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PII: S0165-0327(19)31609-X
DOI: <https://doi.org/10.1016/j.jad.2019.11.125>
Reference: JAD 11372



To appear in: *Journal of Affective Disorders*

Received date: 19 June 2019
Revised date: 29 October 2019
Accepted date: 29 November 2019

Please cite this article as: Marjo Taivalantti , Jennifer H Barnett , Anu-Helmi Halt , Jari Koskela , Juha Auvinen , Markku Timonen , Marjo-Riitta Järvelin , Juha Veijola , Depressive symptoms as predictors of visual memory deficits in middle-age, *Journal of Affective Disorders* (2019), doi: <https://doi.org/10.1016/j.jad.2019.11.125>

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Highlights

- No associations were found between depressive symptoms or change in depressive symptoms and visual memory and new learning scores.
- The result did not change following cut-offs 1.55 and 1.75 for depression.
- Sub-clinical depressive symptoms do not seem to effect visual memory and new learning in the middle-aged population.

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Depressive symptoms as predictors of visual memory deficits in middle-age

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Abstract

Background: Depression has been known to affect memory and other cognitive domains. The objective of this longitudinal cohort study was to investigate longitudinal associations between depressive symptoms at age 31 years and visual memory and new learning at the age of 46 years. We investigated whether depressive symptoms at age 31 predicted visual memory deficits at age 46 years, and whether changes in depressive symptoms between 31 and 46 years predicted visual memory at age 46.

Methods: Participants were members of the Northern Finland Birth Cohort 1966 (NFBC-1966). Depressive symptoms were assessed with the Symptom Checklist-25 (SCL-25) on both occasions. Visual memory and new learning were assessed using Paired Associative Learning (PAL) test at the age 46 follow-up. PAL total errors adjusted and first trial memory score were used as outcomes and basic educational level, relationship status, physical activity and diet at baseline were considered as confounding factors in linear regression analysis.

Results: A total of 5029 (57% female) participants were included in the main analysis. No associations were found between depressive symptoms or change in depressive symptoms and visual memory and new learning scores. The result did not change following cut-offs 1.55 and 1.75 for depression.

Limitations: SCL only measures symptoms during the past week. Only one cognitive domain was assessed.

Conclusions: Contrary to our hypothesis, neither baseline depressive symptoms nor change in depressive symptoms predicted visual memory scores 15 years later. It appears that sub-clinical depressive symptoms do not effect this cognitive domain in the middle-aged population.

Keywords: Depressive symptoms; visual memory; middle-age.

Introduction

Depression has long been known to affect memory (Burt et al., 1995) and other neurocognitive domains (Austin et al., 2001; Snyder, 2013). (Douglas and Porter, 2009; McDermott and Ebmeier, 2009). Depression has also been linked to subjective memory complaints especially among the older population, and has been found to be associated with an increased risk of developing mild cognitive impairment (MCI) in cognitively normal elderly people. (Brigola et al., 2015; Ganguli et al., 2004; Goveas S. et al., 2011; Montejo Carrasco et al., 2017; Ravaglia et al., 2008). However, the direction of the association between affective problems and cognition is not clear.

There are a limited number of studies that have previously studied the association between depressive symptoms and cognition in a middle-aged population. Most of the clinical studies have been cross-sectional. Findings have been similar to those in elderly people, i.e. a negative association between depressive symptoms and cognitive performance. Some cross-sectional studies have noted that depressive symptoms are more strongly associated with subjective measure of cognition than objectively assessed cognitive performance. (e.g. Rowell et al., 2016; Srisurapanont et al., 2017).

To our knowledge, there are only two earlier longitudinal population-based studies investigating the associations between depressive symptoms and cognition in middle-aged people. The Whitehall II study investigated the association between history and frequency of depressive symptoms and cognitive deficits over an 18-year period, the baseline age being 35-55 years. Depressive symptoms were measured 6 times during the research period and a range of cognitive tests were utilised to assess cognition in late midlife. In this cohort, persistent depressive symptoms were a risk factor for poorer cognition in late midlife. (Singh-Manoux et al., 2010).

In a prospective British 1946 birth cohort, Richards et al. 2014 found that affective symptoms spanning ages 13-53 years were more clearly associated with self-reported memory problems at 60-64 years than with objectively measured memory and information processing from age 43 to 60-64. The study included 1688 males and females. Regression analyses did not show clear associations after adjusting for gender, childhood cognitive ability, education and midlife socioeconomic status. (Richards et al., 2014).

In this study, we focused on associations between depressive symptoms and visual memory and new learning in the Finnish middle-aged population. Depressive symptoms were assessed by SCL-

25, a self-report symptom inventory to measure symptoms of anxiety and depression which is derived from Symptom-Checklist of Derogatis. (Derogatis et al., 1974). The CANTAB paired associates learning (PAL) test was used to assess visual memory. (Sahakian et al., 1988).

The aim of this longitudinal cohort study was to study the association between depressive symptoms, visual memory and new learning at the age of 31 years and at the age of 46 years in males and females. The study focused on whether baseline depressive symptoms or the change in depressive symptoms at the follow-up is a stronger predictor of visual memory deficits at the age of 46 years. We investigated the following hypotheses: 1) Baseline depressive symptoms at the age of 31 years predict visual memory deficits at the follow-up at the age of 46 years. 2) The change in depressive symptoms between 31 and 46 years predict visual memory deficits at the follow up.

Methods

The database of the Northern Finland Birth Cohort 1966 (NFBC1966) serves as a foundation for this study. The cohort study was originally founded to study risk factors for perinatal deaths and low birth weight. (Rantakallio 1969). Originally it included 12 231 males and females whose expected year of birth was 1966. The number of live births was 12058. This covered 96.3% of all births in the Lapland and Oulu area in 1966. The cohort database includes pre-birth and postnatal information and four follow-up studies have been conducted at the ages of 1, 14, 31 and 46, in 1967, 1980, 1997-1998 and 2012-2014 respectively. (Rantakallio, 1988; Sorri and Järvelin, 1998). Data on health and lifestyle of the cohort members have been collected at several study points.

The basic population of this study consists of the Northern Finland Birth Cohort 1966 members who were not known to be dead, whose addresses were known and who lived in Finland at January 1st in the year 2013 (N=10 321).

Information about depressive symptoms was gathered by a postal SCL-25 questionnaire. This survey was conducted at baseline in the year 1997 when the subjects were 31 years of age (n=8641). A comprehensive background and lifestyle survey was also conducted by gathering information by postal questionnaire. The SCL-25 survey was repeated and the PAL test taken at the 46 follow-up in 2012-2014. The PAL test was taken at the same time as the cohort members participated in the clinical examination (N=5608).

The subjects for our analysis were those who had answered the SCL-25 at baseline and taken the PAL test at follow up. A total of 5029 subjects were included in the main analysis. (See Figure 1). All included subjects had given an informed consent after receiving information about the study. The study protocol has been approved by The Ethics Committee of the Faculty of Medicine of the University of Oulu and the Ministry of Social and Health Affairs.

Visual memory

PAL test is a non-verbal assessment of visual associative memory and new learning. During the test, the subject learns the location of visual patterns on the screen. PAL has been shown to differentiate subjects with Alzheimer disease and mild cognitive impairment from subjects with depression, and healthy volunteers (Swainson et al., 2001) and is considered reliable for assessing the type and degree of functional loss and the specificity of aging-associated changes. (De Rover et al., 2011). The PAL test has been successfully used for cognitive assessment across different cultures and education levels in both longitudinal and cross-sectional studies. (Barnett et al., 2016). The version used in our study was presented on iPad and took between 2-20 minutes to complete. Clinical examination time was fairly short and administration of PAL via an iPad was a suitable way for evaluation in a clinical setting and could be administered by personnel without neuropsychological training. The test was also included as a baseline for future studies of memory decline as the cohort follow-up continues. To our knowledge, there is a knowledge gap concerning the association between depressive symptoms and visual memory and new learning in unselected, population based cohort compared to clinical studies with study subjects with MDD.

It is known that people with right-sided hippocampal damage are impaired in object-location memory, which is dependent on the functional integrity of the temporal lobe, particularly the entorhinal and transentorhinal cortex areas in the hippocampus. (Smith and Milner 1981, Owen et al., 1995, Barnett et al., 2016). The PAL test has been shown in fMRI studies to activate the bilateral hippocampus making it a suitable test of hippocampal connectivity. (De Rover et al., 2011). The neural basis requires the ability to associate ventral visual stream information with spatial stream information, which coincide in the entorhinal cortex and adjoining hippocampal formation. This is also the area where some of the earliest pathology of Alzheimer's disease occurs. (Barnett et al., 2016).

In this study we investigated two PAL variables. The key outcome measure total errors adjusted (TEA) is the number of times the study subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. First trial memory score (FTMS) is the number of correct box choices that were made on the first attempt during assessment problems.

Assessment of depressive symptoms

SCL-25 is a shorter version of SCL-90 questionnaire which was originally developed to measure symptomatic behaviour of psychiatric outpatients. (Derogatis et al., 1973). Part I of the SCL-25 has 10 items for anxiety symptoms and Part II has 15 items for depression symptoms. The questionnaire measures the self-reported symptom presence and intensity over the previous week scaling from a few (1), somewhat (2), great (3) and very great or severe (4). The questionnaire has been translated in Finnish and validated in Finnish population. (Holi et al., 1998).

The SCL-25 questionnaire was used at the baseline and follow-up to assess depressive symptoms. In this study we used the 13 items that specifically detect depressive symptoms. Items that assess anxiety were left out of the analysis because of the focus on depressiveness in this study. For the analysis a depression sum score average was calculated. For the final analysis, missing data was imputed for 165 study subjects (60 values at 31 years and 105 values at 46 years follow-up) from whom one answer from SCL was missing. Mean-imputed values were used to replace missing values. Imputed figures for the sum score showed no significant change after imputation.

Attrition analysis

To evaluate the representativeness of our study population an attrition analysis was performed. At the baseline 8424 subjects answered the SCL-25 and gave their informed consent. During the follow-up 3453 (40.7%) subjects had been lost. More male subjects (47%) than females were lost. It is known that more subjects with severe depression are expected to be reluctant to participate in the follow-up. We compared the SCL-25 score at 31 years follow-up between our study subject (N=5029) to those who only took part in the 31 years follow up but not 46 years follow-up. Analysis showed a statistically significant difference at 31 years ($p=0.000$), however the absolute difference was only about 0.5 points. For those who did not participate the 46 years follow up SCL-25 mean was 18.1 as for our study subjects 17.6 Those males who were lost had slightly higher

depression sum score (mean 17.6, SD 4.9) compared to those males who participated at the follow-up as well. (Mean 16.8, SD 4.0). This was statistically significant in lost male subjects ($p < 0.001$), but not in females ($p = 0.154$).

Confounders

Confounders were defined as variables shown in literature to have an effect on cognition performance. Education and sex have been considered as markers of cognitive reserve in older adults (e.g. Van Hooren et al., 2007), education may protect against verbal memory deficits in individuals with elevated depressive symptoms. (McLaren et al., 2015). Physical activity and diet has been shown to effect cognition and e.g. may influence Alzheimer's disease risk (Davidson et al., 2014; Kanoski and Davidson, 2011), however further studies need to be conducted since the findings have not been consistent. Marital status has been found to protect from cognitive impairment in older adults. (Feng et al., 2014; Håkansson et al., 2009).

The distribution of confounders at baseline in males and females is presented in table 1. Variable modifications made for the analysis are described below.

Relationship status

Information about relationship status at the baseline was gathered by questionnaire. Response options were: married since; cohabiting since; single; legal separation or divorced since; widowhood since. For the analysis we combined the information into two classes: in a relationship and not in a relationship.

Basic education

Basic education level was acquired at the baseline from the study subjects. Response options were less than; 9 years of basic school; basic school; matriculation examination. For the analysis education was combined into two classes: basic education and matriculation examination.

Diet

In this study we categorised diet to healthy or unhealthy on the basis of vegetable, roots and salad consumption. The diet was considered healthy if the study subject consumed these 3 or more times per week and unhealthy if consuming was 2 times per week or less.

Physical activity

Physical activity was categorised into two classes: active and inactive. Study subjects reporting less than 1 hour of brisk physical activity at a time (brisk defined in the questionnaire causing at least some breathlessness and sweating) were classified as inactive. Those reporting 1 hour or more brisk physical activity at a time were classified as active.

Statistical analysis

Statistical analysis was performed with SPSS version 23. Linear regression analysis was used to assess the association between depressive symptoms and PAL score.

Results

At baseline and at the follow-up females had a slightly higher depression sum score compared to males. The difference was statistically significant. (Mann-Whitney U-test p-value < 0.001). At the follow-up females had slightly lower depression sum score compared to baseline as for males the score was slightly higher. (See table 2).

In our study females had a higher FTMS and lower TEA score compared to males (Mann-Whitney U-test p-value < 0.001). For males the FTMS mean was 19.0 (SD 3.3) and TEA mean 14.4 (SD 14.3). For females FTMS mean was 19.6 (SD 3.3) and TEA mean 11.9 (SD 10.8).

Association between depression symptoms at baseline and visual memory at follow-up

No significant associations were found between depression symptoms at baseline and visual memory scores at the follow-up in males or females. (Table 3). The result did not change after taking into account the confounders. (See supplement 1).

Association between change in depression symptoms and visual memory at follow-up

No significant associations were found between change in depression symptoms and visual memory scores at the follow-up in males and females. (Table 4). The result did not change after taking into account confounders. (See supplement 2).

To confirm our results we also conducted a secondary analysis with study subjects who met cut-offs of 1.55 and 1.75 for depression, which are the conventional recommended thresholds for caseness in SCL-25. (Nettelbladt et al., 1993). Following these cut-offs the results did not change. (See supplement 3).

Those study subjects who were more physically active scored better and made fewer mistakes in PAL test. The effect of physical activity seemed to be statistically significant in male subjects. Longer education seemed to have a similar effect on both sexes. (See supplement 1 and 2).

Discussion

In our population-based cohort study there seemed to be no effect of baseline or longitudinal change in depressive symptoms on visual memory in mid-life.

Previous studies on the effect of depression on cognition have mainly focused on persons with diagnosed major depressive disorder (MDD), but it is appropriate to reflect relevant findings from these studies to our study. A study by Chen et al. 2018 using CogState battery suggest an impairment in the visual, working, and verbal memory in first-episode, drug-naive MDD patients in a Chinese population compared to medicated and healthy controls. (Chen et al., 2018). Another study investigated delayed recall, recognition, and visual-spatial memory assessed by the Rey Complex Figure Test among subjects with major depressive disorder (MDD) following 9 months of recovery from acute depression. In the acute phase, the MDD subjects performed significantly worse compared with control subjects in delayed recall and recognition, but following 9 months of recovery, there were no longer differences between groups. The MDD group made a significant improvement in terms of depressive symptoms and performed better in recall and recognition. (Hammar and Schmid, 2013). It may be so that that cognitive impairment is present in acute MDD, which are to be found in clinical studies. The difference may also be explained by the specific battery used, the state and depth of depression.

Variability in the pattern and severity of depression-related cognitive difficulties has been found across individuals, which has been linked partially to differences in the severity of depressive symptoms, heterogeneous nature of MDD and diversity of assessment methods. (McDermott and Ebmeier, 2009). The previous results about persistence of cognitive deficits beyond the acute state in depression have been inconsistent. Rock et al. (2014) in their systematic review and meta-analysis investigated whether cognitive deficits in executive function, memory and attention occurs separately from episodes of low mood in depression. They conclude that cognitive impairment is a core feature of depression that cannot be considered entirely an epiphenomenon secondary to low mood. (Rock et al., 2014). One mechanism by which depression affects memory is thought to be through hippocampal changes. (Boku et al., 2017). Studies have shown a decreased hippocampal volume in patients with MDD. (Videbech and Ravnkilde, 2004). On the other hand, hippocampal volume decreases in late adulthood, which may lead to impaired memory and is considered an increased risk for dementia. This age related decline in episodic memory can be seen from the 40-50's on. (Barnett et al., 2016).

Cognitive dysfunction may however play a negative role in psychosocial functioning independently of mood disorders. Even after symptomatic remission, cognitive dysfunction may persist and mild cognitive impairment be present in recovery. (Baune et al., 2010; Baune and Air, 2016; Halvorsen et al., 2012). Cognitive domains may also be differentially affected by depression. Lee et al. 2012 in their meta-analysis on neuropsychological deficits in first-episode MDD, psychomotor speed and memory functioning were associated with clinical state, whereas attention and executive functioning were more likely trait-markers showing differences between acute and remitted states. (Lee et al., 2012). It has also been shown that individuals who experience subclinical levels of depression have also been shown to exhibit cognitive deficits. (Dotson, 2014). The effect of subclinical depression symptoms on memory in general population is poorly understood. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) cohort n=2544 study examined the memory correlates of depression symptoms (assessed with the depression subscale of the Hospital Anxiety and Depression Scale (HADS) in the general population. Depression symptoms were related to self-reported memory problems (self-reported yes/no), objective memory (assessed with the delayed recall of a story taken from the Wechsler Memory Scale) and valenced memory assessed with objects positively and negatively valenced and in valence neutral contexts. The frequency of self-reported memory problems increased as a function of subclinical depressive symptoms. In this study however, as with our results, depression symptoms were not associated with memory performance on a standard objective memory measure, when controlled for age,

general cognitive ability and sex. Depression symptoms were associated with poorer memory for objects presented in negative contexts. (Schweizer et al., 2018).

In our study those participants who were physically active and had a healthier diet seemed to perform better in PAL test. Exercise is known to have cognitive benefits, especially pertaining to memory and new learning processes. It may increase the size of the hippocampus and mediate hippocampal neurogenesis by possibly facilitating BDNF expression. (Erickson et al., 2011; Liu and Nusslock, 2018). However opposite results have been published. In a study by Krogh et al. 2014 a pragmatic exercise intervention did not increase hippocampal volume or resting levels of neurotrophins in out-patients with mild to moderate major depression. (Krogh et al., 2014). Some studies have pointed that obesity may be associated with cognitive impairments and may increase a risk of developing dementia and Alzheimer's disease later in life. Western diet high in saturated fat and added sugars has been shown to have negative impact on cognitive function. Mnemonic processes that rely on the integrity of the hippocampus are particularly effected. Links between gut microbiome and dietary- and metabolic-associated hippocampal impairment has been under investigation recently. High fat and/or high sugar diets are thought to alter gut bacteria colonies. The mechanisms for negative impact of these alterations are under investigation. High fat and/or sugar diet increases intestinal permeability and reduces blood brain barrier integrity which may increase vulnerability to the toxins from the circulation to the brain in addition to neuroinflammatory processes and impaired periferal insulin sensitivity. (Noble et al., 2017).

Strengths

Our study had several strengths. First, the study was prospective with a long follow-up period and the study population was relatively large. The participants were middle-aged which age group has not been studied previously thoroughly. The study was based on population. We were able to take into account multiple confounders and we were able to investigate the possible long-term association in study population.

Limitations

In this study only one domain of cognition was tested. However, some cognitive domains may be more affected than others. Visual memory and new learning may be one of those areas that may be less affected. (Égerházi et al., 2007). Life course performance for episodic memory reaches the peak early in life and begins to worsen around the fifth decade. Alzheimer's disease pathology is also known to start in midlife, which may be part of what is driving the follow-up PAL scores. (Barnett

et al., 2016). It is known that the relative easiness of a cognitive test for study subjects may not be enough to differentiate between groups, e.g. study subjects with or without depressiveness. However, in PAL the range in difficulty level within the test is wide, reducing the possibilities for ceiling effects. Increasing difficulty level ranges from two to eight patterns to be remembered. It has been widely used in depression research and there is data about the use of PAL in depression and in younger people as well as older adults. (Rock et al. 2014, Barnett et al.2016).

Information about the depressive symptoms in the original questionnaire asked about symptoms only during the past week and is based on self-report, which may be biased due to personal interpretation.

Measuring depressiveness on the basis of reported symptoms consider depression as a single condition and all symptoms as equally good severity indicators. Some causal associations between symptoms may not be considered in sum-score approach (e.g. sleep difficulties and low mood).

Depression itself is a syndrome consisting of many symptoms; it could be interesting and useful to separately explore the association between the 13 different symptoms and cognition. It would also be interesting to see whether these associations found in middle age population have an impact on clinically meaningful deficits in later life with aging.

Conclusions

Our study suggests that associations previously observed in clinical groups might differ from those in population-based studies such as our cohort study. This study contributes to the augmentation of knowledge about depression symptoms in subclinical individuals and has provided new knowledge about cognitive functioning in this group.

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Figure 1. Flowchart of study participants

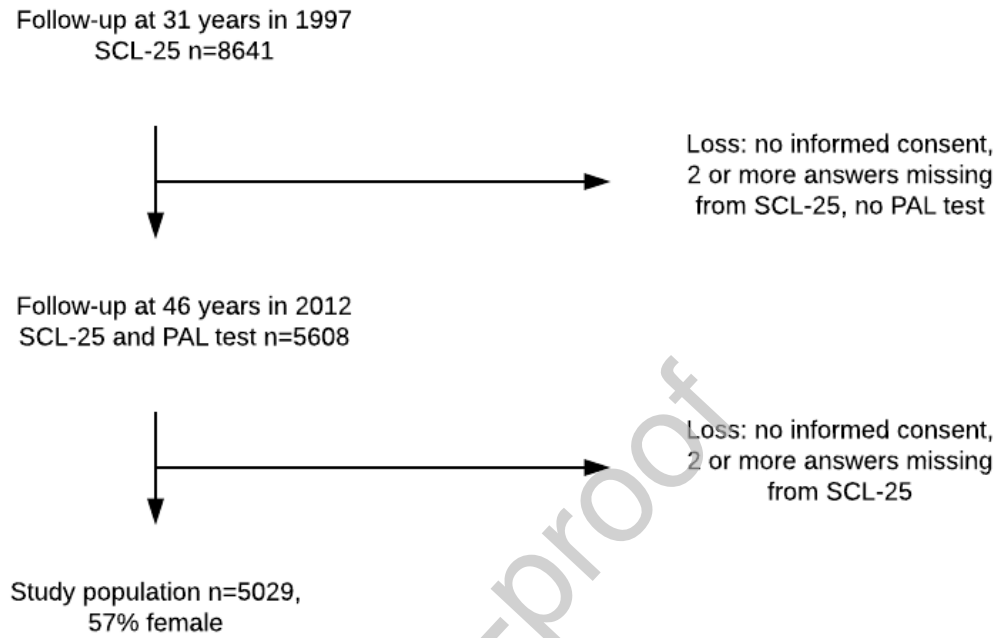


Table 1. Confounder distribution at the baseline

	Male	Female
Sex	43%	57%
Relationship status:		
<i>In a relationship</i>	72,2%	78,7%
<i>Not in a relationship</i>	27,8%	21,3%
Education:		
<i>Basic education</i>	65,4%	45,3%
<i>Matriculation examination</i>	34,6%	54,7%
Diet:		
<i>Healthy</i>	50%	68%
<i>Unhealthy</i>	50%	32%
Physical activity:		
<i>Active</i>	32,5%	21,8%
<i>Inactive</i>	67,5%	78,2%

Table 2. Depression symptoms sum score at the baseline (a.) and follow-up (b.)

	<i>Male</i>		<i>Female</i>		<i>M-W U</i>
	Mean	SD	Mean	SD	p-value
SCL sum score at baseline	16.8	4.0	18.3	5.1	<0.001
SCL sum score at follow-up	17.2	4.8	18.1	5.4	<0.001

Table 3. Association between depressive symptoms at baseline and visual memory at the follow-up

<i>Sex</i>	<i>PAL</i>	Univariate analysis					Multiple variant analysis					
		<i>B</i>	<i>t</i>	<i>p-value</i>	<i>95% CI</i>		<i>B</i>	<i>t</i>	<i>p-value</i>	<i>95% CI</i>		
					<i>Lower bound</i>	<i>Upper bound</i>				<i>Lower bound</i>	<i>Upper bound</i>	
Male	TEA	.058	.737	.461	-.096	.211	-0.51	-.638	.524	-.207	.105	
	FTMS	-.018	-1.022	.307	-.053	.017	.007	.388	.698	-.028	.042	
Female	TEA	.057	1.426	.154	-.021	.134	.047	1.192	.233	-.030	.123	
	FTMS	-.021	-1.705	.088	-.044	.003	-.012	-.985	.324	-.036	.012	

Table 4. Association between change in depressive symptoms during the follow-up and visual memory at the follow-up.

Sex	PAL	Univariate analysis					Multiple variant analysis				
		<i>B</i>	<i>t</i>	<i>p-value</i>	95% <i>CI</i>		<i>B</i>	<i>t</i>	<i>p-value</i>	95% <i>CI</i>	
					<i>Lower bound</i>	<i>Upper bound</i>				<i>Lower bound</i>	<i>Upper bound</i>
Male	TEA	-.028	-.415	.678	-.160	.104	-.037	-.556	.578	-.169	.094
	FTMS	.001	.095	.924	-.028	.031	.004	.271	.786	-.025	.033
Female	TEA	.036	.989	.323	-.035	.108	.035	.952	.341	-.037	.106
	FTMS	-.001	-.091	.927	-.023	.021	-.002	-.138	.890	-.024	.021