Our results are consistent with a number of previous studies [4,16–18,62], but differ from others [4,6,9,11,15]. Few previous studies examining the difference in cognitive deficits in early vs late onset depression have controlled for the effect of depression severity and educational attainment and thereby our study makes an important contribution. There are several

possible explanations for the lack of association between age of onset and cognitive performance on three tasks in our study: Firstly, cognitive differences between EOD and LOD individuals might be masked by the cognitive effects of an ongoing (current) depressive episode. It is further possible that, even if controlling for these effects for both EOD and LOD, different structural changes and mechanisms, like prolonged toxic effects of depression for EOD and age related structural cerebral damage for LOD, may lead to equivalent cognitive impairments [16]. Furthermore, another possibility is that as they age, EOD individuals may subsequently develop similar underlying pathological changes seen in people with LOD and therefore show similar neuropsychological and clinical features [4].

Additionally, the current study revealed that current depression severity is negatively correlated with all four cognitive domains; this substantiates previous findings in the literature [53,63–65]. Nevertheless, no significant correlation was identified between historical depression severity score and visuospatial episodic memory and verbal working memory. This highlights that historical severity of depression might not have an effect on performance in these domains later in life, in contrast to some studies reporting that cognitive impairments persists even after remission [66–69]. Surprisingly, we found a positive relationship between historical depression severity and verbal reasoning, which is at odds with previous findings [66,70–72]. Conversely, we found a negative relationship between performance on the self-ordered search task, which requires both executive and visual working memory processes, and historical depression severity. This is in line with the literature that executive function is negatively associated with depression [66,70–72]. Further assessment of executive function using other tasks would be useful but was unfortunately not available in this dataset.

Another finding of this study is that participants with early-onset depression performed worse on the paired associates learning task than participants with midlife-onset depression, indicating more impaired visuospatial episodic memory in EOD. This result is in line with previous studies that showed episodic memory impairments in individuals with EOD [4,8]. One explanation might be that people with early onset depression have more frequent and longer episodes, which according to the glucocorticoid cascade hypothesis, may lead to hippocampal damage through prolonged activation of the HPA axis [30–32], although this could not be tested with the current dataset. Participants with early-onset depression had better verbal reasoning scores compared to participants with midlife-onset depression and late-onset depression. This is consistent with some studies that have reported differences in executive function between early- and late-onset depression [4,5,7–9] , but not with others that have reported no difference [16,17,65]. This finding shows that the association between LOD and age related brain diseases[45], such as concurrent cerebrovascular disease[40,44,65] and fronto-striatal white matter abnormalities[7,73,74] may differentiate the neuropsychological profiles of LOD and EOD. Of note, the majority of previous studies have only used two age of onset groups; early-onset and late-onset, defining groups by the age of 60 or 65 years. Previous studies have not been able to differentiate between cognitive profiles in early and midlife onset depression. There is a reported increased dementia risk in those with midlife depression [22] and there are a number of psychosocial and hormonal changes that occur in midlife which may be associated with depression and different patterns of cognitive difficulties [37]. There is therefore a need for further investigation into cognitive impairments following midlife-onset depression.

Our results are in keeping with other studies that found that executive function is more impaired in LOD than EOD and this may be helpful when trying to identify whether the

pattern of cognitive impairment in an older adult is consistent with depression or may be related to prodromal dementia. However, the current severity of depressive episode appears to be overall the most relevant factor for cognitive performance, highlighting the need to treat a current depressive episode before being able to clearly assess underlying cognitive function.

Limitations

There are number of limitations which may have influenced the results of the study. A strength of the PROTECT study is the use of an online platform for data collection, allowing the recruitment of large numbers of participants. However, this is also a limitation, as there is no way of objectively verifying the subjective responses of participants. Depression measures and age of onset of depression were collected retrospectively (except current depression severity) through self-report, which may have led to reporting or recall bias. Bias in self-report may have arisen through a 'telescoping' phenomenon, where memories of depressive episodes that happened long ago, are seen as having occurred recently [75] Moreover, older participants tend to forget psychiatric disorder episodes that did not affect them severely, especially the ones that happened many years ago [76]. Rather than self-report, measures using official medical records and established diagnostic criteria for depression may resolve this problem. A prospective study could avoid some of these potential sources of bias and would also provide an opportunity to detect changes in cognitive function and depressive symptoms with age. The PROTECT study aims to follow up participants for 10 years and will therefore provide valuable prospective data on how cognition and depressive symptoms interact with age. Secondly, the effect of participants' past and present prescribed psychotropic medication was not controlled for. Older

antidepressants and first generation antipsychotics are implicated in adverse impacts on cognitive functions [77,78], while latest generation antidepressants were found to exhibit a more benign profile with potential cognitive benefits [79,80]. Thirdly, information on the number of previous depressive episodes, type of depression (with or without psychotic symptoms) and the length of these episodes was lacking and would have provided more robust results. Fourth, the sample was highly selected with regard to education level. As a higher level of education is related to higher scores on cognitive measures, one of the reasons for not being able to detect differences in cognitive scores between the different age of onset groups, contrary to the literature, may be the high baseline education level. Having a highly educated sample of which 78.6% are females introduces a possible selection bias, as the sample is self-selected and over-represents white, highly educated and potentially healthier women than the general population. Whilst this may limit the overall generalizability of the findings, the results still provide important information on the effects of depression on cognition in a large study population. It also provides valuable insight into a self-selecting cohort who are most likely to engage with online interventions and platforms, which are an increasing focus for public health approaches [56]. Lastly, it is also possible that as we included four cognitive tests, there were not sensitive enough to detect differences in impairment between LOD and EOD on three of the four cognitive tasks. Use of a larger neuropsychological battery with more detailed tests of executive function, memory and other domains such as processing speed or language may have demonstrated differential cognitive function between groups. Future work should target more precise age of onset groups and take midlife-onset into consideration as another group distinct from early and late onset depression. Moreover, mechanisms underlying cognitive impairments in depressive disorders require further elucidation.

Conclusion

Our study of depression onset, severity and cognitive function suggests that the most important factor associated with cognitive function is current depression severity. The age of onset of the first depressive episode demonstrated a significant difference between mid-life and early onset depression on two cognitive tasks, and comparison between late onset and early onset depression revealed a significant difference on the verbal reasoning task, when controlling for current depression severity, historical depression severity and other demographic and clinical factors such as education, age, stroke, exercise and gender. The cognitive differences between early-onset (<40 years) and late-onset (<60 years) depression on the verbal reasoning task and the finding of differing patterns of cognitive scores between early-onset and midlife-onset (40-60 years) depression add to a growing body of literature on the importance of the effect of age of depression onset on cognitive trajectories. The results of the present study suggest that although impaired executive function may be associated more with late onset than early onset depression the most significant factor in cognitive impairment in patients with a history of depression is the current severity of depressive symptoms. This highlights the need to effectively treat depression in older adults prior to drawing any conclusions about underlying cognitive function.

Table 1

Demographic information of participants

	Early-onset (<40 yrs)	Midlife-onset (40-60yrs)	Late-onset (>60yrs)
	%	%	%
Education			
GCSE	14.3	16.2	23.9
A Level	11.7	12.7	12.4
Vocational	20.0	21.7	23.2
Undergrad	31.5	31.8	28.4
Postgrad	19.2	14.6	9.7
PhD	3.3	3.0	2.4
Employment			
Employed Full	22.3	22.8	4.5
Employed Part	19.7	17.5	5.0
Self-employed	11.8	10.3	4.7
Retired	42.2	46.0	84.5
Unemployed	4.0	3.4	1.3
Marital Status			
Married	61.8	58.1	45.5
Widowed	4.6	9.7	35.3
Separated	2.0	2.2	2.6
Divorced	14.2	16.4	10.5
Civil Partnership	.7	.7	.8
Co-habiting	8.5	7.0	1.6
Single	8.2	5.9	3.7
Age			
50-54	20.4	14.4	-
55-59	25.1	26.4	-
60-64	25.3	27.1	16.8
65-69	18.2	19.3	36.6
70-74	8.0	9.4	28.2
75-79	2.3	2.6	13.2
80-84	.7	.7	3.7
85-89	.2	.1	1.6
Gender			
Female	81.7	74.0	71.1
Male	18.3	26.0	28.9
Ethnicity			
White	98.1	98.3	97.1
Mixed	.6	.6	.8
Asian	.7	.3	.11
Black	.2	.3	-
Others	.4	.2	1.1
Exercise			
No	31.8	33.4	42.6

Yes	68.2	66.6	57.4
Stroke			
No	98.8	98.3	98.7
Yes	1.2	1.7	1.3

	N	SOS Mean (SD)	DS Mean (SD)	PAL Mean (SD)	VR Mean (SD)	CDSS Mean (SD)	HDSS Mean (SD)
First episode(yrs)							
18-40	4562	7.4624 (.032)	7.3057 (.02029)	4.4664 (.01077)	32.4230 (.13224)	12.79 (.059)	13.46 (.062)
40-60	2402	7.4574 (.04459)	7.3301 (.02830)	4.5174 (.01506)	31.6389 (.17799)	11.95 (.067)	13.04 (.080)
>60	380	7.1010 (.10680)	7.1598 (.07491)	4.2970 (.03786)	28.4235 (.43799)	12.22 (.189)	11.82 (.202)

Table 2

Mean scores for cognitive outcomes

DS = digit span task; PAL = Paired associates learning task; VR = verbal reasoning task; SOS = self-ordered search task; CDS = Current depression severity score; HSS = Historical depression severity score

	R^2	F	df1	df2	p
VR	.1067	46.2483	19	7324	<0.001
DS	.0318	11.7050	19	7324	<0.001
SOS	.2034	918.1516	20	7323	<0.001
PAL	.0481	20.0982	19	7324	<0.001

Table 3

Multiple regression results of overall model

DS = digit span task; PAL = paired associates learning task; VR = verbal reasoning task; SOS = self-ordered search task.

	DS	VR	PAL	SOS
	ß (SE)	ß (SE)	ß (SE)	ß (SE)
First episode (yrs) (ref <40)				
40-60 yrs	.0191 (.0351)	-.4730 (.2144)*	.0620 (.0184)***	-.0217 (.0500)
>60 yrs	.0570 (.0792)	-1.1147 (.4521)*	.0291 (.0408)	-.0087 (.1097)
Historical severity score	-.0051 (.0041)	.0578 (.0248)*	-.0015 (.0021)	-.0118 (.0056)*
Current depression Score	-.0204 (.0045)***	-.0647 (.0278)*	-.0081 (.0024)***	-.0230 (.0065)***
Education (ref GCSE)				
A Level	.1685 (.0630)**	3.1999 (.3910)***	.0406 (.0323)	.1656 (.0880)
Vocational	.0773 (.0539)	2.5800 (.3378)***	.0483 (.0283)	.1781 (.0769)*
Undergrad	.2827 (.0498)***	5.3132 (.3160)***	.1031 (.0264)***	.4371 (.0715)***
Postgrad	.3395 (.0570)***	5.2083 (.3547)***	.0806 (.0296)**	.2255 (.0823)**
PhD	.3297 (.0570)***	5.8280 (.6092)***	.0871 (.0532)	.3629 (.1527)*
Age (ref 50-54)				
55-59	-.0947 (.0493)	-1.0523 (.3288)**	-.0970 (.0265)***	-.1584 (.0710)*
60-64	-.1171 (.0486)*	-1.8125 (.3215)***	-.1851 (.0263)***	-.4214 (.0714)***
65-69	-.1849 (.0530)***	-2.7883 (.3355)***	-.2842 (.0278)***	-.6617 (.0771)***
70-74	-.4484 (.0704)***	-4.7735 (.4123)***	-.4218 (.0336)***	-.9339 (.0947)***
75-79	-.4951 (.1055)***	-6.4779 (.5688)***	-.5962 (.5238)***	-1.3329 (.1411)***
80-84	-1.0361 (.1839)***	-7.9757 (1.1109)***	-.6000 (.1091)***	-1.5088 (.2713)***
85-89	-1.0259 (.3020)***	-9.0484 (2.2881)***	-.8836 (.1450)***	-2.1786 (.6094)***
Stroke	-.1611 (.1511)	-2.1630 (.9172)*	-.0352 (.0832)	-.7600 (.2242)***
Exercise	.1207 (.0342)***	1.0484 (.2142)***	.0313 (.0181)	.0593 (.0493)
Female gender	-.1988 (.0395)***	-.2899 (.2404)	-.0060 (.0210)	-.4092 (.0586)***
(constant)	7.8583 (.1216)***	30.3792 (.7467)***	4.6906 (.0629)***	2.8041 (.1835)***

Table 4

Multiple linear regression models reporting coefficients (standard errors) for the four cognitive tasks
**p < 0.05, **p < 0.01, ***p < 0.001, ref = reference value for regression*
DS = digit span task; PAL = Paired associates learning task; VR = verbal reasoning task; SOS = Self-ordered search task.

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