ARTICLE

The pulvinar nucleus and antidepressant treatment: dynamic modeling of antidepressant response and remission with ultra-high field functional MRI

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Abstract

Functional magnetic resonance imaging (fMRI) successfully disentangled neuronal pathophysiology of major depression (MD), but only a few fMRI studies have investigated correlates and predictors of remission. Moreover, most studies have used clinical outcome parameters from two time points, which do not optimally depict differential response times. Therefore, we aimed to detect neuronal correlates of response and remission in an antidepressant treatment study with 7 T fMRI, potentially harnessing advances in detection power and spatial specificity. Moreover, we modeled outcome parameters from multiple study visits during a 12-week antidepressant fMRI study in 26 acute (aMD) patients compared to 36 stable remitted (rMD) patients and 33 healthy control subjects (HC). During an electrical painful stimulation task, significantly higher baseline activity in aMD compared to HC and rMD in the medial thalamic nuclei of the pulvinar was detected ($p = 0.004$, FWE-corrected), which was reduced by treatment. Moreover, clinical response followed a sigmoid function with a plateau phase in the beginning, a rapid decline and a further plateau at treatment end. By modeling the dynamic speed of response with fMRI-data, perigenual anterior cingulate activity after treatment was significantly associated with antidepressant response ($p < 0.001$, FWE-corrected). Temporoparietal junction (TPJ) baseline activity significantly predicted non-remission after 2 antidepressant trials ($p = 0.005$, FWE-corrected). The results underline the importance of the medial thalamus, attention networks in MD and antidepressant treatment. Moreover, by using a sigmoid model, this study provides a novel method to analyze the dynamic nature of response and remission for future trials.

Introduction

First-line medication of major depression (MD) consists of antidepressant treatment with selective serotonin-reuptake inhibitors (SSRIs) [1, 2]. After non-responsive treatment in the first trial a second trial with an antidepressant with a differential mechanism of action such as a serotonin-noradrenaline reuptake inhibitor (SNRI) is often performed. After both sequential treatments in total about 30–60% achieve remission, leaving about 70–40% of all patients depressed [3, 4]. For medication-naive patients, estimation of future response and remission remains open to clinical judgments [5]. To obtain biological markers of treatment effects, studies investigated blood-oxygen-level dependent (BOLD) signal changes upon antidepressant treatment with fMRI. In the beginning, most of these studies investigated correlates of response [6], only recently fMRI-studies

focused on remission [7]. While neurobiological response markers may be of interest for drug development or clinical research, predictive markers of remission have the potential to be clinically applicable, by allowing patients and physicians to anticipate who will maximally improve before treatment.

A recent fMRI antidepressant trial investigated predictive markers of remission [8]. In this study, dorsolateral prefrontal cortex (dlPFC) activity in a Go/NoGo response inhibition task significantly predicted remission, whereas higher post-treatment dlPFC activity was associated with non-remission. A prior investigation failed to detect baseline differences between remitter and non-remitter using a Stroop Color-Word paradigm [9]. These previous fMRI studies on remission to antidepressant therapy applied lower field strengths at 3 T [8] and 1.5 T [9].

Other neurobiological substrates of depression are the anterior and medial cingulate cortex as well as the insula. Areas that can be activated by various salient stimuli like electrical painful stimulation [10]. In a pilot study we showed that 7 T fMRI had advantageous BOLD responses to transcutaneous electrical stimulation as compared to 3 T in brain areas associated with pain processing [11]. Based on the neuronal activation pattern of painful stimuli and our pilot study, we conducted an antidepressant treatment study at 7 T with the aim of assessing treatment effects in order to investigate correlates of response and discover predictors of remission. Furthermore, we aimed to improve response assessment by modeling clinical outcome parameters from all available study visits. Applying dynamic response modeling we aim to predict response and remission in an explanatory whole-brain approach, without limitation to a priori defined regions of interest. Based on the previous study [10] and our pilot study, we hypothesized that anterior and midcingulate cortex as well as insular, prefrontal and basal ganglia functionality would exhibit significant treatment effects.

Methods

Participants and treatment

All participants gave oral and written informed consent to the study protocol. Subjects were compensated financially for their participation. The study protocol and all study related procedures were approved by the Ethics Committee of the Medical University (EK 103/2011) of Vienna and registered at clinicaltrials.gov (NCT01477203). Study duration was from November 2011 to September 2016. For inclusion and exclusion criteria see supplementary methods.

All medication free acute (aMD) patients underwent an open label, flexible dose, unblinded, but standardized antidepressant treatment for 12 weeks with control visits with possible dosage adjustment every two weeks. fMRI-1 was at week 0 and fMRI-2 was scheduled 12 weeks later. As first line treatment, all aMD patients received escitalopram oxalate for six weeks. A starting dosage of 5 mg was allowed for better tolerance for a maximum of 5 days, afterwards flexible escitalopram dosages between 10–20 mg were given according to clinical judgment by study psychiatrists. Down-titration to 15 or 10 mg was allowed, if 20 mg were not tolerated due to side effects.

If acute patients did not respond to the first-line antidepressant after 6 weeks, defined by at least 50% Hamilton Depression Rating Scale (HAM-D$_{24}$) reduction compared to first visit, they were switched to a second trial with venlafaxine extended release 75–150 mg or mirtazapine 30–60 mg, if venlafaxine was not tolerated. If venlafaxine or mirtazapine was previously not tolerated, escitalopram 10–20 mg was allowed to continue, even if patients did not respond after 6 weeks. The second trial treatment was administered for another six weeks with control visits until fMRI-2 (v1 = inclusion, v2 = fMRI 1 and week 0 of treatment, v3 = week 2, v4 = week 4, v5 = week 6, v6 = week 8, v7 = week 12 and fMRI-2, v8 = follow up). All three groups were measured 12 weeks apart for fMRI-1 and fMRI-2.

Outcome parameters

All patients were assessed by psychiatrists with at least 3 years of experience in clinical psychological testing at every visit with HAM-D$_{24}$, Hamilton Anxiety Rating Scale (HAM-A), Beck Depression Index (BDI), and Clinical Global Impression Scale (CGI). Response (−50% HAM-D$_{24}$ compared to visit 1) was assessed at every visit. Remission was assessed at visits 5 (week 6) and 7 (= fMRI-2, week 12) and defined as <8 on the HAM-D$_{24}$ scale, which was chosen as a conservative cutoff to minimize residual symptoms. Healthy controls and remitted (rMD) subjects were tested with the same questionnaires at baseline visit, fMRI-1 and fMRI-2, as well as at end-of-study examination.

fMRI analyses

The entire pain paradigm and image preprocessing are detailed in the supplementary material and in the pilot studies [11, 12]. Single-subject analysis was conducted using the General Linear Model approach as implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). For each possible anticipation and stimulation condition, a regressor was modeled. Nuisance regressors included 6 realignment parameters, 4 white matter, and 1 ventricles confounding signal.

To test group differences and hence treatment effects between fMRI scans a 3 × 2 repeated measures ANOVA

(rmANOVA) was calculated in SPM12 with group as between-subject and scan as within-subject factor contrasting pain vs. no-pain and expect vs. unsure conditions. This analysis was corrected for sex, age, and an index for the individually calibrated pain stimulation intensity (1−10) at the scan day (= painful intensity−non painful intensity). Post-hoc *t*-tests between every group and scan were performed.

Based on visual inspection of HAM-D$_{24}$ scores across all 8 visits, a sigmoid course was suggested. Therefore, response over visits was fitted in a sigmoidal model with scaling and offset parameters for time between visits and HAM-D$_{24}$ scores with following parameters:

$$\sigma(t) = \frac{a}{1 + e^{bt+c}} + d$$

whereby *a* represented the amplitude between highest and lowest HAM-D$_{24}$ score (i.e., maximum change in HAM-D$_{24}$ score), *b* was the time scaling, i.e., the speed of transition between upper and lower plateau phase, *c* modeled the temporal shift of the curve, and *d* was the lowest HAM-D$_{24}$ value allowed. The parameter *b* was most important for the current study since it reflects the dynamic change of HAM-D$_{24}$ score over time (i.e., the speed how fast a patient experiences changes in HAM-D$_{24}$ score). If model fitting with all available data points lead to implausible results (e.g., reduction of the transition between the plateau phases to a step function), responsible outliers were identified and removed (maximum one per subject). Fitting was accomplished using the MATLAB "fit" function (2013b, The MathWorks, Inc., Natick, Massachusetts, United States, Curve Fitting Toolbox 3.4.) with the "least absolute residuals" method.

To model the dynamic response to antidepressant treatment over 12 weeks in the group of currently depressed patients, the speed of transition values (*b*), i.e., the slopes of the dynamic response function, were used in a regression model with pain, no-pain, expect and unsure contrasts in the pain paradigm in SPM 12 correcting for sex, age, and pain stimulation indices. Imaging results were correlated with escitalopram or venlafaxine plasma values (supplementary methods).

Finally, we assessed predictability or correlates of remission between remitted and non-remitted acute depressed patients after 12 weeks antidepressant treatment. To evaluate the association between the slope of the HAM-D$_{24}$ curve and BOLD responses, a linear regression analysis was performed in SPM12 across the group of currently depressed patients. To test for significant differences in this association between remitter and non-remitter, a voxel-wise ANOVA was carried out [13]. Covariates of non-interest in the model were age, sex, and stimulation thresholds (difference between pain stimuli and non-pain stimuli).

All results were corrected applying the family-wise error rate (FWE) at $p < 0.05$ voxel-level or cluster-level (vFWE or cFWE, as indicated below), the latter following $p < 0.001$ uncorrected voxel-level.

Results

For subject details and clinical outcomes please see Fig. 1, Table 1 and supplementary results.

Neuroimaging results

Treatment effects ANOVA

Acute depressed subjects exhibited significantly different activation (i.e., hyperactivation) in the no pain vs. baseline contrast peaking in the left thalamic pulvinar nuclei, the ventral posterior nucleus, mammillary body and medial dorsal nucleus at baseline ($F_{2,9} = 14.6$, cFWE $p = 0.004$,
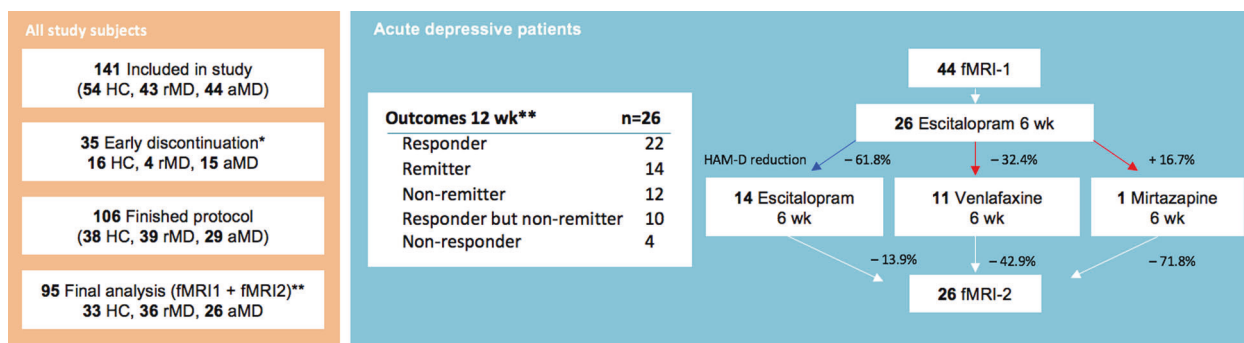

Fig. 1 Subject numbers and outcomes. Numbers of all study subjects are given on the left side. * Early discontinuation reasons are listed at Table S3 in supplemental material. **Numbers correspond to final dataset, reasons for exclusion from data-analyses are given in Table S4. Outcomes after 12 week (wk)-flexible dose antidepressant treatment with escitalopram, venlafaxine, and mirtazapine are presented on the right side. Responder are defined by 50% Hamilton Depression Rating Scale (HAM-D$_{24}$) reduction to baseline or more, remitter by HAM-D$_{24} < 8$. Percentages represent reduction of HAM-D$_{24}$
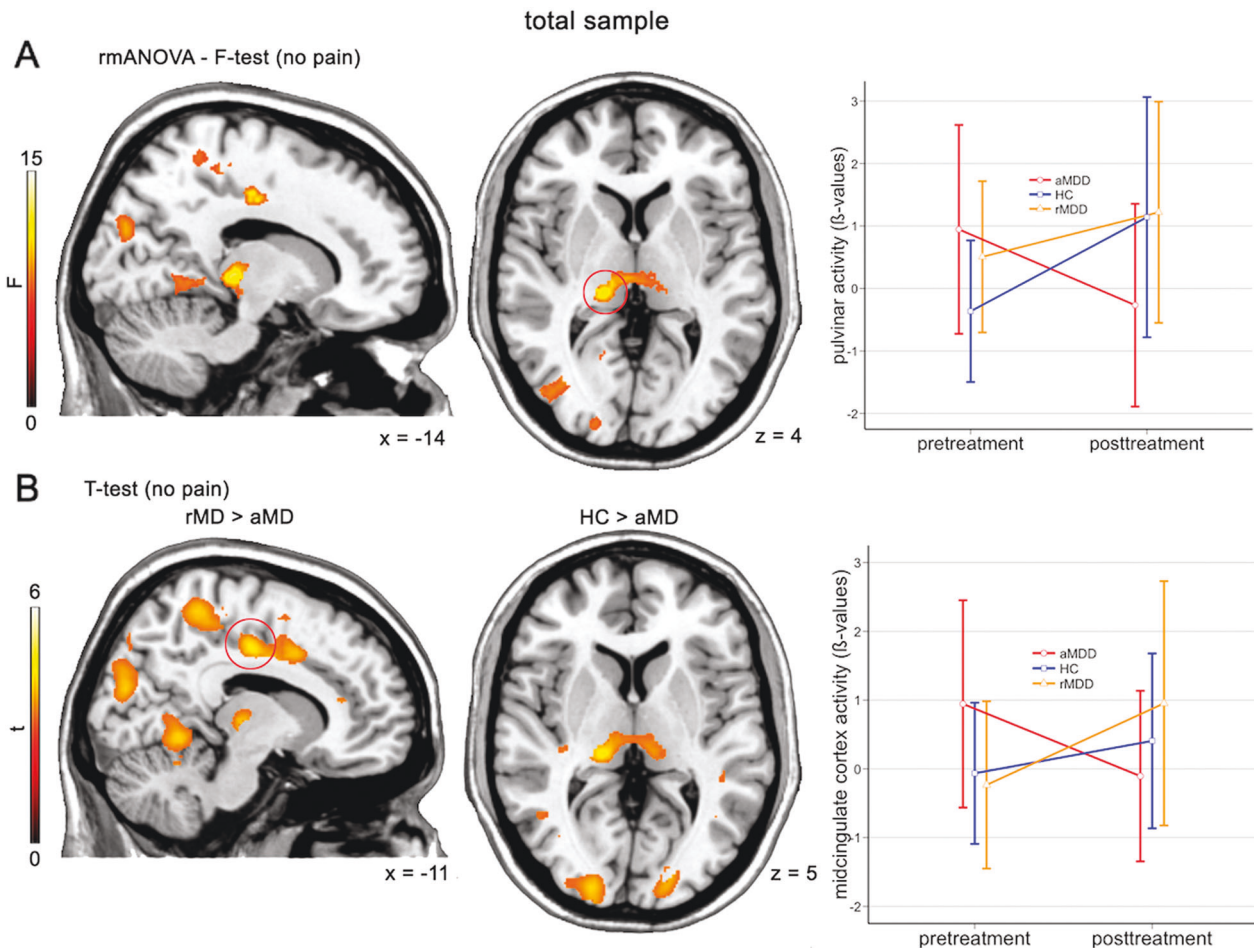
Fig. 2 Reversal of thalamic hyperactivity after antidepressant treatment. Repeated measures analysis of variance (rmANOVA) comparisons between fMRI-1 and fMRI-2 within healthy controls (HC), remitted depressed patients (rMD), and acute depressed patients (aMD). Acute patients were treated with escitalopram or venlafaxine for 12 weeks. **a**, *F*-test results depicts elevated activation of thalamic pulvinar nuclei in acute patients, which reversed to baseline values of HC after treatment. Activations represents difference in *F*-test between fMRI-2 vs. fMRI-1. **b**, Post-hoc *t*-tests revealed elevated activity in midcingulate cortex. Activations represents difference in *t*-test between fMRI-2 vs. fMRI-1. Errorbar-plots represent activation values of red circled-clusters, which survived family-wise error correction (FWE, cluster-level, $p < 0.05$). Left is left. Results are depicted at $p < 0.001$ uncorrected voxel level

see Fig. 2, Figure S4 and for statistics Table S2). Compared to rMD ($t = 4.3$, cFWE $p = 0.019$) and HC ($t = 5.4$, cFWE $p = 0.001$) hyperactivity in aMD was reduced to values of HCs at baseline after 12 weeks of treatment. An additional significant cluster was obtained in the right superior occipital cortex/cuneus ($F_{2,9} = 9.4$, df = 2/9, cFWE $p = 0.003$). A similar pattern, which did not survive statistical correction in the *F*-test was observed in the midcingulate cortex. Here, significantly elevated activation in aMD, which diminished at fMRI-2 with most difference to rMD was observed ($t = 4.8$, cFWE $p < 0.001$). Additionally, rMD subjects exhibited higher signal difference between the two scans in the bilateral precuneus, the occipital cortex and the anterior lobe of the cerebellum (see Table S2). To exclude that the effects are solely driven by variability in the healthy control group, we also tested for significant differences only

for the aMD group. We observed significantly reduced neuronal activation in the pulvinar and middle cingulate cortex at uncorrected levels ($p < 0.001$). There was no statistical difference in the rmANOVA between rMD subjects and HC (all $p > 0.001$) in the no pain vs. baseline contrast. All other tested contrast combination yielded negative results (see supplementary results).

Dynamic response regression

The whole-brain regression analysis in aMD patients with speed of transition values *b* yielded a significant negative correlation between dynamic HAM-D$_{24}$ reduction and perigenual anterior cingulate (pgACC) and medial prefrontal cortex (mPFC) activation ($t = 4.9$, cFWE $p < 0.001$, see Fig. 3). This result was obtained in
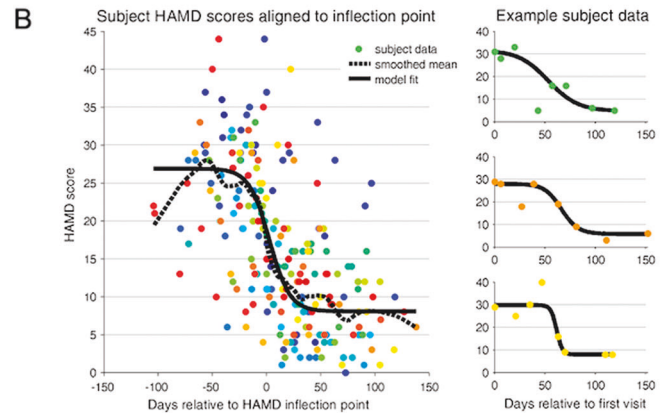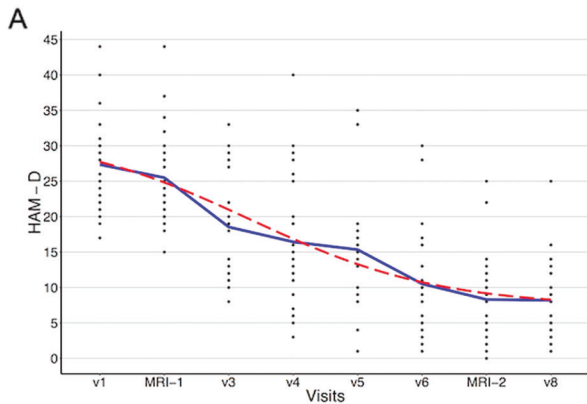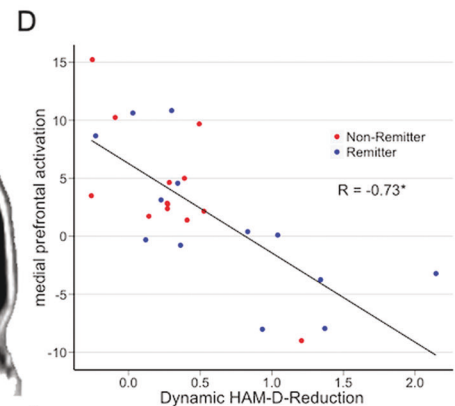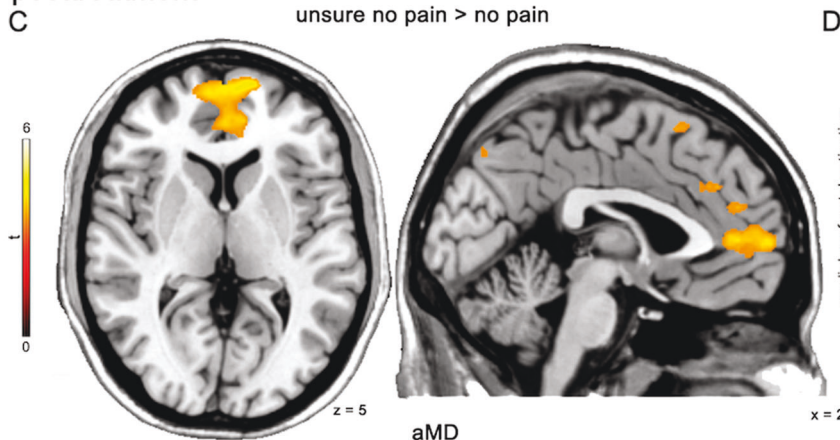
Fig. 3 Dynamic response to antidepressant treatment. **a**, Hamilton Depression Rating Scale (HAM-D_{24}) reduction from baseline visit (v1) to last visit (v8). fMRI-1 and fMRI-2 were 12 weeks apart. The blue line represents means, the red dashed line corresponds to the function in (**b**). **b**, HAM-D_{24} reduction was fitted with a general sigmoid model with days between visits and HAM-D_{24} scores was fitted for each acute depressed (aMD) patient and aligned at 0. Colors of single points represent individual patients. **c, d** The sigmoid function's b (i.e., the

slope of the HAM-D_{24} reduction) was used in a regression model and yielded a significant negative correlation ($p < 0.001$, FWE, cluster-level) between dynamic HAM-D_{24} reduction and perigenual cingulate and medial prefrontal activation at fMRI-2. Non-Remitter (= HAM-D_{24}>8) exhibited higher activation after treatment. Activations represents t-tests between remitter and non-remitter at fMRI-2. * represents Pearson correlation coefficient at $p < 0.05$

the "unsure no pain" vs. "sure no pain" contrast at fMRI-2, there were no other significant results surviving cFWE-correction in other contrasts or fMRI-1. Simply using the difference between HAM-D_{24} scores from MRT-1 and MRT-2 did not result in a significant association with BOLD signal changes ($p > 0.001$ uncorrected). By plotting the activation values of the cluster against b (corrected for age, sex, and difference in stimulation thresholds), we observed that all but one non-remitter exhibited higher activation after treatment, i.e., in these patients this region was not downregulated after treatment. However, this was not specific to non-remitter, since activation with remitters overlapped.

The mean β-values of the cluster in the pgACC/mPFC significantly correlated with escitalopram ($r = 0.77$, $p = 0.005$), but not with venlafaxine plasma values ($r = 0.05$, $p = 0.89$, see Figure S3).

Prediction of remission

Activation in the right temporoparietal junction (TPJ) at fMRI-1 significantly separated remitter from non-remitter in the expect vs. unsure stimuli ($t = 4.1$, cFWE $p = 0.005$, see Fig. 4a). This cluster had an accuracy of 58%, sensitivity of 41.6% and specificity of 71.4%. While remitting patients increased their activation between fMRI-1 and fMRI-2, non-remitter had a decrease of activation at fMRI-2 (Fig. 4a). The difference between fMRI-1 and fMRI-2, i.e., effects of treatment between remitter and non-remitter, was associated with significantly higher activation in the left orbitofrontal cortex in non-remitter ($t = 4.7$, vFWE $p = 0.034$). The cluster is located lateral and inferior to the cluster obtained by the response regression analysis in all subjects (accuracy = 54%, sensitivity = 50%, specificity = 57%). Activation plots show that non-remitter exhibited

Fig. 4 Non-remitter failed to upregulate temporoparietal junction after treatment . **a**, Acute depressed patients who remitted (aMDDrem) after 12 weeks antidepressant treatment had significantly more activity at fMRI-2 in the right temporoparietal junction in the expect vs. unsure contrast (asterisk in **a** represents $p = 0.005$, FWE cluster-level). Remission was defined conservatively by HAM-D_{24}<8. Activation represents t-tests between remitter and non-remitter at fMRI-2. **b**, Non-remitter exhibited significantly increased activity between fMRI-1 and fMRI-2 in the no pain contrast (**represents $p = 0.034$, FWE voxel-level). Activation represents t-tests between remitter and non-remitter between fMRI-2 and fMRI-1
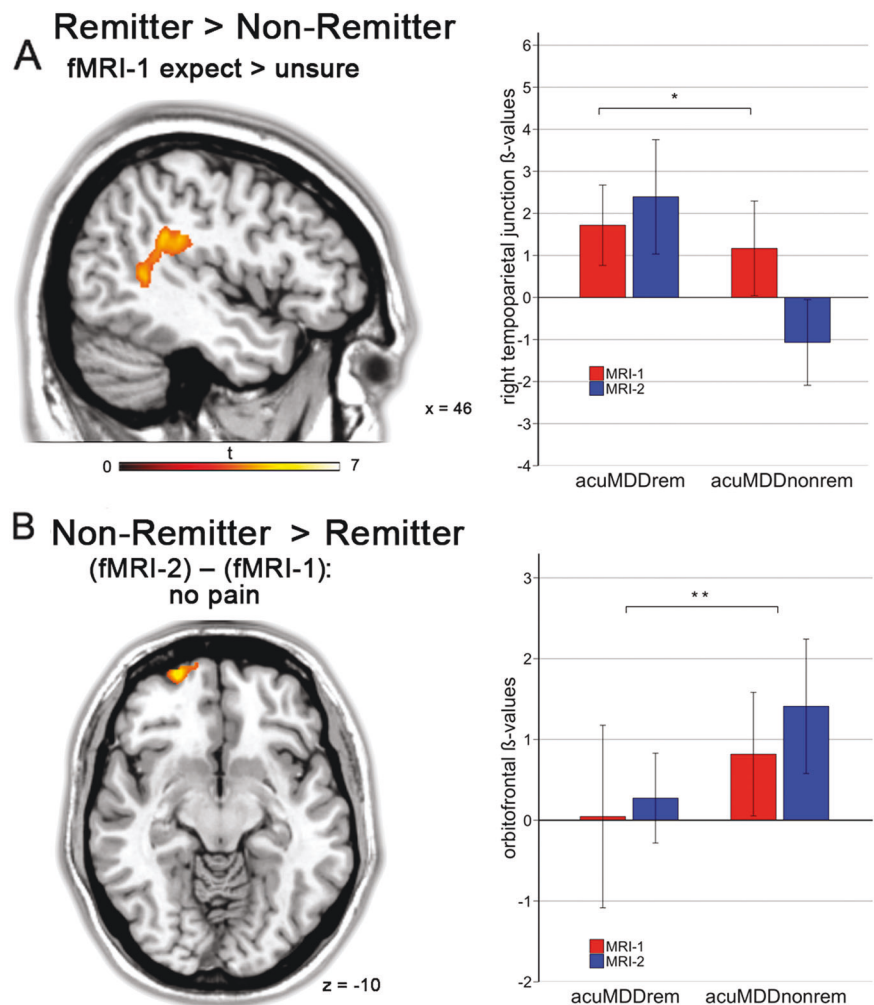
higher baseline activation and increased orbitofrontal activity at fMRI-2 in comparison to remitting patients (Fig. 4b). An ANOVA (time point × group) between remitting and non-remitting MD without the sigmoid model did not yield significant results (all $p > 0.001$, uncorr.).

Discussion

In this 12-week, open-label, antidepressant fMRI study we identified reduction of elevated baseline thalamic activity in the pulvinar and medial thalamus as significant antidepressant treatment effect. These data indicate that antidepressant treatment reverses elevated activity in regions of a major thalamocortical network with strong connections to the limbic system [14]. Furthermore, optimized detection of response and remission was achieved by mapping the dynamic speed of individual treatment response with a sigmoid function. Thereby, aberrant frontal and anterior cingulate activity were confirmed as important correlates of antidepressant response [6, 15–17]. Finally, we detected

that remission was associated with higher pretreatment TPJ activity. Together, these results speak for reversal of hyperactivity in regions within salient and attention networks as an important antidepressant effect.

Our data are not in accordance with those resulting from a prior pain fMRI study [10]. It is striking that the main results were obtained in the no-pain vs. baseline condition, even though pain yielded expected activations (Figure S2). Heterogeneity in the depression group with mixed antidepressant treatments at fMRI-2 or a ceiling-effect at 7 T, which might not be present in lower field strengths during physiologically stronger pain-stimuli, could explain missing results in the pain vs. no-pain contrasts. Between group heterogeneity or measurement time points might not be the main driver of the pulvinar result, since pulvinar changes were detected in aMD only as well. Moreover, these studies differ in regard to the field strengths used, treatment regimens, and comparison groups. Even though 7 T might exhibit superiority for fMRI-statistics for most of the brain regions [11] and provide increased spatial specificity [18], this study in concert with

Table 1 Demographic and clinical characteristics (analyzed sample)

Subjects	HC	rMD	aMD		p
n	33	36	26		
Sex (f/m)	20/13	23/13	19/7		0.592[a]
Age (y)	26.6 ± 6.8	28.5 ± 8.2	30.4 ± 9.7		0.215[b]
Age of onset (y)	–	22.8 ± 6.7	21.6 ± 9.2		0.284[c]
Number of episodes (n)	–	1.7 ± 1.4	3.2 ± 1.6		<0.001[c]
Duration of disease (y)	–	5.8 ± 4.8	9.5 ± 8.8		0.02[c]
Current episode/last episode rMD (m)	–	9.1 ± 6	6.8 ± 12.1		0.128[c]
Previous medication (unclear/yes/no)[d]		5/17/13	0/14/12		
PT during study (unclear/yes/no)	–	2/4/28	4/3/19		
PT before study (unclear/yes/no)	–	8/20/6	3/9/13		
Handedness (r/l)	32/1	34/1	25/1		
Scales			Pretreatment	Posttreatment	
HAM-D$_{24}$	–	2.3 ± 2.5	27.3 ± 6.4	8.3 ± 5.9	
HAM-A	–	2.5 ± 2.4	20.9 ± 5.6	6.7 ± 3.9	
BDI	–	4.2 ± 4.6	21.1 ± 7.2	7.4 ± 5.7	
CGI	–	1.7 ± 0.8	5.3 ± 0.5	3.1 ± 1.2	
Medication during study					
Escitalopram (mg)	–	–	–	13.9 ± 4.5	
Venlafaxine (mg)	–	–	–	98.2 ± 41.7	
Mirtazapine (mg)	–	–	–	30[e]	
Citalopram plasma (ng/ml)	–	–	–	33.7 ± 27.3	
Venlafaxine plasma (ng/ml)	–	–	–	88.4 ± 59.2	
Painful stimulus intensity					
fMRI-1	5.6 ± 5.2	4.5 ± 3.4	5.1 ± 2.8		0.567[b]
fMRI-2	5.6 ± 6	4.3 ± 3.7	5.4 ± 3.7		0.543[b]
Non-painful intensity					
fMRI-1	1.2 ± 1.1	1.3 ± 1.1	1.5 ± 0.8		0.555[b]
fMRI-2	1.7 ± 2.2	1.4 ± 1.1	1.5 ± 0.9		0.722[b]

HC healthy control subjects, *rMD* remitted depressed subjects, *aMD* acute depressed patients *fMRI-1* functional magnetic resonance imaging session one, *HAM-D$_{24}$* Hamilton Depression Rrating Scale (24 item version), *HAM-A* Hamilton Anxiety Rating Scale, *BDI* Beck Depression Index, *CGI* Clinical Global Impression scale, *f* female, *m* male, *y* years, *m* months, *r* right, *l* left

[a]*p*-value chi-square test

[b]*p*-value analysis of variance

[c]*p*-value *t*-test

[d]for detailed medication see supplementary Table S5

[e]only one patient

others show that advantages in group discrimination over lower field strengths might be negligable [19]. For response-prediction markers research, multimodal approaches [20] and machine learning analyses [21] might be more valuable than higher field strengths. For future applications of 7 T fMRI in depression research, determination of potential confounders such as physiological noise will be particularly important. Increases in signal strength come at the cost of increased physiological noise, whereby regions such as the orbitofrontal cortex with proximal air-tissue boundaries are at risk.

Nevertheless, these results match studies reporting altered pulvinar function in MD and highlight pulvinar and thalamic alterations in the pathophysiologic model of depression. Increased pulvinar BOLD-signals and glucose metabolism in untreated MD are substantiated by three meta-analyses [22–24] and elevated baseline glucose metabolism in the pulvinar was demonstrated to be reduced with remission [25]. Our study adds that increased pulvinar BOLD-signal at baseline was reduced after treatment. Thalamocortical coupling is altered in depression and antidepressant therapy targets this connection [26–28].

Antidepressant effects on the pulvinar and the thalamus are substantiated in other fMRI tasks [29–31]. Moreover, thalamocortical connectivity was altered upon ketamine administration [32] and transracial magnetic stimulation to the dorsolateral prefrontal cortex elevated activity in the pulvinar nuclei [33]. These results corroborate reduction of pulvinar hyperactivity by antidepressants, which might not be specific to a pain fMRI paradigm, but a more general effect of antidepressant efficacy.

In the following we discuss potential consequences of altered pulvinar function in MD. The pulvinar nuclei receive the majority of their inputs from the retina and reciprocal connections with striatal, extrastriatal, parietal, temporal, frontal, orbital, cingulate cortices, and the amygdala were described [14, 34]. They provide quick feedback for behaviorally relevant stimuli [35] and monitor attention and/or distraction (reviewed by Pessoa et al. [34]). Irreversible damage to the pulvinar nuclei was associated with visual neglect but also with post-stroke pain [36, 37], which could explain why these results were gathered in a pain-paradigm. Functional changes in the pulvinar, as demonstrated in our study, might contribute to biased acquisition and processing of information, which has been described as important pathophysiological factor in MD [38]. Altered thalamocortical processing was suggested to underlie negativity biases [39], hence, our results might be neurobiological substrates of biased acquisition and retrieval of information, though replication with explicit testing of salience and negativity bias is needed.

The time course of antidepressant response followed a sigmoid function, which has been previously demonstrated [40]. With this optimized model of antidepressant response, we replicated anterior cingulate and ventromedial prefrontal cortex activity as antidepressant treatment response correlate [6, 7, 17, 41]. Without dynamic response modeling, no results on response and remission were yielded in this dataset. Elevated pretreatment anterior cingulate activity is most often reported in resting state or facial emotion tasks [6]. Furthermore, the time points of measurement might impact results, since early response might underlie a different neuronal activity as late response [42, 43]. A sigmoid response indicates that individual patients respond with a moderate decline of HAM-D values in the beginning, followed by at a certain period of faster response and an again flatter decline at the end of observations. A steeper decline in the sigmoid function means that the speed of transition from depression to remission is faster. By describing response with a sigmoid function better fits to interindividual variations in speed of response could be gained. But first replication in larger datasets should be performed. Potentially, differential "response constants" could be then determined for pharmacological and non-pharmacological antidepressant treatments. These would

decrease the number of required data points and could in future be applied to independent datasets.

Applying the model of dynamic response by multiple study visits, we yielded higher baseline activity in the right temporoparietal junction (TPJ) in remitter. Non-remitter exhibited a decrease of activation after treatment. The TPJ is part of the ventral attention network [44] and usually activated in fMRI studies by reorienting attention to salient stimuli [45]. The TPJ is involved in controlling theory of mind-related abilities [46], which were recently shown to be significantly reduced in MD [47] (although see negative results e.g., ref. [48]). MD patients exhibit a reduced visual arousal in the right TPJ [49]. Treatment elevated TPJ-hypoactivity towards activity levels of healthy controls [50]. These studies corroborate a role of the TPJ in enabling internal predictions about external sensory events [51], which might be altered in MD. In our study, remission was associated with increased baseline TPJ-activity in relation to levels of activity in non-remitters. Non-remission was associated with increased activity in the left orbitofrontal cortex between fMRI-1 and fMRI-2. The orbitofrontal cortex is prone to susceptibility artifacts, that is why replication of this result is needed. Both these results were not sensitive and specific enough to promote TPJ activity as potential prognostic marker with clinical applicability. While both regions seem to be affected by MD, future studies could look closer into their potential as clinical marker. In general, clinical applicability of task-based fMRI still remains an unresolved issue. Here, machine learning approaches were previously demonstrated to yield higher accuracies with a low minimum sample size [52]. Moreover, resting state analyses outperformed task-based fMRI in a meta-analysis comparing diagnostic classification by machine learning algorithms [21]. Hence, other imaging modalities and analyses strategies than task-based fMRI and the general linear model might in future be more profitable in finding predictive response or remission markers. Nevertheless, we propose that TPJ-activity should be more frequently investigated in MD, since easy accessibility by non-invasive therapies such as TMS could provide rewarding paradigms.

A few factors must be kept in mind when interpreting these findings. Test-retest reliability remains an issue for potential clinical application of fMRI. Several studies with only fair to moderate ICC values in pain paradigms were reported [53], while others find slightly better values [54]. Yet, spatial activation patterns [55] and noise [56] appear to be stable over measuring time-points. Since we detected significant differences in aMD patients only, we do not conclude that the pulvinar result is solely driven by heterogeneity potentially present between measurements or groups. Second, we did not correct for potential effects of psychotherapy, which might be a limiting factor of the

current study design. However, previous evidence demonstrated differential effects of remission to psychotherapy in the anterior insula and the subgenual cingulate [57, 58], while no effects on the thalamus were demonstrated. The potential influence in our sample, given low numbers of current psychotherapy, might be small, but future studies should control for psychotherapy. A third limitation might be the lack of placebo control. While all applied antidepressants were demonstrated to be superior to placebo [59, 60], this does not rule out unwanted placebo effects in this study. Placebo control in fMRI treatment trials is currently infrequently applied [8, 61, 62]. For translation of pharmacological fMRI findings to clinic placebo-controlled validation might be necessary. In the end, generalization of predictive markers derived from studies as ours to clinical populations remains very hard, because inclusion and exclusion criteria constrain the heterogeneity of major depression in clinical settings.

Conclusion

This antidepressant fMRI treatment study in patients with MD applying a pain-paradigm revealed elevated activity in the medial thalamus, especially in the pulvinar nuclei, which declined after treatment. Thalamic and pulvinar activity are a major contributor to depression pathophysiology. Moreover, we optimized response assessment by modeling the dynamic speed of response using a sigmoidal model with fMRI-data and corroborated the importance of anterior cingulate function in remission. Moreover, our results hint towards temporoparietal junction activity as a potential correlate of non-remission, but confirmation is needed. The main conclusion of this study is that pulvinar activity has a key function in depression and antidepressant treatment, while optimized modeling of response and remission might be a valuable method for future clinical depression trials.

Compliance with ethical standards

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