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REGULAR RESEARCH ARTICLE

Hippocampal Subfields in Acute and Remitted Depression—an Ultra-High Field Magnetic Resonance Imaging Study

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ABSTRACT

Background: Studies investigating hippocampal volume changes after treatment with serotonergic antidepressants in patients with major depressive disorder yielded inconsistent results, and effects on hippocampal subfields are unclear.
Methods: To detail treatment effects on total hippocampal and subfield volumes, we conducted an open-label study with escitalopram followed by venlafaxine upon nonresponse in 20 unmedicated patients with major depressive disorder. Before and after 12 weeks treatment, we measured total hippocampal formation volumes and subfield volumes with ultra-high field (7 Tesla), T1-weighted, structural magnetic resonance imaging, and FreeSurfer. Twenty-eight remitted patients and 22 healthy subjects were included as controls. We hypothesized to detect increased volumes after treatment in major depressive disorder.
Results: We did not detect treatment-related changes of total hippocampal or subfield volumes in patients with major depressive disorder. Secondary results indicated that the control group of untreated, stable remitted patients, compared with healthy controls, had larger volumes of the right hippocampal-amygdaloid transition area and right fissure at both measurement time points. Depressed patients exhibited larger volumes of the right subiculum compared with healthy controls at MRI-2. Exploratory data analyses indicated lower baseline volumes in the subgroup of remitting (n = 10) vs nonremitting (n = 10) acute patients.
Conclusions: The results demonstrate that monoaminergic antidepressant treatment in major depressive disorder patients was not associated with volume changes in hippocampal subfields. Studies with larger sample sizes to detect smaller effects as well as other imaging modalities are needed to further assess the impact of antidepressant treatment on hippocampal subfields.

Keywords: depression, hippocampus, hippocampal subfields, ultra-high field MRI, antidepressant

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Significance Statement

Altered neuronal plasticity and volumetric changes in the hippocampus are correlates of major depression. Antidepressants were demonstrated to induce structural changes in the brain's neuronal networks in rodent studies but results in depressed patients are ambiguous. This study investigated whether subfields—such as the dentate gyrus of the hippocampus—change in response to antidepressant treatment. Against our expectations, we did not find increased subfield volumes after 12 weeks of antidepressant therapy. These negative results provide a basis for further investigations with more refined imaging modalities and larger sample sizes.

Introduction

Hippocampal volume reductions and altered neuronal plasticity are pathophysiological substrates of major depressive disorder (MDD) and other psychiatric disorders (Pittenger and Duman, 2008; Macqueen and Frodl, 2011; Kuhn and Gallinat, 2013), while preclinical results suggest that antidepressants facilitate neuroplasticity (Castrén and Rantamäki, 2010; Duman et al., 2016). Studies in animals and humans indicate that stress and a history of adverse events—both important risk factors for MDD—impact hippocampal neuronal survival, glial cells, and neurogenesis (Pittenger and Duman, 2008; Serretti et al., 2013; Rabl et al., 2014; Saleh et al., 2017). On a hormonal level, stress hormones altered in MDD such as glucocorticoids affect spine synapses and dendrites in the cornu ammonis (CA1-3) (Pittenger and Duman, 2008; Hajszan et al., 2009). In addition, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) were found to closely interact with neurotrophins such as the brain-derived neurotrophic factor (Castrén and Rantamäki, 2010). Treatment with SSRIs was demonstrated to oppose the effects of stress by stimulating hippocampal neurogenesis (Malberg and Duman, 2003; Anacker and Hen, 2017) and increasing synaptic spine volumes in the hippocampus, in particular in the dentate gyrus (Kasper and McEwen, 2008; Kitahara et al., 2016). However, this evidence mostly originated from rodent models and needs to be translated to patients with MDD.

Hippocampal formation volumes represent a surrogate of neuronal plasticity and can be measured in MDD patients in vivo with structural magnetic resonance imaging (MRI) and automatic or manual volume analysis. Several previous studies reported hippocampal formation volume increases after treatment. After 8 weeks of antidepressant treatment with citalopram, hippocampal formation volume increases were demonstrated in patients with MDD (Arnone et al., 2013). An earlier study reported volume increases after 12 weeks of treatment with paroxetine in patients with posttraumatic stress disorder (Vermetten et al., 2003). A third study with a naturalistic inpatient setting and a mixed antidepressant treatment regime detailed posterior hippocampal volume increases after approximately 23 weeks of treatment (Schermuly et al., 2011). Those studies highlight that pro-neuroplastic effects of monoaminergic antidepressants supported by animal literature (Pittenger and Duman, 2008; Malykhin and Coupland, 2015; Duman et al., 2016) could mediate hippocampal volume increases in humans. In contrast, several results found no volume increases after treatment (Frodl et al., 2004; Vythilingam et al., 2004; Phillips et al., 2015). Still, subgroup analyses in 2 of these studies found hippocampal volume increases in remitted and acute patients continuously taking antidepressants (Frodl et al., 2004; Phillips et al., 2015). While the reasons for discrepancies between these results remain unclear, further studies using refined methods are warranted.

Due to its multifaceted cortical structure, volumetric measurements of hippocampal subfields result in greater gains of information (Mueller et al., 2018). Therefore, automatic segmentations such as FreeSurfer's (FS) hippocampal subfield analysis are advantageous, because they do not require (much) prior anatomical knowledge and are time efficient. A cross-sectional study with this algorithm (n = 270) reported larger tail volumes and smaller CA2/3, CA4 molecular layer, granule cell layer, and alveus in medication-free MDD patients compared with controls (Maller et al., 2018). Almost a dozen other cross-sectional studies reported altered subfield volumes in MDD patients; for an overview of these findings see (Maller et al., 2018).

Higher spatial MRI resolutions enabled increasingly detailed delineation of hippocampal subfields. Longitudinal measurements of hippocampal subfields with 7T MRI in MDD could provide further insights into pro-neuroplastic effects of monoaminergic antidepressants. In this study, we analyzed hippocampal subfield volumes in unmedicated patients with MDD and included remitted patients and healthy control subjects as control groups. Based on previous longitudinal results on hippocampal formation volumes, known pro-neuroplastic effects of SSRIs, and advantages of 7T MRI image details, we hypothesized: compared with baseline volumes and between-measurement changes in control groups, unmedicated patients with MDD will exhibit significantly increased volumes of hippocampal subfields and volumes of the hippocampal formation after treatment at MRI-2.

Methods

Participants and Study Design

The study sample consists of subjects previously reported (for detailed sample descriptions, please refer to Spies et al., 2017; Kraus et al., 2019). All participants consented to study participation and protocol procedures by oral and written consent. Subjects were financially compensated for study participation. The study protocol and all study-related procedures were approved prior to the start of the study by the Ethics Committee of the Medical University (EK 103/2011) of Vienna and was registered at clinicaltrials.gov (NCT01477203).

All acute patients had to be within an episode of MDD (aMDD), 18 to 50 years old, and moderately to severely ill as assessed by clinical impression and corroborated by a Hamilton Depression Rating Scale (HAM-D_{24}) score ≥17 at screening. Diagnosis was assured by an experienced psychiatrist conducting the structured clinical interview (SCID-I) for DSM-IV, and any comorbid personality disorders were excluded by SCID-II. All included patients were either medication-naïve or -free for at least 3 months prior to screening. No patient was left untreated to reach the 3 months inclusion limit, the average time between screening

and MRI-1 was 7.9±7 days, and treatment started on the morning after MRI-1. Any other current primary psychiatric disorder (including anxiety disorders or bipolar depression), substance abuse disorder within the last 12 months, or any major medical or neurologic illness were not permitted. Remitted MDD patients had the same inclusion criteria (rMDD), but they had to be in stable remission (HAM-D_{24} <8) including free of medication for at least 3 months.

Healthy subjects had to be free of any psychiatric diagnosis their entire lifetime and absent of any significant illnesses, current medication intake, and current or past substance abuse disorder. During screening, all subjects underwent a medical and neurologic examination with medical history, blood and hormone (thyroid and sex hormones) analyses, urine drug screening, and pregnancy tests as well as an electrocardiogram. For this study, MRI scans from 32 HC, 28 aMDD, and 32 rMDD subjects were available (see Figure 1), and we included 22 HC, 28 rMDD, and 20 aMDD subjects in the final statistical analyses (for details, see next section).

We treated all unmedicated aMDD patients with an open-label, flexible dose, standardized oral antidepressant for 12 weeks, with a mandatory switch of antidepressants on nonresponse to the first medication. The rationale for switching came to mimic a naturalistic treatment regime as performed in previous studies and recommended international guidelines at the time of study design (2009/2010) (Rush et al., 2006; Bauer et al., 2013). Neuropsychological testing and dosage adjustments were done every 2 weeks. Initially, all aMDD patients were treated with escitalopram oxalate (5–20 mg) for at least 6 weeks, with dosage adjustments according to clinical judgment and HAM-D curves by study psychiatrists. Down titration was allowed if any dose was not tolerated. Upon nonresponse to escitalopram after 6 weeks, defined by at least 50% HAM-D_{24} reduction compared with the first visit, a switch to venlafaxine extended release was conducted (allowed dosage range 75–150 mg). The second trial lasted for another 6 weeks. MRI measurements were at week 0 (MRI-1) and week 12 (MRI-2) of treatment. rMDD patients and HC were seen only at screening MRI-1 and MRI-2. None of the rMDD patients relapsed during study duration.

All study psychiatrists had extensive experience in clinical psychological testing. Rating scales administered at every visit were HAM-D_{24}, Hamilton Anxiety Rating Scale, Beck Depression Index, and Clinical Global Impression Scale. Response to antidepressant treatment (–50% HAM-D_{24} compared with visit 1) was assessed at visits of week 6, 8, and 12 (=MRI-2). Remission was defined as <8 on the HAM-D_{24} scale, which was chosen as a conservative cutoff to minimize residual symptoms. Healthy controls and rMDD patients were tested with the same questionnaires at baseline visit, MRI-1, and MRI-2.

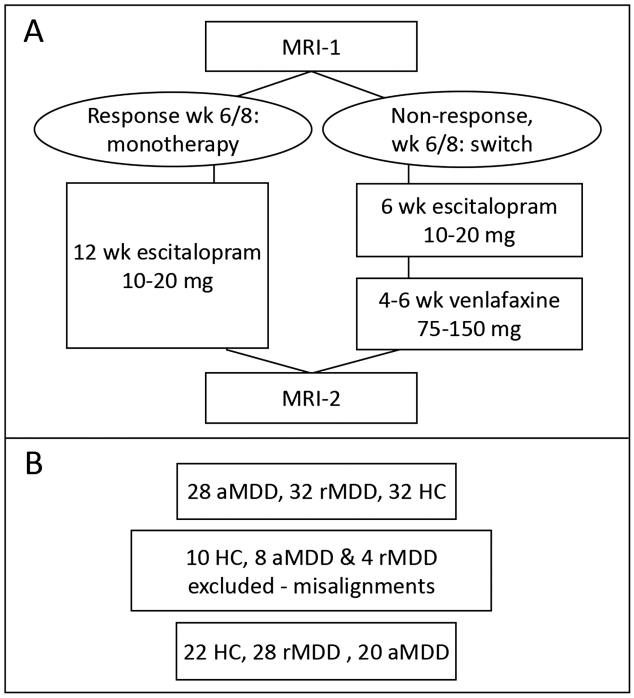

Figure 1. Study diagram outlining study design and patient numbers. (A) Study flow diagram. (B) Subject numbers. Note that 22 subjects had to be excluded due to misalignments (see "MRI Measurements and Hippocampal Subfield Analyses"). aMDD, acute depressed patients; HC, healthy control subjects; rMDD, remitted depressed patients (untreated); wk, week.

MRI Measurements and Hippocampal Subfield Analyses

Every study subject underwent 2 7T MRI scans with a Siemens Magnetom scanner and a 32-channel head coil. We applied a MP2RAGE sequence with TR=4060 milliseconds, TE=3.07 milliseconds, resulting in a total MRI scan time of 11:20 minutes in a field of view of 192×312×384 mm (x/y/z) and a voxel size of 0.74×0.68×0.68 mm (x/y/z). Functional sequences were conducted prior to structural MRI, which are not within the scope of this article and are reported elsewhere. The sequence was previously demonstrated to be appropriate for hippocampal longitudinal analyses, while other regions (e.g., middle and inferior temporal gyri) had worse test-retest values (Seiger et al., 2015). Hippocampal subfield segmentation was performed with the FS image analysis suite v6.0 beta-version for the following subfields (in alphabetical order): CA1, CA3, CA4, fimbria, fissure, granule cell layer of the dentate gyrus, hippocampus–amygdala transition area, molecular layer, parasubiculum, presubiculum, subiculum, and tail (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, http://surfer.nmr.mgh.harvard.edu/) (Iglesias et al., 2015). The whole brain segmentation for calculating total intracranial volume (TIV) and total brain volume were done with SPM-12 (Wellcome Centre for Human Neuroimaging, London, UK, https://www.fil.ion.ucl.ac.uk/spm/) and Matlab 8.3 scripts (The MathWorks, Inc. Natick, MA), while total hippocampal volume was done with FS 5.3, since at the time of analysis only a beta version of FS 6.0 was available online. We previously showed that hyperintensities occurred in our MP2RAGE images at 7T that could distort whole-brain within-subject registrations, especially near air-tissue borders (Seiger et al., 2015). Since this could result in failures of whole-brain registrations, we decided not to use the FS longitudinal pipeline. Instead, we implemented rigorous quality control as follows: (1) image quality was visually checked by R. S. and subfield segmentations were visually inspected after segmentation by R. S. and C. K. independently; (2) an automated quality control analysis used by the ENIGMA consortium (http://enigma.ini.usc.edu, kindly provided by Philipp Säman) was conducted; and (3) outliers in absolute subfield values (5 SDs) were excluded. We excluded 22 subjects (10 HC, 8 aMDD, and 4 rMDD) after step 1 for visible misalignments of the subfield segmentations with the underlying hippocampus, and none after steps 2 and 3. As a result, we included 22 HC, 28 rMDD, and 20 aMDD subjects in the final statistical analyses (see Figure 1 for an overview of the study and subject numbers). The excluded HC were significantly

older than the analyzed HC (34±6.9 years in excluded vs 25.9±6.7 years in the analyzed HC, $t=3.1$ $P=.007$). All other clinical characteristics of excluded subjects in aMDD and rMDD did not differ significantly from the analyzed sample (all $P>.05$). All data are available on request from the corresponding author.

Statistical Analyses

All subfield volumes were checked for normal distribution with histograms, q-q plots, and Shapiro-Wilk tests, and residual diagnostics were performed for statistical models. Based on these procedures, all analyses were done with log-transformed values (see supplemental Material, page 1; figures show untransformed values).

Since test-retest reliability of subfield segmentations with FS 6.0 has not been established, we initially conducted a reliability analysis in healthy subjects only. For this purpose, we calculated the intraclass correlation coefficient (2-way mixed, average measure, absolute agreement) with subfields' volumes between both MRI measurements with SPSS v.23 (IBM Corporation, Armonk, NY). Moreover, we calculated Spearman's correlations between MRI-1 and MRI-2 for volumes of the whole hippocampus as well as each subfield (see supplemental Figures 1 and 2).

According to our hypotheses, we compared total hippocampal volume changes between healthy controls, remitted, and acute patients by fitting a linear model with the "lm"-function in R (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). Logarithmically transformed volumes of both hippocampal formations were added as dependent variables and group × time × hemisphere including combinations of interactions as independent variables, controlling for TIV, sex, and age. Longitudinal changes (between MRI-1 and MRI-2) of hippocampal volumes in both models were investigated with repeated-measures ANOVAs (type-II).

The same procedures were applied for our main hypothesis analyzing subfield volumes. Again, logarithmized values of subfields were dependent variables and group × time × subfield (subfield = each subfield volume) including combinations of interactions as independent variables, controlling for TIV, sex and age. Of note, hemisphere is concatenated in "subfield," which is why it was not necessary to include "hemisphere" as additional independent variable. Following previous literature (Maller et al., 2018), we also investigated the influence of correcting for total hippocampal volume and total brain volume (total gray and white matter). For both total hippocampal formation and subfield ANOVAs, we calculated estimated marginal means with R's "emmeans" package and conducted t tests on contrasts within groups for each MRI time point as well as between MRI time points. All statistical tests assumed an alpha level of $P<.05$. We used Tukey's method to adjust for multiple comparisons in post-hoc t tests; uncorrected P values are reported. Residual distribution indicated adequacy for both ANOVAs with log-transformed values.

Finally, we explored subfield values between remitting (aMDDrem, HAM-D_{24} <8) after treatment and nonremitting patients (aMDDnon-rem, HAM-D_{24} ≥ 8). We computed a model identical to the but restricted analysis within the aMDD patients. Subfield volumes were dependent variables and remission × subfield independent variables, correcting for sex, age, and baseline HAM-D_{24}. Group × time × subfield interactions were tested with type-II ANOVA, and post-hoc comparisons were calculated with the "emmeans" package and t tests on contrasts within groups for each MRI time point as well as between MRI time points. Note that results of comparisons between remitting and nonremitting patients have to be interpreted with caution, since a low n = 10 in each group enhances chances of false positives. For further exploratory analyses, we also correlated psychosocial variables (age at first episode, previous episodes, duration of last episode) in aMDD patients with baseline subfield values.

Results

Clinical Results and Test-Retest Analysis

Clinical results of the sample were previously published (Spies et al., 2017; Kraus et al., 2019). Briefly, 9 aMDD patients had psychopharmacological antidepressant treatment during a previous episode, while 9 were naïve and information on 2 patients was missing. For more detailed information, see our previous work. Hamilton Anxiety Rating Scale, HAM-D_{24}, and Beck Depression Index values significantly decreased after 12 weeks of antidepressant treatment from MRI-1 to MRI-2 in aMDD patients (see Table 1, all $P<.05$). Ten of the 20 patients in the final analysis remitted, and 10 patients were considered as nonremitter (HAM-D_{24}≥8). After 12 weeks of antidepressant treatment with a flexible dose regime at MRI-2, 11 patients were on escitalopram (16.5±4.5 mg) and 9 patients were on venlafaxine (100±37.5 mg). Of the 10 remitting aMDD patients 8 were on escitalopram and 2 on velanfaxine, while in the 10 nonremitting aMDDs 7 were on venlafaxine and 3 on escitalopram. Note that the study design demanded a switch after nonresponse (<50% HAM-D_{24} from visit one) at week 6 and/or 8. Notably, a patient could meet the criterion for response (50% HAM-D_{24} reduction) but not reach the study criterion for remission. Hence, several patients were taking escitalopram at MRI-2.

In the initial test-retest analysis, intraclass correlation coefficients ranged from 0.532 (left hippocampal-amygdaloid transition area [HATA]) to 0.945 (right dentate gyrus) at an intraclass correlation coefficient of 0.87±0.11 (average±SD) for left and 0.9±0.06 for right subfields, leaving all regions but the left HATA with sufficiently high correlations between the measurements (see supplemental Material; supplemental Figure 2; supplemental Table 1). Test-retest analysis revealed positive correlations ranging within $0.59<r<0.93$ of absolute volumes between both measurements in all regions (including total hippocampi) apart from the left HATA ($r=0.35$, $P=.12$; see supplemental Figure 2). Therefore, we left out this region in a separate model in the subsequent analysis (see below).

Hippocampal Formation Volumes

We did not observe group × hemisphere ($F_{2,265}=0.35$, $P=.7$), group × time ($F_{2,265}=0.72$, $P=.49$), or group × time × hemisphere ($F_{2,265}=0.03$, $P=.96$) interactions. Across all scans, we found a main effect of hemisphere ($F_{2,265}=14.32$, $P<.001$), suggesting hippocampal formation volumes were different between sides. This was driven by larger left (3387.56±274.72 mm^3; real values, not estimates) compared with right hippocampal volumes (3289.23±288.54 mm^3, $t=3$, $P=.003$). There was also a significant effect of group ($F_{2,265}=4.21$, $P=.015$), whereby rMDD subjects (3420.05±25.95 mm^3) had significantly larger hippocampi (both sides averaged between measurements±SD) compared with aMDD patients (3271.25±27.76 mm^3, $t=3.9$, $P<.001$) and HC subjects (3295.48±32.79 mm^3, $t=3.1$, $P=.002$), whereas hippocampi did not differ in volume between HC and aMDD ($t=-0.4$, $P=.643$). Post-hoc comparisons are shown in supplemental

Table 1. Clinical Characteristics of the Sample

			aMDD			Subsample (aMDD)					
	rMDD	HC	total		P	aMDDnon-rem			aMDDrem		P
n	28	22	20			10			10		
Age	26.6 ± 5.7	25.9 ± 6.7	30.5 ± 9.6		*	30.5 ± 11.5			30.4 ± 6.6		.49
Sex (f/m)	16/12	12/10	14/6		*	7/3			7/3		—
TIV (MRI-1, cm^3)	1490.3 ± 133.4	1453 ± 133	1416.1 ± 139.1		*	1411.3 ± 123.7			1420.8 ± 159.7		.45
Handedness (r/l)	28/0	22/0	(19/1)								
Previous medication (relation yes/no)	1:1	—	1:1								
Age at first episode (y)	22 ± 5	—	22.8 ± 11.7			26 ± 12.2			20.1 ± 9.7		.046
Previous episodes (n)	1.6 ± 1.4	—	2.9 ± 1.5		*	2.2 ± 0.97			2 ± 0.82		.12
Duration of last (rMDD)/ current (aMDD) episode (months)	8.3 ± 5.4	—	10.1 ± 9		*	6.4 ± 6.3			9.6 ± 18		.21
			MRI-1	MRI-2		MRI-1	MRI-2	P	MRI-1	MRI-2	P
$HAM\text{-}D_{24}$	2.3 ± 2.8	—	27.2 ± 7.5	9 ± 6.9	*	27.1 ± 9.6	14.4 ± 5.7	*	27.3 ± 5	3.6 ± 1.8	*
HAMA	2.6 ± 2.7	—	21.3 ± 6.4	6.8 ± 5.3	*	21.7 ± 8.5	10.7 ± 4.8	*	20.8 ± 3.9	2.8 ± 1.5	*
BDI	4.2 ± 4.9	—	20.6 ± 8.1	8.1 ± 5.8	*	22.3 ± 9	11.5 ± 6.1	*	18.9 ± 7.2	4.7 ± 3	*
CGI	1.5 ± 0.5	—	5.1 ± 0.7	3.5 ± 1.2	*	5.2 ± 0.4	4 ± 0.5	*	5 ± 0.8	3 ± 1.4	*

Abbreviations: aMDD, acute depressed patients; aMDnon-rem; acute MDD patients nonremitting after treatment; aMDDrem, acute depressed patients remitting; BDI, Beck Depression Index; CGI, Clinical Global Impression Scale; $HAM\text{-}D_{24}$, Hamilton Depression Rating Scale; HC, healthy controls; rMDD, remitted depressed subjects; TIV, total intracranial volume. *P < .001; P values from F-tests (ANOVA), chi-square test, or t test.

Table 2, and estimated means by region, measurements, and groups are shown in supplemental Table 3.

Hippocampal Subfield Volumes

We detected no significant effect for the interaction group × time ($F_{2,3213} = 2.99$, $P = .05$) and a significant effect of group on subfield values ($F_{2,3213} = 17.15$, $P < .001$), while other relevant interactions such as group × subfield, time × subfield, and group × time × subfield were not significant (all $P > .05$). To confirm that the influence of group was present at each measurement, we repeated the same linear model without the interaction term "time" at each time point separately. Indeed, at both MRIs, the effect of group on subfield values was significant (MRI-1, $F_{2,1605} = 6.9$, $P = .001$; MRI-2, $F_{2,1605} = 12.28$, $P < .001$), while group × subfield did not change considerably (all $P > .9$). For plots of the interaction group × time and the effect of group (across both MRIs) see supplemental Figure 5. Because of low test-retest correlations in the left HATA, we excluded this region in a separate model. However, the results did not change (i.e., group × time: $F_{2,3213} = 2.95$, $P = .052$). See Figure 2 and supplemental Figure 3 for boxplots of original values and supplemental Tables 4 and 5 and for statistical results of hippocampal subfields.

By testing post-hoc pairwise comparisons with the emmeans "pair" function between groups in all regions, we detected significant differences in subfields of the right hippocampus at single measurements only between groups, not between measurements. Specifically and only at baseline or follow-up scans, the right hippocampal fissure (MRI-1: $t = 3$, $P_{Tukey} = .034$, Cohen's $d = 0.11$; MRI-2: $t = 2.4$, $P_{uncorr} = .016$, $d = 0.08$) and right HATA (MRI-1: $t = 2.13$, $P_{uncorr} = .034$, $d = 0.07$; MRI-2: $t = 3.2$, $P_{Tukey} = .017$, $d = 0.11$) exhibited larger values in rMDD compared with HC at both MRI-1 and MRI-2. Moreover, we detected significantly larger right subiculum values in aMDD patients ($t = 2.02$, $P_{uncorr} = .044$, $d = 0.07$) and rMDD subjects ($t = 2.14$, $P_{uncorr} = .033$, $d = 0.08$) compared with HC at MRI-2 only.

Of note, upon investigating results with alternative covariates, we obtained increased total gray matter volumes in rMDD vs aMDD at both time points (MRI-1: 78.4 ± 24.1, $t = 3.3$, $P_{Tukey} = .004$: MRI-2: −74.6 ± 24.1, $t = 3.1$, $P_{Tukey} = .007$; see supplemental Statistics and Figure 4). Main results remain unchanged on correcting with total gray matter or total brain volume (see Supplementary Material).

Exploratory Analyses: Associations With Response and Remission

We explored differences of hippocampal formation volume and subfields according to remission status in acute patients. This was done by repeating the same linear models within aMDD patients stratified by acute patients remitting (aMDDrem, n = 10) and nonremitting (aMDDnon-rem, n = 10) after treatment. Of note, we did not design the study to investigate differences between remitter and nonremitter. Hence, based on the low number of subjects in these subgroups, results of these ANOVAs have to be interpreted with caution. In the total hippocampus, there was no effect of remission × time ($F_{1,69} = 1.3$, $P = .26$) or each factor alone. On hippocampal subfield values, we found a significant effect of remission × time ($F_{1,860} = 8.14$, $P = .004$) and remission status ($F_{1,860} = 15.24$, $P < .001$), yet no significant interaction between remission × time × subfield ($F_{1,860} = 0.23$, $P = 1$). Post-hoc testing was performed with the emmeans "pair" function between groups in all regions. We found significantly higher values in aMDDnon-rem patients compared with aMDDrem in the right fimbria (MRI-1: $t = 2.8$, $P_{Tukey} = .027$, $d = 0.19$), bilateral presubiculum (MRI-1, right: $t = 2.55$, $P_{uncorr} = .011$, $d = 0.17$; MRI-1, left: $t = 2.1$, $P_{uncorr} = .036$, $d = 0.14$), and right fissure (MRI-1: $t = 2.51$, $P_{uncorr} = .012$, $d = 0.17$). There were no significant differences between aMDDrem and aMDDnon-rem between MRI-1 and MRI-2. For statistical results and means see supplemental Tables 6 and 7 as well as Figure 3. Moreover, we found a positive correlation between age at onset and baseline CA3 volume ($r = 0.48$, $P = .035$), duration of disease and right HATA volume ($r = 0.46$, $P = .047$), and (logarithmized) duration of the episode on left parasubicular volume ($r = -0.5$, $P = .034$; see supplemental Figure 6).

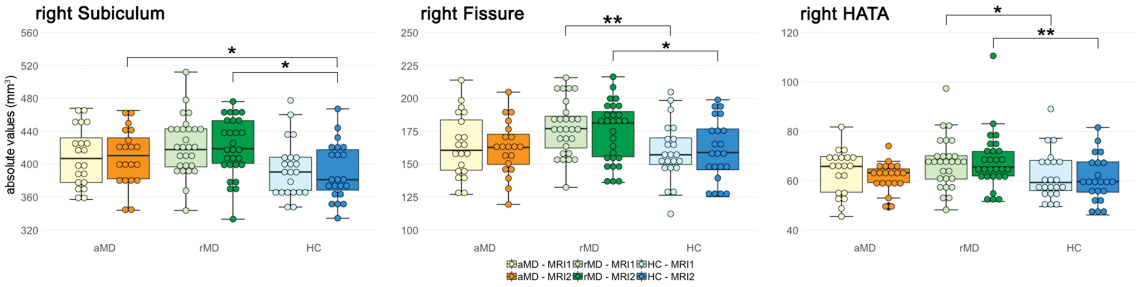

Figure 2. Group differences in 3 hippocampal subfield volumes at MRI-1 and MRI-2. Untransformed hippocampal subfield volumes are plotted by groups and time points. Solely, group differences at each time point were obtained in the right hippocampus in the hippocampal fissure, subiculum, and HATA. All other nonsignificant subfields are shown in supplemental Figure 3. **P < .05, corrected with the Tukey method, *P < .05, uncorrected. aMDD, acute MDD patients received 12 weeks antidepressant treatment between MRI-1 and MRI-2; HATA, hippocampal-amygdaloid transition area; HC, healthy control subjects, both control groups did not take psychopharmaceuticals; rMDD, patients in stable remission before and during the study.

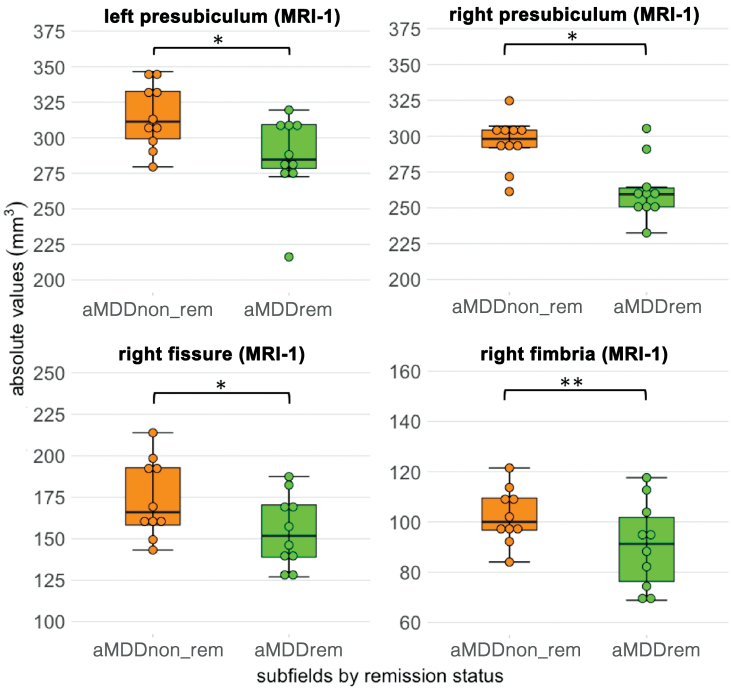

Figure 3. Exploratory analysis of hippocampal subfield differences before treatment in acute depressed patients according to remitter status after 12 weeks of treatment (n = 10/10). Larger subfield volumes were found in the presubiculum, right fissure, and right fimbria in nonremitting depressed patients (aMDDnon_rem) compared with remitting patients (aMDDrem) before treatment. No significant changes were obtained between MRI-1 and MRI-2 or at MRI-2. **P < .05 corrected with Tukey's method, *P < .05, uncorrected.

Discussion

In this 12-week antidepressant treatment study measuring hippocampal subfields in MDD with 7T MRI, we did not detect longitudinal changes of hippocampal formation volumes or hippocampal subfield volumes. Compared with healthy controls, we found hints for larger volumes of the hippocampal formation averaged over both time points in unmedicated, stable remitted patients. Analyses revealed that subfield volumes in remitted depressed patients serving as controls to depressed patients in acute episodes were larger in the subiculum, HATA, as well as the right hippocampal fissure.

Our primary findings are absent hippocampal formation volume and subfield volume changes after antidepressant treatment in depressed patients. These results are in contrast to a study reporting increases of the total hippocampus after 8 weeks of treatment with citalopram (n = 32, 1.5 T; 6-week measurement interval) (Arnone et al., 2013). This study also found larger hippocampal volumes in patients who were remitted, although not in the same pattern as we found (aMDD < HC < rMDD in our study vs aMDD < rMDD < HC in Arnone et al.). A higher number of episodes in their remitted sample might explain this discrepancy, and this study was better matched for sex and age than in our sample. Hippocampal volume increases after paroxetine treatment were found earlier in posttraumatic stress disorder (n = 23, 1.5 T, 12 months (Vermetten et al., 2003). While the first study used a voxel-based morphometry approach with masks, the latter applied manual delineation, which are methodologically different to newer methods (Cao et al., 2017; Maller et al., 2018). Absent volume increases in the total hippocampus as well as absent total hippocampal differences between depressed

patients and controls are in line with a study using FS 4.3 and a mixed antidepressant treatment paradigm (Phillips et al., 2015). Likewise, the authors did not find baseline hippocampal differences between depressed patients and healthy controls. Importantly, this was a more severe treatment-resistant sample undergoing antidepressant therapy with an average scan interval of 331 days in remitters and 420 in nonremitters. Moreover, Philipps et al. found that patients who did not remit over the course of the treatment period exhibited larger baseline volumes. Only patients who remitted exhibited volume increases according to treatment (n = 26, 1.5T, 12 months) (Phillips et al., 2015). Larger baseline volumes in patients who do not remit in are in concert with our results; however, we did not replicate their positive remission × time interaction in the whole hippocampus in our subsample. Increased baseline volumes, however, speak against a meta-analytic finding, indicating that smaller baseline volumes are associated with lower response/remission rates (Colle et al., 2018). At this stage, it is only possible to speculate about reasons for these findings. Studies incorporating disease-inherent heterogeneity with methodologically standardized measurement techniques at comparable time points of the disease phases are needed to better compare hippocampal volume studies.

There is more compelling evidence on cross-sectional hippocampal volume reductions in MDD. Our data indicate smaller volumes of the hippocampal formation of aMDD compared with rMDD (across both scans), but there was no statistically significant difference between aMDD and HC. Of note, hippocampal volume reductions in MDD at cross-sectional levels exhibit small effect sizes even at very large samples (e.g., $d = -0.14$) (Schmaal et al., 2016). In contrast, electroconvulsive therapy appears to have stronger effects on the hippocampus, since increases have been demonstrated with MRI now by several studies (Abbott et al., 2014; Gbyl and Videbech, 2018; Gryglewski et al., 2019).

Increased synaptic plasticity and stimulated neurogenesis is considered as one of several mechanisms of action of SSRIs (Castrén and Rantamäki, 2010; Duman et al., 2016). But the level of existence of neurogenesis in adult humans remains controversial (Boldrini et al., 2018; Sorrells et al., 2018). In that regard, reduced neurogenesis in adult age would fit our findings. Still, increased synaptic plasticity in the dentate gyrus after treatment with various classes of antidepressants was demonstrated (Seo et al., 2014; Patricio et al., 2015). Therefore, discrepancies in existing findings are unlikely to arise from mixed antidepressant paradigms in negative studies, including ours. Moreover, venlafaxine is engaging the serotonin transporter substantially more than the norepinephrine transporter at low doses. The time point of sampling might play an important role but has not been investigated systematically. Interestingly, we found very large variabilities of published hippocampal volumes. For example, total (right) hippocampal volumes of depressed, nondemented patients younger than 60 years in the MRI literature range from 2415 mm^3 to 4363.4 mm^3 (MacQueen et al., 2008; Phillips et al., 2015). Of note, most studies included in a meta-analysis reported bilateral hippocampal volumes between 4794 mm^3 and 8298 mm^3 (Colle et al., 2018). A similar variation exists for subfields, for example, right CA1 volumes in healthy subjects between 34 and 1635 mm^3 are reported (Sone et al., 2016; Voets et al., 2017).

As secondary results of this study, we found a significant main effect of group (although no group × subfield interaction) and significant post-hoc tests in subfields' volumes in remitted subjects in the right HATA, subiculum, and fissure. In the present study, rMDD exhibited larger hippocampi when values of both measurements where combined. In addition, rMDD exhibited larger total brain gray matter. While the reasons for these observations remain unclear, structural and functional hippocampal alterations in remitted depression have been reported (Neumeister et al., 2005). This study compared remitted patients with healthy controls and found decreased total volumes of the hippocampal formation compared with healthy controls. Interestingly and in contrast to this result, we found the same pattern of gray matter—aMDD < HC < rMDD—as another study with unmedicated acute depressed and remitted patients (Salvadore et al., 2011). The authors discussed that increases in gray matter in rMDD might be a subsample-specific trait in patients who are more likely to remit, but they also cannot rule out neurotrophic effects of previous antidepressant exposure. Similar to this study, our rMDD patients were exposed to the same amount of previous medication as the aMDD group but had significantly fewer episodes and therefore less sickness activity (see Table 1 and Kraus et al., 2019) for more details).

To describe our results, the HATA is located between the medial entorhinal cortex, the cortical nucleus of the amygdala, CA1, and the subiculum (DL Rosene, 1987) and shares close connections with amygdalar nuclei. A previous study detailed substantial amounts of intersubject variability in the HATA (Amunts et al., 2005). We also detected low test-retest reliability in the left HATA, while ICC in the right HATA was low as well (0.793). In addition, we found indications of increased HATA values in rMDD compared with HC at both time points, as we did for the right fissure, which exhibited sufficiently high enough ICCs. Enlargement of the hippocampal fissure was previously related to hippocampal atrophy in humans with Alzheimer's (Bastos-Leite et al., 2006) and mice after chronic unpredictable stress (Li et al., 2018). Correlations with psychosocial variables such as onset of disease or duration of the disease constitute an approach to link disease parameters with biology, but these results are only hints for future studies. In addition, our secondary results hinting towards increased subfield volumes in rMDD have to be scrutinized given lower power and a lack of statistically significant interaction of group × subfield.

Mostly negative results in our study between aMDD and HC contradict previous a study reporting volume differences in MDD patients compared with healthy subjects in the tail, CA 2/3, CA 4, and molecular layer (Maller et al., 2018) and another study demonstrating volume reductions in CA1-4, the dentate gyrus, and subiculum (Roddy et al., 2019). Larger subiculum volumes in depressed patients and patients in stable remission in relation to healthy controls, as we found after treatment at MRI-2, contradict a series of studies (Cho et al., 2010; Cole et al., 2010; Wisse et al., 2015; Han et al., 2016), while others undermine cross-sectionally reduced dentate gyrus as well as CA1-4 volumes (Huang et al., 2013; Travis et al., 2015, 2016) or negative results (Cao et al., 2017). Again, interpretation of our findings should be under the premise that this study was designed to obtain longitudinal results. Interestingly, there is heterogeneity between findings comparing subfields in unipolar and bipolar depression as well. Cao et al. (2017) found reduced subfield volumes (CA4, molecular layer, granule cell layer, tail) in bipolar depression; they did not report reduced volumes in unipolar depression. In contrast, a study with FS 6.0 reported reduced volumes in unipolar depression (CA1-CA4, granule and molecular cell layers, tail) in MDD vs HC only and did not find alterations in bipolar depression vs HC (Han et al., 2019). Reasons for these discrepancies remain open so far.

The following limitations that could potentially impact this study have to be reported. We had to exclude 22 subjects (23.9%) due to misalignments after segmentation. Others had to exclude 9.9% (Maller et al., 2018). A systematic comparison suggests T2-weighted images were better suited for subfield segmentations (Mueller et al., 2018). Not recording T2-weighted images might have been a main shortcoming leading to high failure rates of the subfield atlas in our study. Many MRI sequences and analysis approaches have been developed, but optimal methods for 7T have not yet been established (Wisse et al., 2017). An optimal longitudinal subfield's sequence, also allowing application of FS' longitudinal pipeline, is desirable for future studies. Moreover, it would have been optimal for test-retest reliability to conduct scans within several hours/days, since volumes could change in a 12-week period in HC. Still, we consider our test-retest results useful for future studies with 7T and to interpret our results. In addition, our groups were not matched according to age. Acute MDD patients had the highest mean age, suggesting that they would have the highest age-related atrophy, which we did not find in our results. Third, the study was powered for longitudinal effects; results at each separate time point have to be replicated by larger cross-sectional datasets in remitted subjects. Fourth, we did not collect data on years of education in this study, which could have confounded our results and should be addressed in future studies. Finally, there was not enough statistical power to test for group effects of medication. As outlined above, we consider it unlikely that the mixed drug-design obscures positive results. However, a lack of venlafaxine to facilitate neuroplasticity could still be possible.

To conclude, first, we found indications for increased volumes in stable remitted patients, hinting at hippocampal alterations in depression beyond acute episodes, but these results must be scrutinized. Second, we demonstrated with 7T MRI that SSRI and SNRI antidepressant treatment did not yield longitudinal changes in subfield or total hippocampal formation volumes.

Supplementary Materials

Supplementary data are available at International Journal of Neuropsychopharmacology (IJNPPY) online.

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Statement of Interest

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