The drive to control : how affect and motivation regulate cognitive control

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Depression and Conflict Adaptation

"A depressed man lives in a depressed world."

Ludwig Wittgenstein

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Abstract

Negative affect in healthy populations regulates the appraisal of demanding situations, which tunes subsequent effort mobilization and adjustments in cognitive control. We hypothesized that dysphoria in depressed individuals similarly modulates this adaptation, possibly through a neural mechanism involving serotonergic regulation. We tested the effect of dysphoria induced by Acute Tryptophan Depletion (ATD) in remitted depressed patients on conflict adaptation in a Simon task. ATD temporarily lowers the availability of the serotonin precursor L-Tryptophan and is known to increase depressive symptoms in approximately half of remitted depressed participants. We found that depressive symptoms induced by ATD were associated with increased conflict adaptation. Our finding extends recent observations implying an important role of affect in regulating conflict-driven cognitive control.

Introduction

One of the defining symptoms of depression is a depressed mood. Although a depression is certainly undesirable and maladaptive, normal and pathological mood states of sadness lie on a continuum and may actually play an important role in adaptive behavior (e.g., Andrews & Thomson, 2009; Mayberg et al., 1999). The Mood-Behavior-Model (MBM; Gendolla, 2000) proposes that negative affect helps to regulate resource mobilization and behavior via a biased appraisal of situational demands (cf. Ach, 1935; Hillgruber, 1912). Indeed, several studies using mood induction procedures in healthy populations have shown that negative affect increases demand appraisals of difficult situations, which improves subsequent effort mobilization as measured by cardiovascular adjustments (for a review, see Gendolla & Brinkmann, 2005). Recent evidence suggests that behavioral adaptation to fluctuating task difficulty is also subject to this affective regulation. We have recently shown that dynamic behavioral adjustments after demanding, conflict trials in a flanker task are stronger following the induction of a sad or anxious mood than following a happy or calm mood (van Steenbergen et al., 2010). These data suggest that negative affect may facilitate conflict-driven recruitment of cognitive control, as can be measured by trial-to-trial adaptations in conflict tasks that use randomized presentation of compatible and incompatible trials (Gratton et al., 1992; for a review, see Egner, 2007).

Here, we hypothesize that – analogous to these negative mood effects in healthy samples – dysphoria in remitted depressed individuals also improves demand-driven behavioral adaptation. Recent work has demonstrated enhanced demand-driven effort recruitment in depression using cardiovascular measures (Brinkmann & Gendolla, 2007), but no study has yet demonstrated such effects of depressed mood on behavioral adjustments in cognitive control tasks. It is important to note that the majority of past research on the link between depression and cognitive control has compared attentional interference effects only (i.e., calculating main compatibility effects, such as the Stroop effect), and did not address the modulation of trial-to-trial adaptations in control (i.e., a sequential modulation of interference effects). Although this literature has yielded some evidence for depression-related general deficits in cognitive control (for reviews, see Levin, Heller, Mohanty, Herrington, & Miller, 2007; Rogers et al., 2004), it has been proposed that such deficits are mainly driven by factors other than mood state, e.g., increased rumination (e.g., Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Philippot & Brutoux, 2008). Mood induction studies in healthy populations actually

support this suggestion, showing that sad mood in itself does not modulate effort mobilization or interference effects (Chepenik, Cornew, & Farah, 2007; van Steenbergen et al., 2010). These findings are also consistent with the notion that a negative mood in itself does not have general motivational implications, but can regulate effort adaptation via modulated demand appraisals, thus producing context-sensitive effects in tasks using fluctuating task demands (Gendolla, 2000). Thus, in contrast to the analysis of main attentional interference effects, sequential effect analysis may provide a measure that is much more sensitive to depressed-mood modulation.

Increased demand-driven behavioral adaptation in depression may arise from the negativity bias and its associated amplified neural reactivity to adverse and demanding events typically observed in this disorder (Beck, 1976; Olvet & Hajcak, 2008; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). It has been proposed that these neural effects are driven by central serotonin (5-hydroxytryptamine; 5-HT) regulation (Jocham & Ullsperger, 2009; Cools et al., 2008). The impact of central 5-HT on mood and cognition has been investigated with Acute Tryptophan Depletion (ATD), a manipulation that temporarily lowers the availability of L-Tryptophan (Trp), the precursor of serotonin. ATD leads to a transient increase in depressed mood in individuals who are vulnerable to depression (e.g., former patients and first-degree relatives), but not in healthy non-vulnerable individuals (cf. Booij, van der Does, & Riedel, 2003; Ruhe et al., 2007; van der Does, 2001). Some studies have shown that ATD can lower attentional interference independent of mood changes, that is, in both non-vulnerable and depression-vulnerable individuals (Booij et al., 2005; Schmitt et al., 2000; for a review, see Mendelsohn, Riedel, & Sambeth, 2009). However, it is still an open question whether ATD-induced mood changes may modulate conflict adaptation. Recent neuroimaging studies provide some initial support for this hypothesis (for reviews, see Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Fusar-Poli et al., 2006). For example, ATD-induced depressed mood correlates with activity in the Anterior Cingulate Cortex (ACC; Evers, van der Veen, Jolles, Deutz, & Schmitt, 2009), a region playing a prominent role in the generation of adaptive control to demanding situations (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Serotonin polymorphisms have also been linked to changes in post-conflict behavioral adjustments (Holmes, Bogdan, & Pizzagalli, 2010; Osinsky et al., 2009). However, the role of 5-HT accounting for the link between negative mood and conflict adaptation is not known yet.

This study investigates the putative link between conflict adaptation, 5-HT function, and depressed mood. Focusing on trial-to-trial adjustments in performance, we reanalyzed data from an earlier published ATD study (Booij et al., 2005) that only reported overall response-conflict effects, as measured with a Simon task (Simon & Rudell, 1967), in a group of remitted depressed patients after they received ATD. In that study, ATD increased depressive symptoms in about half of the investigated sample and thus provides an excellent design to investigate the associations between depressive symptoms, 5-HT, and conflict adaptation. Similar to the better-known Stroop and flanker tasks, the Simon paradigm is a conflict-inducing task that requires speeded responses to targets that randomly appear in locations that correspond (compatible trial) or do not correspond (incompatible trial) to the location of the correct response key. Incompatible, demanding trials evoke response conflict, which is thought to generate increased cognitive control on subsequent trials (Botvinick et al., 2001). This adaptation to conflict is manifested by reduced compatibility effects in trials following conflict (incompatible) trials as compared to trials following nonconflict (compatible) trials (Gratton et al., 1992; for a review, see Egner, 2007). Given previous theory and evidence for enhanced demand-driven effort mobilization in dysphoria (Gendolla, 2000; Brinkmann & Gendolla, 2007) and after negative mood inductions (Gendolla, 2000; van Steenbergen et al., 2010), and neural evidence suggesting potentiated conflict responses in individuals who show a depressed mood response to ATD (Evers et al., 2009), we hypothesized that ATD may increase conflict adaptation, especially in individuals in whom ATD transiently induced depressive symptoms.

Methods

Twenty-three patients were administered a high-dose and low-dose ATD mixture (100 vs. 25 g amino acids) in a double-blind randomized crossover design with two sessions, separated by at least four days (Booij et al., 2005; Booij, van der Does, Spinhoven, & McNally, 2005). The 100 g and 25 g ATD mixture have previously been shown to lower plasma Trp levels by approximately 90% and 50%, respectively, in this sample (Booij et al., 2005) as well as in other samples (e.g., Booij, van der Does, Haffmans, & Riedel, 2005). The study was approved by an independent medical ethics committee (METIGG, Utrecht), and performed according to their guidelines and regulations. All patients were informed about the study by their

clinician and in detail by one of the investigators (LB), and provided written informed consent.

Participants

The sample has been described in detail previously (Booij et al., 2005). Eligible patients were selected outpatients of a mood disorders clinic. Inclusion criteria were: age between 18 and 65 years; ongoing treatment with an SSRI or a serotonin noradrenaline reuptake inhibitor for at least 4 weeks, meeting DSM-IV criteria for depression in full or partial remission, Hamilton Depression rating Scale (HRSD, 17-items) (Hamilton, 1960) lower than 15 (Frank et al., 1991). Exclusion criteria were: substance abuse within the past 3 months, psychosis (lifetime), major physical illness, lactation, pregnancy. After excluding two drop-outs and two statistical outliers, 19 participants remained for statistical analyses (cf. Booij et al., 2005).

Diagnoses and symptoms

As described in the original paper (Booij et al., 2005), depressive symptoms were assessed with the 10-item Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). The sleep items were omitted, as this could not change within an ATD session. Diagnoses, demographic and clinical background variables were verified with the Structured Clinical Interview for DSM-IV (SCID-I) (First, Spitzer, Gibbon, & Williams, 2005).

Conflict adaptation

The Simon task consisted of 64 trials presented in two consecutive blocks in which the stimulus interval differed (2250 ms fixed versus 2250–5500 ms variable). The word 'left' or 'right' was presented in randomized order either at the left or the right side of the screen. Participants were instructed to respond to the meaning of the word (target) and to ignore its location (distracter), as fast as possible. The same number of compatible (distracter location matches the target word) and incompatible (distracter location conflicts with the target word) stimuli was used.

Procedure

Venous blood (10 ml) was taken in the morning, 6 h after ATD and the next day (t+24) and analyzed for total plasma Trp and the other large neutral amino acids (Fekkes, Vandalen, Edelman, & Voskuilen, 1995). Mood was assessed 1 h before ATD (t−1), 6.5 h later (t+6.5), and the next morning (t+24). The Simon task ("left/right task") was administered (Booij et al., 2005) approximately 5.5 h after

administration of the ATD mixture. Cognitive performance was also assessed at a separate intake and a post-intervention session. The average of these two assessments was taken as baseline measurement (cf. Booij et al., 2005).

Data analysis

Repeated measures ANOVAs were used for sequential analysis of Simon performance, separately for correct reaction time (RT) and percent accuracy. In order to measure sequential adjustments in Simon task performance, we not only included the factor compatibility of the current trial as is usually done, but we also added the factor "compatibility of the previous trial". Standard conflict-adaptation, i.e., the modulation of the compatibility effect as a function of previous-trial compatibility (cf. Figure 1A), should yield an interaction effect between current and previous trial compatibility (Gratton et al., 1992; Egner, 2007).

To analyze direct effects of the ATD manipulation on conflict adaptation, intervention (baseline versus low-dose versus high-dose ATD) was added as a within-subject factor. The effect of mood state on conflict adaptation, for the low-dose ATD and high-dose ATD sessions separately, was analyzed by using mood scores (measured at +6.5 h) as a covariate. To visualize the hypothesized association between mood and conflict adaptation, we calculated standard individual conflict-adaptation scores by subtracting the interference effect following a correct conflict (incompatible) trial from the interference effect following a correct nonconflict (compatible) trial (cf. Figure 1A). Before averaging sequential conditions for each individual, the first trial of each block, trials following an error, and trials with RTs not fitting the outlier criterion (deviating more than 2.5 SD from the individual condition-specific mean) were excluded from analyses.

Results

As described in detail elsewhere (Booij et al., 2005), high-dose ATD but not low-dose ATD led to a both statistically and clinically significant induction of depressive symptoms as measured by MADRS scores 6.5 h after depletion (7.9 ± 7.8 vs. 3.7 ± 3.8, mean ± standard deviation; $t(18) = 3.34$, $p < .005$). The Simon task produced a standard interference effect: incompatible trials produced longer RTs than compatible trials ($F(1,18) = 23.47$, $p < .001$, MSE = 1933.65). The analysis also revealed a robust conflict-adaptation effect as indicated by an interaction between current- and previous-trial compatibility ($F(1,36) = 38.27$, $p < .001$, MSE =

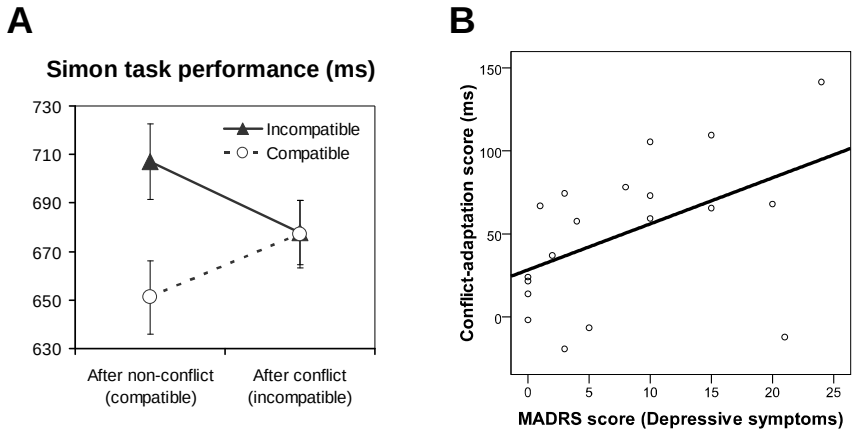

Figure 1. A. *Conflict adaptation in the Simon task as evidenced by a reduced compatibility effect after conflict trials vs. non-conflict trials. Graphs show mean RT (ms) and standard errors.* ***B.*** *More depressive symptoms (MADRS score) after the high-dose ATD intervention are associated with increased conflict adaptation.*

1143.45). As Figure 1A shows, the interference effect was eliminated after conflict (incompatible) trials but not after non-conflict (compatible) trials, indicating standard conflict adaptation, that is, reduced interference after conflict trials. This reduction in interference was driven by both post-conflict speeding of incompatible trials (illustrating that increased conflict-driven control reduces interference; $t(18) = -4.2$, $p < .001$) and by post-conflict slowing of compatible trials (illustrating that increased conflict-driven control reduces facilitation; $t(18) = 4.5$, $p < .001$). Analyses of error rates also showed standard interference ($F(1,18) = 5.38$, $p < .05$, $MSE = 0.001$) and conflict adaptation ($F(1,36) = 6.30$, $p < .05$, $MSE = 0.001$) effects. In addition, it revealed a main effect of previous compatibility ($F(1,18) = 4.46$, $p < .05$, $MSE = .002$) indicating improved accuracy after conflict. Notably, no main effects or interactions with congruency or conflict-adaptation in RT or accuracy were observed for ATD intervention. Thus, ATD did not have an effect on interference (as reported earlier by Booij et al., 2005) and it also did not directly modulate conflict adaptation.

An ANCOVA using mood score as covariate confirmed our hypothesis: depressed-mood scores during the high-dose ATD condition predicted increased conflict adaptation in RT as indicated by a significant three-way interaction

between mood, current-trial compatibility, and previous-trial compatibility ($F(1,18) = 5.30$, $p < .05$, MSE = 396.75). As Figure 1 shows, individuals with more depressive symptoms after the ATD intervention showed more conflict adaptation in the Simon task. As is typically observed (Chepenik et al., 2007; van Steenbergen et al., 2010), mood did not have effects on interference or overall reaction time. Moreover, no mood effects were found for accuracy, thus showing that the effect on conflict adaptation could not be attributed to a speed-accuracy tradeoff. Because the low-dose ATD session did not lead to any mood changes (Booij et al., 2005), data from this session were used for a control analysis: no association between mood and performance emerged.

Discussion

We report the first evidence for a link between low tryptophan concentrations, depressed mood and conflict adaptation in remitted depressed patients: Individuals with higher levels of depressive symptoms following high-dose ATD showed increased conflict adaptation. The ATD manipulation in itself exerted no direct effect on conflict adaptation. This finding is in line with predictions derived from MBM theory (Gendolla, 2000), with earlier behavioral and physiological observations from mood-induction studies in healthy populations (e.g., Gendolla, Abele, & Krusken, 2001; Gendolla & Krusken, 2002; van Steenbergen et al., 2010), and with neural evidence (e.g., Evers et al., 2009). Our study demonstrates for the first time that extra demand-driven recruitment of cognitive control is not limited to conditions of sad mood as induced in healthy volunteers (van Steenbergen et al., 2010), but can also be observed in people with depressive symptoms.

Our observation has important implications for understanding how depressive affect regulates cognitive control. In line with MBM theory (Gendolla, 2000), our data illustrate that depressed mood per se does not have motivational implications (as would be indicated by a modulation in attentional interference effects), but may facilitate increased cognitive control after a behavioral challenge. Interestingly, this effect was observed in a relatively low-demanding Simon task where people were merely instructed to do their best (see also Brinkmann & Gendolla, 2007) and in the context of depression scores that were mainly below the cut-off value for a depression diagnosis, but that were still clinically relevant and much larger than the effect of mood inductions in healthy participants.

However, it is important to note that MBM theory also predicts situations where a negative mood may actually lead to demand-driven disengagement, namely in cases where a demand is perceived as too high to actively cope with (cf. Brehm & Self, 1989). Evidence for this effect has been reported in mood-induction studies and can also be shown in dysphoric participants when they perform tasks with extremely high fixed demands (Brinkmann & Gendolla, 2008). We think that these findings may also provide an interesting account for the recent observation of decreased conflict adaptation when participants received negative feedback concerning their task performance, an effect especially strong in subclinically depressed participants (Holmes & Pizzagalli, 2007). Interestingly, a very recent study by Meiran and colleagues (Meiran, Diamond, Todor, & Nemets, 2011) has reported a reversal of the conflict-adaptation effect in currently depressed patients, which suggests that conflict-driven control may actually break down when people become clinically depressed. In other words, there might be an inverted-U relationship between depressive symptoms and conflict adaptation (cf. Brehm & Self, 1989). It is an important aim for future studies to understand the generalizablilty of these findings and to disentangle the effects of increased negative affect and putative reduced availability of resources (e.g., due to rumination) in depression. MBM theory assumes that the interaction between both factors determines the actual appraisal of the demand, which in turn modulates effort mobilization. This hypothesis now ripe for further testing in other studies using sequential analyses of conflict-task performance.

At the neural level, the joint impact of depressed mood and demand evaluation on subsequent effort mobilization and cognitive control may be associated with (hyper)activation of the anterior cingulate cortex (ACC), a region important for signaling the need for more cognitive effort to the dorsolateral prefrontal cortex (DLPFC) (Botvinick et al., 2001; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Olvet & Hajcak, 2008; Pizzagalli et al., 2006). It has been suggested that dysfunction of this ACC-DLPFC circuit in unipolar depression also produces catastrophic reactions to errors (for a review, see Pizzagalli, 2011). Further study is needed to understand the exact neuromodulating role that 5-HT may play in this affective regulation (cf. Jocham & Ullsperger, 2009). Future studies that combine neuroimaging methods with effort-related physiological and behavioral measures will advance our understanding of the functional role of the ACC in the affective (dys)regulation of adaptive control to fluctuating task demands.

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