Cognitive Complaints Are Associated with Smaller Right Medial Temporal Gray-Matter Volume in Younger Postmenopausal Women

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Disclosure Statement

The authors report no conflicts of interest.

Cognitive complaints affect medial temporal volume

Abstract:

Objective: Menopause is associated with increasing cognitive complaints and older women are at increased risk of developing Alzheimer's disease compared to men. However, there is difficulty in early markers of risk using objective performance measures. We investigated the impact of subjective cognitive complaints on the cortical structure in a sample of younger postmenopausal women.

Methods: Data for this cross-sectional study were drawn from the baseline visit of a longer double-blind study examining estrogen-cholinergic interactions in normal postmenopausal women. Structural MRI imaging was acquired on 44 women, aged 50-60 years and gray-matter volume was defined by voxel-based morphometry. Subjective measures of cognitive complaints and postmenopausal symptoms were obtained as well as tests of verbal episodic and working memory performance.

Results: Increased levels of cognitive complaints were associated with lower gray-matter volume in the right medial temporal lobe (r = -0.445, $p < 0.002$, R^2 = 0.2). Increased depressive symptoms and somatic complaints were also related to increased cognitive complaints and smaller medial temporal volumes but did not mediate the effect of cognitive complaints. In contrast, there was no association between performance on the memory tasks and subjective cognitive ratings, or medial temporal lobe volume.

Conclusions: The findings of the present study indicate that the level of reported cognitive complaints in postmenopausal women may be associated with reduced gray-matter volume which may be associated with cortical changes that may increase risk of future cognitive decline.

Keywords: subjective cognitive complaints, gray-matter volume, menopause, medial temporal lobe, estrogen, memory

Many women report changes in cognition during and following the menopause-transition. [1,2] The reduction of circulating estrogen level with menopause may modify age-related cognitive changes and may accelerate typical aging. [3,4] Estrogens have been observed to be involved in a number of neuroprotective roles, from modulating cholinergic function at the basal forebrain, [5] to interacting with neurofibrillary tau tangles in preclinical AD models. [6] Therefore, the loss of these mechanisms following menopause due to depletion of cortical estrogens is believed to be a driving factor behind the increased risk of women developing Alzheimer's disease compared to men (AD).[7] Thus, the present study investigated whether the endorsement of cognitive complaints after menopause was associated with objective cognition and cortical structure.

Subjective cognitive decline (SCD) is proposed to represent a prodromal stage of Mild Cognitive Impairment (MCI), with reports of deterioration in memory and cognitive performance and is no discernible difference on quantitative measures. [8] Compared to cognitively normal (CN) individuals, adults with SCD are twice as likely to develop MCI or Alzheimer's disease. [9] Despite the lack of objective cognitive deterioration, individuals with SCD are more likely to possess AD biomarkers and neurodegenerative symptomatology compared to CN adults. [10] Older adults with SCD have higher levels of cortical beta-amyloid (Aβ), and also evidence of AD-like cortical atrophy. [11] The deterioration of gray-matter volume (GMV) in adults across aging is varied, however for individuals who develop MCI, the deterioration of the medial temporal lobe is accelerated, [12,13] and SCD is associated with a reduction in hippocampal volume. [14,15]

There is evidence that the changes in estrogen levels following the menopause transition can influence cortical structure. [16] Estrogen has been shown to be involved in hippocampal function, [17] and estrogen treatment can enhance hippocampal volume in postmenopausal women. [18] Additionally, postmenopausal women who reported cognitive complaints performed worse than women not

reporting complaints on objective measures of verbal episodic memory, [19] which may be correlated with decreases in GMV. The presence of cognitive complaints following menopause may represent an early marker of future cognitive decline in some women, however due to the age range of the samples of prior studies, it is difficult to parse the impact of cognitive complaints following menopause from that of typical cognitive aging. [20] The present study examined postmenopausal women aged 50-60 with differing levels cognitive complaints. The aim of this study was to identify whether, in a relatively young sample of postmenopausal women, the level of cognitive complaints endorsed was associated with changes in GMV and objective cognitive performance. This limited age range allows for better characterization of cognitive changes following menopause. Based on our previous work showing hippocampal effects of both estradiol and cholinergic antagonists, [18,21] we hypothesized that higher endorsement of cognitive complaints on the Cognitive Complaints Index (CCI) [11] would be related to smaller GMV in the medial temporal lobe. Additionally, we examined whether the number of endorsed postmenopausal symptoms (hot flushes etc.) endorsed was related to cortical GMV. Finally, to assess risk of further cognitive decline, we assessed whether CCI scores would be associated with objective cognitive performance on tests of verbal episodic and working memory.

Methods

Participants and Screening Procedures

44 postmenopausal women aged between 50-60 years (mean 56.1 ± 2.7 years) completed baseline MRI scans. All participants were postmenopausal, without menses for at least 1 year and had an FSH level greater than 30 mIU/mL. Eight participants had either a hysterectomy or a partial oophorectomy, however all participants had at least one functioning ovary, and went through natural menopause. Eleven women had prior hormone therapy (HT), but had no hormone use for at least a year prior to

entering the study. The study was conducted at both the University of Vermont and at Vanderbilt University, and was approved by both Institutional Review Boards. This study was carried out in accordance with the recommendations of the Declaration of Helsinki, with all participants giving written informed consent prior to participation in the study.

All participants that passed the inclusion and exclusion criteria [22] were screened to ensure normal cognitive functioning and exclude MCI/dementia using the Mini-Mental State Exam (MMSE; [23] Brief Cognitive Rating Scale,[24] and the Mattis Dementia Rating Scale (DRS-2)[25] to establish a Global Deterioration Scale score. [26] Participants were required to have a Global Deterioration Scale score of 1-2 and an MMSE score of greater than 26. Current mood disorder was excluded by a partial Structured Clinical Interview (SCID) [27] and the Beck Depression Inventory (BDI score < 13). [28]

Subjective Measures of Cognitive and Symptomatic Complaints

Following screening, participants completed the Cognitive Complaints Index [11] to determine their level of subjective cognitive decline. The CCI consists of the Memory Functioning Questionnaire (MFQ), [29] Memory Self-Rating Questionnaire,[30] Neurobehavioral Function and Activities of Daily Living Rating Scale,[31] Informant Questionnaire on Cognitive Decline in the Elderly (IQCDE),[32] 4 items related to cognition from the Geriatric Depression Scale (GDS),[33] 12 items from a telephone-based screening for mild cognitive impairment (MCI), and 20 items from the Memory Assessment Questionnaire adapted in part from the Functional Activities Questionnaire (FAQ). Responses to 114 questions were dichotomized as representing an endorsed or unendorsed complaint. The CCI score was expressed as the percent of all items endorsed. To assess the severity of current postmenopausal symptoms we used the menopause symptom checklist (MSC); [34,35] which includes physiological and emotional symptoms that are commonly experienced following menopause (e.g. hot flashes, abdominal pain).

Measures of Verbal Episodic and Working Memory

Immediate and delayed episodic memory was assesses using The Selective Reminding Task (SRT). [36] This task involves word list learning and selective reminding over 8 trials and a delayed recall trial after a 20-minute delay. SRT total immediate recall was the number of correctly recalled words across trials 1–8, recall consistency was the number of words correctly on two consecutive trials across trials 1–8, recall failure was the number of words not recalled on two consecutive trials across trials 1–8, and delayed recall was the number of words correctly recalled after a 20-min delay.

A visually presented N-back sequential letter task was used to assess working memory performance. Four conditions were presented: 0-back, 1-back, 2-back, and 3-back. The 0-, 1-, 2-, and 3-back conditions were performed in two blocks of 27 trials each for a total of 216 trials. The main outcome variable of the n-back task was sensitivity (d') for each of the four conditions, calculated as Z (Hit) − Z (False Alarms).

MRI Image Acquisition

Imaging data collected at both the University of Vermont and Vanderbilt University were collected using identical Philips Achieva 3T MRI scanners (Philips Medical Systems, Inc., Best, Netherlands). Both scanners were identical in software and used an 8-channel head coil. Each participant completed a Sagittal T1-weighted 3D Turbo Field Echo Sensitivity Encoding (TFE SENSE) sequence perpendicular to the anterior commissure-posterior commissure line, repetition time of 9.9 ms, echo time of 4.6 ms, a flip angle of 8°, number signal averages 1.0, a field of view of 256 mm, a 256x256 matrix, and 1.0 mm slice thickness with no gap for 140 contiguous slices.

Preprocessing and Voxel Based Morphometry

For each participant, the T1 image was segmented using the standard processes in SPM12. [37]. We then

used the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) tools in

SPM12 to create a study specific template, warps for each participant to this template, and the

transform of the template to Montreal Neurological Institute (MNI) space. The warps and transform

were then applied to the gray-matter change images to create images in MNI space for comparison.

VBM analysis was performed using the SPM12 package [37] in combination with MATLAB 2017b

(Mathworks, Sherborn, MA, USA). The smoothed gray matter images were entered into a voxel-wise

regression analysis to investigate the variability in the regional GMV. Visualization and labeling of the

significant brain regions resulting from the analyses was performed using xjView

(http://www.alivelearn.net/xjview8/).

Statistical Analyses

To assess the effect of endorsed cognitive complaints on GMV, we ran a linear regression model in

SPM12 with CCI score as the continuous between-subject's factor. To correct for multiple comparison

thresholds, cluster size for the whole-brain analysis was set at 62 contiguous voxels reflecting a

corrected threshold of $p<0.05$ (uncorrected $p=0.05$). Scanner site was not included in these analyses, as

it has been included in a prior analysis that included this data set using the imaging data collected at

both sites and no significant site effect was observed. [18] Following the SPM analysis, GMV for each of the

clusters that were significantly related to CCI were extracted. These values were then compared to the

MSC levels and the cognitive outcome measures using Pearson correlations. To control for the

collinearity between the MSC, BDI and the CCI due to the presence of some cognitive and affective items listed in the MSC, we removed 10 of the cognitive and affective items (forgetfulness, nervous tension, mood swings, irritability, anxiety, panic attacks, worry needlessly, depression, loss of Interest, & crying).

To assess the impact of either prior HT or previous surgery (hysterectomy or partial oophorectomy), we ran partial correlations with each of the binary variables as controlling factors. We used non-parametric tests due to the unequal sizes of these groups. Summary data from the cognitive measures were compared to CCI and GMV data using Pearson correlations. Correlations are reported with the coefficient, significance, R-squared and achieved power values. To determine performance on the n-back, we ran a one-way repeated measures analysis of variance with within-subjects contrasts to compare each level of the n-back task. We ran a series of mediation analyses to determine if the relationship between CCI and GMV was driven by postmenopausal or depressive symptoms. Descriptive information for both the cognitive and demographic data, as well as all partial and full correlations were run in IBM SPSS version 20 (IBM Corp, Armonk, New York, USA). Mediation analyses were run using the PROCESS macro for SPSS. [38]

Results

Demographics

Table 1 summarizes the demographic information for the participants. Median years post-menopause was 5 years. 28 of the 44 participants were in Stage 1, the remainder were in Stage 2 according to the STRAW+10 model. [39] We found a significant relationship between scores on the MSC and CCI, indicating that women who experienced more somatic symptoms also endorsed more subjective cognitive complaints ($r=0.535$, $p<0.001$; $R^2=0.29$). Neither scores on the CCI or MSC were associated with age,

education or years since menopause (all p>0.1). Despite no participant meeting clinical criteria for depressive symptoms, scores on the BDI were correlated with both age (r=0.332, p=0.028, R^2=0.11) and CCI score (r=0.41, p<0.005, R^2=0.17).

Differences in gray matter volume

The results of the whole brain VBM regression model between GMV and CCI score showed a significant cluster located in the right medial temporal area (MTL), encompassing parts of the hippocampus and the parahippocampal gyrus (Figure 1; cluster size: 132 voxels; coordinates X: 26.89; Y: -39.95; Z: 1.127). This region was negatively related to the CCI score, indicating that participants who endorsed more cognitive complaints had lower gray-matter volume at the right MTL (Figure 2; r=-0.445, p<0.002, R^2=0.2). In addition, greater endorsement of depressive or somatic symptoms was also significantly associated with smaller right MTL volume (BDI: r=-0.3, p=0.045, R^2=0.09; MSC: r=-0.3, p=0.048, R^2=0.09). When we controlled for the effect of years of education, prior HT or whether participants had a hysterectomy or partial oophorectomy, the association between CCI score and gray-matter volume remained significant (Education: r=-0.45, p<0.002 R^2=0.2; Surgery: r=-0.44, p<0.003 R^2=0.19; HT: r=-0.47, p<0.001 R^2=0.22).

Cognitive Results

The results of the cognitive data are summarized in Table 2. One participant was not included in the analysis of the SRT (n=43), and two participants were not included in the analysis of the N-back task (n=42) due to incomplete data. Overall participants showed better accuracy for immediate vs delayed recall; as well as for 0- and 1-back blocks. However, there was no score from either the N-back or SRT that was significantly associated with either CCI or GMV values (all p>0.1).

Mediation analyses

As we saw significant associations between CCI, MSC and MTL volumes, we conducted an exploratory

analysis using mediation modelling to assess whether MSC affected the relationship between CCI score

and GMV values (Figure 3A). The total effect of cognitive complaints on right MTL volume was very

strong (β=-72.4, *p*=0.002). There was a significant relationship between the mediator and CCI scores

(β=36.62, *p*<0.002), but not with GMV (β=-0.24, *p*>0.4). The model showed that the direct effect of CCI

on gray-matter was slightly weaker than the total effects model (β=-63.4, *p*=0.017). These results imply

that MSC scores did not significantly mediate the relationship between cognitive complaints and gray-

matter volume. We also ran this model using BDI as the mediator (Figure 3B), and this did not

significantly affect the association between CCI and right MTL volume (β=-62.7, *p*=0.015). While

exploratory, these analyses suggest that the association between CCI and MTL volume is not driven by

either depressive or somatic symptoms despite the strong intercorrelation.

Discussion

The main finding of the present study was that greater endorsement of cognitive complaints was

associated with lower volume of the right MTL in postmenopausal women aged 50-60. This is partially

consistent with our hypothesis; however, we did not predict the lateralization of the effect. In addition,

greater depressive and somatic symptom endorsement was also associated with smaller right MTL

volumes. Furthermore, the association between cognitive complaints and the structure of the MTL was

not mediated by the number of depressive or somatic symptoms. In contrast to the subjective scores,

neither the verbal episodic or working memory performance of participants was related to CCI score or the volume at the MTL.

The findings of the present study indicate the potential for cognitive complaints as an early marker of the risk of pathological cognitive decline in postmenopausal women, as the relationship is similar to the effects found in adults with SCD. The present study goes beyond previous work in that it looks at the impact of differing levels of subjective cognitive complaints on the cortical structure of younger postmenopausal women. Volume of the MTL, in particular the hippocampus, decreases across aging, and more rapidly with dementia-like pathology. [12] Therefore, the identification that increased levels of cognitive complaints and symptoms is associated with smaller right MTL gray-matter volume may reflect a dysfunctional pathway or circuitry in the cortex in some women, that may lead to future vulnerability to pathological cognitive decline. It is also important to note that due to the narrow age range and the because there was not a relationship between age and CCI, we are confident that the present findings represent the impact of postmenopausal cognitive symptoms independent of age on cortical structure. Moreover, the fact that neither depressive nor somatic symptoms could account for the relationship between cognitive complaints and GMV at the MTL indicates that this effect is driven by more than just physiological symptomatology. The results of this study also highlight the importance of taking subjective measurements into consideration in addition to objective cognitive performance, as subjective reports of cognitive symptoms may be more sensitive at an early stage of illness, prior to any definitive performance deficits on cognitive tasks. [40] These results suggest that while the menopause transition is associated with both structural and functional changes, [3,41] women who endorse more cognitive complaints have smaller right MTL volumes compared to those who do not.

The results of the present study are consistent with a number of studies that have shown that volumetric differences associated with SCD are stronger for the right hippocampus compared to the left

hippocampus. Specifically, the GMV of the right hippocampus has been observed to be smaller in older adults endorsing SCD compared to those who do not. [14,42,43] This pattern has also been seen in longitudinal studies, with right hippocampal volume at baseline showing the strongest prediction values for a future MCI diagnosis. [43] While bilateral hippocampal loss is predictive of objective cognitive performance declines, the volume of the right hippocampus is more sensitive to subjective measures at early stages of decline. [40] Therefore, the fact that we saw only an association between cognitive complaints and GMV for the right MTL, may be due to the relatively young age of the women in the present study. The fact that the women who had more cognitive complaints also had more depressive and somatic symptoms is consistent with prior research displaying links between somatic and cognitive markers of disease progression. [44]

A limiting factor of this cross-sectional dataset is we are unable to directly answer predictive questions of how cognitive complaints may lead to further decline in these women. Nonetheless, based on the results of this study, we propose that the impact of menopause is not the proximate cause of cognitive symptoms, but potentially to provoke them in women who may be at higher risk for late-life cognitive decline. As noted above, the finding that neither the depressive or somatic symptoms could account for the relationship between CCI and GMV indicates that there may be other underlying processes that may account for this relationship. For some women, the changes in the cortical hormonal balance following menopause may reduce the ability to compensate, through both the reduction of cholinergic signaling, [4] and also the ability of estradiol to interact with misfolded proteins. [6] Therefore, menopause may act as an accelerator for further cognitive decline in vulnerable women by removing the protective effects of estradiol in the cortex, rather than a direct cause. A limitation of the mediation models used in the exploratory analyses is that due to the sample size of the current study, they were slightly underpowered. However, we believe these analyses is still important as it highlights how neither affective or somatic symptoms can explain the relationship between CCI and GMV. Another

consideration is the somatic scale for postmenopausal symptoms used in this study was different from

previously validated scales, such as the Menopause Rating Scale. [45,46] However we believe that the MSC

used in the present study is comparable, as it asks participants to rate the same somatic symptoms.

Moreover, the MSC breaks down the broader symptom categories, which may allow for more

differentiation between participants. Finally, while not a direct hypothesis of the study, HT has

previously been shown to have an impact on cognitive performance and neurodegenerative pathology, [3]

and estrogen or estradiol trials have shown beneficial effects on both cognitive function, as well as on

GMV in the hippocampus. [18] However, when we controlled for either the prior HT use or past

hysterectomy or partial oophorectomy, there was still a significant negative relationship between CCI

and volume at the right MTL.

Conclusion

In conclusion, the increasing levels of cognitive complaints were associated with lower GMV in

the right MTL in postmenopausal women aged 50-60 years. Very modest elevations in depressive

symptoms and somatic complaints were related to higher CCI score and smaller medial temporal

volumes, however neither mediated the relationship between cognitive complaints and gray-matter

volume. The findings of the present study identify the relationship between the cognitive complaints

and structural differences in younger postmenopausal women. Future studies should examine

longitudinally whether increasing levels of cognitive complaints early in the postmenopausal period

leads to a greater proportional cortical atrophy as well as an increased incidence of neurodegenerative

pathology.

Author Contributions

Alexander C. Conley contributed to the processing and analysis of data, and the preparation and revision of the manuscript.

Kimberly M. Albert contributed to the processing and analysis of data, and the preparation and revision of the manuscript.

Brian D. Boyd contributed to the processing and analysis of data.

Shin-Gyeom Kim contributed to the processing and analysis of data.

Sepideh Shokouhi contributed to the analysis of data and the revision of the manuscript.

Brenna McDonald contributed to the project design and the revision of the manuscript.

Andrew J. Saykin contributed to the project design and the revision of the manuscript.

Julie A. Dumas contributed to project design and implementation, and the revision of the manuscript.

Paul A. Newhouse contributed to the project design and implementation, and the revision of the manuscript.

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Figure Legends

Figure 1. Association between gray matter volume at the medial temporal lobe and the cognitive complaint index (CCI) as identified by voxel-based morphometry. Significant clusters are shown in the Axial, Coronal and Sagittal planes. Colorbar indicates t-scores between 0-5.

Figure 2. Relationship between cognitive complaint index (CCI) and the gray-matter volume at the right medial temporal lobe (r = -0.445, p < 0.002, R^2 = 0.2).

Figure 3. Mediation models showing total relationship between cognitive complaint index (CCI) and gray-matter volume of right medial temporal lobe at the top; and below with either menopause symptom checklist score (MSC; 3A) or Beck Depression Inventory as a mediator (BDI; 3B). Beta values represent standardized coefficients, and direction of arrows reflects theoretically plausible relationships.

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Tables

Table 1. Demographic and menopause symptoms (means, standard deviations and ranges).

Demographic Variable	Mean ± SD	Range
Age (y)	56.1 ± 2.7	51-60
Body Mass Index	24.5 ± 2.95	20-30.1
Education (y)	16.3 ± 2	12-21
Years since menopause transition (y)[a]	5 ± 3.8	2-16
Prior Hormone Use (Yes/No)	11/33	
Mini-Mental State Exam	29 ± 1.2	26-30
Menopause Symptom Checklist [b]	14.7 ± 7.6	2-37
Cognitive Complaint Index Score (%)	19.5 ± 13	0-51
Beck Depression Index	3.4 ± 3.12	0-12

Notes: Body mass index calculated as weight [kg]/height [m^2)]. Cognitive Complaint Index determined as % of complaints endorsed); [a] Listed as Median (SD) not Mean (SD); [b] Menopause Symptom Checklist was derived from a total of 50 items not the original 60 used in Newhouse et al. (2010).

Table 2. Cognitive performance data (means and standard deviations) for the Selective Reminding Test and N-back task, and the correlation to the Cognitive Change Index Score.

| Task	Measure	N	Mean ± SD	Correlation with CCI Score
Selective	Total Immediate Recall	43	84.2 ± 15.8	0.21
Reminding Task	Recall Consistency	43	50.95 ± 21	0.27
	Recall Failure	43	10.42 ± 7.8	-0.08
	Delayed Recall	43	9.8 ± 3.8	0.17
N-back Task	0-back d'	42	5.25 ± 1.28	-0.04
	1-back d'	42	5.09 ± 1.395	0.07
	2-back d'	42	3.277 ± 1.27	0.07
	3-back d'	42	2.54 ± 0.9	-0.152

Notes: d' defined as standardized hits minus standardized false alarms (Z (Hit) – Z (False alarms)).

Differences between levels of the n-back were assessed by one-way ANOVA with within-subject contrasts. [a]$p<0.05$
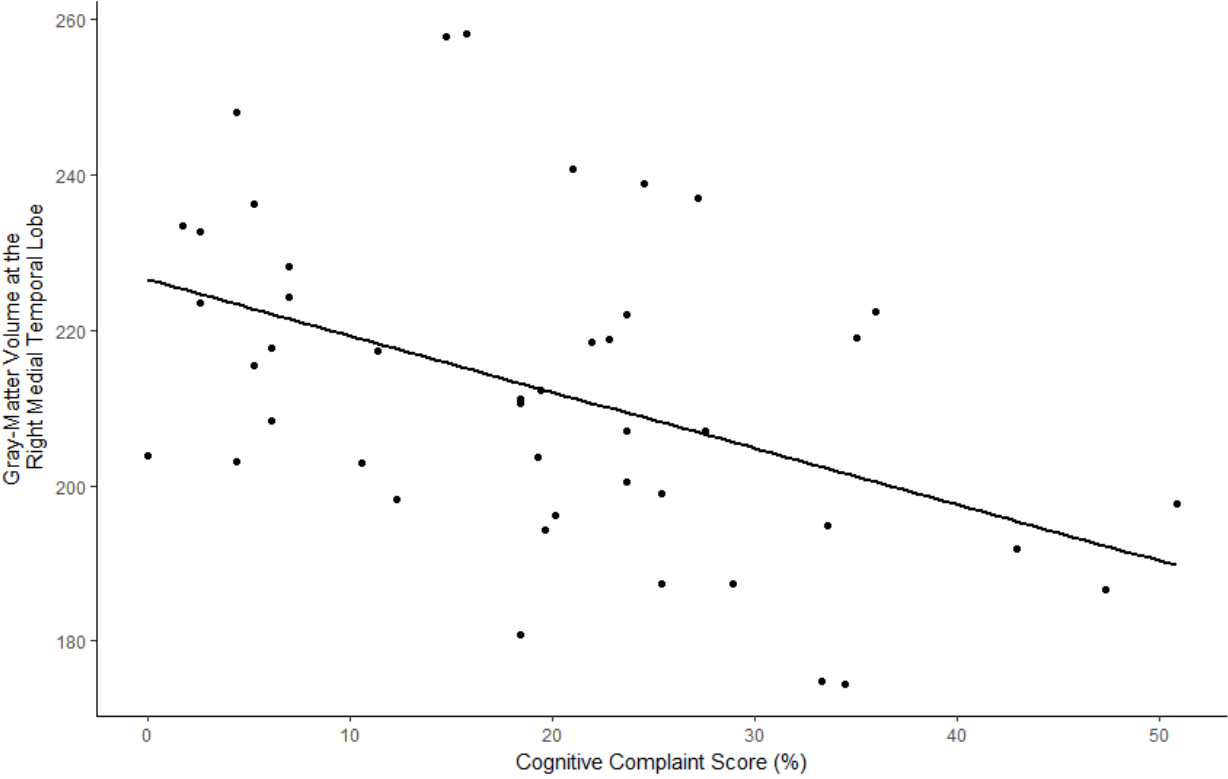
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Figure 1.
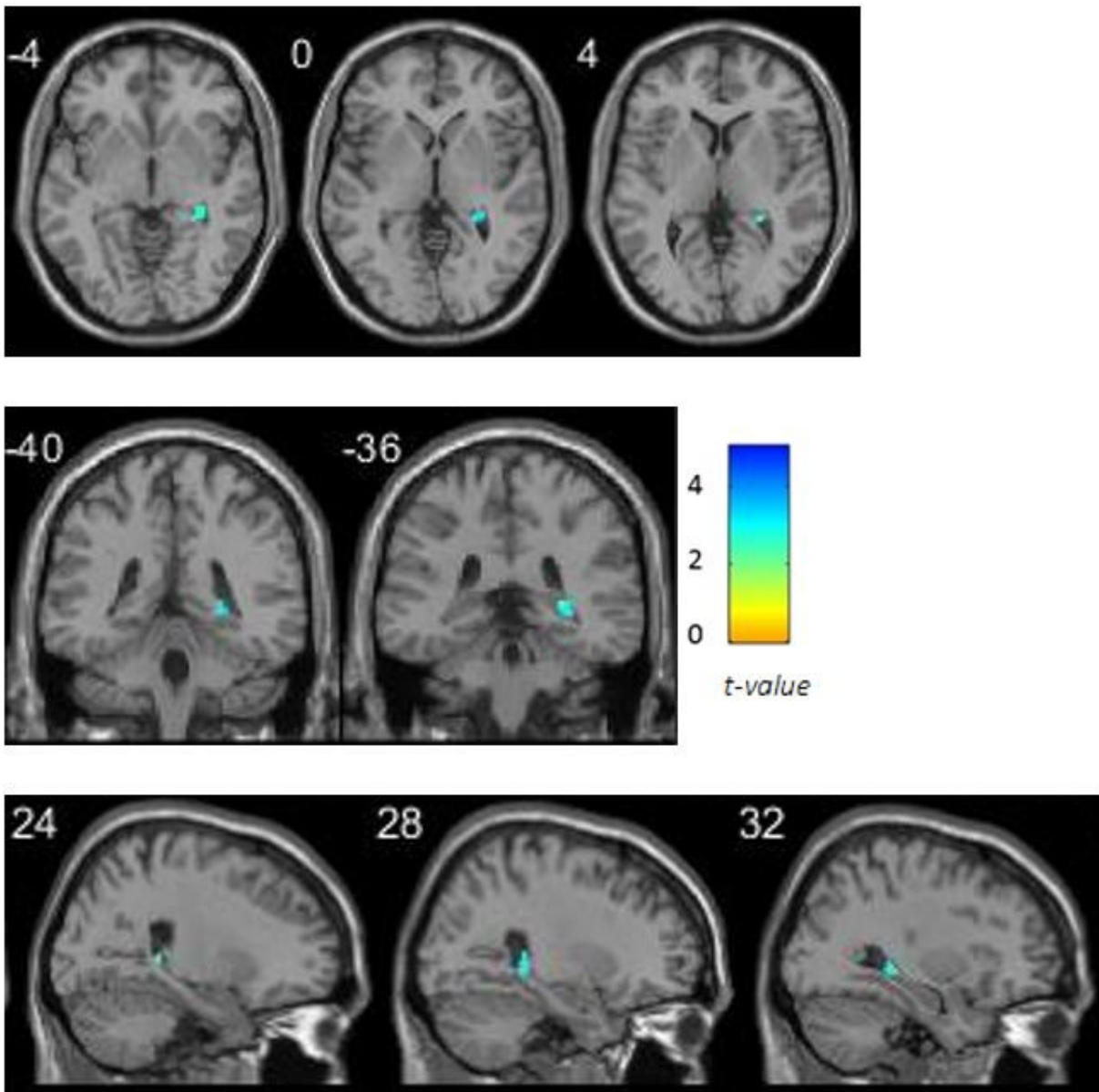
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Figure 2.

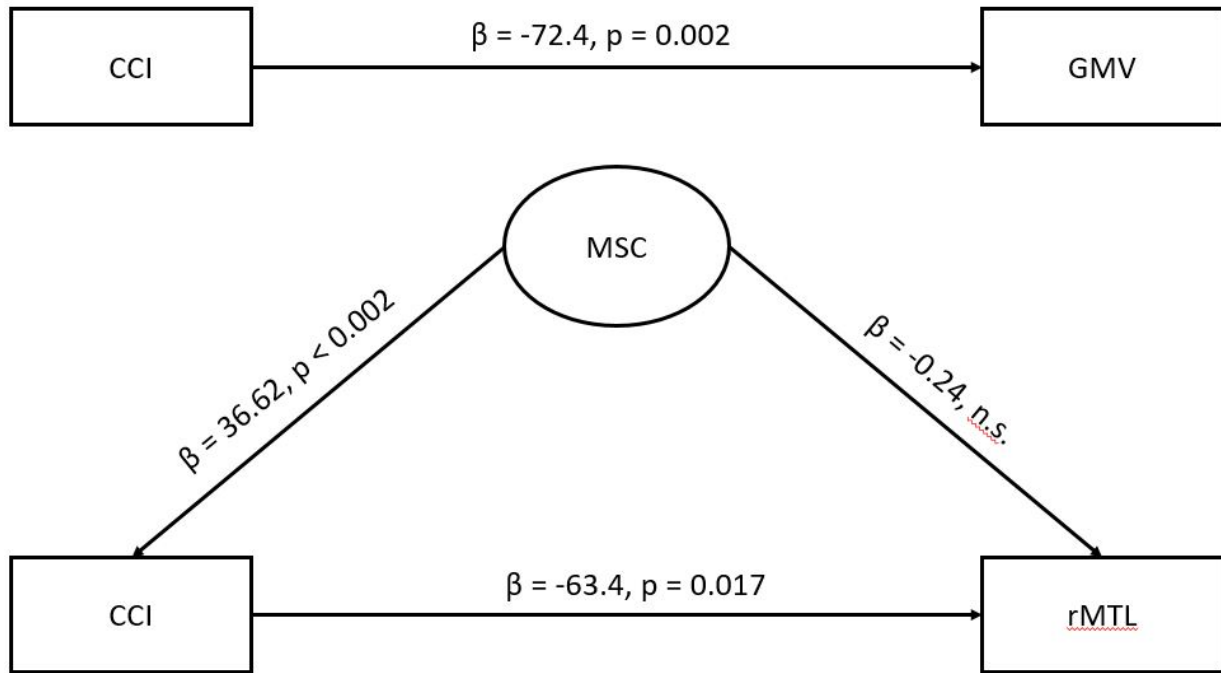Cognitive complaints affect medial temporal volume

Figure 3A.

Figure 3B.