



Cerebral perfusion in depression: Relationship to sex, dehydroepiandrosterone sulfate and depression severity

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ABSTRACT

Background: Major depressive disorder (MDD) is a leading cause of disease burden and shows a marked sexual dimorphism. Previous studies reported changes in cerebral perfusion in MDD, an association between perfusion and dehydroepiandrosterone sulfate (DHEAS) levels, and large sex differences in perfusion. This study examines whether perfusion and DHEAS might mediate the link between sex and depressive symptoms in a large, unmedicated community sample.

Methods: The sample included 203 healthy volunteers and 79 individuals with past or current MDD. Depression severity was assessed with the Hamilton Depression Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). 3 T MRI perfusion data were collected with a pseudocontinuous arterial spin labelling sequence and DHEAS was measured in serum by LC-MS/MS.

Results: Large sex differences in perfusion were observed ($p < 0.001$). Perfusion was negatively correlated with DHEAS ($r = -0.23$, $p < 0.01$, $n = 250$) and with depression severity (HAM-D: $r = -0.17$, $p = 0.01$, $n = 242$; partial Spearman correlation, controlling for age and sex), but not with anxiety. A significant sex*perfusion interaction on depression severity was observed. In women, perfusion showed more pronounced negative correlations with depressive symptoms, with absent or, in the case of the MADRS, opposite effects observed in men. A mediation analysis identified DHEAS and perfusion as mediating variables influencing the link between sex and the HAM-D score.

Conclusion: Perfusion was linked to depression severity, with the strongest effects observed in women. Perfusion and the neurosteroid DHEAS appear to mediate the link between sex and HAM-D scores, suggesting that inter-individual differences in perfusion and DHEAS levels may contribute to the sexual dimorphism in depression.

1. Introduction

Major depressive disorder (MDD) represents one of the leading causes of global disease burden (Bruffaerts et al., 2012; Lopez & Murray, 1998; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004; WHO, 2008), with reported lifetime prevalence rates between 10% and 30% (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Kruijshaar et al., 2005). Previous studies have shown a marked sexual dimorphism in depression vulnerability (Weiss, Longhurst, & Mazure, 1999), and in depression symptomatology (Gobinath, Choleris, & Galea, 2017;

Labonté et al., 2017; Paus et al., 2010). While the underlying basis for the sexual dimorphism in MDD is not yet fully understood, large sex-specific differences in cerebral blood flow or perfusion have also been reported between men and women (Cosgrove, Mazure, & Staley, 2007; Ghisleni et al., 2015; Gur & Gur, 1990; Liu et al., 2012) and may potentially underlie sex differences in depression. Previous studies revealed a link between perfusion and depression, reporting both increases and decreases in perfusion in frontal, striatal, and limbic regions in the context of MDD (Duhameau et al., 2010; Li et al., 2018; Lui et al., 2009; Orosz et al., 2012; Vasic et al., 2015). Another recent study found

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reduced cerebral blood flow (CBF) in the right parahippocampal gyrus, the thalamus, and fusiform and middle temporal gyri as well as the bilateral insula, and increased CBF in the bilateral inferior parietal lobules in depressed adults (Cooper et al., 2019a).

In a previous study investigating the effect of neurosteroid levels on perfusion, plasma concentrations of the neurosteroid dehydroepiandrosterone sulfate (DHEAS) were observed to explain some of the variance in global and regional brain perfusion between men and women (Ghisleni et al., 2015). Since DHEAS has been linked to anxiety (Hsiao, 2006) and depressive symptoms (Peixoto et al., 2020; Souza-Teodoro et al., 2016; ter Horst et al., 2019), and shows significant sex differences (Leblhuber et al., 1993; Orentreich, Brind, Rizer, & Vogelmann, 1984), perfusion and DHEAS may represent potential mediators for differences in depression vulnerability between men and women. However, to date, the interaction between sex and perfusion on depression has not been examined directly, and it is not yet known to what extent DHEAS may mediate the relationship between perfusion and depressive symptoms.

The purpose of this study was to examine the link between perfusion, depressive symptoms, and potential mediating variables (e.g. sex, DHEAS), in a large, unmedicated community sample including healthy subjects as well as those exhibiting (mostly mild) MDD symptoms. Severity is an important characteristic of depression, related to aetiology and treatment response. Frequently, depression and excessive anxiety occur at the same time and a high anxiety level is an important predictor of chronic course and treatment non-response to MDD treatment. As a result, we examined depression severity as well as anxiety levels in this study, as applied previously in search of the neural correlates of depression (Alexander et al., 2020; Bjelland et al., 2009; Insel et al., 2010; Majd et al., 2020).

2. Materials and methods

2.1. Recruitment

Participants were recruited by advertisements in local newspapers or by blackboard webpages of the University of Zurich for this ongoing cohort study, resulting in a sample of young adults from the general population ($N = 282$, of which 203 were healthy, 56 had a history of past MDD, and 23 met the diagnostic criteria for current MDD, see Table 1 for a descriptive overview). After a full explanation of the goals and risks of the study and after giving their verbal consent in a first step, participants were admitted to the study. All participants were aged between 18 and 40 years, had not taken any psychopharmacological medication for three months prior to the study assessments and abstained from caffeine, nicotine, and alcohol on the day of testing, to minimize the possible effects on the brain. Subjects with a history or family history of severe psychiatric disorders, such as psychosis, substance abuse and acute eating disorders, as well as a personal history of neurological and severe physical disorders, such as heart disease, were excluded. The local ethics committee approved the study (Kantonale Ethikkommission Zürich) and

written informed consent was obtained from all participants. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Procedure

After giving first verbal consent, the participants were screened for magnetic resonance (MR) safety via telephone, followed by a standard checklist for psychological disorders with the screening part of the structural clinical interview for DSM disorders (SCID-IV). Subsequently, the participants completed an extensive online battery of psychological and physiological questionnaires. Validated German versions of all instruments were used. Finally, an approximately five-hour long face-to-face session at the Children's Hospital in Zurich was conducted, during which participants gave written consent, completed interviews of the psychological rating scales, including the Hamilton Depression Scale (HAM-D) (Hamilton, 1960) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1977), supervised by a trained psychologist. Participants also completed questionnaires such as the Beck's Depression Inventory (BDI) (Beck et al., 1961) and the Beck's Anxiety Inventory (BAI) (Beck et al., 1988) and underwent MRI scanning, including a pseudocontinuous arterial spin labelling (ASL) perfusion MRI sequence, at the Children's Hospital in Zurich.

2.3. Blood sample

For the assessment of DHEAS concentrations a venous blood sample was taken shortly before commencing the MRI scan (mean time 14:04, $SD = 55.5$ min). Analysis of DHEAS serum concentration was conducted at the division of Clinical Chemistry and Biochemistry of the University Children's Hospital Zürich applying an accredited diagnostic LC-MS/MS method using an ACQUITY UPLC® HSS T3 column (Waters AG, Baden, Switzerland) on a Shimadzu Nexera X2 UHPLC System (Shimadzu Schweiz GmbH, Reinach, Switzerland) with a SCIEX TripleQuad 6500⁺ MS/MS detector (AB Sciex Switzerland GmbH, Baden, Switzerland). The method has a coefficient of variation of 8.2% at 8.7 $\mu\text{mol/L}$.

2.4. MRI data acquisition and analyses

MRI data were obtained with a 3.0 GE MR750 whole-body MRI scanner (GE Healthcare, Milwaukee, WI, USA), equipped with an eight-channel receive-only head coil and a body transmit coil. Collection of perfusion images was carried out during rest and with the subjects' eyes closed. A background-suppressed, pseudocontinuous ASL (pcASL) sequence with a 3D stack of spirals fast spin echo readout was used for image acquisition (Dai et al., 2008). We collected thirty-two axial slices with a repetition time of 4.2 s and an echo time of 25 ms, a slice thickness of 4 mm, a field of view of 24 cm, 3 Nex, a nominal in-plane resolution of $1.9 \times 1.9 \text{ mm}^2$, and a total scan time of 4 min 20 s. We used a 1.5 s post-labelling delay to ensure minimal errors from transit

Table 1
Group demographics and depression scores.

	Female participants				Male participants			
	Overall	Healthy	Past MDD	Current MDD	Overall	Healthy	Past MDD	Current MDD
Variable	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)	Mean (n, SD)
Age	24.7(189, 4.65)	24.9(128, 4.48)	23.9(41, 4.34)	24.9(20, 6.23)	25.1(92, 4.58)	24.8(71, 1.53)	23.4(9, 2.88)	27.8(12, 3.93)
HAMD	3.65*(161, 5.62)	1.05(105, 2.33)	6.65(40, 4.87)	13.3(16, 8.26)	2.60*(81, 5.39)	0.639(61, 1.53)	4.11(9, 2.26)	12.3(11, 9.27)
MADRS	3.96(188, 6.26)	1.32(128, 2.46)	7.63(40, 5.45)	13.5(20, 10.60)	3.15(92, 5.65)	1.30(71, 2.17)	6.11(9, 4.78)	11.9(12, 10.20)
BDI	5.53*(189, 7.52)	2.30(128, 3.07)	9.56(41, 6.38)	17.9(20, 12.00)	4.44*(93, 6.99)	2.25(72, 3.83)	5.56(9, 5.08)	16.8(12, 9.89)
BAI	5.94**(188, 6.78)	4.01**(128, 4.10)	8.15(40, 8.09)	13.8(20, 10.20)	3.64**(92, 3.82)	2.35**(71, 2.52)	6.44(9, 3.36)	9.17(12, 4.67)

Abbreviations: MDD, major depressive disorder; n, sample size; SD, standard deviation.

Stars indicate different levels of significance in a non-parametric one-way ANOVA with Dwass-Steel-Critchlow-Fligner pairwise comparisons.

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$ (comparison female versus male participants).

time effects (Alsop & Detre, 1996). The perfusion data were normalised to a study specific template using FSL-FLIRT, and the whole brain perfusion was extracted using a grey matter mask from the automated anatomic labelling (AAL atlas). A grey matter mask was used in order to reduce confounds from partial volume effects, since perfusion is sensitive to the relative proportion of grey matter, white matter, and CSF within each imaging voxel. For further details regarding the pre-processing steps, please see Ghisleni et al. (2015).

2.5. Statistics

Statistical analyses of the average whole-brain perfusion data were performed with SPSS 25 and RStudio, and voxel-based analyses were conducted with FSL randomise. Since neither perfusion data nor depression scores were normally distributed ($p < 0.01$, Kolmogorov-Smirnov test), we investigated sex differences in whole brain (WB) perfusion with an independent two-group Mann-Whitney test. Sex * depression interactions on WB perfusion were calculated using log-regression with dichotomized outcome variables (median split of depression rating scales). Post-hoc partial Spearman correlation analyses were performed in the male and female subgroups separately to disentangle interaction effects, and additional, voxel-based analyses were performed to disentangle global and regional perfusion effects. Voxelwise tests for significant correlations between depression scores and perfusion were performed using the nonparametric permutation testing methods implemented in FSL randomise, controlling for multiple comparisons with threshold-free cluster enhancement. A mediator analysis with DHEAS and WB perfusion as the mediators, was conducted utilising the sem package for RStudio.

3. Results

We observed a pronounced, highly significant difference in perfusion between men and women, both in the whole brain analysis (Males =

47.8 ml/min/100 ml, Females = 58.8 ml/min/100 ml; ($W = 2799$, $p < 0.001$), see Fig. 1A), and in the voxel-based analysis, which revealed a single significant cluster extending into every voxel included within the brain mask (see Fig. 1B). The whole-brain perfusion was negatively correlated with DHEAS levels in the full participant group ($r = -0.23$, $p < 0.01$, $n = 250$) (See Fig. 2). Females and males did not significantly differ in age (Mann-Whitney- U test: rank biserial correlation = 0.0621, $p = 0.397$), or between groups (Non-parametric one-way ANOVA with Dwass-Steel-Critchlow-Fligner pairwise comparisons: Healthy vs. past MDD ($W = -1.97$, $p = 0.341$), Healthy vs. current MDD ($W = 0.99$, $p = 0.760$), past MDD vs. current MDD ($W = 2.321$, $p = 0.229$)).

Log-regression with dichotomized questionnaire scores (median split) revealed a significant sex * perfusion interaction on HAM-D ($z(239) = -2.364$, $p < 0.02$, $n = 242$), a trend-level interaction on MADRS ($z(277) = -1.939$, $p = 0.053$, $n = 280$), and nonsignificant sex*perfusion interactions on both BDI ($z(279) = -1.142$, $p < 0.3$, $n = 282$), and BAI ($z(277) = -1.257$, $p = 0.2$, $n = 280$) (see Fig. 3A).

Partial Spearman correlations, corrected for sex and age, revealed significant negative correlations between WB perfusion and HAM-D score ($\rho = -0.17$, $p = 0.01$, $n = 242$), MADRS score ($\rho = -0.12$, $p = 0.03$, $n = 280$), as well as BDI score ($\rho = -0.12$, $p = 0.03$, $n = 282$), but not between whole brain perfusion and BAI score ($\rho = -0.04$, $p = 0.16$, $n = 280$).

Spearman correlations within the subgroups of men and women, corrected for age, showed significant negative correlations between the depression scales and WB perfusion in the female subgroup (HAM-D ($\rho = -0.26$, $p < 0.01$, $n = 166$), MADRS ($\rho = -0.19$, $p < 0.01$, $n = 193$), BDI ($\rho = -0.17$, $p < 0.02$, $n = 194$)) but no significant correlation of anxiety levels and WB perfusion ($\rho = 0.09$, $p = 0.24$, $n = 192$). In the male subgroup, only the MADRS score showed a significant positive correlation with WB perfusion ($\rho = 0.19$, $p = 0.045$, $n = 107$), but no significant correlations were observed between global perfusion and other measures of depressive and anxiety symptoms, (HAM-D ($\rho = 0.14$, $p = 0.17$, $n = 93$), BDI ($\rho = 0.01$, $p = 0.9$, $n = 106$), BAI ($\rho =$

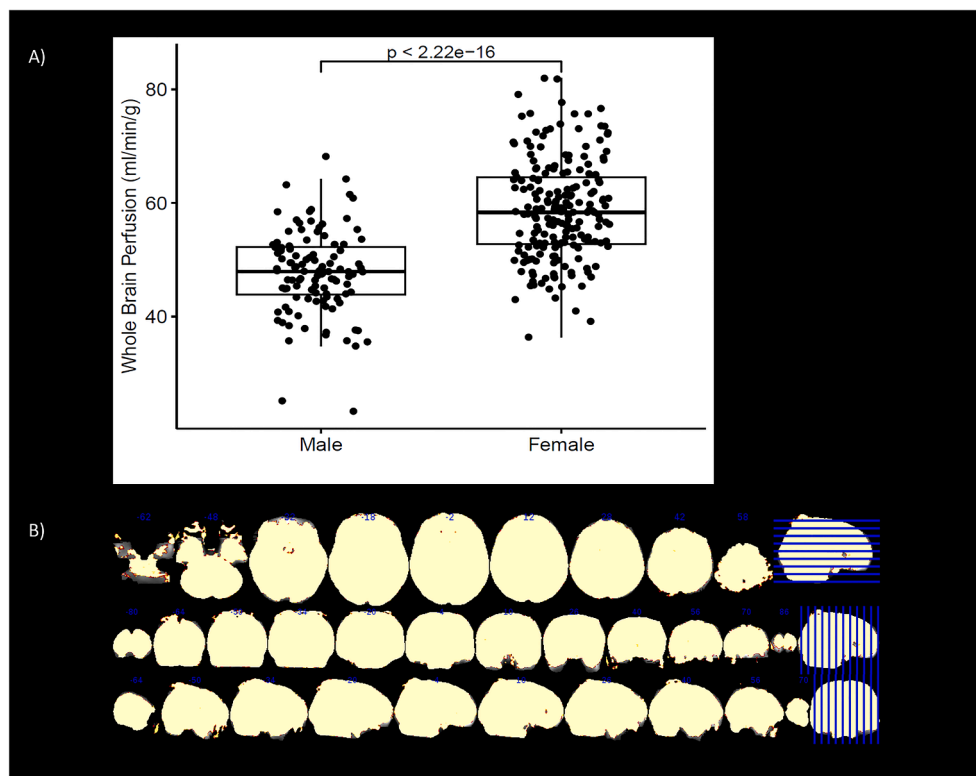


Fig. 1. Sex difference in perfusion A) Average whole-brain perfusion in females and males ($p < 2.2 \times 10^{-16}$); B) Voxel-based analysis of perfusion differences between men and women, at $p < 0.05$, corrected for multiple testing, female subgroup > male subgroup.

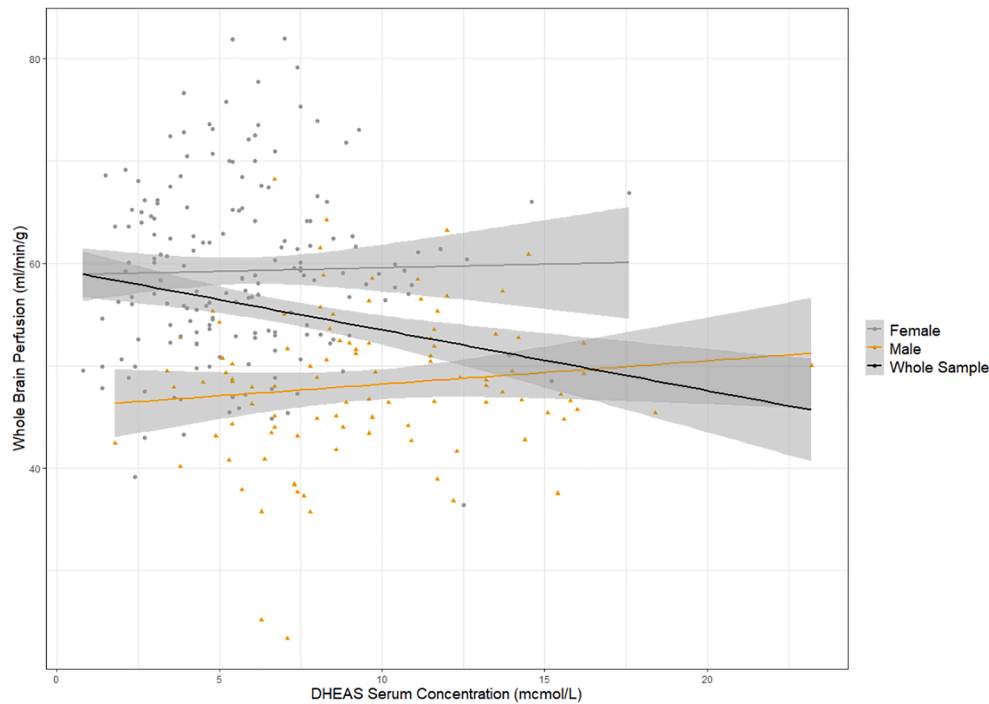


Fig. 2. Scatterplot showing the association between whole-brain perfusion and dehydroepiandrosterone sulfate serum levels in the whole group ($r = -0.23$, $p < 0.01$, $n = 250$) and in the female and male subsamples (female: $r = 0.07$, $p = 0.33$, $n = 166$; male: $r = 0.04$, $p = 0.46$, $n = 84$) corrected for age.

0.12, $p = 0.21$, $n = 108$)).

A voxel-based correlation analysis in the sex subgroups between WB perfusion and the questionnaire scores, corrected for multiple testing, revealed a significant negative correlation in the female subgroup for the HAM-D ($p < 0.05$, $n = 161$), the MADRS ($p < 0.05$, $n = 188$), and the BDI ($p < 0.05$, $n = 189$) (see Fig. 3B). A significant positive correlation between perfusion and depressive symptoms was seen in the male subgroup, for the MADRS only ($p < 0.04$, $n = 92$) (see Fig. 3C). There was no significant association between perfusion and anxiety scores in the voxel-based analysis, in either the male or the female subgroups (see Fig. 4 for scatterplots of the sex subgroup analyses). After including the whole-brain perfusion as a covariate in the voxel-based analysis, the correlations between perfusion and depression scores were no longer significant, but a significant correlation was observed between regional (relative) perfusion and anxiety, quantified from the BAI ($p < 0.05$, $n = 283$, Fig. 5).

Finally, the mediator analysis, corrected for age, with DHEAS and WB perfusion as the mediating variables (bootstrapped, 1000 iterations), yielded a significant mediating effect of perfusion and DHEAS regarding the association between sex and depression scores, as assessed using the HAM-D, but not for the other measures of mood and anxiety symptoms (see Fig. 6). DHEAS was a significant mediator of the effect of sex and age on perfusion for all analyses.

4. Discussion

In this large and ongoing cohort study, we investigated the link between sex-specific differences in perfusion and depressive symptom severity. Our analyses included a mediation analysis to assess the potentially mediating role of the neurosteroid DHEAS on perfusion and depressive symptoms. In a population of young adults, we were able to replicate the well-known perfusion differences between the sexes and showed that the association between perfusion and depression severity differed between sexes.

Log-regression with dichotomized outcome variables (median split) revealed a significant interaction of sex and perfusion on MDD symptom severity as measured with the HAM-D, but not with the other measures

of depression severity. The significant link between sex-specific differences in perfusion and HAM-D, and the absence of such a link in the other depression rating scales may have arisen due to the HAM-D's stronger focus on somatic symptoms than the MADRS' and BDI's. In addition, the face-to-face administration of the HAM-D and the MADRS allowed for more detailed and focused follow-up questions to be administered to clarify the participants' responses when compared to the BDI, which might have led to more sensitivity in detecting the presence and severity of symptoms.

Partial Spearman correlations of all subjects, corrected for sex and age, revealed significant negative associations between depression severity (symptom scores) from all depression rating scales and WB perfusion, which appear to be driven by the female subsample, given that the results were more pronounced in the female subsample. The male subsample showed a significant positive correlation between MDD symptoms and WB perfusion, only for the MADRS. The largely absent effects in the male subsample may be due to lower statistical power, since fewer men were included in the cohort, but the effect sizes describing the association between depressive symptoms and perfusion are also smaller in the male subsample, except for the symptom scores quantified by the MADRS. Overall, these results seem to confirm previous evidence (Eid et al., 2019; Seney et al., 2018; Slavich & Sacher, 2019) for different mechanisms underlying the pathophysiology of depression in men and women. It is possible that because women tend to exhibit, in general, higher baseline perfusion, depressive symptoms might be linked to lowered perfusion in women while in men, brain perfusion might not be associated with MDD symptoms. Using machine learning algorithms based on whole-brain CBF, and the contributing factors sex and regional CBF of cortical, limbic and paralimbic regions, Ramasubbu et al. (2019) were able to classify healthy controls and MDD subjects with a high degree of accuracy, indicating that patterns of whole-brain and regional perfusion, as well as sex might represent important factors in the pathophysiology of depressive symptoms.

The mediation analysis identified the neurosteroid DHEAS (Ghisleni et al., 2015) as a possible mediator of these effects, with women exhibiting lower DHEAS concentrations, which in turn are associated with higher WB perfusion. Previous studies have reported negative

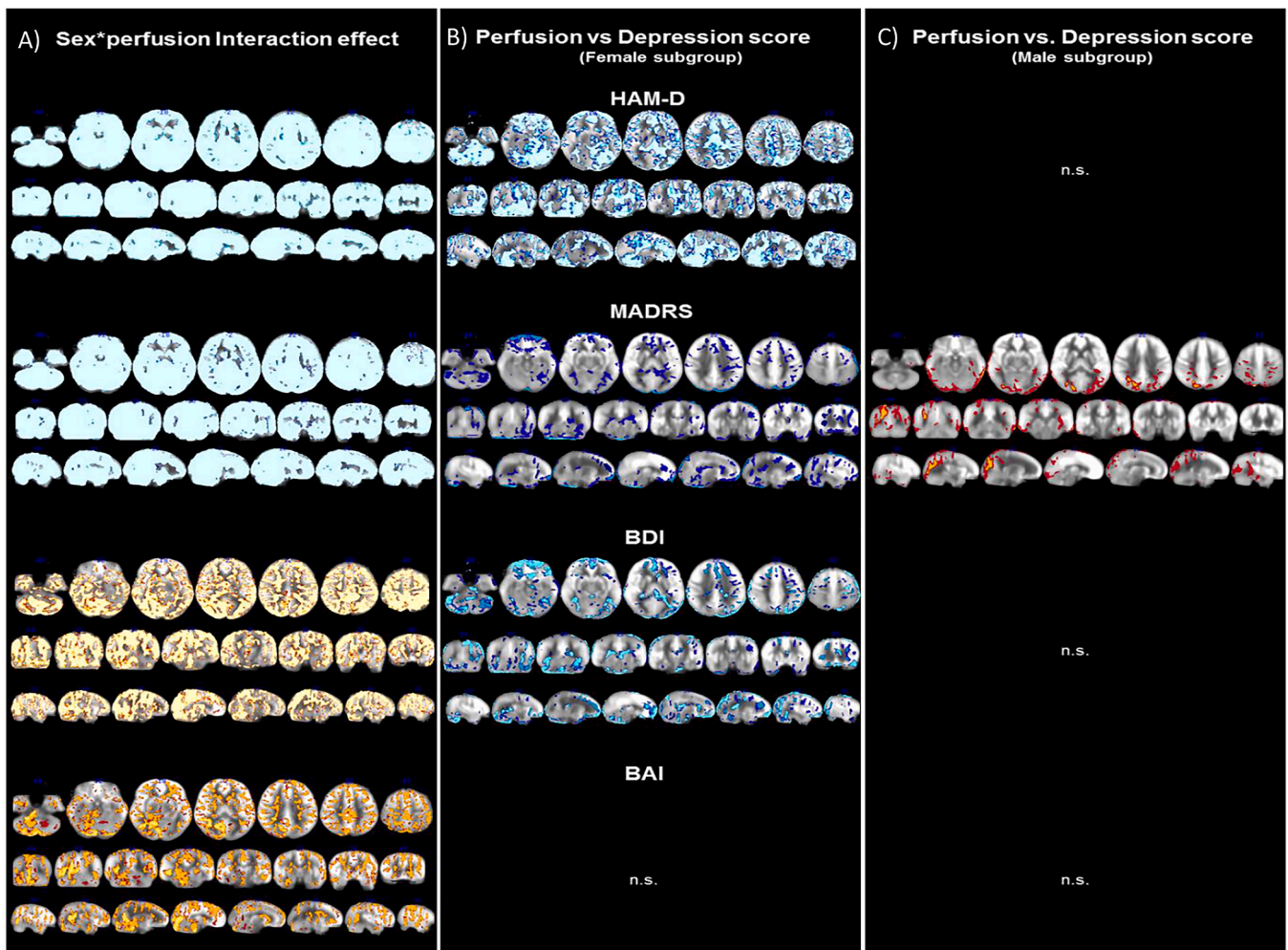


Fig. 3. A) Sex*voxel-based perfusion interaction on Hamilton Depression Scale (HAM-D) total score ($p < 0.05$, $n = 242$), on Montgomery-Asberg Depression Rating Scale (MADRS) total score ($p < 0.05$, $n = 280$), on Beck's Depression Inventory (BDI) total score ($p < 0.05$, $n = 282$), and on Beck's Anxiety Inventory (BAI) total score ($p < 0.05$, $n = 280$) in the whole group, B) voxel-based correlation of cerebral perfusion and HAM-D total score ($p < 0.05$, $n = 166$), of MADRS total score ($p < 0.05$, $n = 193$), and of BDI total score ($p < 0.05$, $n = 194$) in the female subgroup, C) and voxel-based correlation of cerebral perfusion and MADRS total score ($p < 0.05$, $n = 193$) in the male subgroup. *Note.* Nonsignificant results are denoted with n.s.

associations of DHEAS and risk of depression, depression symptom severity, and risk of relapse (Tipton, 2019), and higher baseline DHEAS in MDD remitters before and after SSRI treatment when compared to non-remitters (Hough et al., 2017). Higher baseline DHEAS serum concentration was also identified as a predictor for SSRI response in MDD patients (Hough et al., 2017). In their meta-analysis, Peixoto et al. (2020) also proposed DHEAS as a possible treatment in itself, demonstrating a significant effect of the neurosteroid when compared to placebo, possibly acting via GABA-ergic modulation (Genud et al., 2009). This difference in baseline DHEAS concentration and its interaction with baseline perfusion might, in part, account for the higher prevalence of MDD in women and act protectively in women with higher DHEAS concentrations than the average.

Perfusion has also been linked to treatment response with antidepressants such as sertraline (Cooper et al., 2019b) and escitalopram (Kaichi et al., 2016), and brain stimulation such as repetitive transcranial magnetic stimulation (TMS) (Nord et al., 2019; van Wingen et al., 2020; Weiduschat & Dubin, 2013), suggesting that sex differences in perfusion may represent a potential mediating factor for the sex-specific response to antidepressant and other treatments. On the other hand, perfusion changes due to treatment were found in different brain regions such as in sensory and limbic networks after ketamine treatment (Sahib et al., 2020), in the precuneus after TMS (Dumas et al., 2012),

and in overall baseline perfusion after cognitive behavioural therapy (Susic-Vasic et al., 2017), suggesting that normalisation of brain perfusion may be a mechanism of therapeutic action.

The observation of a significant correlation between relative perfusion and anxiety is consistent with reported links between perfusion, anxiety, and depression in mild traumatic brain injury (Papadaki et al., 2020), and between anxiety and hypoperfusion in cardiovascular disease (Alosco et al., 2015). While the introduction of the whole brain perfusion as a covariate caused the correlations between perfusion and depression scores to diminish in significance, covarying for the whole brain perfusion increased the significance of the correlation between perfusion and BAI. This result suggests that the association between perfusion and depression may be more global, while anxiety might be linked to regional differences in perfusion, underscoring the importance of examining both absolute and relative changes in perfusion in association with behavioural variables.

The interpretation of results in the present study is limited by the nature of the sample used: subjects were generally young, highly educated, and there was a lack of subjects with severe MDD. Additionally, the relationship between DHEAS and whole-brain perfusion diminished to trend level for a one-tailed comparison when controlling for sex, indicating a predominant role of sex in the link between the two. While the perfusion values for the voxelwise analysis were not corrected

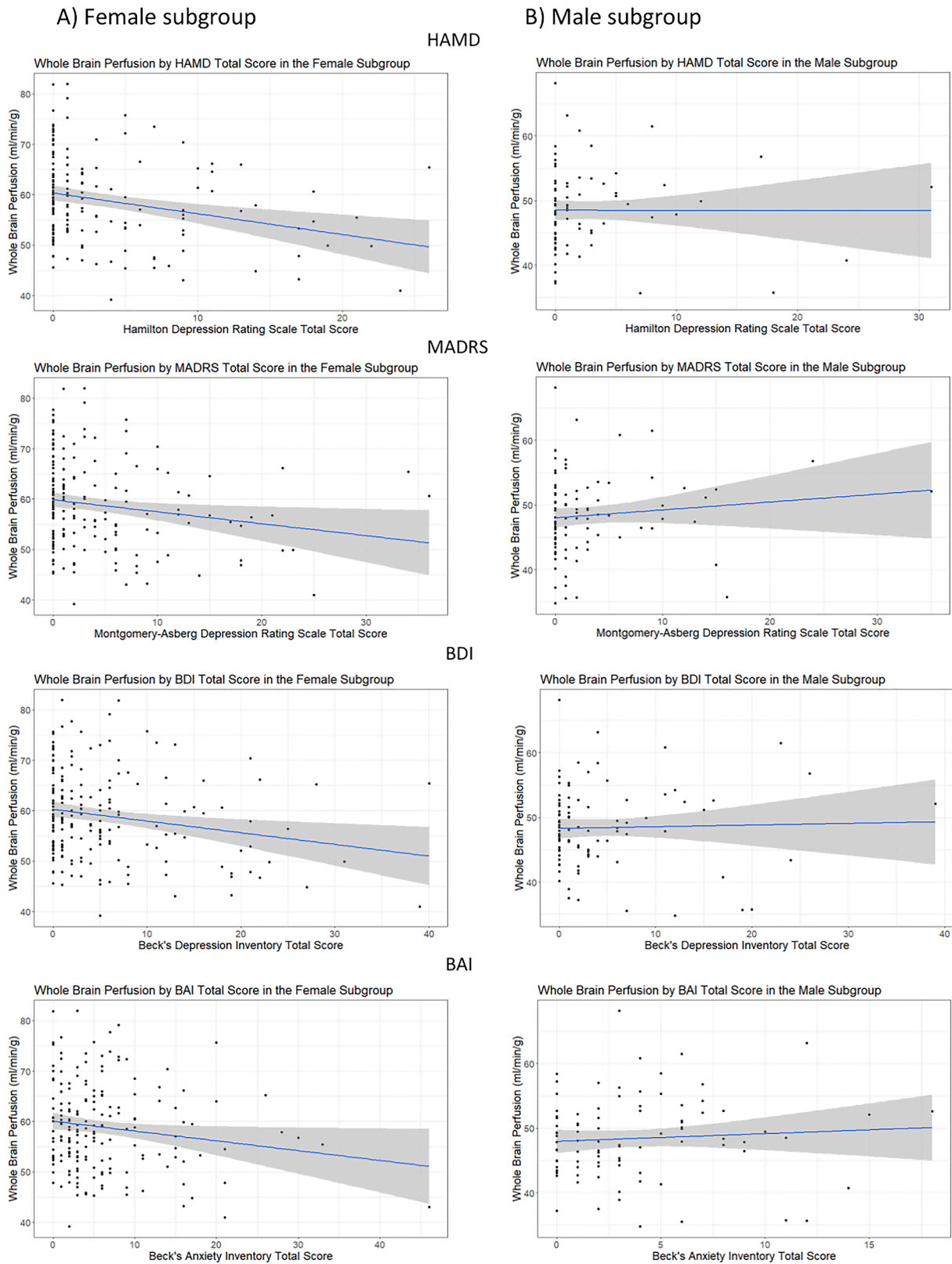


Fig. 4. Scatterplots of whole-brain perfusion by total scores of depression/anxiety rating scales of the female and male subgroups. Voxel-based correlation of whole-brain perfusion and Hamilton Depression total score (female: $\rho = -0.26$, $p < 0.01$, $n = 166$; male: $\rho = 0.14$, $p = 0.17$, $n = 93$), of Montgomery-Asberg Depression Rating Scale total score (female: $\rho = -0.19$, $p < 0.01$, $n = 193$; male: $\rho = 0.19$, $p = 0.45$, $n = 107$), of Beck's Depression Inventory total score (female: $\rho = -0.17$, $p = 0.02$, $n = 194$; male: $\rho = 0.01$, $p = 0.9$, $n = 106$), and of Beck's Anxiety Inventory total score (female: $\rho = 0.09$, $p = 0.24$, $n = 192$; male: $\rho = 0.12$, $p = 0.21$, $n = 108$) in the female and male subgroups.

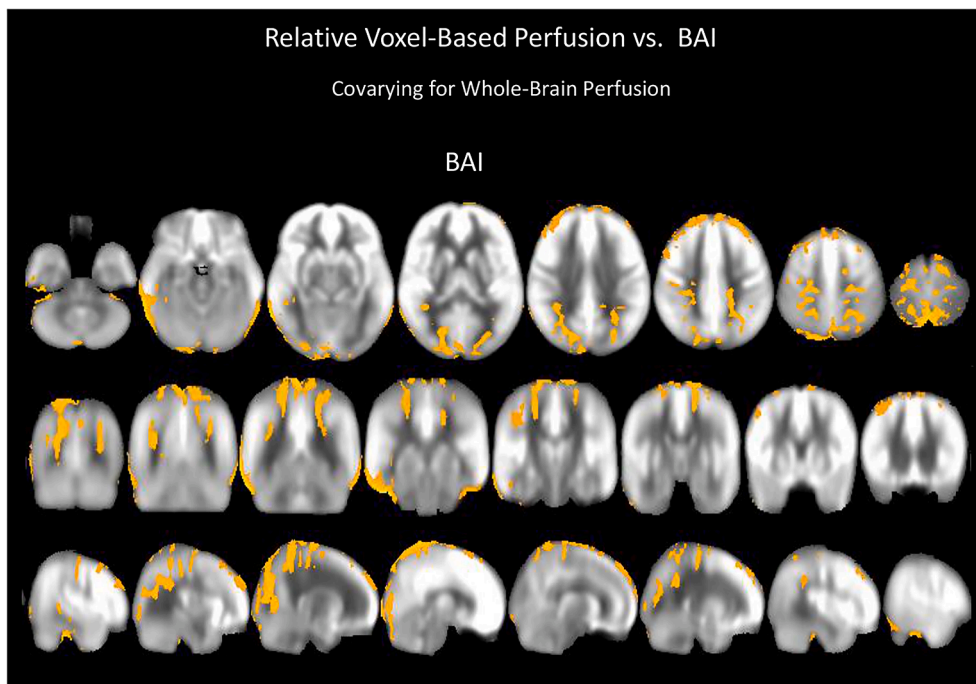


Fig. 5. Relative voxel-based correlation of cerebral perfusion and Beck's Anxiety Inventory total score covarying for whole-brain perfusion ($p < 0.05$, $n = 283$).

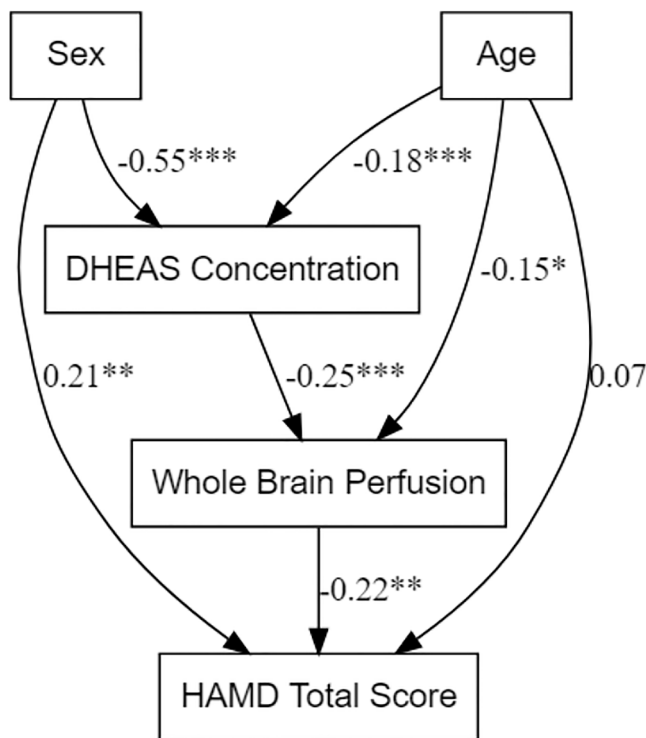


Fig. 6. Mediation analysis calculated using the sem package in R, corrected for age. Significant direct effect of sex on Hamilton Depression Scale (HAM-D) total score (Cohen's $d = 0.21$, $p < 0.01$), as well as a significant indirect effect via dehydroepiandrosterone sulfate and whole-brain perfusion on HAM-D total score (Cohen's $d = 0.14$, $p < 0.001$).

for partial volume effects, the results were concordant with those from the whole brain perfusion analysis, where a grey matter mask was used to mitigate potential confounds from partial volume effects within the imaging voxels. In a previous perfusion study in Alzheimer's disease, the

partial volume corrected and uncorrected perfusion maps were reported to give comparable results, with the sensitivity to pathological changes reportedly higher in the uncorrected maps (Leeuwis et al., 2017), but it is important to consider potential confounds from atrophy or associated partial volume effects, particularly in perfusion studies in older adults, or in cohorts with increased atrophy. The strengths of this study include the relatively high number of subjects, the community-based recruitment, and the fact that subjects were exclusively non-medicated.

Future studies incorporating a longitudinal design or direct manipulation of DHEAS blood concentration via injection, may be able to clarify the directionality between DHEAS and MDD symptom severity and elucidate the causality of the connection between the two.

CRediT authorship contribution statement

Christopher Ritter: Writing – original draft, Methodology. **Andreas Buchmann:** Data curation. **Sabrina Theresia Müller:** Data curation. **Martin Hersberger:** Data curation. **Melanie Haynes:** Data curation. **Carmen Ghisleni:** Data curation. **Ruth Tuura:** Conceptualization, Methodology. **Gregor Hasler:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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