Exploring Cortisol's Impact on Brain Structure in Late Mild Cognitive Impairments and Mild Dementia Due to Probable Alzheimer's Disease

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ABSTRACT

Introduction

Aging involves cognitive decline and structural impairments in the brain. Understanding the mechanisms responsible for these detriments is essential for developing strategies to preserve brain robustness in the elderly. Hormonal factors, such as cortisol, are crucial to brain health. Differences in cortisol's impact have also been observed between men and women. However, research in elderly populations remains limited, as gaps in understanding the effect of cortisol on brain function in advanced age persist.

Objective

This study aims to explore the link between cortisol and structural brain alterations in elderly individuals, with a particular emphasis on uncovering potential sex-specific effects.

Methods

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to examine associations between plasma cortisol levels and changes in brain structure among 80 elderly subjects diagnosed with late mild cognitive impairment (LMCI) due to probable Alzheimer's disease (AD) or have mild dementia due to probable AD. Baseline and one-year follow-up plasma

cortisol levels, along with T1-weighted MRI scans, were analyzed using linear mixed-effects (LME) models to examine the associations between cortisol and cortical thickness, volume, and area. Partial correlations were also used to assess the associations between cortisol and subcortical brain volume.

Results

LME models examining the impact of baseline cortisol on cortical brain structure at follow-up revealed sex-specific patterns. Men displayed positive correlations in brain thickness, mainly within the parietal lobe, while women exhibited positive correlations across brain thickness, volume, and area spanning multiple cortical regions. Additionally, partial correlation analyses examining the association between cortisol and subcortical brain volumes across several structures revealed that changes in cortisol were linked to volume changes in regions like the caudate and putamen, with notable associations in the left caudate for women.

Conclusions

This research on the association between cortisol and brain structure underscores significant sex differences, highlighting a more pronounced impact on women compared to men. Elevated cortisol is associated with structural changes in critical brain regions related to cognitive functions. These findings are intended to inform future studies investigating the influence of stress hormones on age-related cognitive decline. The study also emphasizes the need for sex-specific considerations

in future research to better understand the possible impacts of cortisol on cognitive health across sexes.

RÉSUMÉ

Introduction

Le vieillissement entraîne le déclin cognitif et les déficiences structurelles du cerveau. Il est essentiel de comprendre les mécanismes responsables de ces troubles pour élaborer des stratégies visant à préserver la robustesse du cerveau chez les personnes âgées. Les facteurs hormonaux, comme le cortisol, sont essentiels à la santé du cerveau. Des différences dans l'impact du cortisol ont également été observées entre les hommes et les femmes. Cependant, les recherches sur les populations âgées restent limitées, puisque des lacunes persistent concernant l'effet du cortisol sur les fonctions cérébrales à un âge avancé.

Objectif de l'étude

Cette étude vise à explorer le lien entre le cortisol et les altérations structurelles du cerveau chez les personnes âgées, en mettant particulièrement l'accent sur la découverte d'effets potentiels spécifiques au sexe.

Méthodes

Des données ont été obtenues auprès de l'Alzheimer's Disease Neuroimaging Initiative (ADNI) afin d'examiner les associations entre les niveaux de cortisol plasmatique et les modifications de structure cérébrale chez 80 personnes âgées diagnostiqués avec des troubles cognitifs légers et tardifs dû à une probable maladie d'Alzheimer ou souffrent de démence légère dû à une probable maladie d'Alzheimer. Les niveaux de cortisol plasmatique de base et de suivi d'un an, ainsi que les IRM pondérées en T1, ont été analysés à l'aide de modèles linéaires à effets mixtes afin d'examiner les associations entre le cortisol et l'épaisseur, le volume et la surface du cortex. Des corrélations partielles ont également été utilisées pour évaluer les associations entre le cortisol et le volume cérébral sous-cortical.

Résultats

Les modèles statistiques examinant l'impact du cortisol de base sur la structure corticale du cerveau au moment du suivi ont révélé des schémas spécifiques au sexe. Les hommes ont montré des corrélations positives dans l'épaisseur du cerveau, principalement dans le lobe pariétal, tandis que les femmes ont montré des corrélations positives dans l'épaisseur, le volume et la surface du cerveau dans plusieurs régions corticales. En outre, les analyses de corrélation partielle examinant l'association entre le cortisol et les volumes cérébraux sous-corticaux dans plusieurs structures ont révélé que les changements de cortisol étaient liés à des changements de volume dans des régions telles que le caudé et le putamen, avec des associations notables dans le caudé gauche chez les femmes.

Conclusions

Ces recherches sur l'association entre le cortisol et la structure cérébrale soulignent des différences significatives entre les sexes, mettant en évidence un impact plus prononcé sur les femmes que sur les hommes. Un taux élevé de cortisol est associé à des changements structurels dans des régions cérébrales critiques liées aux fonctions cognitives. Ces résultats devraient servir de base à de futures études sur l'influence des hormones de stress sur le déclin cognitif lié à l'âge. L'étude souligne également la nécessité de prendre en compte les spécificités de chaque sexe dans les recherches futures afin de mieux comprendre les impacts possibles du cortisol sur la santé cognitive des hommes et des femmes.

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STATEMENT OF CONTRIBUTION

This research project was done in collaboration with Sherif Karama, Yasser Iturria-Medina, Gleb Bezgin, and Leah Abdul-Reda.

Introduction

LAR drafted the introduction, conducted the literature review, and stated the objectives of the research.

SK provided feedback on drafts and helped with the literature review direction.

Methods

LAR developed the study design, handled data collection, and conducted statistical analyses.

SK, YIM, and GB advised on methodology, reviewed statistical approaches and assisted with data collection.

Results

LAR conducted data analysis, generated visual representations, and interpreted findings.

SK, YIM, and GB reviewed the data analysis and provided input on data presentation.

Discussion

LAR drafted the discussion, integrated findings with existing literature, and addressed study limitations.

SK provided feedback on drafts.

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LAR drafted the conclusion and highlighted the significance of the research.

SK provided feedback on drafts.

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
LMCI	Late mild cognitive impairment
LME	Linear mixed effects
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
RFT	Random Field Theory
AD Group	Participants with mild dementia due to probable Alzheimer's disease
LMCI Group	Participants with mild cognitive impairments due to probable Alzheimer's disease

INTRODUCTION

Cognitive capabilities in individuals normally decline as they age. Aging is primarily associated with significant morphological and physiological changes in the brain (Cadar, 2018). These changes lead to a debilitating decline in cognitive skills encompassing executive functions, including attention, reasoning, learning, creativity, and impulse control. Moreover, memory gets compromised with age, making it harder for people to navigate daily routines and habits (Cadar, 2018). Thus, comprehending the underlying factors that exacerbate the impact of aging on the brain in general and cognition in specific is critical to better understanding the physiological mechanisms contributing to cognitive decline.

Multiple factors can impact the brain and cognitive aging

With aging, several factors affect the brain and contribute to cognitive decline. Thus, understanding these factors can potentially help mitigate cognitive decline and preserve brain robustness. Such factors include biological changes in the brain. It has been estimated that the brain's volume tends to decrease at a 5% rate after age 40 (Svennerholm et al., 1997), with other studies suggesting that such a rate could increase after age 70 (Scahill et al., 2003). Much of the decrease in brain volume is related to the shrinking of the grey matter that has been attributed to either direct neuronal cell death or perhaps to the decrease of the neuronal cells' volume rather than their number (Murphy et al., 1996). Given this major morphological change, dendritic sprouting is said to take place as a compensatory mechanism against cell death (Anderton, 2002). Studies

have shown that aging is associated with a decreased number of dendritic synapses (Bliss et al., 2003).

Genetics are also another major factor that is found to directly affect cognitive aging. Multiple studies have found that single-nucleotide polymorphisms (SNPs) in several genes related to Alzheimer's disease (AD), such as *ADAMTS9, BDNF, CR1, DNMT3A, REST, SRR,* and *TOMM40,* may play a role in enabling cognitive decline within the aging population (Lin et al., 2017).

Furthermore, hormones contribute to various functions in the human body, and their fluctuations across the lifespan have a substantial impact on the brain. Several hormones tend to play a major role in maintaining cognition. This includes sex hormones such as estrogen, progesterone, and testosterone. These hormones are associated with preserving brain functions via mechanisms, namely neuroprotection, stimulation of neuronal outgrowth, synaptogenesis, and dendritic branching (Ali et al., 2018).

Effect of hormones and hormonal change with age on the brain

Several studies have tackled the effect of hormonal change with age on the brain and subsequent cognitive decline. Taking estrogen as a first example, it has been put forward that this hormone plays a role in major brain regions that are typically affected by AD, including the nucleus basalis of Meynert. Another cross-sectional study examined the association between serum estradiol and cognitive functions among elderly American women. The findings showed that higher estrogen levels are significantly associated with higher cognitive performance, which encompasses better

processing, sustained attention, and working memory (Xu et al., 2024). A different study also examined the effect of hormonal changes with age on middle-aged women, where a multiple linear regression was conducted to examine the various factors that could contribute to cognition. Results revealed that better semantic memory performance was significantly associated with higher total levels of estradiol and free estradiol (Ryan et al., 2012). Similarly for progesterone, a cross-sectional study was conducted to investigate its effect on cognition in middle-aged menopausal women, whose progesterone levels were significantly decreased. It was found that progesterone concentrations are significantly and positively associated with several neuropsychological measures, including verbal memory and overall cognition, but not with executive functions (Henderson et al., 2013). In addition, pertaining to testosterone, a study consisting of middle-aged and elderly subjects aimed to explore its impact on the brain by measuring testosterone in both men and women. The results show that higher testosterone levels are positively associated with better semantic memory, episodic memory, and visual-spatial abilities in men. However, this association is negative in the female group (Thilers et al., 2006). It has also been suggested that decreases in testosterone levels might be related to an increased risk of developing dementia. A longitudinal study followed up on a sample of middle-aged and elderly men to test the association between serum and free testosterone concentrations and neuropsychological measures, including memory performance. Findings found that men with a higher ratio of testosterone to sex hormone binding globulin (SHBG) at baseline performed better on various cognitive tests and were less likely to develop AD (Moffat et al., 2002).

Building on these findings, which suggest that fluctuating hormone levels affect the brain over time, research has extended its efforts to test hormonal therapy and its implications for enhancing

several brain functions in various populations. For example, a clinical study was implemented to examine the effect of estrogen replacement therapy (ERT) on cognitive decline in a sample of 288 post-menopausal women. Those who received ERT, which is suggested to play a protective factor against cognitive aging, performed better on short-term visual memory and visual perception tasks (Resnick et al., 1997). Similarly, a study found that women who received hormonal therapy performed better on verbal and visual memory tasks in comparison to women who did not receive the treatment (Resnick & Maki, 2001). Additionally, both groups significantly differed in the level of brain activation in regions associated with those tasks (Resnick & Maki, 2001). On the other hand, some studies examined the effect of androgen deprivation therapy (ADT), as it reduces the concentration of testosterone levels in men. A study recruited 82 men split into two groups: those who received ADT and those who did not. Results showed that men who received ADT performed worse in some of the attention and memory tasks, with half of them presenting significant cognitive decline after a 6-months follow-up, whereas the other group showed no change (Green et al., 2002).

Sex differences and receptor distribution variations

Estrogen and progesterone are more predominant among women, whereas testosterone is more present among men. Such differences suggest that aging impacts women and men's brains in distinct ways. Given the effects of estrogen and progesterone on cognition, studies have focused on exploring the impact of menopause with aging on brain functions, as well as the risk of developing dementia-related illnesses. A study investigating the risk of developing AD among elderly men and women revealed that women have a higher risk of developing AD compared to

men (Andersen et al., 1999). Such findings call for exploring the distribution of hormone receptors in the brains of men and women, which might elucidate the differential impact of hormones on brain health. Concerning estrogen, its receptors are distributed throughout various regions of the adult brain, including the hypothalamus, amygdala, cerebellum, and cortex, with regional size and volume differences observed between men and women volume (Sato et al., 2023). Additionally, progesterone receptors are found in the hippocampus and frontal lobes (Brinton et al., 2008), with sex differences present at the level of receptor immunoreactivity in certain regions such as the anteroventral periventricular nucleus (AVPv) and the medial preoptic nucleus (MPN) (Quadros et al., 2002). As for testosterone, a study has indicated sex differences in the distribution of androgen receptors within the hypothalamus (Fernández-Guasti et al., 2000), with males showing stronger receptor immunoreactivity compared to women (Kruijver et al., 2001). Thus, these differences shape how hormones impact the brain, particularly in the context of aging.

Role of cortisol

Another important hormone that has been widely studied within the context of brain aging is cortisol. Cortisol is a glucocorticoid hormone, a steroid, that has various functions that concern body regulations and cognitive appraisal. In addition to playing a critical role in the stress and fear body response, it has a significant contribution to energy metabolism and behavioural adaptation to external and internal changing circumstances (Erickson et al., 2003). Furthermore, cortisol affects the nervous system by implicating neuropeptide and neurotransmitter systems within the brain's parenchyma (Erickson et al., 2003).

Cortisol is synthesized from cholesterol in the zona fasciculata layer of the adrenal gland (Thau et al., 2023). The production of cortisol is regulated by the hypothalamus-pituitary-adrenal (HPA) axis. It circulates the bloodstream along carrier proteins called corticosteroid-binding globulin (CBG). Under basal conditions, 90-95% of the cortisol circulating in the bloodstream is bound to CBG (Perogamvros et al., 2012). Cortisol has often been described as a stress hormone, and is found in high concentrations during stressful situations (Erickson et al., 2003). Elevated levels of cortisol have been detected in both healthy individuals (Adam & Gunnar, 2001) and those with physical or psychiatric illnesses (Cleare et al., 2001; Weber et al., 2000). Therefore, cortisol is not only primarily associated with the stress response, but also extends to cover other bodily functions such as energy metabolism and neural function.

In what concerns cognition, cortisol contributes to various vital roles. Stimulating arousal is a major role for cortisol. Normally, the secretion of cortisol into the bloodstream increases arousal in humans, with its release being inhibited during sleep and elevated in the morning (Huang et al., 2022). This increase in cortisol concentrations earlier in the day is attributed to an increase in energy for individuals to start their day, then the concentration continually decreases till the evening hours, following the human natural circadian rhythm (Huang et al., 2022; Mohd Azmi et al., 2021). Attention is also impacted by cortisol levels. It has been associated with periodic elevations of cortisol levels in the plasma (Henckens et al., 2012). However, chronic elevations in cortisol levels negatively affect attention; in contrast, short-term spikes of cortisol aid in sustaining attention (Erickson et al., 2003). Additionally, cortisol plays a role in emotion regulation. Emotions are generally processed in the amygdala, prefrontal cortex, and medial temporal regions, as these brain regions are essential for interpreting and processing perception and episodic memory

(Erickson et al., 2003). For example, when the amygdala is stimulated by an emotional stimulus such as fear, the release of cortisol is elicited to regulate the bodily response to fear (Roberts et al., 2022). Moreover, cortisol administration is said to regulate the response to negative stimuli when it is given in a dose-dependent manner (Erickson et al., 2003). Cortisol also impacts memory, with studies showing that both low and high levels are negatively associated with memory functioning, with only specific concentrations being essential to stimulate memory consolidation (Kim et al., 2015). This is illustrated in the hippocampus, which is shown to function best when it's under moderate levels of glucocorticoids (Kim et al., 2015).

Elevated cortisol is associated with impaired memory and reduced executive functions

It is worth noting that elevated cortisol has been significantly detected as a part of normal aging (Butler et al., 2017). Thus, understanding the effect of elevated cortisol on the brain is important. An association between elevated levels of cortisol and impaired cognitive tasks, including memory and overall executive functioning, has been established based on several research studies. A research study investigated the impact of psychosocial stress in a sample of 20 young healthy men. Findings showed that a high concentration of cortisol, which is attributed to high loads of stress, is significantly associated with slow working memory function, in addition to impaired recalling of moderately emotional memories (N. Y. L. Oei & Bermond, 2006). These results build on those reported by Wolf et al., who conducted a study on a sample of middle and old-aged individuals who were with (n = 27), or without (n = 19) subjective memory complaints. It was found that those who declared memory complaints had higher basal cortisol levels, as well as higher levels of

cortisol, even after the administration of dexamethasone, a synthetic glucocorticoid (Wolf et al., 2005).

To further consider the effects of cortisol elevation on memory and executive functioning, Sheilds et al. investigated whether chronic stress, as displayed by elevated cortisol levels, is associated with problematic core executive functioning (Shields et al., 2016)**.** Thus, a meta-analysis was conducted focusing on three major executive functions: working memory, inhibition, and cognitive flexibility. Results showed that there is a significant association between impaired working memory and stress. As for inhibition, the overall effect size was moderate in comparison to that of the working memory. Moreover, cognitive flexibility was significantly impaired by acute stress (Shields et al., 2016). Another study was implemented to determine cortisol awakening response (CAR) in relation to impairment in executive functions. A total number of 109 healthy males were recruited for the study. It was reported that individuals who had elevated levels of CAR were more likely to perform poorly in a problem-solving task (Butler et al., 2017).

Prolonged exposure to high cortisol levels can lead to structural changes in the brain

Increased levels of cortisol have been related to eliciting structural changes in the brain. Lupien et al. conducted a study to test whether prolonged elevation of serum cortisol in healthy individuals is associated with decreases in the hippocampal volume. Results revealed that the hippocampal volume within the high cortisol level group was significantly decreased (14%) when compared to the moderate cortisol level group. However, no significant volumetric differences were detected in other brain regions, including the parahippocampal and fusiform gyri (Lupien et al., 1998).

Similarly, Dronse et al. examined the association between serum cortisol level and the volume of the hippocampus and gray matter between a healthy aging group and a group of individuals with AD. Within the healthy aging group, higher serum cortisol levels were significantly associated with smaller left hippocampal volumes and lower gray matter volume in the hippocampus, and temporal and parietal regions in the left hemisphere (Dronse et al., 2023). In addition, to explore the effects of early morning serum cortisol on cognition and brain structural changes, a study recruited dementia-free subjects from three different generations where the results showed that higher cortisol levels are significantly associated with worse memory and visual perception, and lower gray matter volume in the total brain, occipital, and frontal lobar regions (Echouffo-Tcheugui et al., 2018).

Increased cortisol predicts a more rapid cognitive decline in individuals with MCI and AD

Elevated cortisol levels are said to increase cognitive decline in people who are suffering from Mild Cognitive Impairment (MCI) or AD. Ouanes et al. examined the association between cortisol levels, cognitive impairment, and AD through a review of the literature. The summary of the results reported showed that participants with dementia and MCI due to AD tend to have higher levels of cortisol than cognitively healthy aging individuals. It was suggested by the authors that elevated cortisol in the cerebrospinal fluid (CSF) may have contributed to the rapid cognitive decline in patients with MCI due to AD (Ouanes & Popp, 2019). Similarly, White et al. explored the impact of plasma cortisol on hippocampal volume and disease progression in patients with MCI. A total of 304 MCI patients were recruited for a longitudinal study. Findings showed that higher cortisol

levels are associated with a faster decrease in hippocampal volume over time. Additionally, a small hippocampal volume has predicted the risk of developing AD (White et al., 2023).

Sex differences in the association between cortisol and cognitive decline

When considering the relationship between elevated cortisol and cognitive decline, there are sex differences that come into play. In a research study that recruited healthy males and females to investigate the impact of acute stress, with the stress response measured by estimating cortisol levels, on memory function, it was reported that elevated cortisol levels are negatively associated with memory performance, with the correlation being significant among men, and not among women (Wolf et al., 2001). To assess the impact of cortisol on executive functioning among men and women, a study utilized the Wisconsin Card Sorting Test (WCST) and measured salivary cortisol. Results showed that higher cortisol concentrations are associated with more errors while performing the said test. This association was more pronounced in women than men; however, it is worth mentioning that cortisol levels at the time of the test were lower among men (McCormick et al., 2007). Concerning brain structure, a previously mentioned study which explored the relationship between early morning cortisol levels and brain structure revealed that higher cortisol levels are negatively correlated with cerebral brain volume in women, but not in men (Echouffo-Tcheugui et al., 2018).

Objectives

Given the previous findings, it becomes rather critical for researchers to delve deeper into the association between cortisol levels and cognition, whilst considering the effects of aging, physical changes in the brain, and sex differences among men and women. Most studies in the literature are focused primarily on middle-aged groups, and when older adults are included, they are often grouped with middle-aged participants. Moreover, studies that explore hormonal influences on brain aging generally emphasize brain function over structure. Henceforth, the following study adopts a whole brain approach to examine the local and global impacts of cortisol on structural brain changes in a sample of participants who were either suffering from late mild cognitive impairment (LMCI) due to probable Alzheimer's disease (AD) or have mild dementia due to probable AD. This study seeks to elucidate the complex relationship between cortisol and structural brain changes, to advance our understanding of how hormonal fluctuations can contribute to neurobiological alterations. By examining these interactions, the research aims to provide valuable insights that can inform future studies exploring the broader implications of cortisol in the context of cognitive aging and neurodegenerative processes. Ultimately, the findings may help clarify the role of stress-related hormones in age-related cognitive decline.

METHODOLOGY

Study Overview

Data for this study were sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and directly downloaded from the ADNI data resource webpage (https://adni.loni.usc.edu). The primary objective of ADNI is to evaluate if neuroimaging, other biological markers, and clinical and neuropsychological assessments can be integrated to track the progression of mild cognitive impairment (MCI) and Alzheimer's disease (AD). For the latest information, visit www.adni-info.org.

All study participants provided written informed consent for blood sampling, cognitive and clinical assessments, and neuroimaging before being included in the study. Ethics approval for the ADNI study was obtained from the institutional review boards of all participating institutions.

Study Participants

This study is based on the ADNI 1 cohort investigating biomarkers of disease progression that are most promising to explore in future trials for the prevention and treatment of AD. All enrolled subjects were between 55 and 90 (inclusive) years of age, had a study partner able to provide an independent evaluation of functioning, spoke either English or Spanish, and were willing and able to undergo all testing procedures including neuroimaging and agree to longitudinal follow-up. For further information regarding the study protocol and details on inclusion/exclusion criteria, see

https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-1_Protocol.pdf.

Participants diagnosed with late mild cognitive impairments (LMCI) due to probable AD and participants diagnosed with mild dementia due to probable AD were chosen from the ADNI I cohort, based on the availability of the following assessments: (i) baseline and one-year follow-up plasma cortisol level measurements, and (ii) baseline and one-year follow-up T1-weighted magnetic resonance imaging (MRI) full brain scans. The final sample for this study consisted of 80 participants (Table 1).

Assessments

Plasma cortisol levels

Plasma cortisol levels, obtained from the Biomarkers Consortium Plasma Proteomics Project, were retrieved from the ADNI database.

Neuroimaging data

Structural T1-weighted MRI scans were acquired following standardized MRI acquisition protocols (Jack Jr et al., 2008). Baseline and follow-up anatomical scans were processed using Freesurfer 5.0 neuroimage analysis suite, which is documented and freely available for download

online (http://surfer.nmr.mgh.harvard.edu/), and CIVET human brain image processing pipeline (version 2.1.0) developed at the Montreal Neurological Institute (Lepage et al., 2017).

Statistics

Statistical analyses were performed using MATLAB/Simulink R2024a (https://www.mathworks.com).

Linear Regression Model

Vertex-level linear mixed effects (LME) models were implemented using the MATLAB toolbox SurfStat (Worsley et al., 2009). SurfStat is designed for analyzing cortical data with mixed effects models, providing correction for multiple comparisons using random field theory (RFT) (Worsley et al., 2004). It can also be used for Gaussian smoothing, surface inflation, and for the visualization of results.

LME analysis was performed to examine the relationship between baseline plasma cortisol levels and changes in the brain over a one-year study duration. The model included baseline cortisol, age, sex, baseline brain measurements (cortical thickness, volume, or area) (to account for baseline differences in brain characteristics among subjects and rendering them all on the same scale), education, Mini-mental state examination (MMSE) scores, and the interaction term "Cortisol by Sex," whereas the relative change in total brain thickness, volume, and area was entered as a response.

To illustrate the effect of cortisol on the brain, we also conducted a cross-sectional analysis, using the same model, to determine the relationship between baseline cortisol levels and baseline brain characteristics.

Regression equations are included, below, for each model tested, where the first model is used to assess cross-sectional baseline results, and the second model tests the annual change in the brain (to compute the change, we extracted the difference in the measurement and divided it by the time difference):

1. Brain Baseline = intercept + β1 (Baseline Cortisol) + β2 (Age) + β3 (Sex) + β4(Baseline Brain) + β5 (Education) + β6 (MMSE) + β7 (Cortisol × Sex)

2. Brain Change = intercept + β1 (Baseline Cortisol) + β2 (Age) + β3 (Sex) + β4 (Baseline Brain) + β5 (Education) + β6 (MMSE) + β7 (Cortisol × Sex)

In addition, to gain a deeper understanding of potential differences in the effect of cortisol levels on brain characteristics across sexes, we used a recentering approach to better interpret the interaction term Cortisol by Sex and isolate the findings separately for males and females. We conducted separate analyses for both sexes while preserving the complete sample size to maintain statistical power. This is achieved by manipulating the binary coding of the sex variable in the interaction term. Initially, men and women are coded as 1 and 0, respectively, which reflects the effect of cortisol specifically for males because females (coded as 0) effectively eliminate the

interaction term from their analysis. Following that, men and women are coded as 0 and 1, respectively, which similarly focuses on the effect of cortisol primarily for females.

To enhance the validity of our regression outcomes, we performed multiple comparisons correction using RFT. This method enables us to address the inherent randomness in the data and enhance the reliability of our results.

Partial Correlation

Partial correlation analysis was performed to evaluate the relationship between the change in plasma cortisol and the change in subcortical brain volume throughout the one-year study duration. This analysis controlled for age, sex, and baseline intracranial volume.

Considering the numerous comparisons in our investigation (18 partial correlations), we employed a Bonferroni correction to mitigate the heightened risk of Type I error. Recognizing that the 18 subcortical volume measures were moderately correlated at baseline, with a mean correlation of 0.468, we adjusted the correction to account for this non-independence among variables. Following the adjustment, we set a significance threshold of 0.0249 to target an overall 0.05 level of significance across all analyses of subcortical structures. Partial correlations were thus deemed statistically significant if the p-value was below this adjusted threshold.

RESULTS

Demographics

The sample of subjects included in the following study encompassing participants with late mild cognitive impairment due to probable Alzheimer's disease (LMCI Group) and participants with late dementia due to probable Alzheimer's Disease (AD Group). In turn, demographic data were collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the following comparisons were established (Table 1). It can be noted first that the LMCI Group contains 63 subjects, while the AD Group has 17, which amounts to a total of 80 participants. The average age of participants in the LMCI Group is 73.5 years old (SD = 8.1; range = 55 – 88) whereas the mean age of participants in the AD Group is 74.0 years old (SD = 10.1; range = 56 – 89). The men-to-women ratio is quite different across both samples of participants, where within the sample of participants in the LMCI Group, the ratio is 41 men to 22 women; however, in the sample of participants in the AD Group, this ratio shifts to 8 to 9. Pertaining to education, both groups of participants have a close number of years spent in education, with the LMCI Group having average years of 15.8 (SD = 3.3; range = 6 – 20); equivalently, the mean number of education years in the AD Group is 15.5 (SD = 2.8; range = 12 – 20). Mini-mental state examination (MMSE) scores were also considered when extracting demographic data. The mean MMSE score in the LMCI Group is 26.7 (SD =1.8; range = 23 – 30), while in the AD Group it's 22.9 (SD =1.9; range = 20 – 26).

Moreover, comparisons were also established between men and women across the baseline biomarker characteristics of cortisol levels and total brain volume (Table 2). Regarding cortisol levels, women have a mean of 2.16 ng/ml (SD = 0.11; range = 1.98 – 2.28), whereas men have a mean of 2.19 ng/ml (SD = 0.13; range = 1.80 – 2.50). As for total brain volume, the mean volume in women is 5.45 L (SD = 0.54; range = 4.60 – 6.80), which is lower than that of men, who have a mean of 6.16 L (SD = 0.85; range = 3.05 – 7.67).

Association between cortisol levels and subcortical brain volume

Partial correlation analyses were used to examine the relationship between cortisol levels and subcortical brain volume in the following brain structures: accumbens, amygdala, caudate, cerebellum cortex, cerebellum white matter, hippocampus, pallidum, putamen, and thalamus. The analyses were performed on the entire sample and separately for men and women. The following three sections show the results of these analyses.

Association between baseline cortisol levels and baseline subcortical brain volume

When testing the associations between baseline cortisol levels and baseline subcortical brain volume, results showed that the associations were non-significant (p-value > 0.0249) for the entire sample (Table 3). However, upon separating the analysis by sex, men showed no significant associations (Table 4), but women revealed significant associations in the left (p-value = 0.002) and right (p-value = 0.009) hippocampi, with the left amygdala nearing significance (p-value = 0.030) (Table 5).

Association between baseline cortisol levels and change in subcortical brain volume

When testing the associations between baseline cortisol levels and the change in subcortical brain volume, which measured the difference between baseline and one-year follow-up, the results showed that the associations were non-significant (p-value > 0.0249) across the whole sample (Table 6), as well as when the analysis was separated by sex (Tables 7 and 8).

Association between change in cortisol levels and change in subcortical brain volume

When testing the associations between the change in cortisol levels and the change in subcortical brain volume, which measured the difference between baseline and one-year follow-up, the results showed significant associations across the whole sample (Table 9), within certain brain structures and with varying significance levels. These regions encompassed the left caudate (p-value = 0.023), right caudate (p-value = 0.023), left putamen (p-value = 0.009)**,** and right cerebellum white matter (p-value = 0.021), with the left thalamus nearing significance (p = 0.027). Further statistical analyses were applied to estimate the nature of this association in light of sex differences. Henceforth, it was revealed that men showed no significant associations (Table 10); however, women had significant associations specifically in the left caudate (p-value = 0.020) (Table 11).

Associations between cortisol levels and cortical brain structures

Linear mixed effects (LME) models were used to evaluate the association between baseline cortisol levels and cortical brain morphological measures at baseline and after a year of follow-up for both men and women. The next two sections show the results pertaining to both analysis instances.

At baseline

In men, baseline cortical brain thickness analyses showed significant positive correlations in the right frontal lobe (Figure 1) and significant negative correlations in the left temporal lobe (Figure 2). However, no significant correlations were reported when measuring baseline cortical brain volume and area.

Conversely, baseline cortical brain thickness analyses in women exhibited significant positive correlations in the right prefrontal cortex (Figure 3) and significant negative correlations in the left temporal and parietal lobes (Figure 4). Similar to men, no significant correlations were reported for baseline cortical brain volume and area in women.

At one-year follow-up

At the one-year follow-up, significant results were reported for men in terms of change in cortical brain thickness only, with positive correlations present in the left parietal and occipital lobes (Figure 5). No significant correlations were reported for changes in cortical brain volume and area.

In contrast, after follow-up, women exhibited significant correlations across both hemispheres for all brain metrics. For changes in cortical brain thickness (Figure 6), positive correlations were reported within the prefrontal cortices and frontal lobes. Pertaining to changes in cortical brain volume (Figure 7), positive correlations were identified in the frontal, parietal, temporal, and occipital lobes. Lastly, for changes in cortical brain area (Figure 8), positive correlations were reported in the frontal, parietal, and occipital lobes. It is worth noting that the highest observed cluster was in the left medial frontal lobe.

DISCUSSION

The following research aims to take a whole-brain approach of the brain under the effect of cortisol to speculate its impact locally, on specific brain regions and functions, and globally on neural network connectivity, systemic physiological functions, and neuroendocrine interactions. Moreover, the study here considers the differences between men and women separately. Our findings suggest that baseline cortisol is significantly associated with brain structural changes, with the specific regions and extent of significance varying across men and women. Women were predominantly impacted by cortisol when considering brain structural changes across all metrics (thickness, volume, and area), whereas men showed significance only at the level of brain thickness.

Further, no significant associations across the entire sample were observed between baseline cortisol levels and baseline subcortical brain volume. However, when considering each sex separately, no significant associations were reported for men, but they were reported for women in the left and right hippocampi. On the other hand, when considering the association between the change in cortisol levels and the change in brain subcortical volume, significant associations were revealed across the entire sample, with significant associations in several brain regions including the left and right caudate, left putamen, as well as the right cerebellum white matter. Besides that, these results were further investigated in terms of sex, where a significant association in the left caudate was seen in women only.

Sex-specific differences in the association between cortisol levels and brain structure and function

The impact of high cortisol levels on cortical thickness can be contemplated in light of the great number of glucocorticoid receptors present in many brain regions. The number of receptor which can be negatively affected b chronic elevated cortisol levels, potentially concentration, leading to impaired neuroplasticity and, ultimately, neuronal loss (Liu et al., 2015). While it is important to point out that our findings also highlight a significant association with cortical thickness in men, significant results were more pronounced in women when investigating the association between cortisol levels and brain structural changes, as previously mentioned. Our findings are consistent with those found in the literature. In a study that investigated the impact of cortisol levels on cognition and brain overall structure among subjects from three different generations using magnetic resonance imaging (MRI), findings revealed that higher cortisol levels are significantly and inversely associated with brain volume in women, rather than in men (Echouffo-Tcheugui et al., 2018).

This finding can be interpreted in light of several important facts attributed to the physiological brain differences present between men and women. Across the entire lifespan of women, they are under the influence of two main ovarian sex hormones estrogen and progesterone. These two hormones have been thoroughly examined to identify their various effects on brain structure and function. It has been suggested that both estrogen and progesterone have neuroprotective properties which encompass promoting synaptic plasticity by modulating dendritic spines and synaptic density in various brain regions that include the hippocampus, nucleus accumbens, and the amygdala (Micevych & Christensen, 2012). Additionally, the hormones' neuroprotective property also involves protection against neuroinflammation and oxidative stress (Brotfain et al., 2016), by inhibiting the production of inflammatory cytokines and free radicals by microglia,

which normally take part in the inflammatory damage of neurons (Brann et al., 2007)**.** As women age, especially after menopause, estrogen and progesterone levels decline significantly. Thus, a reduction in these hormones may make the brain more susceptible to the negative impacts of cortisol, particularly among brain regions that contain high concentrations of estrogen and progesterone receptors including the hippocampus, hypothalamus, and amygdala (Catenaccio et al., 2016; Rocca et al., 2010).

Besides the previous plausible explanation behind the pronounced impact of cortisol on women's brains, sexual dimorphism plays a crucial part in understanding the differences characterizing men's and women's brains at the structural and functional levels (Sacher et al., 2013). Regional differences exist in the hippocampus, with women having a larger posterior hippocampal region compared to men and a significant difference in connectivity (Yagi & Galea, 2019). Studies have found a positive correlation between blood flow to the hippocampus and stressful stimuli in women, while in men, this correlation was found to be negative (Wang et al., 2007). In addition, women tend to be more vulnerable to stress than men; thereby, they are at a higher risk of developing stress-based disorders (Killgore & Yurgelun-Todd, 2001). Given the amygdala's critical role in regulating emotional responses, including stress, its activation is more prominent in women (Kogler et al., 2016), despite men having a larger amygdala (Killgore & Yurgelun-Todd, 2001). To add to that, the hypothalamus-pituitary-adrenal (HPA) axis is more enhanced in women when they are presented with a stressor (Heck & Handa, 2019). Furthermore, women generally have a larger and more active prefrontal cortex than men (Goldstein et al., 2005). The greater reliance on this region in women might explain why changes in that region are more significant. Regarding brain connectivity, there are sex differences in the parietal and occipital lobes (Koscik

et al., 2009), with the possibility that women might have different patterns of brain aging in these areas. These findings suggest that women are more susceptible to cortisol-related changes.

Implications

Our study highlighted several primary brain regions in both sexes that were affected by the levels of cortisol, pointing to the possible complex interplay between cortisol and cognitive aging. These regions included lateral and medial parts of the frontal lobe, parietal lobe, and occipital lobe. Highlighted brain regions in the frontal lobe, which include the prefrontal cortex, are involved with various significant executive functions, which encompass attention, judgment, reasoning, working memory, problem-solving, creativity, impulse control, emotional regulation, and inhibitory control (Fuster, 2002; Scott & Schoenberg, 2010). As for the regions within the parietal lobe, they perform a higher-order process referred to as sensory integration (Berlucchi & Vallar, 2018). The precuneus, which is found medially, has an essential role in memory retrieval and consciousness (Dadario & Sughrue, 2023). Regarding the occipital lobe, the identified regions are involved in visual processing, perception, object and face recognition, and memory formation (Rehman & Al Khalili, 2019). However, all these cognitive functions tend to decline with age, and elevated levels of cortisol are perhaps exacerbating this decline via different plausible mechanisms. Therefore, studying and comprehending these mechanisms is crucial for developing targeted interventions to mitigate the presumed impact of stress and cortisol on cognitive aging.

Of these probable mechanisms is the neurotoxic effects brought by high levels of cortisol. Elevated levels of cortisol or chronic stress have been associated with a decreased brain volume in regions

with high concentrations of glucocorticoid receptors, including the hippocampus and the prefrontal cortex, due to neuronal damage and regional atrophy (Lupien et al., 2018). Therefore, an impairment in cognition is expected, in addition to a cascade of effects that impacts connected regions (Farooqi et al., 2018). Moreover, another neurotoxic effect related to the high levels of cortisol is promoting oxidative stress and increasing the concentration of amyloid β (Aβ) in the hippocampus. This may increase the rate of neurodegeneration, causing an increased risk of developing dementia diseases like Alzheimer's disease (AD) (Ouanes & Popp, 2019; Qiu et al., 2022).

Reduced plasticity is another mechanism that can play a role in exacerbating cognitive decline through cortisol. Cortisol can affect synaptic plasticity, reducing the brain's ability to adapt and reorganize, which is crucial for maintaining cognitive functions in aging (Zak et al., 2018). This happens through the stimulation of hypermetabolism and decreased synaptic density, mainly in the hippocampus and prefrontal cortex (Reser, 2016). Besides this mechanism, neuroinflammation is also a process through which cortisol can impair cognition. Excessive cortisol induces neuroinflammation where glucocorticoid receptors are downregulated in response to excessive production of cortisol. It is important to note that in normal conditions, glucocorticoids including cortisol regulate inflammation by inhibiting proinflammatory cytokines and stimulating anti-inflammatory cytokines, through an action elicited in the cytoplasm of immune cells (Knezevic et al., 2023). Thereby, through the interplay of immune responses, cytokine release, and absence of down-regulation by glucocorticoids, neuroinflammation persists (Knezevic et al., 2023). This persisting inflammation leads to brain atrophy, causing pronounced changes in structure and function in crucial brain regions like the hippocampus (Vyas et al., 2016).

Another plausible mechanism is the dysregulation of the HPA axis. The HPA axis is a major stress system within the human body, and it is vulnerable to aging which could lead to altered cortisol secretion patterns. This dysregulation can particularly affect brain regions involved in the feedback regulation of the HPA axis (Milligan Armstrong et al., 2021). Studies have shown that dysregulation of the HPA axis is associated with impaired cognition, including a disturbance in memory functions (Wingenfeld & Wolf, 2011), in addition to the development of various psychological illnesses like depression (Reppermund et al., 2007).

Strengths and limitations

The given research holds several limitations that are important to be mentioned. Female to male ratio is a significant shortcoming, especially among the sample of participants in the LMCI group, where the number of males was around double that of females; however, this limitation was not present among the sample of participants in the AD Group, as the numbers of males and females were close in number. Another caveat is the diagnosis of subjects that made up our sample, as not all subjects were attributed the same diagnosis (i.e. LMCI due to probable AD versus mild dementia due to probable AD); thus, introducing variability in the analyses performed. Moreover, cortisol levels were taken at only two different time points under the same conditions: at baseline and at a one-year follow-up. Unfortunately, given that cortisol is a hormone with a diurnal pattern, it would have been beneficial to provide cortisol measurements at different times during the day, securing more insight into the variations in cortisol levels. On top of that, brain structural changes were also measured at these previously mentioned two time points only.

Despite these limitations, our study holds multiple strengths that are worth pointing out. To begin with, our study focused on investigating the association between cortisol levels and brain structural changes while adopting a whole-brain approach that considers the whole brain instead of just selected brain regions. In addition to that, we took into consideration sex differences between men and women, with the sample of participants showing no significant variability between sexes at the levels of age, education, and MMSE scoring.

CONCLUSIONS

The study of cortisol's impact on structural brain changes offers crucial insights into the intricate interplay between stress hormones and brain health. It is particularly compelling as it provides a whole-brain view of the brain, encompassing a wide range of cortical regions. Furthermore, it underscores the need for sex-specific approaches in research. In light of the major findings that were revealed from this study, future research is necessary to investigate the significance of the association between cortisol levels and cognition, given the effect of cognitive decline caused by aging, in addition to accounting for differences between men and women. Thus, a cohort study is strongly recommended to better comprehend these associations, and it should include reporting cortisol levels at different times during the day, measuring brain changes at various points throughout the year, and various neuropsychological measures to assess cognition. Building on the previous, future research should maintain the controls in the study by matching men and women based on age, education, recruited number of subjects, and diagnosis to cancel any controllable variabilities that might affect the study's results.

FIGURES

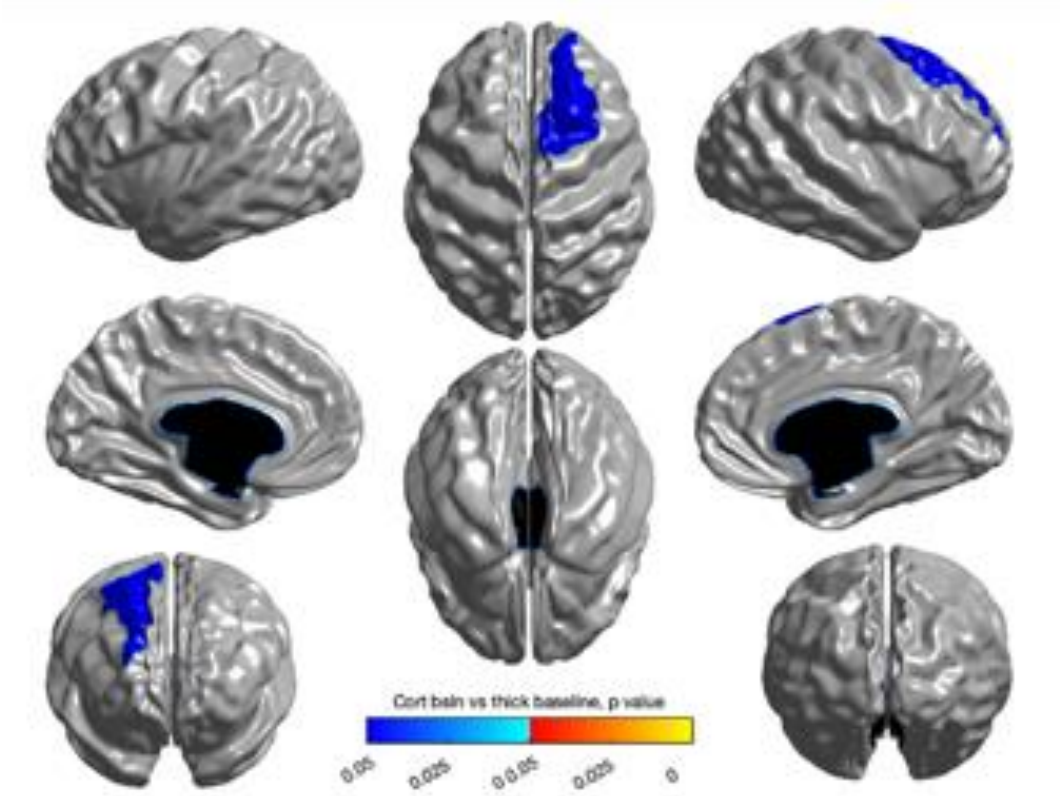

Figure 1: Men: RFT corrected maps showing a positive correlation between baseline cortisol and baseline cortical thickness

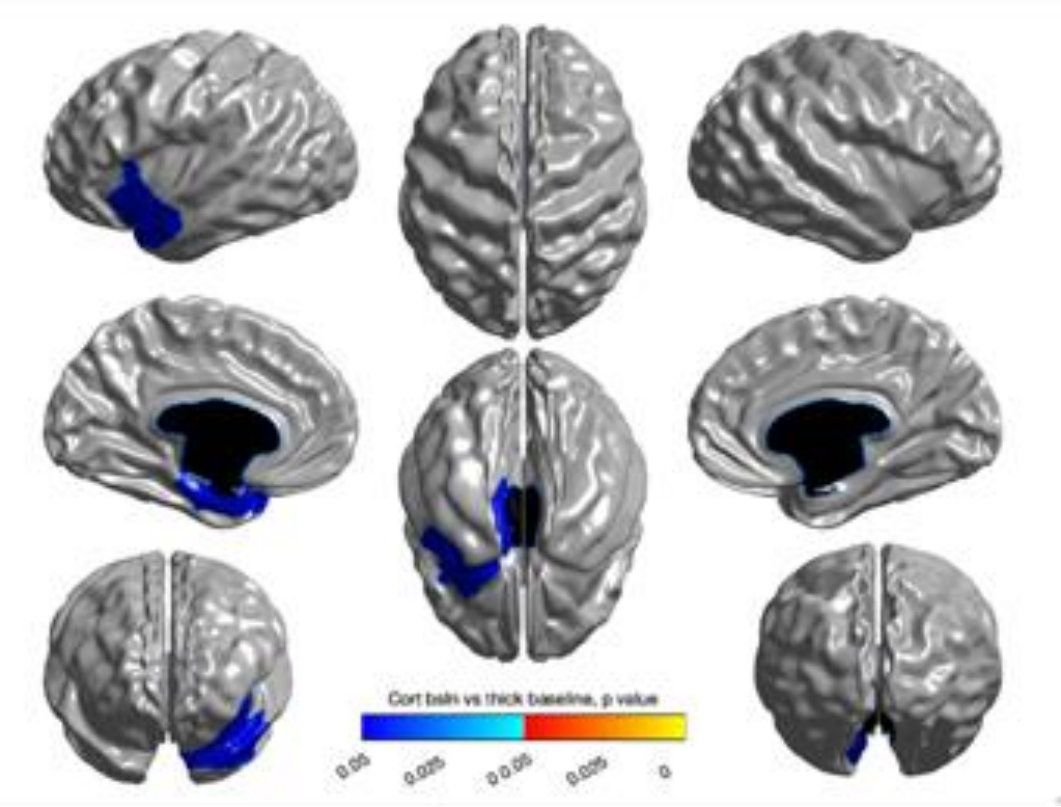

Figure 2: Men: RFT corrected maps showing a negative correlation between baseline cortisol and baseline cortical thickness

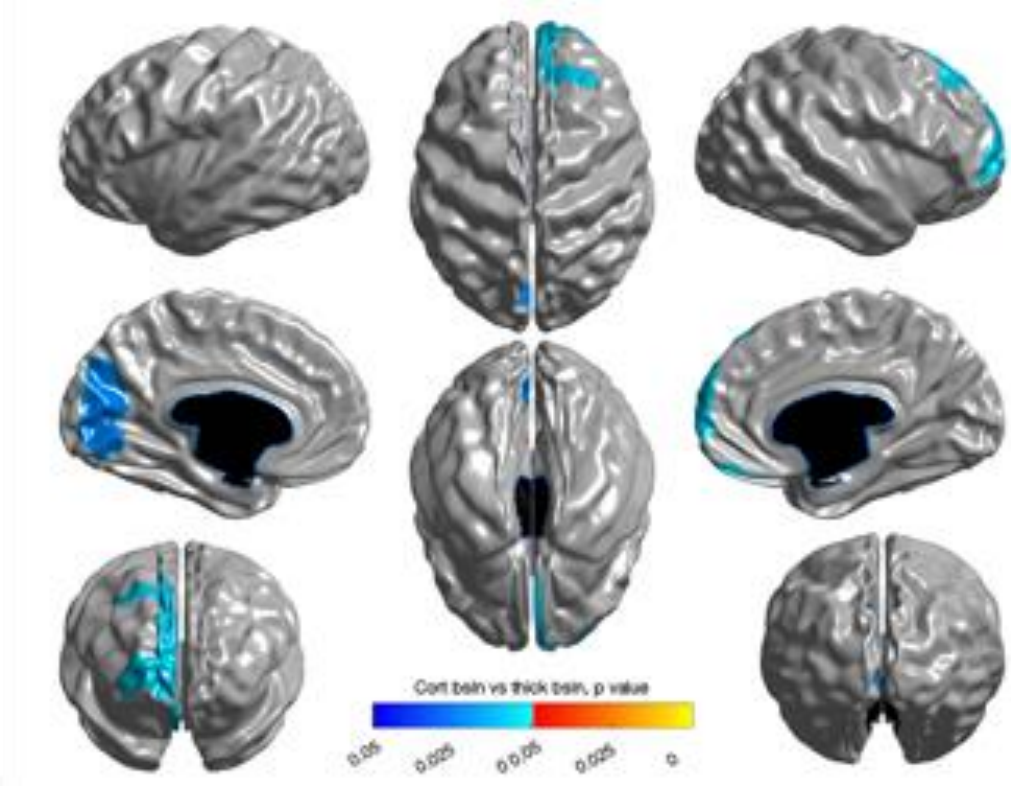

Figure 3: Women: RFT corrected maps showing a positive correlation between baseline cortisol and baseline cortical thickness

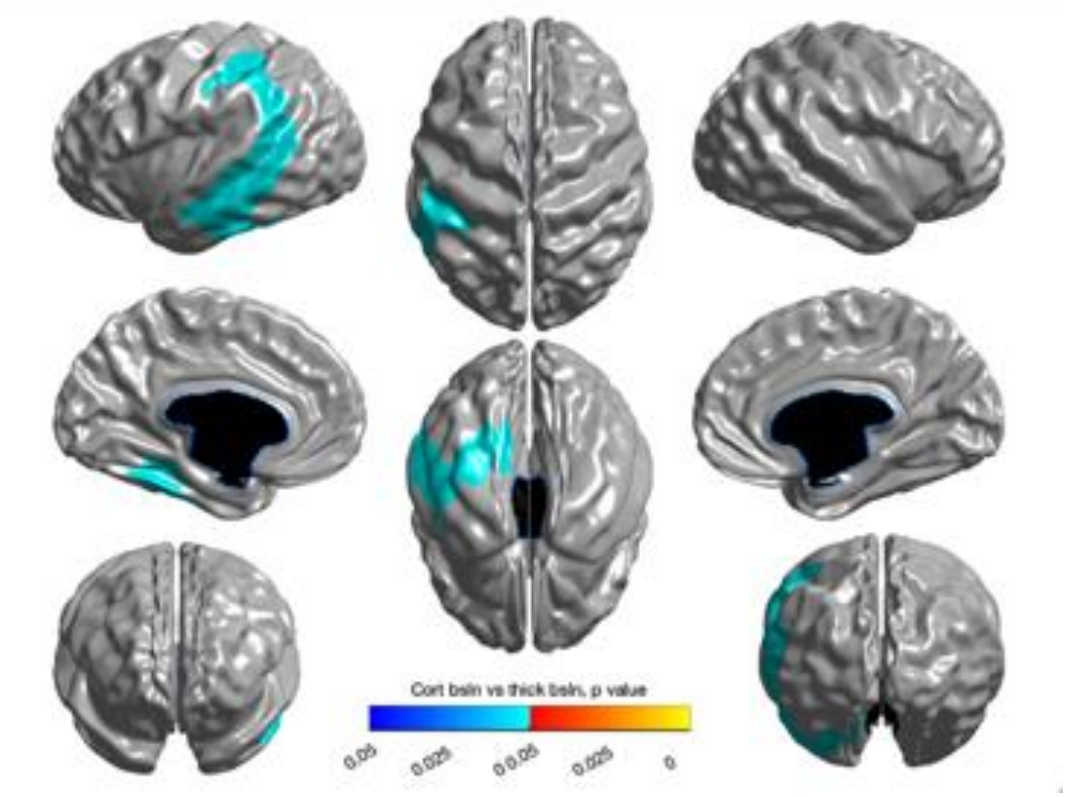

Figure 4: Women: RFT corrected maps showing a negative correlation between baseline cortisol and baseline cortical thickness

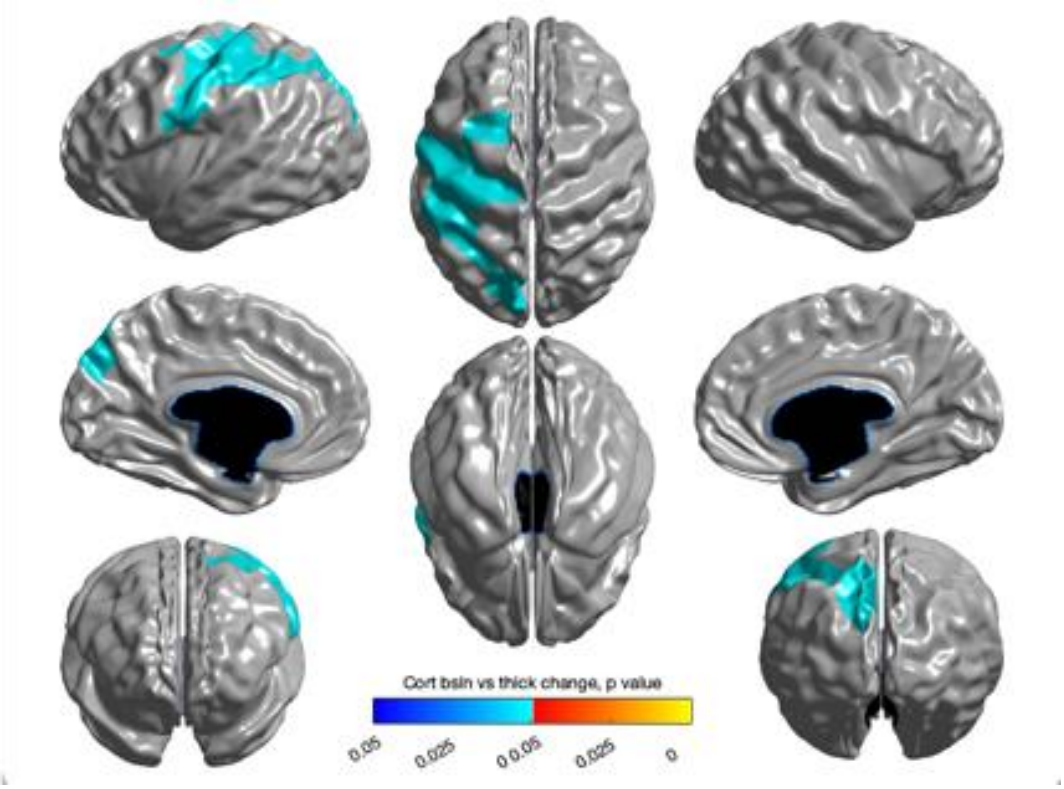

Figure 5: Men: RFT corrected maps showing a positive correlation between baseline cortisol and change in cortical thickness

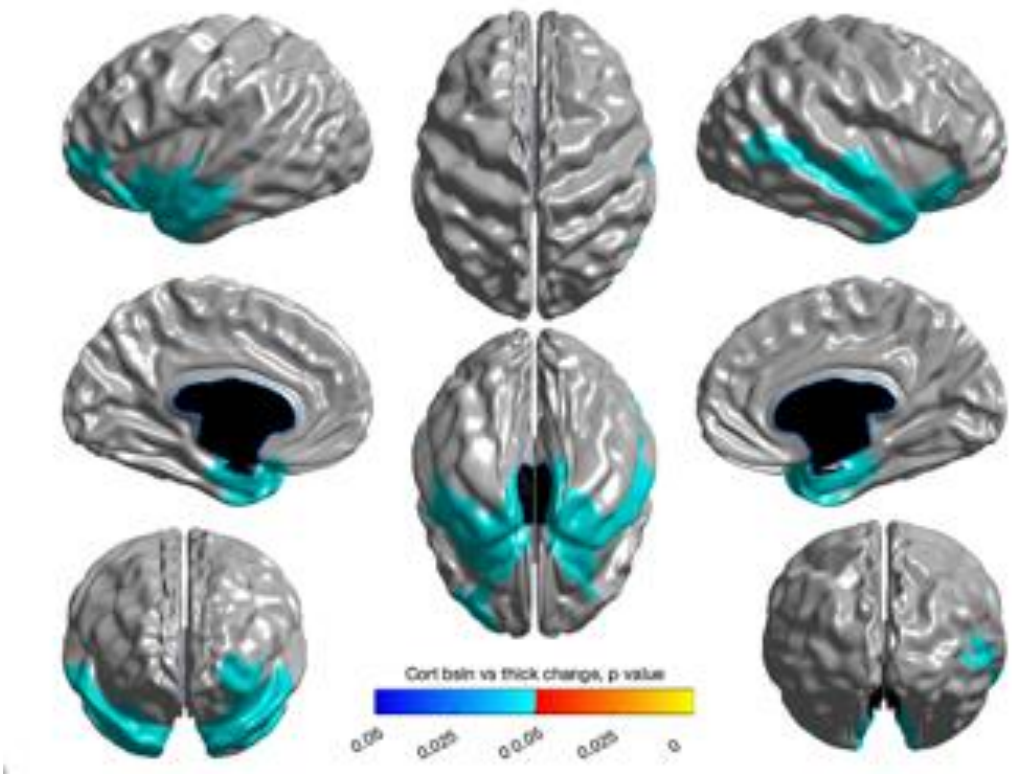

Figure 6: Women: RFT corrected maps showing a positive correlation between baseline cortisol and change in cortical thickness

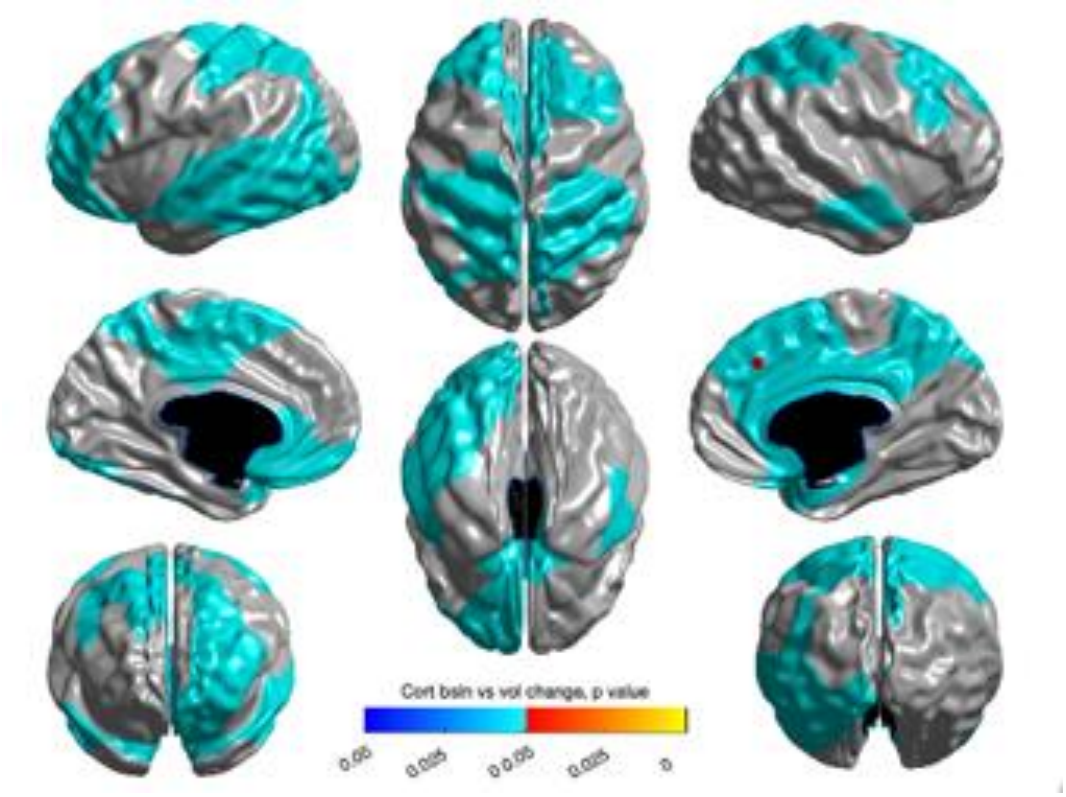

Figure 7: Women: RFT corrected maps showing a positive correlation between baseline cortisol and change in cortical volume

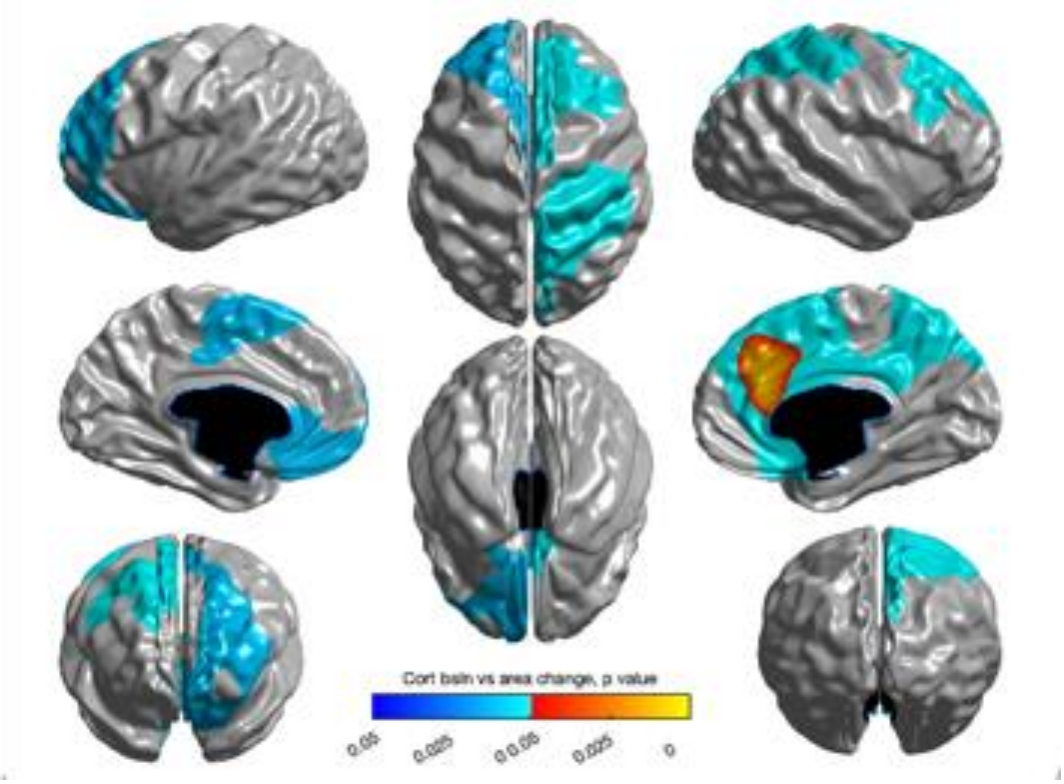

Figure 8: Women: RFT corrected maps showing a positive correlation between baseline cortisol and change in cortical area

TABLES

Table 1 : Demographic information

	LMCI (n = 63)	**AD (n = 17)**
Age	73.5 ± 8.1 (55-88)	74.0 ±10.1 (56-89)
Sex (Men: Women)	41:22	8:9
Education	15.8 ± 3.3 (6-20)	15.5 ± 2.8 (12-20)
MMSE	26.7 ± 1.8 (23-30)	22.9 ±1.9 (20-26)

These numbers represent the mean ± standard deviation and (range); MMSE, mini-mental state examination; AD, Alzheimer's disease; LMCI, late mild cognitive impairment.

Table 2: Men and women: baseline biomarker characteristics

	Women	**Men**
Cortisol (ng/mL)	2.16 ± 0.11 (1.98-2.28)	2.19 ± 0.13 (1.80-2.50)
Total Brain Volume (L)	5.45 ± 0.54 (4.60-6.80)	6.16 ± 0.85 (3.05-7.67)

These numbers represent the mean ± standard deviation and (range).

Table 3: Men and women: partial correlations between baseline cortisol levels and baseline subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.577
Left amygdala	0.784
Left caudate	0.299
Left cerebellum cortex	0.092
Left cerebellum WM	0.914
Left hippocampus	0.573
Left pallidum	0.215
Left putamen	0.773
Left thalamus	0.539
Right accumbens	0.393
Right amygdala	0.396
Right caudate	0.428
Right cerebellum cortex	0.239
Right cerebellum WM	0.755

Right hippocampus	0.686
Right pallidum	0.798
Right putamen	0.668
Right thalamus	0.656

Table 4 Men: partial correlations between baseline cortisol levels and baseline subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.587
Left amygdala	0.264
Left caudate	0.291
Left cerebellum cortex	0.206
Left cerebellum WM	0.610
Left hippocampus	0.167
Left pallidum	0.130
Left putamen	0.793
Left thalamus	0.292

Right accumbens	0.593
Right amygdala	0.952
Right caudate	0.396
Right cerebellum cortex	0.520
Right cerebellum WM	0.382
Right hippocampus	0.218
Right pallidum	0.444
Right putamen	0.700
Right thalamus	0.272

Table 5 Women: partial correlations between baseline cortisol levels and baseline subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.826
Left amygdala	0.030
Left caudate	0.418
Left cerebellum cortex	0.281

Left cerebellum WM	0.384
Left hippocampus	0.002*
Left pallidum	0.863
Left putamen	0.867
Left thalamus	0.564
Right accumbens	0.310
Right amygdala	0.132
Right caudate	0.664
Right cerebellum cortex	0.206
Right cerebellum WM	0.224
Right hippocampus	0.009*
Right pallidum	0.097
Right putamen	0.803
Right thalamus	0.233

* Indicates a statistically significant result ($p < 0.0249$).

Table 6 Men and women: partial correlations between baseline cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.515
Left amygdala	0.445
Left caudate	0.070
Left cerebellum cortex	0.647
Left cerebellum WM	0.573
Left hippocampus	0.723
Left pallidum	0.380
Left putamen	0.793
Left thalamus	0.805
Right accumbens	0.285
Right amygdala	0.141
Right caudate	0.121
Right cerebellum cortex	0.430
Right cerebellum WM	0.863
Right hippocampus	0.408
Right pallidum	0.771
Right putamen	0.071

Right thalamus	0.721

Table 7: Men: partial correlations between baseline cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.903
Left amygdala	0.315
Left caudate	0.195
Left cerebellum cortex	0.626
Left cerebellum WM	0.748
Left hippocampus	0.614
Left pallidum	0.125
Left putamen	0.356
Left thalamus	0.556
Right accumbens	0.421
Right amygdala	0.089
Right caudate	0.270

Right cerebellum cortex	0.586
Right cerebellum WM	0.897
Right hippocampus	0.161
Right pallidum	0.577
Right putamen	0.144
Right thalamus	0.454

Table 8: Women: partial correlations between baseline cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.222
Left amygdala	0.795
Left caudate	0.346
Left cerebellum cortex	0.778
Left cerebellum WM	0.474
Left hippocampus	0.821
Left pallidum	0.223

Left putamen	0.157
Left thalamus	0.294
Right accumbens	0.359
Right amygdala	0.957
Right caudate	0.539
Right cerebellum cortex	0.357
Right cerebellum WM	0.669
Right hippocampus	0.865
Right pallidum	0.589
Right putamen	0.545
Right thalamus	0.245

Table 9: Men and women: partial correlations between change in cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.898
Left amygdala	0.254

Left caudate	0.023*
Left cerebellum cortex	0.084
Left cerebellum WM	0.155
Left hippocampus	0.212
Left pallidum	0.667
Left putamen	0.009*
Left thalamus	0.027
Right accumbens	0.083
Right amygdala	0.090
Right caudate	0.023*
Right cerebellum cortex	0.248
Right cerebellum WM	0.021*
Right hippocampus	0.679
Right pallidum	0.033
Right putamen	0.223
Right thalamus	0.377

* Indicates a statistically significant result ($p < 0.0249$).

Table 10: Men: partial correlations between change in cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.331
Left amygdala	0.123
Left caudate	0.296
Left cerebellum cortex	0.102
Left cerebellum WM	0.328
Left hippocampus	0.386
Left pallidum	0.221
Left putamen	0.040
Left thalamus	0.080
Right accumbens	0.077
Right amygdala	0.144
Right caudate	0.129
Right cerebellum cortex	0.311
Right cerebellum WM	0.096

Right hippocampus	0.372
Right pallidum	0.064
Right putamen	0.944
Right thalamus	0.511

Table 11: Women: partial correlations between change in cortisol levels and change in subcortical brain volume

Subcortical structure	P-value
Left accumbens	0.197
Left amygdala	0.799
Left caudate	0.020*
Left cerebellum cortex	0.669
Left cerebellum WM	0.177
Left hippocampus	0.465
Left pallidum	0.098
Left putamen	0.153
Left thalamus	0.276
Right accumbens	0.946

Right amygdala	0.975
Right caudate	0.084
Right cerebellum cortex	0.451
Right cerebellum WM	0.135
Right hippocampus	0.558
Right pallidum	0.509
Right putamen	0.103
Right thalamus	0.466

* Indicates a statistically significant result ($p < 0.0249$).

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