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Biological profiling of prospective antidepressant response in major depressive disorder: Associations with (neuro)inflammation, fatty acid metabolism, and amygdala-reactivity

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ABSTRACT

Background: A better understanding of factors underlying antidepressant non-response may improve the prediction of which patients will respond to what treatment. Major depressive disorder (MDD) is associated with alterations in fatty acid metabolism, (neuro)inflammation and amygdala-reactivity. However, their mutual relations, and the extent to which they are associated with prospective antidepressant-response, remain unknown.
Purpose: To test (I) alterations in (neuro)inflammation and its associations with fatty acid metabolism and amygdala-reactivity in MDD-patients compared to controls, and (II) whether these alterations are associated with prospective paroxetine response.
Methods: We compared 70 unmedicated MDD-patients with 51 matched healthy controls at baseline, regarding erythrocyte membrane omega-6 arachidonic acid (AA), inflammation [serum (high-sensitivity) C-reactive protein (CRP)], and in a subgroup amygdala-reactivity to emotional faces using functional magnetic resonance imaging (fMRI) (N = 42). Subsequently, we treated patients with 12 weeks paroxetine, and repeated baseline measures after 6 and 12 weeks to compare non-responders, early-responders (response at 6 weeks), and late-responders (response at 12 weeks).
Results: Compared to controls, MDD-patients showed higher CRP (p = 0.016) and AA (p = 0.019) after adjustment for confounders at baseline. AA and CRP were mutually correlated (p = 0.043). In addition, patients showed a more negative relation between AA and left amygdala-reactivity (p = 0.014). Moreover, AA and CRP were associated with antidepressant-response: early responders showed lower AA (p = 0.018) and higher CRP-concentrations (p = 0.008) than non-responders throughout the study.
Conclusion: Higher observed CRP and AA, their mutual association, and relation with amygdala-reactivity, are corroborative with a role for (neuro)inflammation in MDD. In addition, observed associations of these factors with prospective antidepressant-response suggest a potential role as biomarkers. Future studies in independent samples are needed to replicate and test the clinical applicability of these biological predictors for treatment response to result in a precision/personalized medicine approach for treatment.

1. Introduction

Antidepressant-response in Major Depressive Disorder (MDD) remains variable and unpredictable (Kato and Serretti, 2010; Mocking et al., 2015). Understanding underlying biological mechanisms may help to identify biomarkers for response. Identification of pathways modulating antidepressant-response could both guide identification of biomarkers and thereby facilitate selecting the right treatment for each patient, and might also provide novel targets for add-on therapy (Kato and Serretti, 2010; Mocking et al., 2015; Sarris et al., 2016).

An interesting line of evidence suggests that antidepressant-response is modulated by (neuro)inflammatory pathways (Miller and Raison, 2016). MDD is characterized by low-grade

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inflammation, revealed by higher concentrations of inflammatory biomarkers such as C-reactive protein (CRP) (Dahl et al., 2014; Duivis et al., 2013; Howren et al., 2009; Valkanova et al., 2013). Moreover, in MDD-patients, inflammation has been associated with antidepressant non-response, suggesting an interaction between inflammatory processes and antidepressant's effects (Eller et al., 2008; Hannestad et al., 2011; Strawbridge et al., 2015; Thase, 2014; Uher et al., 2014). However, the precise mechanisms underlying the relation between inflammation, MDD, and (non-response to) antidepressants remain unknown. Here, we aim at further unraveling these mechanisms by focusing on a theoretical framework in which we relate (neuro)inflammation in MDD with omega-6 polyunsaturated fatty acid (PUFA) arachidonic acid (AA) and amygdala-reactivity, which we will introduce below.

AA may play an important underlying role in explaining increased inflammation in MDD, because AA is the main precursor of pro-inflammatory eicosanoids (Calder, 2006). MDD has been associated with higher AA (Anders et al., 2013; Dantzer et al., 2008; Dinan, 2009; Irwin and Miller, 2007; Kiecolt-Glaser et al., 2015; Mazereeuw et al., 2015; Zunszain et al., 2013), which may result from dietary intake and/or altered endogenous metabolism (Assies et al., 2014). Of note, while AA has been suggested to directly influence increases in inflammatory markers (e.g. CRP) in MDD (Dinan et al., 2009; Kiecolt-Glaser et al., 2007; Lotrich et al., 2013; Maes, 1999; Zunszain et al., 2013), we are not aware of studies that reported the relation between AA and CRP specifically in MDD. The closest available evidence observed no relation between AA and CRP in a mixed sample of depressed and non-depressed medicated post-myocardial infarction patients (Schins et al., 2007).

Given the relation between AA and inflammation, an association between AA and non-response could also be expected. Especially since a relation with non-response has been observed for (anti-inflammatory) omega-3 PUFAs (also in the present study's sample), which are – at least partly – thought to antagonize omega-6 PUFA's pro-inflammatory effects (Dinan et al., 2009; Kiecolt-Glaser et al., 2011; Kiecolt-Glaser et al., 2012; Mocking et al., 2015). However, the only two studies investigating this relation for AA could not corroborate an association between AA and antidepressant-response (Dinan et al., 2009; Fiedorowicz et al., 2010). This may be because – with sample-sizes of 36 and 23 MDD-patients, respectively – these two studies were relatively small, retrospective, cross-sectional, and did not assess diet.

In addition, it remains unclear how markers of peripheral inflammation and AA relate to alterations in brain activity that have also been associated with MDD and antidepressant-response. One particularly stable finding regarding altered brain activity in MDD is increased reactivity of the amygdala in response to negative facial expressions (Hamilton et al., 2012; Palmer et al., 2015), as was also found in the present study's sample (Ruhé et al., 2012). As part of the cortico-limbic circuit, the amygdala is important for emotion regulation (Drevets, 2003). Of note, several fMRI-studies – including one in the present study's sample – suggest that amygdala-reactivity could also be used to predict antidepressant-response (Fu et al., 2013; Lener and Iosifescu, 2015; Nathan et al., 2014; Ruhé et al., 2012).

Interestingly, a number of studies suggest a link of amygdala-reactivity with AA and inflammation, which makes it an interesting factor to include in our theoretical framework. For example, AA is incorporated into neuronal and glial cell membranes and thereby regulates several brain processes including neurotransmission, cell survival and neuroinflammation in e.g. the amygdala (Bazinet and Laye, 2014). In addition, the wide variety of bioactive AA-derivatives – including lipoxins and endocannabinoids – have numerous neuromodulating effects (Bazinet and Laye, 2014). Moreover, pro-inflammatory cytokines (e.g. endotoxin induced IL-6 and TNF-α) have been found to enhance amygdala-reactivity to threatening stimuli in healthy participants (Inagaki et al., 2012; Redlich et al., 2015), and a strong positive correlation between CRP and amygdala-reactivity was observed in breast cancer survivors (Muscatell et al., 2016). These cross-links of amygdala-reactivity with AA and inflammation could play a mediating role in the cascade of changes leading to MDD and response to antidepressants. However, thus far, no study yet addressed these relationships between (amygdala) brain activity, AA and CRP in MDD.

In sum, we propose a framework of mutually related alterations in AA, inflammation and amygdala-reactivity that may be involved in the pathophysiology of MDD and influence antidepressant-response. In this study, we aim at testing this framework by addressing the following hypotheses in initially unmedicated MDD-patients that are prospectively treated with the antidepressant paroxetine. Cross-sectionally, we hypothesized that: *(I)* unmedicated MDD-patients would have higher levels of AA and CRP compared to matched controls, and *(II)* AA, CRP and amygdala-reactivity would be mutually associated. Longitudinally, we hypothesized that: *(III)* higher AA and CRP would be associated with non-response to twelve weeks paroxetine treatment. Finally, we exploratively tested *(IV)* whether the association of AA with CRP and amygdala-reactivity differed between response-groups.

2. Methods

2.1. Participants

Data collection took place within the framework of the DELPHI-study (ISRCT44111488), as reported previously (Mocking et al., 2015; Ruhé et al., 2009; Ruhé et al., 2015). After institutional ethical committee approval and written informed consent, we included patients from primary and psychiatric care that fulfilled the following criteria: aged 18–70; current MDD episode as assessed by the Structured Clinical Interview for DSM-IV Disorders (SCID-I); antidepressant free ($\geq$4weeks) and a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)-score >18 (First et al., 1996; Hamilton, 1960). Exclusion criteria were severe suicidal thoughts, pregnancy, primary anxiety/substance abuse, bipolar disorder, depression due to a general medical condition, systemic corticosteroid use, psychotic symptoms and neurological, endocrinological or other systemic disorders. We matched healthy controls to patients based on age ($\pm$2.5yrs) and gender. We applied the following additional exclusion criteria for controls: Beck Depression Inventory score >9 (Beck et al., 1961), current or lifetime psychiatric disorders according to the SCID-I, anamnesis of first-degree relative with a psychiatric disorder, use of psychotropic medication, >4 alcoholic beverages/day or drug use $\leq$1 month ago.

2.2. Study design

In a cohort design, we measured clinical, biochemical and imaging parameters in patients and controls at study-entry (T0), after which we started patients on open label selective serotonin reuptake inhibitor (SSRI) paroxetine (20 mg/day). In addition to biweekly clinical visits, we measured all parameters in patients again six weeks after study-entry (T1), at which point we determined clinical response. We kept responders at the same dose of paroxetine. Within the cohort study, at T1, we randomized non-responders to either real paroxetine dose-escalation (10 mg capsules/day increase per 5 days, up to 50 mg/day) or placebo dose-escalation (continued on 20 mg/day paroxetine, with placebo-capsules of '10' mg/capsule to increase up to '50' mg/day), as described previously (Ruhé et al., 2009; Ruhé et al., 2015). Because the randomized placebo-controlled dose-escalation had no clinical effects (Mocking et al., 2015; Ruhé et al., 2012; Ruhé