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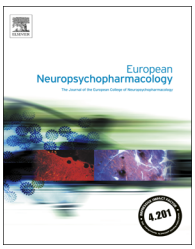

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# Effects of serotonin depletion on punishment processing in the orbitofrontal and anterior cingulate cortices of healthy women

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**Abstract**
Diminished synthesis of the neurotransmitter serotonin (5-HT) has been linked to disrupted impulse control in aversive contexts. However, the neural correlates underlying a serotonergic modulation of female impulsivity remain unclear. The present study investigated punishment-induced inhibition in healthy young women. Eighteen healthy female subjects (aged 20–31) participated in a double-blinded, counterbalanced, placebo-controlled, within subjects, repeated measures study. They were assessed on two randomly assigned occasions that were controlled for menstrual cycle phase. In a randomized order, one day, acute tryptophan depletion (ATD) was used to reduce 5-HT synthesis in the brain. On the other day, participants received a tryptophan-balanced amino acid load (BAL) as a control condition. Three hours after administration of ATD/BAL, neural activity was recorded during a modified Go/No-Go task implementing reward or punishment processes using functional magnetic

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resonance imaging (fMRI). Neural activation during No-Go trials in punishment conditions after BAL versus ATD administration correlated positively with the magnitude of central 5-HT depletion in the ventral and subgenual anterior cingulate cortices (ACC). Furthermore, neural activation in the medial orbitofrontal cortex (mOFC) and the dorsal ACC correlated positively with trait impulsivity. The results indicate reduced neural sensitivity to punishment after short-term depletion of 5-HT in brain areas related to emotion regulation (subgenual ACC) increasing with depletion magnitude and in brain areas related to appraisal and expression of emotions (mOFC and dorsal ACC), increasing with trait impulsivity. This suggests a serotonergic modulation of neural circuits related to emotion regulation, impulsive behavior, and punishment processing in females.


## 1. Introduction

Dysfunction of the neurotransmitter serotonin (5-HT) plays a decisive role in many neuropsychiatric disorders characterized by inappropriate impulse control, such as attention deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD) (Kötting et al., 2013; Lis et al., 2007). Previous research suggests an influence of altered serotonergic neurotransmission on inhibition processes, which are closely related to impulse control and inhibited or, with respect to the outlined psychopathologies, disinhibited behavior. With respect to gender, a PET study comparing serotonin synthesis rates, measured as pmol/g/min, within different brain regions of male and female subjects found that female subjects had a 52% lower rate of central 5-HT synthesis compared with male subjects (Nishizawa et al., 1997), suggesting a disproportionately higher vulnerability to central nervous system 5-HT dysfunction in females. There is considerable evidence that sex hormones interact with central 5-HT availability (Carretti et al., 2005; Rubinow, 1998). Likewise, activation of specific brain areas during response inhibition tasks is affected by menstrual cycle phase, e.g., in the dorsolateral prefrontal cortex (dlPFC), the inferior frontal gyrus, the anterior cingulate cortex (ACC) and the insular cortex (Amin et al., 2006; Bannbers et al., 2012; Protopopescu et al., 2005; Roberts et al., 2008). Activation during response inhibition in the ACC and dlPFC was increased during the luteal phase compared with the follicular phase (Amin et al., 2006); activation was also increased in the left insula of healthy controls during the follicular phase and during the luteal phase of patients with premenstrual dysphoric disorder (PMDD) (Bannbers et al., 2012). In an emotional linguistic Go/No-Go task, medial OFC activity was increased for negative words compared with neutral words during the premenstrual and postmenstrual phases; this increase was enhanced in an inhibitory task context (Protopopescu et al., 2005). Activation in the inferior frontal gyrus was significantly reduced during successful inhibitions only during the follicular phase of the menstrual cycle. Brain activation in the ACC was enhanced during inhibitory errors (Roberts et al., 2008).

So far, the available literature is scarce regarding aspects of underlying neural correlates of serotonergic modulation of impulsivity in female subjects. Impulsive behavior and central nervous serotonin function are known to be closely linked. A major dilemma in the field of research on impulsivity is its exact definition. According to the International Society for Research on Impulsivity (ISRI), impulsivity can be defined as a lack of inhibitory control when confronted by negative consequences. Furthermore, the link between the neurotransmitter 5-HT and inhibition appears to be particularly specific to aversive contexts. As shown by Crockett et al. (2009, 2012), acute tryptophan depletion (ATD – a physiological challenge procedure to reduce brain 5-HT synthesis) abolished punishment-induced inhibition, which is defined as "the general suppression of responding in aversive contexts" (Gray and McNaughton, 2000) in a reward- and punishment-implementing Go/No-Go task. After the administration of a control condition, participants' responses were slower under punishment conditions compared with reward conditions; this difference was extinguished after ATD (Crockett et al., 2009). In the present study, we utilized this particular paradigm in an fMRI environment to investigate changes in brain activation related to diminished 5-HT synthesis during response inhibition in aversive contexts. As the relevant behavioral results by Crockett et al. (2009) mainly rely on RTs solely detectable for Go-stimuli, using an fMRI-based set up allows expanding the investigation of punishment-induced inhibition to the neural correlates of the critical inhibition demanding No-Go-stimuli.

One previous study reported that individual differences in trait impulsivity correlated with activation in the dorsal ACC, amygdala and prefrontal cortex (PFC). In particular, trait impulsivity was positively correlated with activity in the bilateral ventral amygdala, parahippocampal gyrus, dorsal anterior cingulate gyrus (BA 32), and bilateral caudate. Conversely, trait impulsivity was negatively correlated with activity in the dorsal amygdala and ventral PFC (BA 47). In another study, ATD strongly impaired the ability to adequately adapt responses to incentive-motivational cues in individuals with high levels of impulsivity (Cools et al., 2005). Together with the aforementioned finding regarding the reduction of punishment-induced inhibition by ATD, we expected that neural activation during the Go/No-Go task would be modulated by trait impulsivity and that these subjects with higher trait impulsivity might be more vulnerable to the effects of ATD, thus showing more brain activity in corticolimbic behavioral arousal areas and less activity in control circuits after ATD utilizing an incentive inhibition paradigm.

A review by Evers et al. (2010), which examined studies that applied ATD to Go/No-Go tasks in fMRI analyses, concluded that ATD attenuates brain activation in the inferior/orbitofrontal cortex, ACC and dorsomedial PFC during response control and negative feedback tasks. This review states that, during emotional processing, ATD modulates blood-oxygen-level dependent