Psychiatry Research: Neuroimaging 173 (2009) 52–58

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

The effect of acute tryptophan depletion on performance and the BOLD response during a Stroop task in healthy first-degree relatives of patients with unipolar depression

Elisabeth A. T. Evers[a,*], Frederik M. van der Veen[b], Jelle Jolles[a], Nicolaas E. P. Deutz[c], Jeroen A. J. Schmitt[d]

[a]Department of Psychiatry and Neuropsychology, Brain and Behavior Institute, Maastricht University, Maastricht, Netherlands
[b]Department of Psychiatry, Erasmus Medical Centre, Rotterdam, Netherlands
[c]Center for Translational Research on Aging & Longevity, Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[d]Department Nutrition and Health, Nestlé Research Centre, Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 11 April 2007
Received in revised form 9 August 2008
Accepted 16 September 2008

Keywords:
Serotonin
Functional MRI
Family history of depression

ABSTRACT

Previous research has shown that low central serotonin, induced by acute tryptophan depletion (ATD), results in depressed mood and impairs cognition in healthy volunteers with a predisposition for depression. It remains unknown whether ATD affects emotional processing via mood changes or directly. In the present study we investigated the interaction between vulnerability for depression and the effect of ATD on mood, cognition and the associated brain activation. In a previous functional MRI study, we tested the effect of ATD during a combined cognitive and emotional Stroop task in healthy women without a family history of depression (FH−). In this study, we present the data of an additional group of 12 healthy women with a positive family history of unipolar depression (FH+). The effect of ATD on mood and Stroop performance was different for the FH+ group as compared with the FH− group. Scores on the depression sub-scale of the Profile of Mood States (POMS) did not correlate with performance changes, but did correlate with the anterior cingulate cortex response during Stroop interference. This study showed that a family history of unipolar depression interacts with the effect of ATD.

1. Introduction

Major depression, a disorder characterized by depressed mood and cognitive dysfunction, has been associated with disturbed serotonergic functioning (Risch and Nemeroff, 1992). To gain more insight into the etiology and symptoms of depression, acute tryptophan depletion (ATD), a model for reduced central serotonin (e.g. Hood et al., 2005), has been used (e.g. Neumeister, 2003; Salomon et al., 1993; Van der Does, 2001). ATD is a well-established method to temporarily lower central serotonin (5-HT) (Nishizawa et al., 1997; Williams et al., 1999; Young et al., 1999). In line with the cognitive disturbances found in depressed patients, ATD impaired memory consolidation (Riedel et al., 1999; Schmitt et al., 2000) and cognitive flexibility (Park et al., 1994; Rogers et al., 1999) in healthy volunteers. In addition, ATD has been used to study individual vulnerability of the 5-HT system (e.g. Jans et al., 2006; Booij et al., 2005a; Walderhaug et al., 2007. Previous studies showed that risk factors for developing depression (e.g. the serotonin transporter (5-HTTPR) short allele polymorphism, previous depressive episodes, being female, a positive family history of affective disorder) are associated with a depressed mood after ATD (Benkelfat et al., 1994; Booij et al., 2002; Ellenbogen et al., 1996; Klaassen et al., 1999; Neumeister et al., 2002; Riedel et al., 2002, 2003). Participants without a susceptibility to depression do not show a depressed mood after ATD (for review see Van der Does, 2001).

Only a few studies have investigated the association between depressed mood induced by ATD and emotional processing (Booij et al., 2005b; Munafo et al., 2006; Merens et al., 2008). Booij et al. (2005b) showed that ATD induced a depressed mood and impaired the processing of positive words on an emotional Stroop task in remitted depressed patients. Merens et al. (2008) showed that a mood response in remitted depressed patients after ATD tended to increase accuracy of sadness recognition. Furthermore, Munafo et al. (2006) showed that ATD induced a depressed mood and increased interference from social threat words in recovered depressed patients on medication during an emotional Stroop task. It remains unclear, however, whether individual changes in depressed mood after ATD are related to individual changes in emotional processing. To gain more insight into the association between a transient lowering of

* Corresponding author. Department of Psychiatry and Neuropsychology (DRT 10), Maastricht University, P.O. Box 616, 6200 MD Maastricht, Netherlands. Tel.: +31 43 3884086; fax: +31 43 3884092.
E-mail address: l.evers@np.unimaas.nl (E. A. T. Evers).

0925-4927/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2008.09.006

central 5-HT, mood and emotional processing we examined the effect of ATD on healthy women with a first-degree family member who has been diagnosed with unipolar depression (FH+) during a combined cognitive and emotional Stroop task. These data were statistically compared with published data from healthy women without such family history (FH−; Evers et al., 2006). A major strength of this study is that by studying unaffected relatives we are able to study vulnerability markers without the confounding influence of symptoms related to the illness.

Previous ATD studies showed inconsistent effects of ATD on Stroop performance in healthy volunteers. Some previous studies showed that ATD improved (Coull et al., 1995; Rowley et al., 1997; Rosse et al., 1992; Scholes et al., 2007), whereas other studies showed that ATD did not change Stroop performance (Gallagher et al., 2003; Horacek et al., 2005; Sobczak et al., 2002). Also neuroimaging studies are inconclusive. In an event-related fMRI study, Horacek et al. (2005) showed that ATD increased the activation in the bilateral mediofrontal cortex, anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex during Stroop interference without affected performance. In an earlier report about the FH− data (Evers et al., 2006), we showed that ATD decreased the interference score and increased the activation in the anterior cingulate cortex (ACC) during Stroop interference in the first Stroop block. Factors like a susceptibility to depression may influence not only the effect of ATD on mood, but also the effect of ATD on Stroop performance and brain activation.

In this study we tested the following hypotheses: 1) ATD triggers depressed mood in FH+ but not in FH− participants, 2) ATD affects Stroop performance and the associated brain activation patterns differently in FH+ and FH− participants, and 3) depressed mood is associated with the effect of ATD on Stroop performance and brain activation.

2. Methods

Fifteen healthy FH− women performed a combined cognitive and emotional Stroop task in a balanced (BAL) and a tryptophan depleted (TRP−) session (Evers et al., 2006). In the present study, we report the data of an additional group of healthy FH+ women that was recruited and tested in the same time period as the FH− group (exact same paradigm), and statistically compare the results of these two groups.

2.1. Participants

Fifteen healthy FH− women were successfully tested (19–33 years old; mean age 22.1 (S.D. = 3.5); mostly university students). In the FH+ group, fourteen healthy women (19–42 years old; mean age 23.5 (S.D. = 5.7); mostly university students), with a first-degree relative who had been diagnosed with unipolar depression, were included. The family members (12 mothers, 1 father and 1 sister) gave permission to check the diagnosis with their general practitioner or psychologist, who received a small questionnaire by fax (see Table 1). The diagnosis of unipolar depression was confirmed for all relatives. The health states of the participants were checked by a medical questionnaire, evaluated by a medical doctor. All participants were free of present or past mental or physical illness, did not use medication at the moment of inclusion, had never used antidepressants or ecstasy, and were screened for MRI contraindications. One participant was Asian, the rest was Caucasian. The participants were recruited by local advertisements and were paid 75 euros.

This study was approved by the Medical Ethics Committee of Maastricht University Hospital, the Netherlands. All participants gave written informed consent before inclusion.

2.2. Experimental design

Participants were tested in a double-blind placebo-controlled within-subject design. The researchers were blind to the composition of the drink, but not to the FH status of the participants. Due to a lack of personnel the first author both recruited and tested the participants. When the participants arrived at the laboratory they first completed mood and health complaints questionnaires, then a blood sample was taken and thereafter the TRP− or BAL amino acid (AA) drink was consumed. After a four and a half hour break they filled out another set of questionnaires and a second blood sample was taken. Then the participants were scanned at the Maastricht University Hospital radiology department. In each scan session the participants performed two blocks of the Stroop task (9 min each) and halfway through a structural scan was made (10 min). In addition, the participants performed a facial recognition task (Van der Veen et al., 2007). Before the first test session the participants were trained in a dummy scanner.

Table 1
The small questionnaire about the depression of the family members of the FH+ participants, that was completed by the general practitioners or psychologist.

Questions	Answer and frequency		
Has the diagnose unipolar depression been given?	Yes	No	
	14	0	
What was the severity of the depression?	Minor	Moderate	Severe
	3	8	3
Was a diagnostic instrument used?	Yes	No	
	1	13	
If yes, which instrument and what was the score?	Zung: 84		
Is there co morbidity?	Yes[a]	No	
	7	7	
Is depression prominent?	Yes	No	
	14	0	

[a] Co morbidities: atrial fibrillation; hypertension; early COPD; rheumatic artritus; symptoms of borderline; symptoms of OCD; OCD.

2.3. Stroop task

In this task every two seconds a word printed in colored ink was presented against a black background (programmed in E-Prime; Psychological software Tools, 2002). A word stayed on the screen until a response was made. A black screen was shown between the response and the next stimulus. The participants had to report the color of the ink in which the word was printed by pressing one button of the left or right hand response device: left middle finger for blue, left index finger for red, right index finger for green, right middle finger for yellow. These associations had to be learned by heart. In case memory failed, the color-response correspondence was written in small white letters at the bottom of the screen along with each presented word. No feedback was given.

Participants completed two blocks of the modified Stroop task in each test session. Each block contained 152 words in total: 40 congruent color (CC) words (e.g. 'red' written in red ink), 40 incongruent color (IC) words (e.g. 'red' written in blue ink), 24 positive (POS), 24 negative (NEG) and 24 neutral (NEU) words. Each block lasted about 5.5 min. Within each block these different word types were mixed in a semi-randomized way (never the same word type or color three times in a row). Randomization effectively jittered the time between successive onsets of the same stimulus type (Huettel et al., 2004). For example, the time between two IC words was minimal 2 s and maximum 40 s. Each word type was presented equally often in each of the four colors. During the CC and IC words the name of the color was the distracter, during the emotional words the emotional meaning of the word was the distracter. Each block started with ten NEU words which were not included in the analysis (each block contained in total 162 stimuli). In the dummy scanner the participants performed two training blocks that each contained 40 CC, 40 IC and 72 NEU words.

The following performance measures were collected: the mean reaction times (RT) and the number of errors for IC, CC, POS, NEG, and NEU words, and the interference scores for 1) IC compared to CC words ((RT for IC words − RT for CC words) / RT for CC words), 2) POS compared to NEU words and 3) NEG compared to NEU words.

The effect of ATD on RTs and the number of errors was analyzed (SPSS version 11.5) using GLM repeated measures with Treatment (BAL or TRP−) and Word Type (IC and CC words, or NEU, POS and NEG words) as within-subject variables, Group (FH− or FH+) as between-subject variable and Order (BAL or TRP− first) as a covariate. The effect of ATD on the interference scores was analyzed using GLM repeated measures with Treatment as within-subject variable, Group as between-subject variable and Order as a covariate.

2.4. Acute tryptophan depletion

The TRP− mixture was a 75 g AA mixture without TRP (for the exact composition see Evers et al., 2006). In the BAL mixture 3.0 g TRP was added. The mixtures were prepared with 200 ml tap water.

Blood samples (10 ml) were taken to determine the plasma TRP level and the TRP/ΣLNAA (LNAA: large neutral amino acids) ratio ([TRP / [tyrosine + leucine + phenylalanine + isoleucine + valine]). For blood sample analysis see Evers et al. (2006). The effect of ATD on plasma TRP level and the TRP/ΣLNAA ratio was analyzed using GLM repeated measures with Time ($t0$ and $t5$) and Treatment as within-subject variables, Group as between-subject variable and Order as a covariate. A One-Way ANOVA, with Group as factor, was used to compare baseline plasma TRP values (baseline values from both tests days).

2.5. Mood

A visual analogue version of the Profile of Mood States (POMS) was used to assess mood (McNair et al., 1988). This questionnaire consists of 32 bipolar sets of adjectives, which measure five mood dimensions: anger, depression, fatigue, tension and vigor.