

Late-Life Depression, Hippocampal Volumes, and Hypothalamic-Pituitary-Adrenal Axis Regulation: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: We systematically reviewed and meta-analyzed the association of late-life depression (LLD) with hippocampal volume (HCV) and total brain volume (TBV), and of cortisol levels with HCV, including subgroup analyses of depression characteristics and methodological aspects.

METHODS: We searched PubMed and Embase for original studies that examined the cross-sectional relationship between LLD and HCV or TBV, and 46 studies fulfilled the inclusion criteria. Standardized mean differences (Hedges' *g*) between LLD and control subjects were calculated from crude or adjusted brain volumes using random effects. Standardized Fisher transformations of the correlations between cortisol levels and HCVs were calculated using random effects.

RESULTS: We included 2702 LLD patients and 11,165 control subjects from 35 studies examining HCV. Relative to control subjects, patients had significantly smaller HCVs (standardized mean difference = -0.32 [95% confidence interval, -0.44 to -0.19]). Subgroup analyses showed that late-onset depression was more strongly associated with HCV than early-onset depression. In addition, effect sizes were larger for case-control studies, studies with lower quality, and studies with small sample size, and were almost absent in cohort studies and studies with larger sample sizes. For TBV, 2523 patients and 7880 control subjects from 31 studies were included. The standardized mean difference in TBV between LLD and control subjects was -0.10 (95% confidence interval, -0.16 to -0.04). Of the 12 studies included, higher levels of cortisol were associated with smaller HCV (correlation = -0.11 [95% confidence interval, -0.18 to -0.04]).

CONCLUSIONS: While an overall measure of LLD may be associated with smaller HCVs, differentiating clinical aspects of LLD and examining methodological issues show that this relationship is not straightforward.

Keywords: Aging, Cortisol, Hippocampus, Late-life depression, Meta-analysis, MRI

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Major depressive disorder (MDD) is the most common psychiatric disorder, with a lifetime prevalence of about 15% to 20% worldwide (1,2). MDD is a severely disabling disorder, but treatment success is relatively low—only one in three patients may achieve remission after treatment (3). Consequently, it is important to understand the underlying pathophysiology of MDD. Many studies observed morphological brain changes related to MDD showing that particularly hippocampal, medial prefrontal cortex, and basal ganglia areas are affected by MDD in adult populations (4–8).

At older age, MDD is relatively rare, but clinically relevant elevated depressive symptoms frequently occur (9) and often persist over years (10). Several studies have shown that depression later in life is associated with brain volume reductions (11,12) and an increased risk of dementia (13,14). One often-proposed explanation for this relationship is the neurotoxic effect of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis

(15). Functional changes of the HPA axis have consistently been reported in MDD (16), and these may be even more apparent later in life (17), because with increasing age the HPA axis is less adaptive in its responses, leading to a flattened diurnal rhythm (18). Moreover, several studies, predominantly in rodents, found that stress-related increase of glucocorticoids was associated with morphological brain changes, particularly hippocampal volume (HCV) loss (19,20). However, few studies in older human populations have examined the relationship between late-life depression (LLD), HPA axis activity, brain volume loss, and the risk of dementia. In addition, because of the lack of longitudinal studies, the direction of association is unclear, and we do not know whether depression is a contributor to this increased risk or a consequence of brain volume changes and incipient dementia. In addition, LLD is defined as depression occurring later in life (>50 years of age), regardless whether it is or is not the first episode of depression. Thus, LLD includes first-onset

depression (i.e., late-onset depression [LOD]) and early-onset depression (EOD). EOD is defined as a first onset earlier in life and may be recurrent or chronic until later life; it may also be a single episode earlier in life until it recurs later in life. As such, it encompasses different categories with different etiologies. It is therefore possible that the morphological brain changes are different for EOD and LOD. It has also been suggested that EOD is more strongly associated with HCV loss than LOD (12). A possible explanation for this finding is that because of the earlier onset and often recurrent nature of MDD, the hippocampus has had more exposure to the potentially detrimental effects of HPA axis dysregulation associated with (chronic) MDD (21). A recent meta-analysis on morphological brain changes in LLD showed that the most consistent evidence for brain volume reductions were found for the hippocampus but not for any of the other brain areas (22). In this meta-analysis, no distinction was made between EOD and LOD. Thus, an updated meta-analysis is needed that elucidates the influence of age of depression onset.

Another aspect that needs clarification is to what extent depression characteristics, such as assessment of LLD (clinical diagnosis vs. depressive symptom questionnaire), and recurrence and duration of depression are differentially related to HCV. Also, methodological issues such as design and sample size need to be examined. We will also examine lateralization effects in the hippocampus; several studies have found that MDD differentially affects the left and right hippocampus (7,8).

In addition to examining the relation between LLD and brain volumes in greater detail, we will also review and meta-analyze one of the most often proposed explanations for this relationship, which is dysregulation of the HPA axis (23).

Our aim was to systematically review and meta-analyze 1) the relation between LLD and hippocampal and total brain volumes (TBVs), including subgroup analyses of early or late onset, depression assessment, design, and sample size; and 2) the relation between HPA axis dysregulation and HCVs at older age.

METHODS AND MATERIALS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (24).

Literature Search and Study Selection

We searched PubMed and Embase for studies published before June 15, 2015 (for LLD with HCV or TBV) or August 28, 2015 (for HPA axis with HCV) using the search terms shown in [Supplemental Table S1](#). We used broad eligibility criteria for inclusion to be able to examine clinical and methodological moderators ([Supplemental Table S2](#)). We performed quality assessment of studies with the Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies (www.ohri.ca/programs/clinical_epidemiology/oxford.asp) and performed stratified analyses on lower and higher quality of studies. Inclusion and exclusion criteria for studies on HPA axis and HCV are described in [Supplemental Table S2](#). Studies were selected first by screening title and abstract. If a study appeared relevant, the full text was reviewed to identify whether it fulfilled the inclusion and exclusion criteria.

Both authors independently performed study selection, with discrepancies resolved by consensus.

Statistical Analysis

To investigate the relationships of LLD with HCV and TBV, we extracted from all studies the fully adjusted means, or crude means if adjusted were not reported, for participants with and without LLD. For nine articles, authors were contacted (11,12,25–31). Using the “meta” package (version 4.3-0) in R (version 3.2.1; www.r-project.org/), we modeled the standardized mean differences (SMDs, Hedges’ g) between LLD and control subjects with the restricted maximum-likelihood estimator for tau squared, using random effects in the function “metacont.” Heterogeneity was assessed with I^2 . Metaregression and subgroup analyses were run for the following moderators: mean age, percentage female, sample size (continuous and $n < 100$ vs. $n \geq 100$ participants), study design (case-control vs. cohort study), setting (community, in- and outpatients combined, and outpatients only), quality of studies (<6 vs. ≥ 6 stars), year of publication, depression assessment (clinical diagnosis vs. cut-off of depressive symptoms questionnaire), age of onset (EOD vs. LOD), duration of LLD (calculated as mean age at time of magnetic resonance imaging [MRI] minus mean age at first onset), current or remitted LLD, hemisphere (left vs. right HCV), manual versus automated segmentation of the hippocampus, adjustment for cardiovascular risk factors, and exclusion of dementia.

To investigate the relation between cortisol levels and HCVs in older age, we extracted from all studies the fully adjusted or crude correlations if adjusted correlations were not reported. We modeled the standardized Fisher transformations of the correlations between HCVs and cortisol levels, using random effects in the “metacor” function. First, the overall correlation was estimated regardless of timing of cortisol measure, and then subgroup analysis was run to investigate the effect of time of cortisol sampling (morning, evening, diurnal mean, and morning cortisol after dexamethasone suppression test).

To examine publication bias, we computed funnel plots and computed Egger’s t statistics.

RESULTS

LLD and Brain Volumes

The initial search identified 994 records in PubMed and 1345 records in Embase. After exclusion of duplicates, 1807 records were screened on title and abstract, 255 of which were read in full text, and 44 were included in the meta-analysis. Two articles were additionally included from reference lists (snowballing; [Supplemental Figure S1](#)) (11,12,25–68).

[Supplemental Table S3](#) presents the study characteristics. [Table 1](#) presents the main findings of the 46 included studies. LLD was assessed with clinical diagnostic criteria in 33 studies (72%). A case-control design was used in 35 studies (76%). In 22 studies (48%), the total sample size was ≥ 100 participants. In 36 studies (78%), current LLD was reported; in 8 studies, lifetime LLD, including current LLD and remitted LLD, was reported; and in 2 studies, remitted LLD was reported. EOD was distinguished in 15 studies (33%) and LOD also in 15 studies. Medication use was reported in 26 studies (54%), of

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