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Reduced hippocampal and anterior cingulate expression of antioxidant enzymes and membrane progesterone receptors in Alzheimer's Disease with depression

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Abstract

Background: Major depressive disorder (MDD) is a risk factor for dementia including that caused by Alzheimer's Disease (AD). Both MDD and AD have a higher prevalence in women than men, and estrogen-related processes have been implicated in this sex difference.

Objective: To identify if enhanced oxidative stress and decreased expression of the memory enhancer insulin-like growth factor 2 (*IGF2*), each implicated separately in MDD and AD, are exaggerated in individuals with both AD and MDD compared to those with AD.

Methods: Expression of target genes are determined by qPCR in postmortem hippocampus (Hip) and anterior cingulate cortex (ACC) of individuals with dementia and autopsy confirmed AD and those of AD+MDD.

Results: Transcript levels of the antioxidant enzymes catalase (*CAT*) and superoxide dismutase 1 (*SOD1*), as well as *IGF2* and its receptor (*IGF2R*) were significantly lower in the Hip and ACC of individuals with both AD and MDD compared to those with AD and no MDD. Expressions of Progestin and AdipoQ Receptor Family Member 7 (*PAQR7,* alias progesterone receptor alpha, *mPRα*) and *PAQR8* (*mPRβ*), receptors that bind neurosteroids, were also lower in the Hip and ACC of AD+MDD samples compared to those of AD without MDD. Correlations among these transcripts revealed that estrogen receptor 2 (*ESR2*) and *mPRβ* are direct or indirect regulators of the expression of the antioxidant enzymes and IGF2R.

Conclusion: Reduced levels of antioxidant enzymes, decreased *IGF2* expression, and diminished estrogen or membrane progesterone receptor-dependent processes might be more pronounced in the subpopulation of individuals with AD and MDD than without MDD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

Keywords

depression; molecular vulnerability; antioxidant enzymes; insulin like growth factor 2; membrane progesterone receptor; sex/gender differences

INTRODUCTION

Millions of people live with dementia, and 50–70% of all late-onset dementia cases are caused by Alzheimer's Disease (AD) neuropathology [1] in isolation, or accompanied by additional pathologies [2]. The number of AD cases is increasing, predicted to reach 12.7 million by 2050 in the US, and 152 million worldwide. The disease process related to AD starts long before symptom onset and lasts approximately 15–20 years. It is widely believed that early detection of possible precursors and treatment of modifiable risk factors of AD is very important. Emotional, physical, or cellular stressors are known risk factors for cognitive decline and have been implicated in earlier onset and more marked progression of AD [3]. Stress-related disorders like depression have been linked to a state of accelerated biological or cellular aging [4], affecting the hippocampus and subsequently leading to pathological cognitive aging [5–14]. Major depressive disorder (MDD) is a risk factor for the development of AD [3, 15] and the MDD prevalence rate is 37% in those with dementia [16]. Even moderate depression increases risk of progression from cognitively healthy to dementia [17]. Additionally, there may be a limited overlap in the etiology of these illnesses, as a moderate level of polygenic overlap has also been found between MDD and AD [18].

In a recent study, we found that increased stress-reactivity and predisposition to depression-like behavior exaggerated cognitive aging in female rats [19]. Hippocampus-dependent contextual fear memory in the inbred Wistar Kyoto More Immobile (WMI) females declined by middle age, compared to same age controls, the Wistar Kyoto Less Immobile (WLI) females, which do not exhibit enhanced stress responses or depressive behaviors. At a young age, there is no difference in memory between these nearly isogenic strains. Hippocampal transcript levels of the antioxidant enzymes, catalase (*Cat*) and superoxide dismutase1 (*Sod1*) and the learning and memory-stimulant insulin-like growth factor 2 (*Igf2*), and its receptor *Igf2r* were lower in the middle-aged WMI hippocampus compared to the young of both strains [19]. These findings in the animal model promise to be relevant to human illnesses, as enhanced oxidative stress has been implicated in both MDD [21–23] and AD [20, 21]. Furthermore, attenuated levels of hippocampal IGF2 have also been proposed to contribute to AD pathology [22]. IGF2 binds with high affinity to the IGF2 receptor (IGF2R), which reduces the bioavailability of IGF2 by targeting it to lysosomes. Thus, it is demonstrated that the effects of IGF2 in memory enhancement and recovery of function in disease models are dependent on its binding to IGF2R [23–25].

Prevalence of both MDD [10, 26] and dementia [27, 28] are higher in women than in age-matched men. Both the progression of cognitive decline and its association with MDD shows that females are particularly vulnerable [29, 30]. Women also show faster cognitive decline after a clinical diagnosis of mild cognitive impairment (MCI) or AD dementia [31]. Higher risks of cognitive decline and dementia and higher levels of AD neuropathology have

been associated with early, surgically induced menopause, indicating that menopause before the age of 40–45 represents a female-specific risk factor for AD dementia [32, 33].

Reduced peripheral levels of 17β-estradiol and testosterone are observed in female and male patients with AD, respectively, compared to appropriate matched controls [34]. Sex hormones have been proven to improve cognitive functions and alleviation of depression upon treatment with estrogens in both females and males, mainly in rodent models, but also in humans [see recent reviews: 35, 36]. Recently, expression of membrane progesterone receptors, Progestin and AdipoQ Receptor 7 and 8, respectively (*PAQR7*; *mPRα* and *PAQR8*; *mPRβ*), have been assessed in the blood of pregnant and postpartum women with varying degree of depressive symptoms [37]. It was found that blood transcript levels of both *ESR2* and *mPRβ* correlated significantly, but inversely, with depression scores. Thus, lower levels of these receptor transcripts were associated with higher depression scores.

The hippocampus is particularly vulnerable in AD [38–40]. Studies have shown volume loss in the hippocampus during the progression of AD has a direct relationship with cognitive decline. Functional connectivity between the hippocampus and other brain regions, including the ventral anterior cingulate cortex, is disrupted in AD patients [41]. Furthermore, the anterior cingulate cortex (ACC) is a brain region with metabolic decline in aging [42]. ACC is a fundamental hub of the memory network and plays a major role in cognitive control during complex tasks [43]. Hypoactivity in the ACC is associated with depression in AD [44], making it a brain region of importance in this study.

Here, we aimed to determine if the hippocampal molecular deficits found in the animal model can be replicated in human postmortem brain samples from individuals with AD with, and without, a history of MDD. We hypothesized that the increased prevalence of AD in older women could be associated with substantially reduced estrogen and progesterone-dependent processes, and MDD may directly affect these pathways. To answer this, we also examined the expression of estrogen receptors and membrane progesterone receptors in these brain regions.

METHODS

Samples

Postmortem tissue samples (male and female, aged 41–96 years old) were acquired from the Brain Bank of the Mesulam Center for Cognitive Neurology and Alzheimer Disease. Two populations were studied: individuals with AD dementia and neuropathologic changes of AD, with prior depression (n = 19) and individuals with AD dementia and neuropathologic changes of AD, without prior depression (n = 19). Neuropathological diagnosis of AD was as described using the NIA-AA guidelines [45]. Prior depression was assessed from health records. The hippocampus and anterior cingulate cortex (ACC) were studied given their association with AD dementia. Tissues for both brain regions were not available in some cases, making the final sample sizes for hippocampus: AD male, N=9; female, N=10; AD+MDD male, N=8; female, N=7, and for ACC: AD male, N=9; female, N=10; AD+MDD male, N=10; female, N=9. Tissues were received frozen and maintained at −80 °C until RNA isolation.

All participants in the Clinical Core of the Northwestern Alzheimer's Disease Research Center, the source of brain donations, had provided informed consent to be evaluated annually during life and donated their brains at death. The parent study was approved by the institutional review boards of Northwestern University. Informed consent had included agreement to share data and tissue resources with collaborating investigators.

Expression analyses

Total RNA was isolated using the Direct-zol™ RNA MiniPrep kit (Zymo Research, Orange, CA, USA) and was reverse transcribed with SuperScript VILO™ Master Mix (Invitrogen, Carlsbad, CA, USA). Quantitative PCR (qPCR) was carried out as described previously [19]. Briefly, 5 ng of cDNA was amplified with SYBR Green Master Mix (Applied Biosystems, Foster City, CA, USA) and primer sequences specific to various genes of interest. The primer sequences are shown in Supplemental Table 1. Target transcript levels were normalized relative to *GAPDH*, a housekeeping gene previously demonstrated to show similar expression across various conditions. Relative quantification (RQ) was determined using transcript levels from one human female (75-year-old) hippocampal and ACC sample with no AD and no MDD diagnosis as the calibrator, using the $2^{-(\Delta\Delta CT)}$ method. Please note that using the ΔCT method, the same results were obtained, of course inversely to RQ. Data are presented in RQ to provide an easier interpretation of the results.

Technical outliers were defined as samples where either the target or the housekeeping gene showed abnormal amplification or melting curve characteristics. Therefore, these outliers (n=1–3 in the different qPCR runs) were removed.

Statistical analysis

All statistical analyses were performed using GraphPad Prism v9.3.1 (GraphPad Software, La Jolla, CA). Statistical significance for gene expression differences was determined by two-way ANOVA (sex and comorbidity), followed by False Discovery Rate (FDR) corrected *post-hoc* analyses. Post hoc significances are marked in the figures as $q<0.05$ or <0.01, when controlled for multiple comparisons, or $p < 0.05$ as individual p values. When there were no significant main effects for sex or comorbidity in the two-way ANOVA, we combined male and female expression data to test the hypothesis that the presence of MDD diagnosis altered the gene expression. This analysis was conducted by Student's t-test. Data are presented as mean ± standard error of mean. Pearson correlations across transcript levels were carried out using the GraphPad Prism v9.3.1. software and significance values were corrected for multiple comparisons. The modified Kolmogorov-Smirnov "goodness to fit" test was used to verify normal distribution with the GraphPad software.

RESULTS

Table 1 shows descriptive data of the participants. There were no significant differences between the female or male groups of AD and no MDD vs. AD + MDD in age or postmortem interval (PMI). Females AD vs. AD + MDD, age: 81.7 +/− 1.7 vs. 71.7 +/− 6.3; PMI: 12.4 +/− 2.8 vs. 16.1 +/ 2.7 Males AD vs. AD + MDD, age: 76.2 +/− 3.3 vs. 74.2 +/− 4.2; PMI: 14.6 +/− 2.7 vs. 14.0 +/ 2.4. Although AD+MDD females were slightly

younger, including two individuals under 50 years of age, the age distribution was still normal in all groups confirmed by the Kolmogorov-Smirnov test.

Expression of Superoxide Dismutase 1 and Catalase in the Hippocampus and the Anterior Cingulate Cortex

Compared to individuals with AD and no prior depression, individuals with AD and prior depression show reduced hippocampal expression of antioxidants as indicated by two-way ANOVA (comorbidity: *SOD1*, F[1,29]=6.3, p=0.018; *CAT*, F[1,27]=5.8, p=0.023). No significant main effects of sex, or sex by comorbidity interactions were found for the expression of either gene (sex, *SOD1*, F[1,29]=0.49, NS; *CAT*, F[1,27]=0.44, NS). However, post-hoc analyses indicated that hippocampal *SOD1* expression was significantly ($q<0.05$) lower in females with AD + MDD compared to AD (Figure 1A). Similarly, post-hoc comparison showed that hippocampal *CAT* expression was also lower in females of the AD + MDD group compared to those of AD at the individual p value (<0.05) level.

Similarly, *SOD1* levels were significantly lower in AD + MDD in the ACC brain region, but that of *CAT* expression did not reach significance by two-way ANOVA (comorbidity, *SOD1*, F[1,32]=7.33, p=0.011; *CAT*, F[1,32]=1.63, NS; Figure 1B). While there were no significant main effects for sex (*SOD1*, F[1,32]=1.77, NS; *CAT*, F[1,32]=1.63, NS), there was a sex by comorbidity interaction for *SOD1* (F[1,32]=4.8, p=0.036). Post-hoc analysis indicated that *SOD1* expression is significantly ($q <0.05$) lower in the female AD + MDD ACC, compared to that of AD and no depression (Figure 1B). For hypothesis testing, and because there were no sex differences in *CAT* expression in the ACC, we combined the sexes and carried out a Student's t- test. This sex-combined expression of *CAT* was significantly lower in the ACC of the AD + MDD group compared to those of AD alone (t=2.27, df=32, p=0.030).

Furthermore, the cumulative reduction in *SOD1* and *CAT* in individuals with AD and MDD compared with individuals with AD and no MDD was 57.1% in male hippocampi, while it was 85.7% in female hippocampi. The reduction was 18.5% in males and 65.4% in females in the ACC.

Expression of Insulin-like Growth Factor and its Receptor in the Hippocampus and the Anterior Cingulate Cortex

Individuals with AD and no MDD did not show significantly different hippocampal *IGF2* transcript levels from those with AD + MDD analyzed by two-way ANOVA (comorbidity, F[1,22]=3.63, p=0.07; Figure 2A). There was also no significant main sex effect (F[1,22]=1.47, NS), or a sex by comorbidity interaction. Therefore, we combined the male and female data and compared it between the AD and the AD+MDD groups using Student's t-test. This comparison showed a significantly lower *IGF2* expression in the hippocampus in the AD + MDD group compared to those of AD (t=2.53, df=24, p=0.018).

In contrast to hippocampal *IGF2* expression, both a significant sex difference and an effect of MDD comorbidity was observed in the ACC (sex, F[1,26]=4.29, p=0.048; comorbidity, F[1,26]=4.44, p=0.045) without any significant interaction effect. Specifically, *IGF2* expression in the AD no MDD female ACC was higher at the individual p level

($p<0.05$) in comparison to *IGF2* expression in the ACC of females in the AD + MDD group (Figure 2B).

No significant main effects of comorbidity or sex were found for the hippocampal *IGF2R* expression between the groups. *IGF2R* transcript levels did not differ between the sexes in the ACC (sex, F[1,30]=0.93, NS), but were significantly lower in the AD + MDD ACC compared to AD in both males and females using two-way ANOVA (comorbidity, F[1,30]=9.03, p=0.005). These differences were significant at the level of q=0.05 for both males and females at the post-hoc comparisons (Figure 2B).

Expression of estrogen receptors and membrane progesterone receptors in the hippocampus and the anterior cingulate cortex

Hippocampal expression of estrogen receptor 1 and 2 (*ESR1* and *ESR2*) showed significantly higher expression in females compared to males in the two-way ANOVA (sex, *ESR1*, F[1,20]=11.45, p=0.003; *ESR2*, F[1,20]=11.94, p=0.003; Supplemental Figure 1A). No main effect of comorbidity was found for the expression of either estrogen receptors (comorbidity, *ESR1*, F[1,20]=0.07, NS; *ESR2*, F[1,20]=0.05, NS). Sex differences reached significance (q=0.004) in *ESR1* expression between males and females in the AD no MDD group, but not in the AD + MDD group (Supplemental Figure 1A). However, sex differences reached significance in both groups for *ESR2* expression ($q<0.01$ for AD no MDD and $q<0.05$ for AD + MDD).

Estrogen receptor levels were significantly different in the ACC by sex and comorbidity. Specifically, *ESR1* transcript levels were significantly higher in female AD samples compared to those of males, and the presence of MDD symptoms in female AD subjects reduced this expression significantly (sex, F[1,20]=29.59, $p<0.001$; comorbidity, F[1,20]=23.45, $p<0.001$; sex x comorbidity, F[1,20]=28.76, p<0.00; Supplemental Figure 1B). The comorbidity difference in *ESR1* expression was clearly significant in females ($q<0.0001$), as shown by the post-hoc comparison. Interestingly, *ESR2* expression showed a very similar profile (sex, F[1,20]=28.36, $p<0.001$; comorbidity, F[1,20]=15.60, $p<0.001$; sex x comorbidity, F[1,20]=28.78, $p<0.001$). *ESR2* expression in the ACC was significantly different ($q<0.0001$) between females in the AD and AD + MDD groups also (Supplemental Figure 1B).

Hippocampal expression of the Progestin and AdipoQ Receptor Family Member 7 (*PAQR7*), also named as membrane progesterone receptor alpha (*mPRa*), did not differ between males and females, but was significantly lower in the AD + MDD hippocampus compared to those of AD without MDD (sex, F[1,24]=0.04, NS; comorbidity, F[1,24]=8.11, p=0.009). Specifically, *mPRa* expression in the AD + MDD male hippocampus was significantly lower ($q<0.05$) in comparison to *mPRa* expression in the AD no MDD males (Figure 3A). Hippocampal *PAQR8* (*mPRb*) expression did not differ significantly between male and female individuals, but showed a significant main effect of comorbidity (sex, F[1,24]=3.14, NS; comorbidity, F[1,24]=4.56, p=0.043). *mPRb* expression in the hippocampus was also significantly lower ($q<0.01$) in the AD + MDD males compared to AD no MDD males (Figure 3A).

In contrast to the hippocampal expression, *mPRa* expression in the ACC was higher in males than females in general, but lower in individuals with AD + MDD compared to AD no MDD (sex, F[1,26]=13.14, p=0.001; comorbidity, F[1,26]=5.07, p=0.033). Post-hoc comparison identified that *mPRa* transcript levels were lower in the AD+MDD males at the individual p value level ($p<0.05$) compared to AD no MDD males (Figure 3B). There were no main sex effects in *mPRb* expression in the ACC, but the main effect of comorbidity was highly significant (sex, F[1,26]=0.58, NS; comorbidity, F[1,26]=9.96, p=0.004). The expression of *mPRb* was significantly lower in female individuals with AD + MDD compared to those with AD no MDD ($q<0.01$; Figure 3B).

Correlations

Correlations between the variables revealed that all measured hippocampal transcript levels correlated significantly with *ESR2* expression, except *mPRα* (Table 2). Similarly, *mPRβ* significantly correlated with all measures except that of *IGF2* in the hippocampus. In contrast, *ESR2* only correlated with *IGF2* and *ESR1* expression in the ACC, and *mPRβ* did not show a significant correlation with *ESR1* and *ESR2* in the ACC (Table 3).

DISCUSSION

The novel findings of this study are the biochemical worsening of many molecular processes in the brain in participants with autopsy-confirmed AD and depressive symptoms. These include the decreased expression of antioxidant enzymes in the hippocampus and ACC of individuals with AD + MDD compared to those with AD. The other major result is the sex specificity of decreased antioxidant enzyme expression, where expression was significantly decreased in female AD + MDD samples. Furthermore, the brain region- and sex differences observed for *mPRβ* transcript levels between subjects with AD no depression compared to those with AD + MDD suggest that neurosteroids and their receptors may play a significant role in MDD being a risk factor for AD.

The observed decrease in *SOD1* expression in both the hippocampus and the ACC of female subjects with AD + MDD is novel. The significance of this finding is strengthened by the decreased expression of *CAT* enzyme in the same group. There is a substantial body of literature suggesting vulnerability to oxidative damage particularly at an early stage of AD pathology [46, 47]. Blood-based redox alterations have also been found in AD, including decreased levels of SOD [48]. In contrast, a metanalysis found no changes in the expression of SOD1 or CAT in AD brain regions [49].

There are also conflicting results for SOD1 and CAT in the literature of MDD [50–53], although malfunctioning antioxidant defense has been repeatedly implicated in depressive disorders [54–56]. In animal studies, reduced hippocampal Cat and Sod activity has been reported in parallel with stress-induced depression-like behavior [54, 57], similar to our findings in the genetically stress-reactive middle-aged WMI animals [19].

The overall trend of *IGF2* and *IGF2R* expression showed a decrease in the brain regions of individuals with AD + MDD compared to those with AD and no MDD. Decreased *IGF2* expression has been shown previously in some brain regions of individuals with AD

[58, 59]. Whether the decreased *IGF2* expression in AD + MDD is the result of MDD exaggerating the decrease of *IGF2* expression in AD brains cannot be determined in the present study. However, exogenous Igf2 administration can enhance cognitive function [60, 61], and fluoxetine and metformin treatment can enhance *Igf2* expression and decrease depression-like behavior at the same time in animal studies [62]. Thus, increasing Igf2 levels could be a potential mechanism to ameliorate both cognitive dysfunction and depression, and interestingly it has been suggested that increasing Igf2 levels would attenuate oxidative damage in the brain [63].

Aging and female gender are the most common risk factors of AD, leading to increased prevalence in women compared to men [64]. Estrogen and progesterone show protective activity on brain functions, and thus loss of these steroid hormones at menopause is an important risk factor for AD progression in females [65]. Furthermore, women with AD have reduced levels of brain estrogen [66]. As estradiol can increase choline acetyltransferase activity [67], and major depletion of this enzyme is a hallmark of AD [68], this potential mechanism adds to the list of sex difference etiologies in AD. Sex steroids, via androgen and estrogen receptors, have been identified as drivers of disrupted homeostatic processes in AD neurons [69, 70]. The present findings of reduced transcript levels of *ESRs* in the ACC of AD + MDD cases compared to those with AD and no MDD suggest that MDD affects the abundance of *ESRs*. Since selective ESR2 agonists can reduce depression-like behaviors [71], *ESR2* may participate in the molecular processes of MDD becoming a risk factor for AD.

Hippocampal *ESR2* expression was positively correlated with transcript levels of antioxidant enzymes, and those of *mPRβ*. Estrogen receptor beta (ESR2) and mitochondria are co-localized in the female brain, but in AD, both the expression of *ERβ* and its association with the mitochondria are reduced [72]. The reduction of *ERβ* expression in mitochondria is accompanied by decreases in mitochondrial function, which could have resulted from oxidative damage to mitochondrial DNA. The authors suggest that females with AD could have exaggerated accumulation of oxidative stress because of the mitochondrial defect, compared to controls. Thus, it is feasible that estrogen-regulated processes contribute to the female vulnerability to AD.

Progesterone is known to have neuroprotective effects via different receptors including those of mPRs [73, 74]. *mPR*β is expressed in higher levels in the rat brain than *mPR*α, similarly to the higher prevalence of mPRβ in the human brain [75, 76]. The neurosteroid allopregnanolone, metabolized from progesterone, binds to mPRs and affects anti-apoptotic actions [77]. Thus, decreased transcript levels of *mPRβ* in the hippocampus of male, and in the ACC of female AD + MDD cases, could suggest increased apoptotic processes. In addition, allopregnanolone concentration is reduced in the AD brain [78, 79] and in depression [80], suggesting a potential double hit of reduced levels and reduced receptors for this neurosteroid in AD that is further exaggerated in AD + MDD.

A limitation of this study includes the lack of age-matched postmortem samples from control subjects and those with MDD only. Future studies would need to increase the number of postmortem samples and include age matched MDD, and no AD no MDD

samples as well. Nevertheless, the current data suggest that MDD presents the background for a biochemical risk factor for AD, via exaggerating processes known to occur in the brains of individuals with AD. Given the lack of effective disease-modifying treatments for AD, this study highlights the need to place increased efforts on early identification and intervention in MDD. Effective treatment for MDD may therefore not only improve wellbeing in the context of depression but could attenuate the risk for Alzheimer's Disease as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Response to reviewers:

Reviewer 1.

1. Graphs from Figures 1–3 should include all individual data points

   The graphs have been updated as requested.

2. A further revision of the manuscript for English language and abbreviations is recommended.

   Revision for English language and abbreviation has been completed and marked on the document.

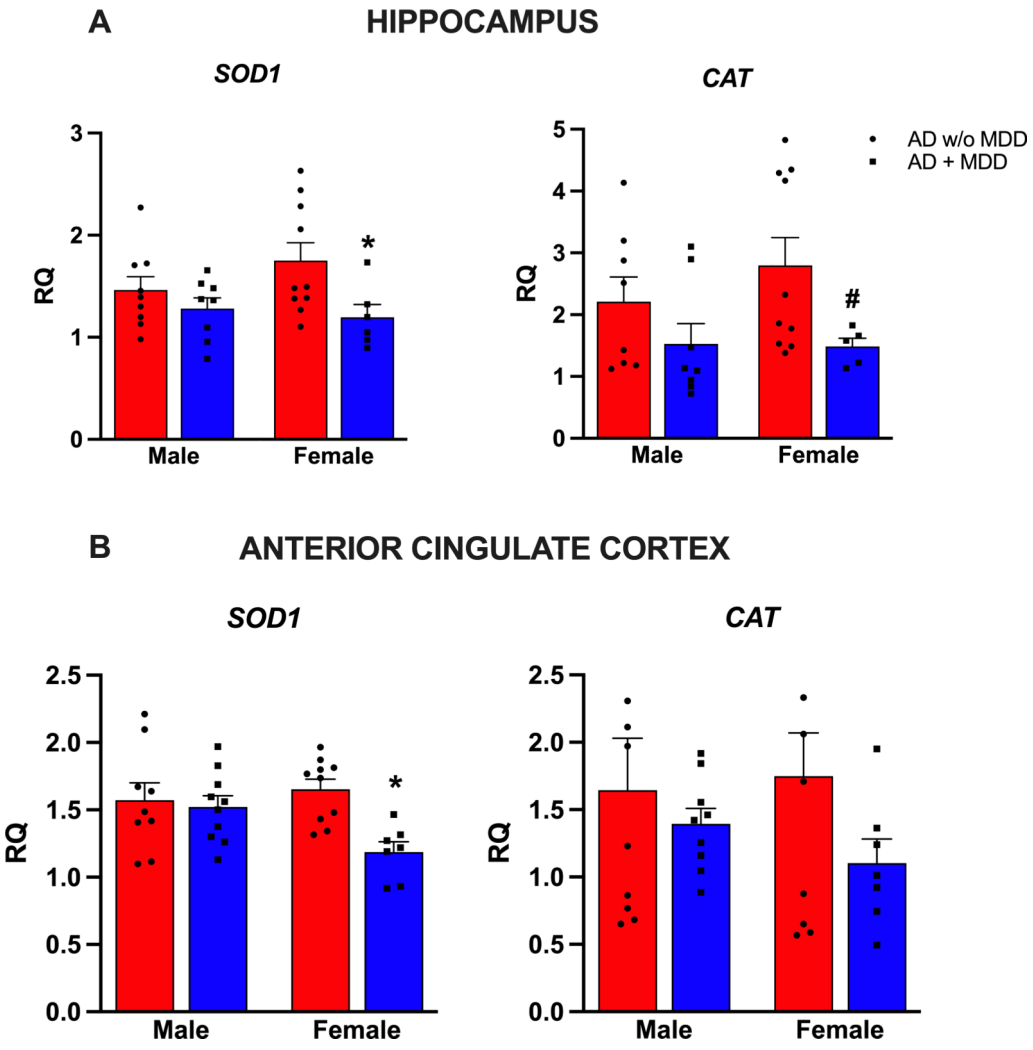

Figure 1. Decreased transcript levels of *SOD1* and *CAT* in the hippocampus (A) and anterior cingulate cortex (B) of individuals with AD+MDD (blue), compared to AD without MDD (red). RNA was isolated from postmortem brain regions and reverse transcribed prior to qPCR analysis for each brain region of study subject. Expressed as mean relative quantification (RQ), as described in the Methods section. The numbers included in the analyses: AD w/o MDD: male N=9 hippocampus, N=8 ACC; female N=10 hippocampus, N=7 ACC; AD+MDD: male N=8 hippocampus, N=8 ACC; female N=6 hippocampus, N=7 ACC. Data were analyzed by two-way ANOVA followed by two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli. Statistically significant differences between the groups are indicated, where $*q < 0.05$ is post-hoc significance corrected for multiple comparisons, while $\#p < 0.05$ refers to individual p value significance between the different comorbidity groups.

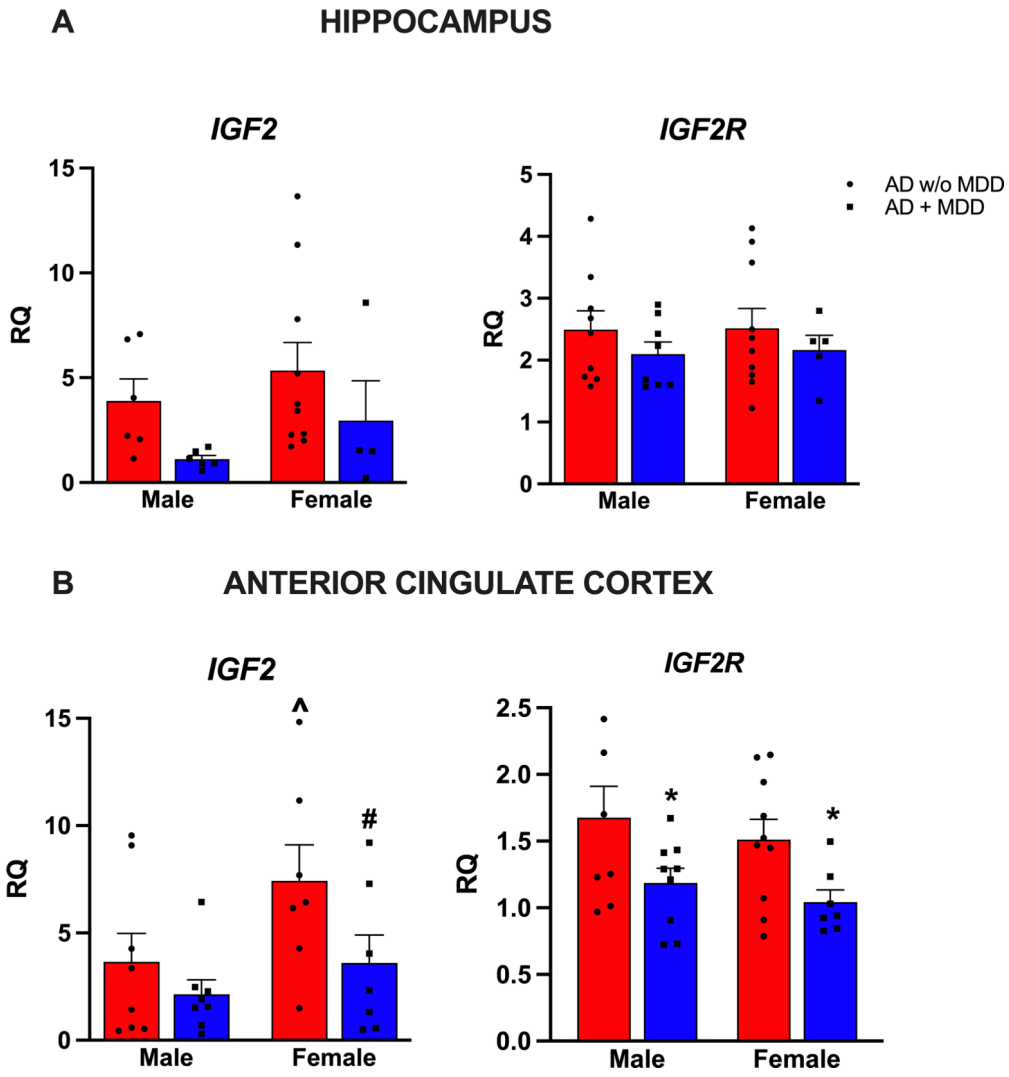

Figure 2. A trend toward decreased transcript levels of *IGF2* and *IGF2R* in the hippocampus (A) and anterior cingulate cortex (B) of individuals with AD+MDD (blue), compared to AD without MDD (red).

Transcript levels were measured as described in Figure 1 and Methods. The numbers included in the analyses: AD w/o MDD: male N=6 hippocampus, N=8 ACC; female N=10 hippocampus, N=7 ACC; AD+MDD: male N=6 hippocampus, N=8 ACC; female N=6 hippocampus, N=7 ACC. ∗q< 0.05; #p< 0.05 between the different comorbidity groups, and ^p < 0.05 indicate sex difference.

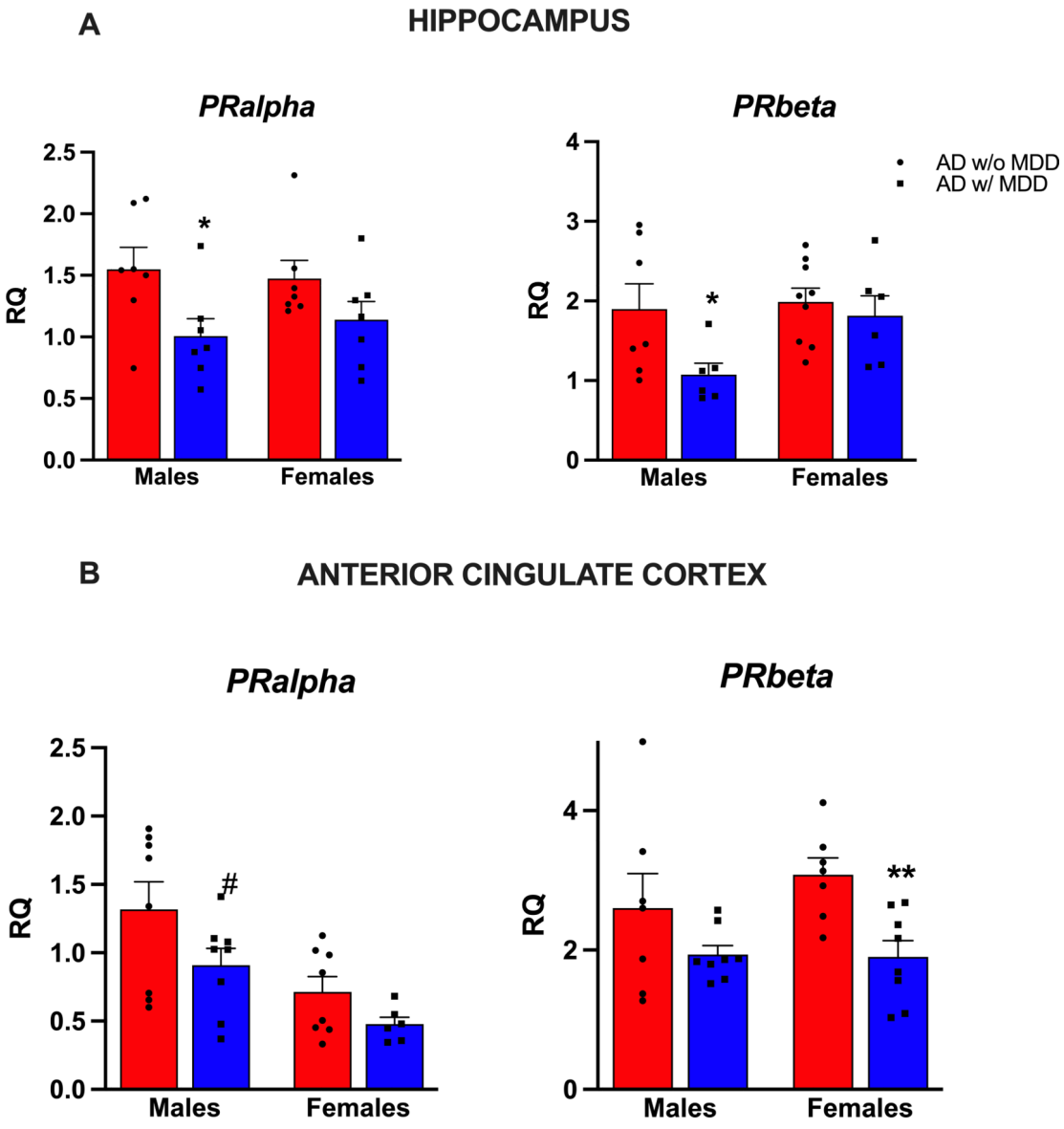

Figure 3. Decreased transcript levels of *PRα and PRβ* the hippocampus (A) and anterior cingulate cortex (B) of individuals with AD+MDD (blue), compared to AD without MDD (red).

Transcript levels were measured as described in Figure 1 and Methods. The numbers included in the analyses: AD w/o MDD: male N=7 hippocampus, N=8 ACC; female N=7 hippocampus, N=8 ACC; AD+MDD: male N=7 hippocampus, N=8 ACC; female N=7 hippocampus, N=6 ACC. ∗q < 0.05; **q <0.01; #p < 0.05 between the different comorbidity groups.

Table 1.

Description of postmortem samples

Group	Age	Gender	PMI[a]	Race[b]	Pathologic Diagnosis[c]
AD+MDD	56	M	8	C	AD (ADNC high - A3, B3, C3)
AD+MDD	60	M	30	H	AD (ADNC high - A3, B3, C3)
AD+MDD	63	M	16	C	AD (ADNC high - A3, B3, C3)
AD+MDD	69	M	8	C	AD (ADNC high - A3, B3, C3)
AD+MDD[acc]	70	M	11	C	AD (ADNC high - A3, B3, C3)
AD+MDD	75	M	14	C	AD (ADNC high - A3, B3, C3)
AD+MDD[acc]	77	M	20	C	AD (ADNC high - A3, B3, C3)
AD+MDD	86	M	9	C	AD (ADNC high - A3, B3, C3)
AD+MDD	90	M	19	C	AD (C, V, high)
AD+MDD	96	M	5	C	AD (ADNC intermed .- A3, B2, C3)
AD+MDD	41	F	12	H	AD (ADNC high - A3, B3, C3)
AD+MDD	48	F	8	H	AD (ADNC high - A3, B3, C3)
AD+MDD	56	F	6	C	AD (C, VI, high)
AD+MDD	74	F	23	C	AD (ADNC high - A3, B3, C3)
AD+MDD	74	F	16	C	AD (ADNC high - A3, B3, C3)
AD+MDD[acc]	85	F	27	AA	AD (ADNC high - A3, B3, C3)
AD+MDD	87	F	16	AA	AD (ADNC high - A3, B3, C3)
AD+MDD[acc]	89	F	10	C	AD (ADNC high - A3, B3, C3)
AD, MDD	91	F	27	C	AD (ADNC high - A3, B3, C3)
AD	61	M	24	H	AD (C, VI, high)
AD	68	M	--	C	AD (C, VI, high)
AD	71	M	12	C	AD (C, VI, high)
AD	73	M	4	C	AD (C, V, high)
AD	74	M	21	C	AD (ADNC high - A3, B3, C3)
AD	75	M	16	C	AD (ADNC high - A3, B3, C3)
AD	84	M	23	C	AD (ADNC high - A3, B3, C3)
AD	87	M	7	C	AD (C, VI, high)
AD	93	M	10	C	AD (C, V, high)
AD	67	F	11	C	AD (C, VI, high)
AD	77	F	21	C	AD (C, VI, high)
AD[hip]	80	F	4	C	AD (C, V, high)
AD	82	F	7	C	AD (C, V, high)
AD	83	F	26	C	AD (C, VI, high)
AD[acc]	84	F	13	C	AD (C, VI, high)
AD	84	F	6	C	AD (C, VI, high)
AD	85	F	26	C	AD (C, VI, high)
AD	85	F	5	C	AD (C, VI, high)

Group	Age	Gender	PMI[a]	Race[b]	Pathologic Diagnosis[c]
AD	86	F	5	C	AD (C, V, high)
AD	86	F	--	C	AD (C, V, high)

acc Only ACC sample

hip Only hippocampal sample

[a] Postmortem Interval

[b] Race C: Caucasian; H: Hispanic; AA: African American

[c] Pathologic Diagnosis: A, B and C severity scores as described in Montine et al., 2016, ADNC: Alzheimer's Disease Neuropathologic Change

Table 2.

Pearson correlation coefficients for hippocampal gene expression.

	CAT	IGF2	IGF2R	SOD1	ESR1	ESR2	PRalpha	PRbeta
CAT		0.56	0.79	0.81	0.66	0.68	0.37	0.73
IGF2	**0.56** *		0.36	0.51	0.77	0.76	0.28	0.44
IGF2R	**0.79** **	0.36		0.59	0.40	0.47	0.45	0.67
SOD1	**0.81** **	**0.51** *	**0.59** **		0.63	0.61	0.21	0.47
ESR1	**0.66** **	**0.77** **	0.40	**0.63** **		0.98	0.25	0.47
ESR2	**0.68** **	**0.76** **	**0.47** *	**0.61** **	**0.98** **		0.24	0.48
PRalpha	0.37	0.28	0.45	0.21	0.25	0.24		0.82
PRbeta	**0.73** **	0.44	**0.67** **	**0.47** *	**0.47** *	**0.48** *	**0.82** **	

* $p<0.05$

** $p<0.01$ after correction for multiple comparison

Table 3.

Pearson correlation coefficients for gene expression in the anterior cingulate

	CAT	IGF2	IGF2R	SOD1	ESR1	ESR2	PRalpha	PRbeta
CAT		0.53	0.71	0.64	0.35	0.29	0.55	0.72
IGF2	**0.53** **		0.18	0.09	0.84	0.83	0.13	0.21
IGF2R	**0.71** **	0.18		0.87	0.01	−0.02	0.64	0.90
SOD1	**0.64** **	0.09	**0.87** **		−0.02	−0.06	0.43	0.89
ESR1	0.35	**0.84** **	0.01	−0.02		0.97	0.08	0.08
ESR2	0.29	**0.83** **	−0.02	−0.06	**0.97** *		0.04	0.08
PRalpha	**0.55** *	0.13	**0.64** **	0.43	0.08	0.04		0.47
PRbeta	**0.72** **	0.21	**0.90** **	**0.89** **	0.08	0.08	**0.47** *	

* $p<0.05$

** $p<0.01$ after correction for multiple comparisons