Serotonergic modulation of response inhibition: a fMRI study

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Abbreviations

5-HT	Serotonin
ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
ADHD	Attention-deficit / hyperactivity disorder
ATD	Acute tryptophan depletion
BA	Brodmann area
BOLD	Blood Oxygen Level Dependency
BPD	Borderline personality disorder
DLPFC	Dorsolateral prefrontal cortex
DMStr	Dorsomedial Striatum
C_{max}	Maximal plasma concentration
fMRI	Functional magnetic resonance imaging
fMRT	Funktionelle Magnetresonanztomographie
IFC	Inferior frontal cortex
mCPP	m- chlorophenylpiperazine
NA	Noradrenaline
OCD	Obsessive-compulsive disorder
OFC	Orbito frontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
RT	Reaction time
SD	Standard deviation
SMA	Supplementary motor cortex
SNRI	Selective noradrenalin reuptake inhibitor
SOA	Stimulus onset asynchrony
SPM 5	Statistical Parametric Mapping Software
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
SSRT	Stop signal reaction time
STN	Subthalamic nucleus

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Abstract

In animal and human studies, the neurotransmitter serotonin (5-HT) has been implicated in inhibitory control. Using functional magnetic response imaging (fMRI), the present study investigated the acute effects of pharmacological modulation in the serotonergic system on brain activations during response inhibition in healthy human volunteers. In all, 14 male participants received either a single oral dose of selective serotonin reuptake inhibitor (SSRI) escitalopram (10 mg) or placebo in a randomized double-blind placebo-controlled cross-over design. At the time of the expected plasma peak participants performed a stop change task during fMRI. Functional images were analyzed using Statistical Parametric Mapping software (SPM5). Escitalopram did not affect behavioral inhibitory performance as the main effect did not reveal significant differences of stop signal reaction time (SSRT). Likewise no differences were found for reaction time on go-trials (goRT) as well as for reaction time on trials of unsuccessful response inhibition (StopRespondRT). However, escitalopram was associated with alterations in brain activation patterns compared to placebo. Escitalopram enhanced brain activations in right prefrontal cortex, including right OFC, in right supplementary/pre motor and bilateral cingulate cortex as well as in subcortical regions during successful response inhibition. Also, escitalopram modulated a widespread network of brain regions, including anterior cingulate, right parietal cortex, right OFC, areas in right temporal cortex and subcortical regions during failed inhibition. During the go-process escitalopram increased brain activations in numerous regions like right anterior and posterior cingulate and in right prefrontal, parietal and temporal cortex as well as in subcortical areas. Our findings implicate an involvement of 5-HT in neural regulation of response inhibition. Moreover, this study provides evidence that 5-HT influences not only action restraint but also action cancellation through modulation of activations of brain areas. In addition, we found modulating effects of serotonin also on activations during failed inhibition. Especially, the anterior cingulate seems to play a critical role here. Results of this study support the assumption of an involvement of the anterior cingulate in error-detection. The results also implicate a fronto-striatal-circuitry for response inhibition in conjunction with serotonin.

Zusammenfassung

Sowohl Tierstudien als auch Studien mit menschlichen Probanden belegen, dass der Neurotransmitter Serotonin (5-HT) eine entscheidende Rolle in der Handlungskontrolle spielt. Diese plazebokontrollierte, randomisierte Doppelblindstudie im cross-over Design beschäftigt sich mit den akuten Effekten einer pharmakologischen Modulation im serotonergen System in Bezug auf Handlungskontrolle. Dabei wurden Verhaltens- und Aktivierungsunterschiede im Gehirn während der Bearbeitung einer Stop-Change-Aufgabe mit Hilfe von funktioneller Magnetresonaztomografie (fMRT) erfasst. 14 männliche, gesunde Probanden erhielten eine orale Dosis von 10 mg Escitalopram oder Plazebo und absolvierten zum Zeitpunkt des erwarteten Plasmapeaks die Stop-Change-Aufgabe während der fMRT-Messungen. Die funktionellen MRT-Bilder wurden mit der Software Statistical Parametric Mapping (SPM5) analysiert. Escitalopram beeinflusste weder die Reaktionszeit (GoRT) noch die Stopsignalreaktionszeit (SSRT), was sich darin zeigte, dass es keinen signifikanten Haupteffekt des Faktors Substanz gab. Auch die Reaktionszeit während des erfolglosen Stoppens wurde nicht beeinflusst. Im Vergleich zu Plazebo bewirkte Escitalopram jedoch Veränderungen von Gehirnaktivierungen. Während des Stoppens verstärkte Escitalopram Aktivierungen im rechten präfrontalen Cortex, einschließlich des rechten Orbitofrontalcortex, im rechten supplementären/prämotorischem Cortex, beidseitig im Cingulum sowie in subkortikalen Regionen. Auch während erfolglosen Stoppens modulierte Escitalopram ein weitreichendes Netzwerk von Gehirnregionen, einschließlich des vorderen Cingulums, des rechten parietalen und temporalen Cortex und subkortikaler Bereiche. Während des Go-Prozesses verstärkte Escitalopram Gehirnaktivierungen in vielen Regionen, unter anderem im rechten vorderen und hinteren Cingulum sowie im rechten präfrontalen, parietalen und temporalen Cortex und auch hier in subkortikalen Regionen. Diese Ergebnisse implizieren, dass Serotonin Einfluss auf die menschliche Handlungskontrolle nimmt. Außerdem liefert diese Studie Hinweise darauf, dass 5-HT nicht nur „ action restraint“, sondern auch „action cancellation“ durch Modulation von Gehirnaktivierungen beeinflusst. Weiterhin zeigte sich in dieser Studie, dass Serotonin die Gehirnaktivierungen auch während des erfolglosen Stoppens veränderte. Vor allem das anteriore Cingulum scheint hier eine entscheidende Rolle zu spielen. So bestärken unsere Ergebnisse die bestehende Annahme, dass diese Region an der Erkennung von Fehlern beteiligt ist. Außerdem implizieren die Ergebnisse dieser Studie die Existenz

eines fronto-striatales Netzwerkes für die Vermittlung von Handlungskontrolle in Verbindung mit Serotonin.

Introduction

Response inhibition is an important executive function providing control over responses in changing situations. It is required in many common everyday life situations, e.g. braking abruptly while driving a car. Whenever the environment alters unexpectedly people need to adapt and sudden change of behavior might be necessary if it turns out that the current process is inappropriate and a new and different goal of action is needed immediately. Stopping is the first step to undertake. Moreover, stopping is an extreme form of action-control resulting in the decision not to do something (Logan, 1994).

Response inhibition, i.e. the ability to stop a motor response after initiation, can be measured by using the stop signal task, a well-established paradigm to investigate inhibitory function in laboratory settings (Logan, 1994). The stop signal task consists of a computerized choice reaction time task in which subjects execute a simple motor response. Two kinds of trials are required in the procedure: to respond to two different go-signals, i.e. either circle or triangle (go-task) and on the other hand to withhold the execution of the motor response when the go-signal is followed by a stop-signal (stop-task). The success to inhibit the response to the original go-signal depends upon the delay between go-signal and stop-signal (stop-signal delay) as the probability for successful stopping increases the sooner the stop-signal follows the go-signal. Key measure to characterize response inhibition is the stop signal reaction time (SSRT), the time it takes to stop the motor response. Stop signal reaction time achieves times between 200 – 400 ms, especially young adults are able to stop in about 200 ms (Logan, 1994). The underlying theory for estimation of SSRT is described by the so-called horse race model (Logan, 1994; see Figure 1). According to this model there are two critical processes (go-process and stop-process) operating independent of one another. Performance of inhibition is considered as a race between these two processes and whichever finishes first wins the race producing either motor response execution or response inhibition, respectively. Another widely used method to investigate response inhibition is a similar paradigm known as the go/no-go task (e.g. Rubia et al. 2005; Liddle et al. 2001).

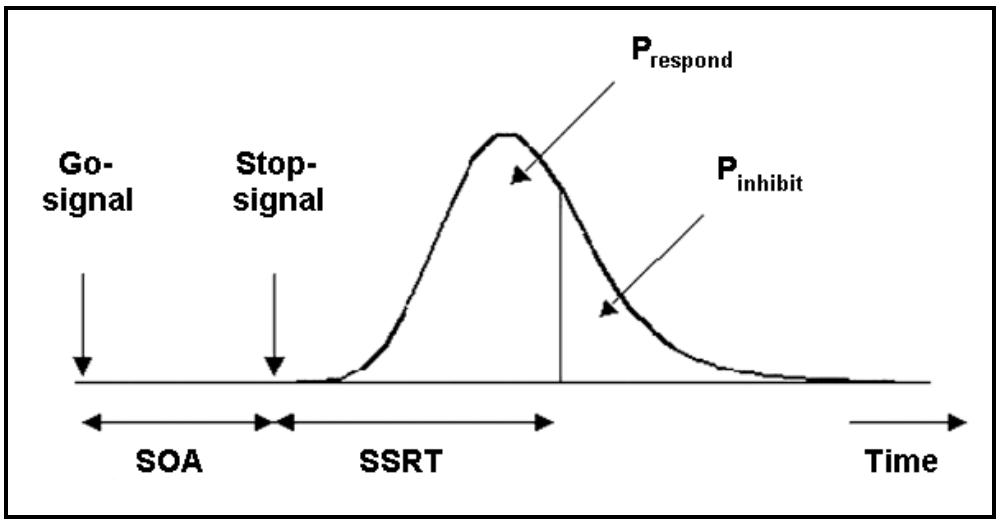

Figure 1. The horse race model

This task likewise requires a response following the presentation of a go-signal though, unlike the stop signal task, this paradigm does not consist of a stop-signal delay. The crucial difference between both tasks is therefore the temporal location of the stop signal within the motor response task. Thus, the go/no-go task measures prepotent responses, i.e. the ability to withhold from responding as the stop-signal is presented before or concurrently with the go-signal. By contrast the stop signal task measures inhibition of already initiated responses ensuring a higher sensitivity for inhibition of ongoing responses. Recently, Schacher et al. (2007) defined two kinds of response inhibition, namely action restraint (describing motor response inhibition before the response has been started) and action cancellation (describing inhibition of an ongoing response). Whereas action restraint is investigated via go/no-go task, action cancellation is measured by the stop signal task.

Patients with several brain disorders show impairment of inhibitory control. For example, neurological disorders have been implicated in deficient inhibitory control: Gauggel et al. (2004) demonstrated deficits in response inhibition in patients suffering from Parkinson´s disease. Furthermore, deficits in response inhibition have been shown in mental disorders like attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) etc. Results of a novel meta-analysis of ADHD-studies suggested a generalized deficit in attention more than in behavioral inhibition as core feature of ADHD, at least in children (Lijffijt et al. 2005; Alderson et al. 2007), but a recent study showed that ADHD was characterized with deficient response inhibition in both action restraint and action cancellation (Schacher et al. 2007). Studies with

patients suffering from other mental disorders like OCD, trichotillomania and borderline personality disorder (BPD) also indicate that impairment of response inhibition obviously plays an important role in the psychopathology of these disorders (Chamberlain et al. 2006; Nigg et al. 2005).

The cognitive deficits may be related to deficits in neurotransmitter functioning in these disorders. The fact that mental disorders being associated with deficient cognitive flexibility show abnormal serotonin (5-HT) functioning for example, leads to the assumption that 5-HT is also involved in response inhibition (Del-Ben et al. 2005; Rubia et al. 2005; Cools et al. 2008). Serotonin is one of the central monoamine neurotransmitters and has been implicated in the etiology and psychopathology of several mental disorders which are associated with cognitive deficits such as major depression, anxiety and impulse-control-disorders (Meltzer 1989; Chamberlain et al. 2005; Schmitt et al. 2006; Dolan et al. 2002). Furthermore, in the treatment of right these disorders selective serotonin reuptake inhibitors (SSRIs), 5-HT neurotransmission enhancing drugs, have proven efficacy. SSRIs are considered to increase central 5-HT concentrations as they result in elongated serotonin availability in the synaptic cleft (Burke 2002; Aronson & Delgado 2004; Wade et al. 2002). Yet, it remains unclear how cognitive processes like response inhibition are affected by 5-HT. Further evidence for an involvement of 5-HT in inhibition processes comes from an animal study by Clarke (2007) who found a deficit in a serial discrimination reversal (SDR) task after prefrontal serotonin depletion. This deficit was not due to a failure to approach a previously unrewarded stimulus, instead it was due specifically to a failure to inhibit responding to the previously rewarded stimulus. Eagle et al. (2008) also found a selective impairment in inhibition performance in rats after serotonin depletion, but only in ‘waiting’ and not in SSRT. She suggests ‘waiting’ and SSRT to be different measures of behavioral inhibition.

In contrast to the suggested involvement of 5-HT in response inhibition previous work rather showed that 5-HT had no effect on task performance in studies with healthy volunteers using the stop signal task (for a review Eagle et al. 2008; Robbins 2007; Chamberlain and Sahakian 2007). In a study of Chamberlain et al. (2006) response inhibition performance was compared in two groups, one treated with SSRI citalopram, another treated with SNRI atomoxetine. While inhibition of central NA reuptake enhanced response inhibition, SSRT remained unaffected by inhibition of central serotonin reuptake. Another well-established method in serotonin research is a dietary challenge which decreases central 5-HT, the so-called acute tryptophan depletion

(ATD) procedure. ATD likewise had no effect on performance in the stop signal task (Clark et al. 2005; Eagle et al. 2008) related this matter of fact to the different forms of action inhibition mentioned-above. Whereas 5-HT did not influence action cancellation, results of studies using the go/no-go task thus measuring action restraint clearly indicated influence of serotonin (see Eagle et al. 2008).

With progress in neuroimaging techniques research also focussed on specified localization of brain areas linked to response inhibition. In lesion and neuroimaging literature several brain regions like the dorsolateral, inferior, superior, orbital and mesial frontal cortex, the supplementary and pre-supplementary motor area, the anterior cingulate gyrus, the temporal and parietal lobes as well as the basal ganglia have been associated with motor response inhibition (Aron et al. 2003; Aron et al. 2004; Aron and Poldrack 2006; Rubia et al. 2003; Eagle et al. 2008). The concrete localization of response inhibition still appears to be difficult. However, evidence that the right inferior frontal cortex (IFC) is critical for inhibiting an already initiated motor response accumulated in neuroimaging studies with the stop signal task since response inhibition consistently activated this particular region (Aron et al. 2004; Rubia et al. 2003). In a functional magnetic resonance imaging (fMRI) study of patients with lesions of the right frontal cortex the authors succeeded to show that damage to the right inferior frontal gyrus is crucial for response inhibition, specifically BA 45 (Aron et al. 2003). Results of a near-infrared spectroscopy study as well pointed to association of stopping and activation of right-lateralized prefrontal cortex (Böcker et al. 2006). Recent research has also implicated the subthalamic nucleus (STN) in response inhibition which is an inhibitory output structure of the basal ganglia (Aron and Poldrack 2006; Li et al. 2008). Aron and Poldrack (2006) suggested that response execution is inhibited by a hyperdirect pathway via STN, which again suppresses the basal-ganglia thalamocortical output. Evidence for an involvement of the basal ganglia also comes from a study with patients suffering from Parkinson´s disease (Gauggel et al. 2004).

In addition, different activation patterns for successful versus failed response inhibition have been described. Failure to inhibit has been related to the prefrontal cortex including anterior cingulate and inferior parietal lobes bilateral (Rubia et al. 2003). This is consistent with findings of go/no-go studies implicating an involvement of the rostral anterior cingulate in error processing (Kiehl et al. 2000; Menon et al. 2001). However, this aspect was not completely confirmed by Aron and Poldrack (2006) who, as well, focussed additionally on processes underlying failed inhibition in their study. They found

an activation pattern similar to successful inhibition in right IFC and STN and putamen though the latter region was even more activated during successful inhibition.

Though rarely published the go-process has been associated with activations in bilateral putamen and left-lateralized thalamus, STN and globus pallidus as well as left motor cortex and left SMA during a stop signal task (Aron and Poldrack 2006). Activations were observed mainly left-hemispherical consistent with right-handed response. Aron and Poldrack (2006) related this activation pattern to a fronto-striato-pallidal pathway. Using a go/no-go task Liddle et al. (2001) found activations of anterior cingulate, SMA, contralateral motor cortex, bilateral parietal lobe, superior temporal gyrus and cerebellum during go trials.

Cognitive functions such as response inhibition are related to the prefrontal cortex (PFC). As reviewed above the PFC has been implicated clearly in response inhibition via neuroimaging techniques. This region is reached by ascending serotonergic projections from dorsal and median raphe nuclei localized in the brain stem (see Cools et al. 2008; Hornung 2003). Mental disorders such as depression, ADHD and OCD which have been implicated in serotonergic dysfunction have also been associated with abnormalities in the prefrontal cortex (for a review Drevets et al. 2008; Rubia et al. 1999; Chamberlain et al. 2005; Clark et al. 2007). The combination of cognitive task performance, neuroimaging techniques and neuromodulation via drug administration offers a suitable possibility for further investigation of 5-HT involvement in cognitive processes. A well-established method to challenge the serotonergic system is the administration of antidepressants, especially SSRIs which increase 5-HT neurotransmission by blocking the reuptake of 5-HT into the presynaptic neuron (Burke 2002; Aronson & Delgado 2004; Cools et al. 2008). So far, analysis of modulating effects of serotonin on brain activation during response inhibition produced inconsistent results. Yet, only few previous fMRI studies investigated the effects of serotonergic modulation on cortical activation while healthy volunteers performed an inhibition performance task. The above-mentioned ATD procedure has been used likewise for fMRI studies. Rubia et al. (2005) found that ATD did not affect inhibition performance in a go/no-go task, but reduced right orbitoinferior prefrontal activation (BA 47, BA 45, BA 6) during the no-go condition by contrast with go trials and increased activations in right and left temporal cortices (BA 21, BA 37, BA 22). The authors conclude that these findings provide evidence for serotonergic modulation of right inferior prefrontal cortex during response inhibition. In another study also using a go/no-go task no effect of ATD was found on task performance as well as on cortical activations (Evers et al. 2006). In

a review Evers et al. (2007) analyzed the two ATD studies named above coming to the conclusion that ATD unlikely impairs response inhibition taking into account that the majority of behavioral studies did not show any effects of ATD on response inhibition. In a fMRI study using the go/no-go task and intravenous administration of SSRI citalopram researchers succeded to demonstrate modulatory effects of citalopram on inhibition. Citalopram enhanced activations in right lateral OFC (BA 47), DLPFC and middle temporal gyrus, whereas attenuations were seen in the medial orbitofrontal cortex (BA11) more left-hemispheric, bilateral supramarginal gyri and right superior temporal gyrus. By reason of these results the authors supported the involvement of 5-HT in response inhibition (Del-Ben et al. 2005).

The aim of the present study was to investigate the acute effects of pharmacological manipulation of 5-HT on brain activation patterns during response inhibition in healthy volunteers. As results of previous work were inconsistent we wanted to investigate the effects of manipulation in the serotonergic system using the most selective SSRI escitalopram. Moreover, to verify response inhibition as precise as possible we chose a stop signal paradigm more specific than the go/no-go tasks which were used in previous research as mentioned above. To our knowledge, no prior study investigated serotonergic modulation by using a combination of performance on a stop signal task and pharmaco-fMRI in healthy volunteers. On the basis of the above-reviewed literature, showing that modulation of 5-HT did not affect SSRT in healthy volunteers, we hypothesized that performance of response inhibition would not be affected. However, we hypothesized in line with previous research with SSRIs (Del-Ben et al. 2005) that escitalopram would modulate brain activations, especially in right PFC associated with response inhibition. In addition, we expected that escitalopram would likewise alter brain activations especially in anterior cingulate during failed inhibition.

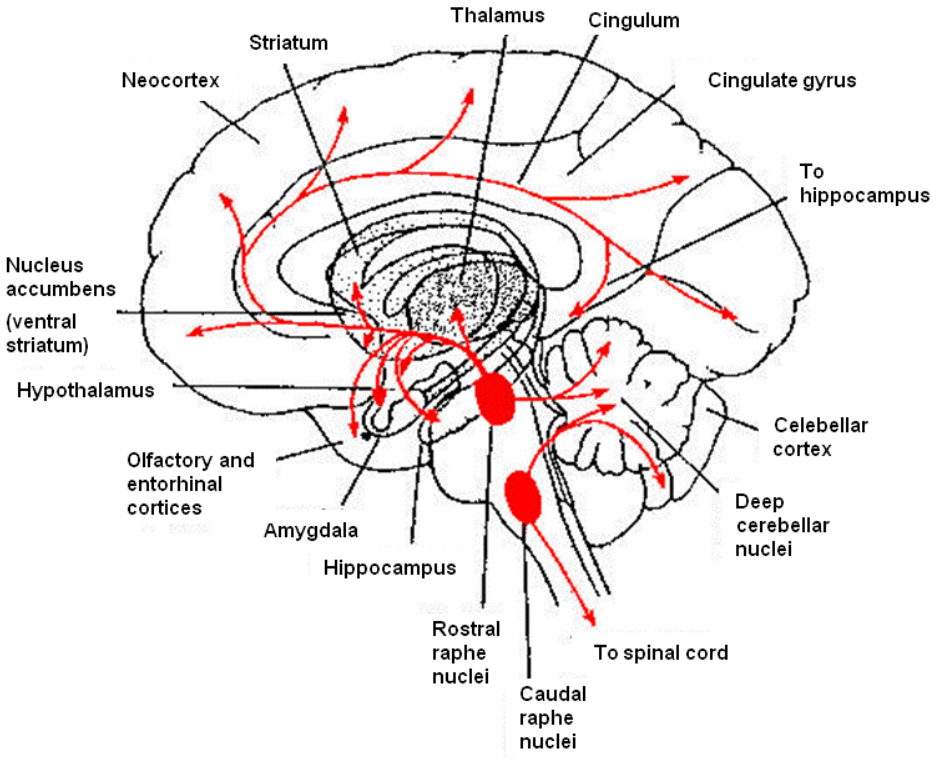

Figure 2. Schematical illustration of serotonergic projections (according to Törk, 1990)

Methods

Participants

A total of 14 male subjects participated in the study. All of them were healthy volunteers at the age of 18 to 39 (mean age 23.9 years, SD 2.3) who declared to be non-smokers and drug-free. All participants were right-handed and had normal or corrected-to-normal vision and hearing. They were recruited via poster advertisement and e-mail. Their means and standard deviation for body weight (kg) and height (cm) are 77.5 ± 8.7 kg and 182 ± 8.3 cm. Nearly all of them were students though varying in the specialization. Participants were questioned concerning their medical and psychiatric history based on a health questionnaire and an interview worked out by medical staff. Also, each participant agreed to take blood samples for blood analysis before attendance in order to verify physical health. Any evidence for medical or mental disorders either acute or chronic led to exclusion from the study. For safety during MRI scanning all participants affirmed to be free of any kind of metal, pacemaker and tattoos. On the date of the tests participants were not allowed to smoke, to drink alcohol, to eat chocolate, nuts or bananas.

All subjects gave written informed consent after detailed information of the study, the procedure, the substance and possible adverse events of the drug and MRI scanning. They were paid for study participation approximately 20 Euros per hour. The participants were allowed to quit the experiment at any time. All participants finished the trial though. The study was approved by the Ethics Committee of RWTH Aachen University and the National Institute for pharmaceutical and medical products (BfArM).

Design and procedure

The study was performed as a randomized double-blind cross-over design with two treatment levels (placebo, 10 mg escitalopram [Cipralex®]) as a single oral dose. 14 participants received on the date of the trial a single oral dose of either 10 mg escitalopram or placebo, half of them receiving the drug in the first session and placebo in the second one, the other half vice versa. Each administration was separated by a washout period of seven days. The blinding was kept until both testing sessions were finalized.

The present study was part of a larger research project. So due to completeness the entire procedure of one session will be described.

In the following one testing day will be described as shown in Figure 3: Starting time varied since the beginning of MRI scanning delayed occasionally at a time period of half an hour. Participants arrived at our institute at 1:45 p.m. or latest at 2:15 p.m. They were weighed and measured as well as blood pressure and heart rate were taken. They got a permanent intravenous cannula and a first baseline blood sample was taken directly. According to starting time administration of the drug (either escitalopram or placebo) was performed at 2:00 p.m. or 2:30 p.m. Afterwards participants started to complete several personality questionnaires which will not be described in detail as they are not objective of this study. One hour after drug-intake another blood sample was taken likewise two hours and twenty minutes after administration. Data of blood parameters will be analyzed separately, too. Then participants practised the stop change task as a start outside the MRI scanner. Three hours after drug-intake subjects started to accomplish the stop change task as this is, respectively, the point in time of mean maximal plasma concentration of escitalopram (Sogaard et al. 2005). At the same time functional neuroimaging via MRI scanning of the brain was performed. The participants took two sessions of the stop change task. Each session lasted 18 minutes in between a short break was offered. In a final step an anatomic scan for 9 minutes was made. At the end of a testing day the last blood sample as well as blood pressure and heart rate were taken. Also participants were asked to evaluate if they got either verum or placebo at their own opinion. One testing day lasted a total of 4.5 hours. Throughout the trial participants stayed at our institute and the Department of Radiology for MRI scanning. They were monitored continuously with regards to any adverse events. All participants completed the study.

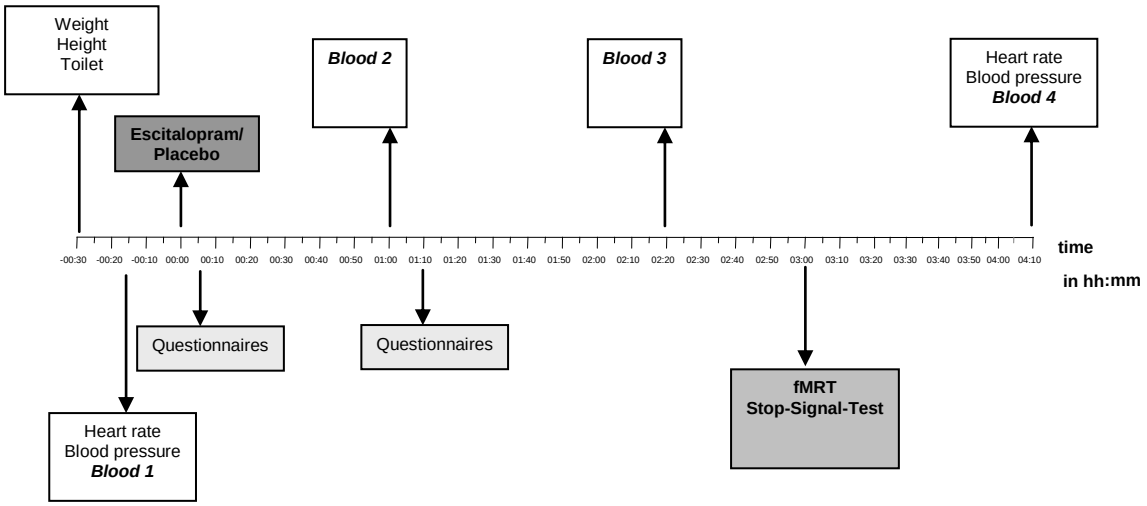

Figure 3. The test procedure

Escitalopram

Escitalopram (Figure 4) is a selective serotonin reuptake inhibitor (SSRI) with high affinity and the greatest selectivity tested so far for the human 5-HT transporter. Escitalopram is the S-enantiomer of SSRI citalopram since pharmacological studies showed that the therapeutic activity of citalopram resides in the S-enantiomer (Burke 2002). It is indicated for the treatment of major depression and anxiety disorders (Burke 2002). Following oral administration escitalopram is rapidly absorbed, maximal plasma concentrations are achieved approximately 3 - 4 h after drug-intake (Sogaard et al. 2005). It exhibits linear and dose-proportional pharmacokinetics with mainly hepatic biotransformation and shows a plasma elimination half-life ($t_{½}$) of 27 - 33 h consistent with once-daily dosing (Rao 2007). Steady state plasma concentrations are reached within approximately one week with once-daily administration of 10 -20 mg, the commonly used dose (Aronson and Delgado 2004). Compared to placebo, first improvements of symptoms are seen within 1−2 weeks after commencing treatment verified on depression rating scales (Burke 2002). Escitalopram is generally well tolerated in clinical trials due to the fact that its high affinity and selectivity for the 5-HT transporter results in no or little affinity to other receptors and therefore less adverse events. However, most commonly observed side-effects associated with the substance (incidence of approximately 5% or greater or at a greater rate than placebo) are nausea, insomnia, ejaculation disorder, diarrhoea, dry mouth and somnolence whereas only nausea occurred in over 10% of escitalopram-treated patients (Burke 2002).

For our study we used the drug Cipralex® and placebo manufactured by Lundbeck.

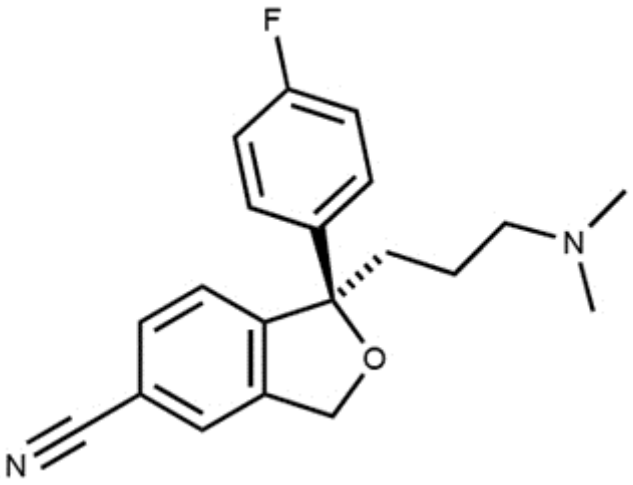

Figure 4. Chemical structure of escitalopram

Stop change paradigm

The stop change task is a computer based test developed to evaluate response inhibition and response re-engagement. As the present study just focuses on inhibition the change task will be described for reasons of completeness though analyzed separately.

The stop change paradigm (see Figure 5) was composed of four different trial types: the go-trials, stop-trials, change-trials and null events. The first three trial types will be referred to as stimulus trials. The duration of the stimulus trials was 3350 ms whereas the null events either lasted 2800 or 3350 ms.

The go-trials required to execute a simple motor response following the presentation of two stimuli. They made up 70% of the stimulus trials and were part of a simple choice reaction time task in which participants had to discriminate a black circle and a black triangle on a computer monitor. Depending on which of the two go-stimuli was presented, participants had to respond either with a left or right key press using index and ring fingers of their right hand. On stop-trials (15% of stimulus trials) the choice reaction time task was followed by an occasionally and unpredictable auditory stop signal (a 1000 Hz tone of 500 ms duration) after a variable delay (stimulus onset asynchrony, SOA). It signalled the participants to inhibit the execution of their response to the choice reaction time task. In another 15% of the stimulus trials a change signal (a 400 Hz tone of 500 ms duration) likewise was presented after a variable delay. This signal indicated that participants should now inhibit their response to the choice reaction

time task and press instead the middle of the three response buttons with their right middle finger.

The stop signal delay (stop-SOA) and the change signal delay (change-SOA) were fixed by a staircase-tracking algorithm (Kaernbach, 1991) that adapted to the response rate. The stop-SOA and the change-SOA were adjusted independently that way participants reached an inhibition rate of approximately 50% (stop condition) or a change rate of likewise approximately 50% (change condition). Setting an accuracy of 50% ensures equal probability for stopping as well as for not stopping, i.e. the probability of stopping is neither overestimated nor underestimated. The staircase-tracking algorithm worked as follows: Initially the stop-SOA and the change-SOA were set at 250 ms. Depending on the success in response inhibition on stop-trials or success in changing on change-trials the SOA was increased by 50 ms in the following stop-trial or change-trial. Thus, a greater difficulty for participants to inhibit or change their responses was produced. If, however, participants failed to inhibit or change their response, the SOA was decreased by 50 ms in the next stop- or change-trial, enhancing the chance of successful inhibition or changing. This tracking procedure provides a possibility to estimate inhibition performance, the stop signal reaction time (SSRT), which is relatively stable against any violations of independence between go- and stop-processes. Moreover, the individual adjustment of stop signal delay and change signal delay allows maintaining a high level of difficulty in inhibition and at the same time homogeneity across subjects by making the participants work in the edge of their inhibitory capacity.

Participants trained the paradigm as follows: Four blocks, containing 44 trials each, were performed to introduce the different types of trials. Participants were instructed to respond as fast as possible while keeping a high level of correctness. They were briefed not to slow down and wait for a possible stop or change signal thus delaying their response, but then to try hard to withhold the response after hearing a stop signal or change the response after the corresponding change signal. To prevent them from developing a strategy participants were told that they would not be able to withhold the response at all times since the computer would adapt to their results aiming for a success rate of 50%.

The participants took two sessions of the stop change task with 308 trials each (196 go-trials, 42 stop-trials, 42 change-trials and 28 null events) while fMRI scanning. The visual stimuli were presented via a head-mounted video display designed to meet MR requirements. If necessary vision was adjusted to normal by placing correcting lenses in

the goggles. The auditory stimuli were presented via headphones at an individually adapted volume-level which was able to penetrate MRI scanner noise.

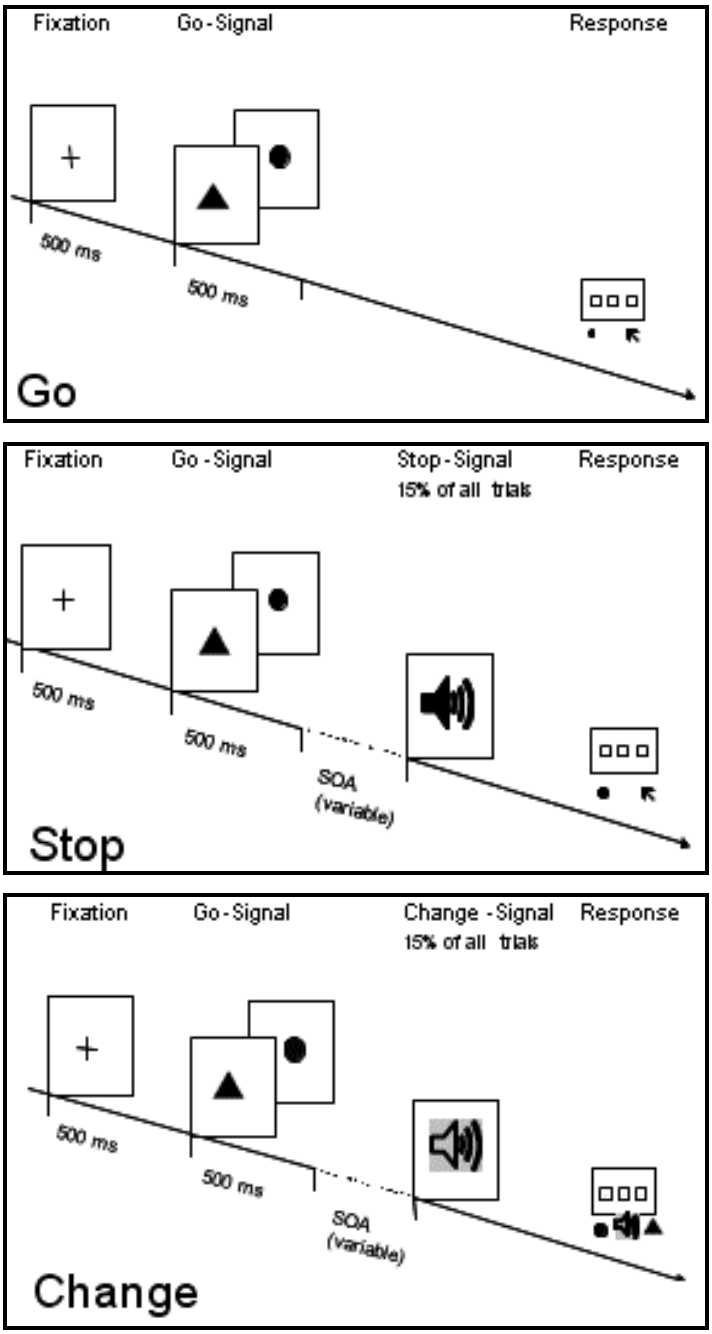

Figure 5. The stop change paradigm

fMRI acquisitation

MR images of the subjects´ brains were acquired at the Department of Radiology of the University Hospital of RWTH Aachen University using a 1.5 Tesla Philips Gyroscan NT with standard head coil and foam padding to restrict movements. Axial multislice T2-weighted images were obtained with a gradient-echo planar imaging sequence (TE = 50

ms; TR = 2800 ms; 64 x 64 matrix; flip angle = 90°; 30 slices, 3.4375 x 3.4375 mm in-plane resolution; slice thickness 3.75 mm; no gap; voxelsize 3.75 x 3.75 x 3.75) covering the entire brain. The scanning session consisted of two subsessions, each starting with 10 dummy scans that were not recorded for data analysis allowing tissue to reach steady state magnetization. During each subsession 380 volumes were acquired.

Inherent to the stop change paradigm is the fact that the experimenter does not know in advance on which of the stop- and change-trials the participant will successfully inhibit or change the initiated response and on which he will fail. However, to ensure an optimized scanning of the hemodynamic response in all brain slices for all four critical stop- and change-conditions, namely StopInhibit, StopRespond, StopChange and ChangeRespond, the experiment was programmed the following way: The TR-time was subdivided into four equally sized so called TR-classes (TR1: 0-700, TR2: 700-1400, TR3: 1400-2100, TR4: 2100-2800). An adaptive TR-class tracking algorithm used from the beginning of the second subsession guaranteed that approximately the same proportion of StopInhibits, StopResponds, StopChanges and ChangeResponds fell into each TR-class. This was achieved by taking the probable answer of participants into account (on the basis of whether the stop-or change-SOA was increased or decreased in the next stop- or change-trial) and so by altering the original onset of the respective trial.

Statistics

Behavioral data

Behavioral data were analyzed using Statistical Package for the Social Sciences (SPSS) Version 16.

Following parameters of the stop change paradigm were determined for this part of the study: goRT for correctly answered go-trials and stop-SOA for stop signal delay. On the basis of these parameters SSRT for successful inhibited responses was estimated via subtracting the delay of the mean reaction time of go-trials (SSRT = mean goRT minus stop-SOA). Also, we determined StopRespondRT for trials of unsuccessful inhibition but correctly answered to the original choice reaction time task.

To verify the working of the tracking algorithm the rate of successful stopping was determined which had to range between 40% and 60%.

A one factorial analysis of variance (ANOVA) for repeated measures with a repeated measurement factor “substance” (10 mg escitalopram versus placebo) was performed to analyze the dependent variables SSRT, RT on go-trials and RT on StopRespond. All

data were screened for outliners. Since few, though slight, outliners were detected, results were compared once outliners excluded, once included. Due to the fact that no change of significance was seen on statistical level and no changes of activations were found in fMRI data, we decided to keep all 14 participants in our analysis supporting the maximal number of participants for further analysis of fMRI data.

fMRI data

Functional images were analyzed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/).

Preprocessing procedures included realignment to correct for motion artefacts using the very first scan as a reference. Images were normalized into standard stereotactic space using Montreal Neurological Institute (MNI) templates. Finally images were spatially smoothed using a Gaussian kernel of 8 mm full-width at half maximum (FWHM) to facilitate intersubject averaging. No participant had to be excluded from further analysis due to movement artefacts.

First-level analysis was performed on each subject to generate a design matrix using a random effect model with following events: StopInhibit, StopRespond, Go and null-event. The hemodynamic response function was modelled to the onset of the responses. On second-level analysis a full factorial ANOVA with factors “substance” and “condition” was performed. Six contrasts were calculated using whole brain analysis to asses the effect of escitalopram: $StopInhibit_{escitalopram} > Stopinhibit_{placebo}$, $StopInhibit_{placebo} > Stopinhibit_{escitalopram}$ and $StopRespond_{escitalopram} > StopRespond_{placebo}$, $StopRespond_{placebo} > StopRespond_{escitalopram}$ and $Go_{escitalopram} > Go_{pacebo}$, $Go_{placebo} > Go_{escitalopram}$. Statistical maps were thresholded at $p < 0.005$ uncorrected with cluster sizes of 5 or more voxels. In addition, another complex contrast which is of interest on account of its repeated presence in the literature was calcultated: *StopInhibit minus* $Go_{escitalopram} >$ *StopInhibit minus* $Go_{placebo}$ and, vice versa, *StopInhibit minus* $Go_{placebo} >$ *StopInhibit minus* $Go_{escitalopram}$. Statistical maps were thresholded at $p < 0.01$ uncorrected with cluster sizes of 5 or more voxels for this contrast.

Results

Behavioral data

Means ± SD for goRT are 465.06 ± 168.09 ms for placebo and 399.96 ± 63.81 ms for escitalopram (Figure 6). Means ± SD for SSRT are 229.81 ± 54.21 ms for placebo and 246.52 ± 45.34 ms for escitalopram (Figure 6). Means ± SD for StopRespondRT are 431.59 ± 148.82 ms for placebo and 380.50 ± 35.16 ms for escitalopram (Figure 6). Analysis of variance revealed for the main effect of factor "substance" no significant differences for goRT ($F = 2.2$, $df = 1$, $p = .162$) and SSRT ($F = 1.052$, $df = 1$, $p = .324$) and StopRespond RT ($F = 1.828$, $df = 1$, $p = .199$) which means that results with escitalopram did not differ from placebo results.

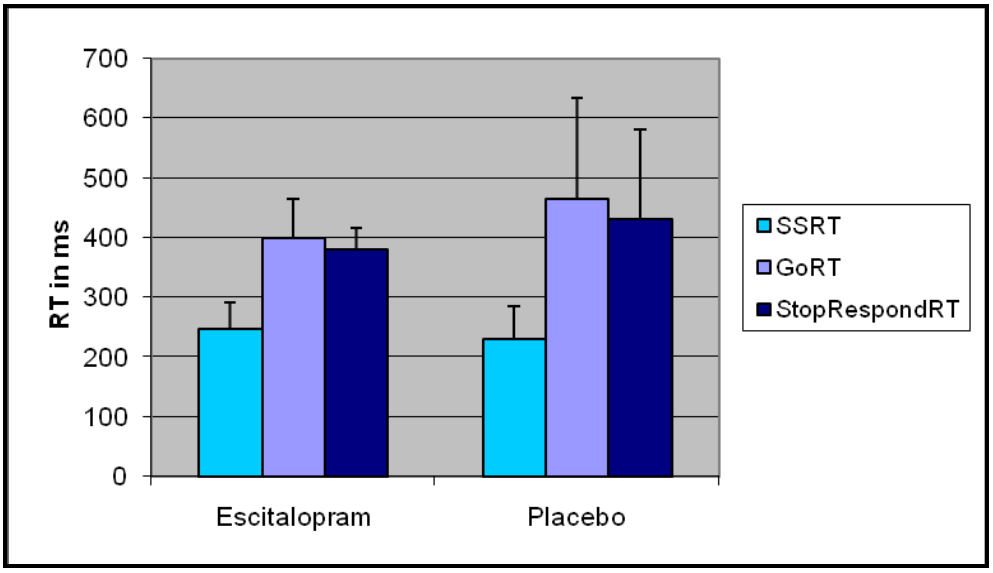

Figure 6. Performance on the stop signal task following escitalopram and placebo

fMRI data

Response Inhibition

Results of brain activations during response inhibition are represented in Table 1. Successful response inhibition for $StopInhibit_{escitalopram}$ > $StopInhibit_{placebo}$ was associated with increased activations at $p < 0.005$ uncorrected in right orbito frontal cortex (OFC) (BA 10/11, see figure 8) as well as right middle frontal gyrus (BA 8) and right cingulate (BA 24). Left lateralized activations were seen in cingulate (BA 31), also anterior cingulate (BA 25), precuneus (BA 7) and middle temporal cortex (BA 21).

Although activations were bilaterally located the focus was right-lateralized. Brain activations for $StopInhibit_{escitalopram}$ > $StopInhibit_{placebo}$ are shown in Figure 7. In the contrary condition, response inhibition for $StopInhibit_{placebo}$ > $StopInhibit_{escitalopram}$ brain activations were found bilaterally in the superior frontal gyrus (BA 8).

Table 1. Brain activations during successful response inhibition

Region	**BA**	**Hemisphere**	**x**	**y**	**z**	**Z-Score**
a) Escitalopram > Placebo						
Cingulate gyrus	31	left	-20	-57	25	3.48
Parietal lobe precuneus	7	left	-16	-68	29	3.08
Medial frontal gyrus	10/11	right	8	42	-12	3.43
Middle temporal gyrus	21	left	-48	-8	-13	3.32
Anterior cingulate	25	left	-4	7	-10	3.24
Superior/middle frontal gyrus	8	right	24	14	40	3.15
Cingulate gyrus	24	right	16	-1	48	3.14
b) Placebo > Escitalopram						
Superior frontal gyrus	8	right	8	38	53	3.02
Superior frontal gyrus	8	left	-4	42	53	2.95

Statistical maps were thresholded at $p < 0.005$ uncorrected.

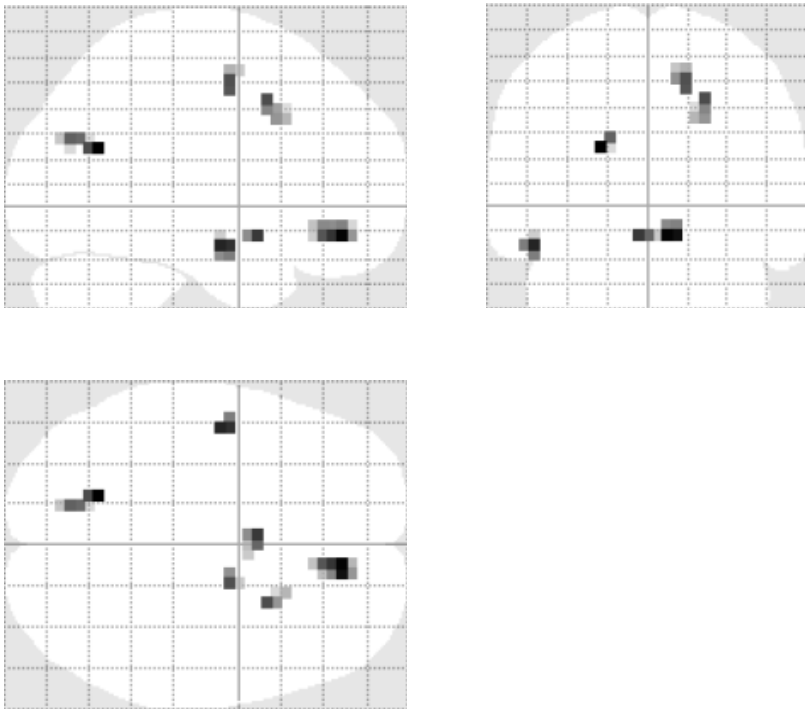

Figure 7. Brain activations during successful response inhibition for escitalopram > placebo

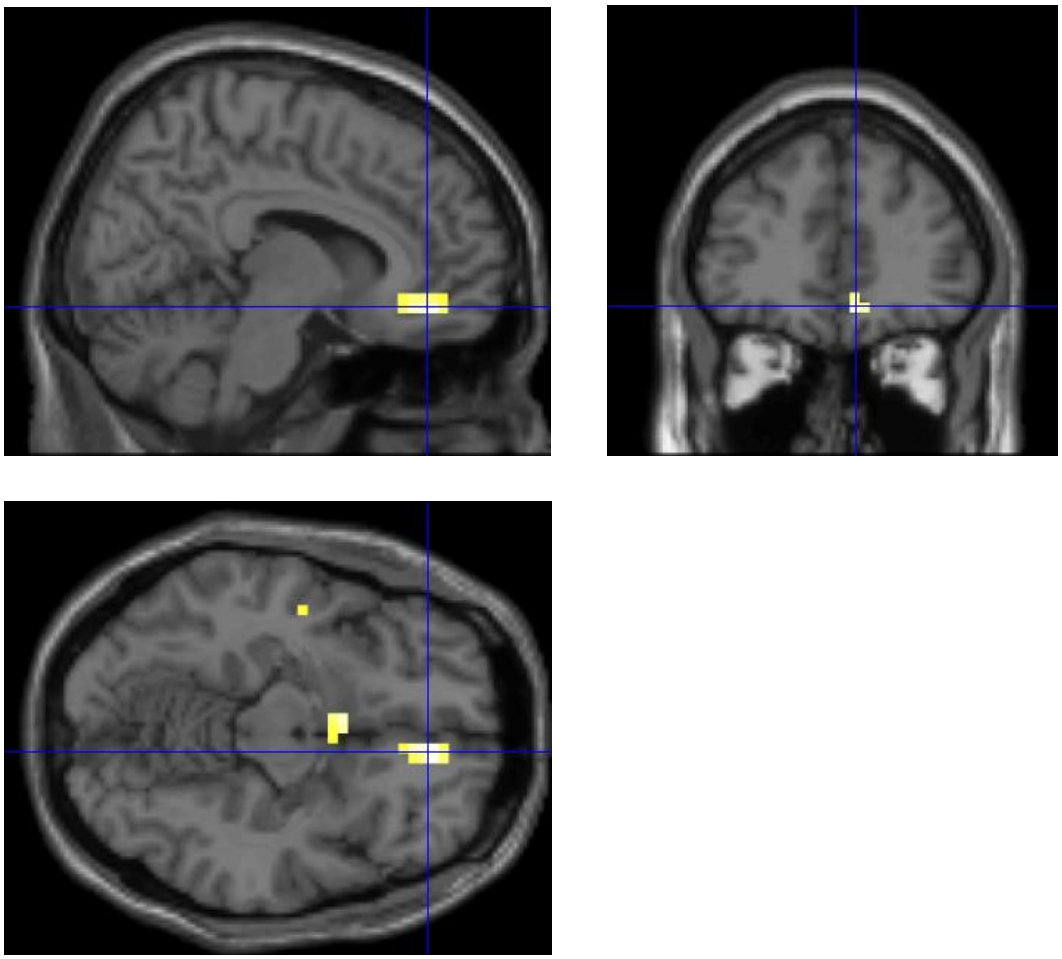

Figure 8. Enhanced brain activation in BA 10/11during response inhibition with escitalopram

Response inhibition minus go

Brain activations for *StopInhibit minus* $Go_{escitalopram}$ > *StopInhibit minus* $Go_{placebo}$ are listed in Table 2 and presented in Figure 9. The contrast *StopInhibit minus* $Go_{escitalopram}$ > *StopInhibit minus* $Go_{placebo}$ at $p < 0.01$ uncorrected was associated with significant activations in bilateral parietal lobe (BA 7), left hemispheric insula (BA 13), claustrum (BA 13), lentiform nucleus and caudate. Also activations were found in right-lateralized posterior cingulate (BA 29), thalamus, middle frontal gyrus (BA 6) as well as red nucleus. The contrast *StopInhibit minus* $Go_{placebo}$ > *StopInhibit minus* $Go_{escitalopram}$ showed activations in right thalamus and left cingulate (BA 31).

Table 2. Brain activations for the contrast *StopInhibit minus Go*

Region	**BA**	**Hemisphere**	**x**	**y**	**Z**	**Z-Score**
a) Escitalopram > Placebo						
Parietal lobe precuneus	7	left	-20	-68	48	4,06
Superior parietal lobule	7	right	28	-63	51	3,23
Insula	13	left	-40	8	14	3,22
Claustrum	13	left	-28	9	18	3,10
Posterior cingulate	29	right	12	-42	17	2,99
Thalamus		right	8	-35	9	2,74
Thalamus		right	28	-31	2	2,98
Lentiform nucleus Putamen		left	-24	-7	19	2,98
Caudate		left	-20	-10	26	2,75
Insula	13	left	-32	-6	26	2,66
Middle frontal gyrus	6	right	24	-6	41	2,87
Frontal lobe sub-gyral	6	right	20	-1	55	2,5
Midbrain red nucleus		right	4	-27	-5	2,73
Claustrum		left	-24	20	14	2,72
b) Placebo > Escitalopram						
Cingulate gyrus	31	left	-20	-30	31	3,08
Thalamus		right	8	-4	4	2,93

Statistical maps were thresholded at $p < 0.01$ uncorrerected.

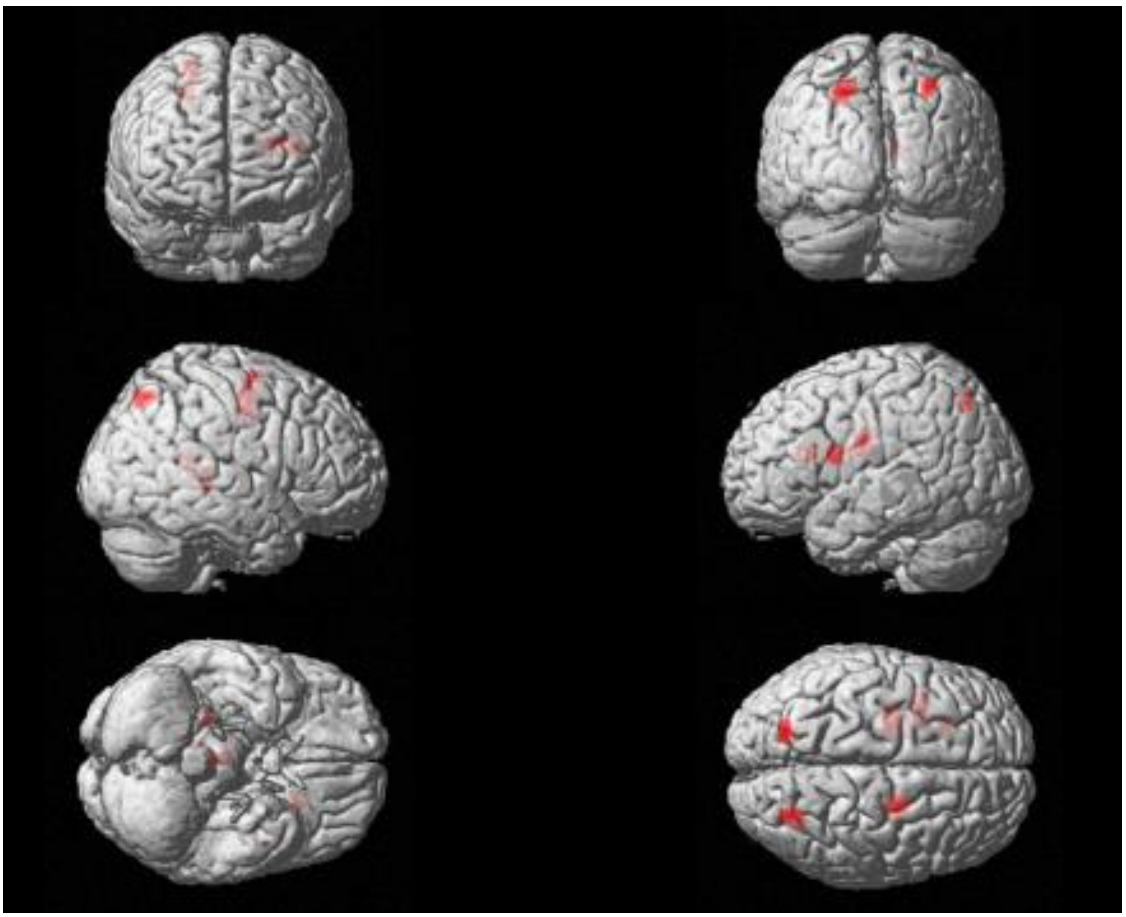

Figure 9. Enhanced brain activations by escitalopram compared to placebo for the contrast *Stopinhibit minus Go*

Failed response inhibition

Results of brain activations during failed response inhibition are represented in Table 3. $StopRespond_{escitalopram}$ > $StopRespond_{placebo}$ significantly activated ($p < 0.005$ uncorrected) right somatosensory cortex (BA 3), right primary motor cortex (BA 4), right cingulate (BA 24/32), right middle and superior temporal gyrus (BA 21, BA 38), right medial frontal gyrus (BA 25) as well as right putamen. Left-hemispherical activations were observed in the parahippocampal gyrus, caudate head and in the temporal cortex (BA 37). Also left auditory cortex (BA 19, BA 22) was activated. Brain activations of this contrast are demonstrated in Figure 10. There were no activations found for the reverse condition placebo > escitalopram.

Table 3. Brain activations during failed inhibition

Region	BA	Hemisphere	x	y	Z	Z-Score
a) Escitalopram > Placebo						
Postcentral gyrus	3	right	51	-17	56	4,28
Parahippocampal gyrus	35	left	-24	-24	-22	3,86
Cingulate gyrus	24/32	right	16	17	25	3,81
Middle temporal gyrus	21	right	48	2	-34	3,78
Middle/superior temporal gyrus	19/22	left	-32	-58	10	3,73
Caudate head		left	-8	19	-4	3,68
Precentral gyrus	4	right	20	-21	49	3,57
Superior temporal gyrus	21/38	right	48	3	-10	3,36
Medial frontal gyrus	25	right	12	7	-14	3,11
Lentiform nucleus, Putamen		right	16	7	-7	2,72
Putamen		right	16	7	-7	2,72
Middle temporal gyrus	21	left	-51	-5	-13	3,09
Fusiforme gyrus	37	left	-48	-51	-11	2,87

No increased activations in the placebo condition compared with escitalopram were found. Statistical maps were thresholded at $p < 0.005$ uncorrected; listing of strongest activations

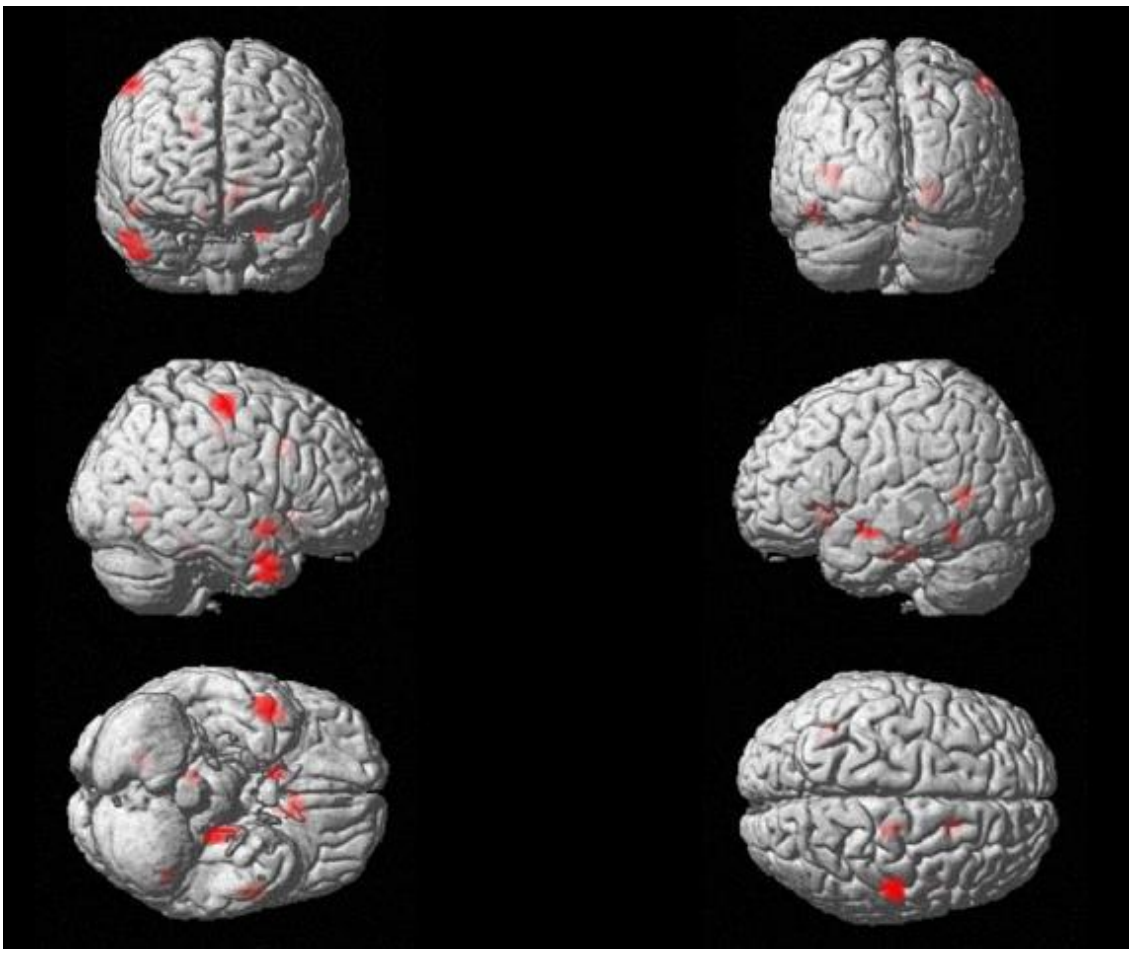

Figure 10. Brain activations during failed inhibition for escitalopram > placebo

Going

Brain activations for go-trials are listed in Table 4. Enhanced activations on go-trials for $Go_{escitalopram} > Go_{placebo}$ were observed at $p < 0.005$ uncorrected obviously right-lateralized: Insula (BA 13), anterior and posterior cingulate (BA 30, BA 32), superior temporal gyrus (BA 38, BA 13), postcentral gyrus (BA 1) and in the middle frontal gyrus (BA 9). Left-lateralized activations were located in the subthalamic nucleus and middle temporal gyrus (BA 21). Brain activations during going for escitalopram > placebo are shown in Figure 11. Go-trials for $Go_{placebo} > Go_{escitalopram}$ were as well associated with a right-lateralized network of brain regions in the middle frontal gyrus (BA 10, BA 11, BA 6), medial frontal cortex including supplementary motor cortex and precentral gyrus (BA 6), superior frontal gyrus (BA 8, BA 10), caudate head, precuneus (BA 7) and middle temporal gyrus (BA 21). Also left medial and middle frontal cortex (BA 6) as well as superior frontal gyrus (BA 10) showed activations.

Table 4. Brain activations during going

Region	BA	Hemisphere	x	y	z	Z-Score
a) Escitalopram > Placebo						
Insula	13	right	44	-7	8	4,02
Subthalamic nucleus		left	-8	-12	-3	3,53
Posterior cingulate	30	right	12	-54	6	3,44
Superior temporal gyrus/sub-gyral	38/13	right	44	3	-10	3,37
Anterior cingulate	10	right	12	34	-12	3,28
Middle temporal gyrus	21	left	-44	-1	-27	3,15
Postcentral gyrus	1	right	67	-14	27	3,14
Anterior cingulate	32	right	4	43	-2	3,09
Middle frontal gyrus	9	right	28	32	21	2,85
b) Placebo > Escitalopram						
Middle frontal gyrus	10/11	right	36	54	-9	4,79
Medial frontal gyrus	6	left	-8	-17	56	4,04
Medial frontal gyrus	6	right	12	-17	56	3,92
Superior frontal gyrus	10	right	36	56	23	3,70
Superior frontal gyrus	8	right	20	33	46	3,65
Middle frontal gyrus	6	right	32	2	37	3,54
Middle frontal gyrus	47	left	-36	39	-5	3,49
Caudate head		right	16	27	-1	3,43
Parietal lobe precuneus	7	right	16	-79	48	3,41
Middle temporal gyrus	21	right	59	-28	-15	3,15
Caudate		right	24	-38	13	3,40
Superior frontal gyrus	10	left	-36	48	23	3,11
Precentral gyrus	6	right	55	-3	26	2,81

Statistical maps were thresholded at $p < 0.005$ uncorerrected; listing of strongest activations.

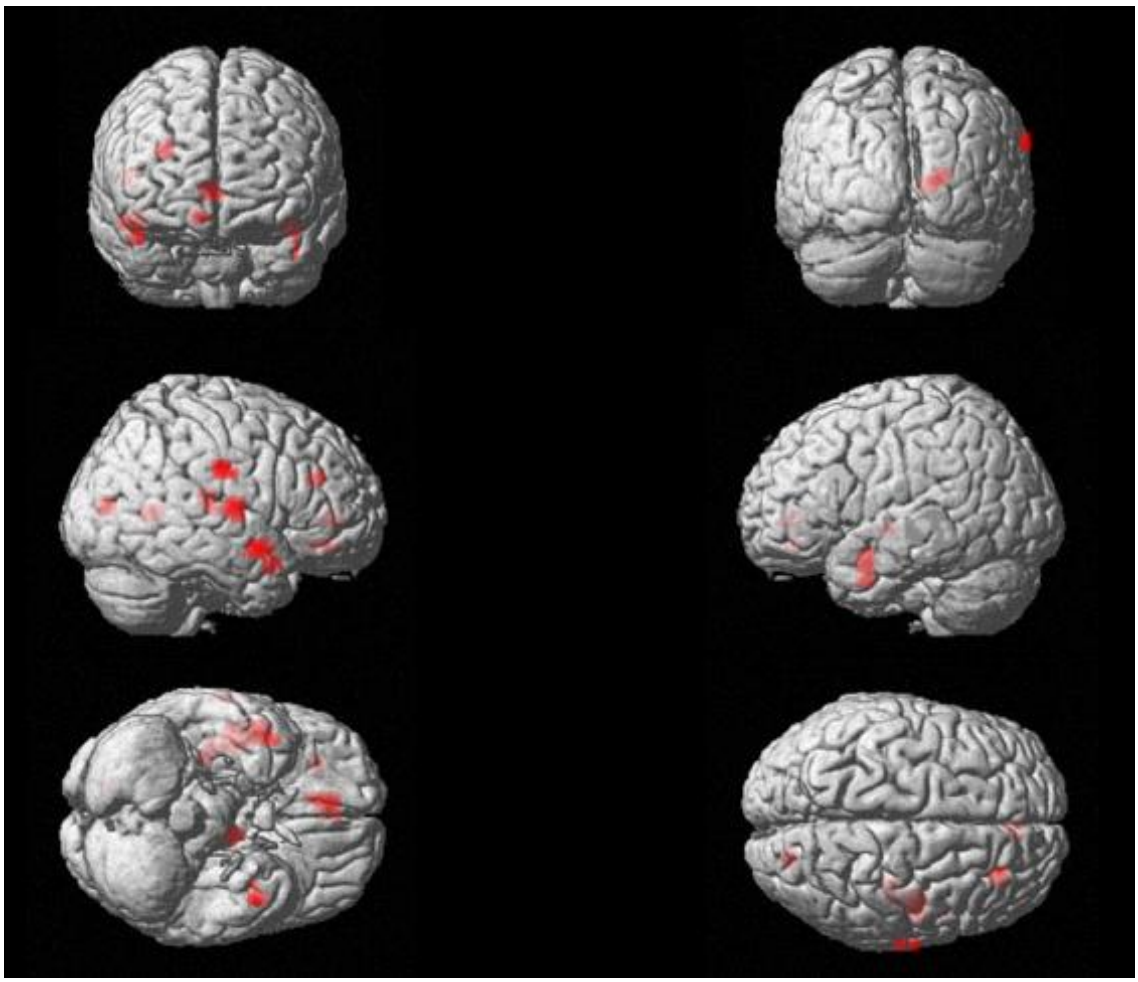

Figure 11. Brain activations during going for escitalopram > placebo

Discussion

The present study investigated the acute effects of pharmacological modulation of 5-HT on brain activations during response inhibition in healthy volunteers. 14 male participants performed a stop signal task after oral administration of SSRI escitalopram. Escitalopram did not affect inhibitory performance as the main effect did not reveal significant differences of SSRT, but was associated with alterations in brain activation patterns compared to placebo. Escitalopram enhanced brain activation in right prefrontal cortex, including right OFC, in right supplementary / premotor and bilateral cingulate cortex as well as in subcortical regions during response inhibition. In the condition of failed stopping escitalopram activated a widespread network of brain regions, including anterior cingulated, right parietal cortex, right OFC, areas in right temporal cortex and subcortical regions. During the go-process escitalopram increased activations in numerous regions like right anterior and posterior cingulate and in right prefrontal, parietal and temporal cortex as well as in subcortical areas.

The lack of effects of escitalopram on task performance is in line with various studies that as well did not find effects of 5-HT modulation on response inhibition using either a stop signal task (Clark et al. 2005, Chamberlain et al. 2006) or a go/no-go task (Del-Ben et al. 2005; Evers et al. 2006; Rubia et al. 2005). The stop signal task and go/no-go task differ in design of paradigm and, as a result, in determination of inhibitory performance. However, the lack of effects of 5-HT on task performance seems to be steady across paradigms. These studies also used different methods of intervention in the 5-HT system. The fact that indeed none succeeded to demonstrate an effect on inhibitory performance implicates that modulation of the serotonergic system has no effect on response inhibition at least not reflected in task performance.

Focus of our interests was the role of escitalopram. Yet, for reasons of control we also reviewed fMRI data of response inhibition in the placebo condition. During the stop process we found activated areas that have been related consistently to response inhibition, including right lateral IFC, right DLPFC, the right supplementary motor area and temporal regions (data not presented here). These brain areas have been associated with response inhibition in multiple fMRI studies and they are considered as relevant brain regions for response inhibition (Aron et al. 2003; Aron et al. 2004; Aron and Poldrack, 2006; Rubia et al. 2003). Since we were able to reproduce these crucial stopping areas we assumed that our study measured stopping performance,

respectively. Furthermore, we therefore assumed that alterations of brain activation patterns were induced by escitalopram.

Our findings of enhanced brain activations in right prefrontal cortex, including right OFC with escitalopram during response inhibition are consistent with results of previous research (Del-Ben et al. 2005; Rubia et al. 2005). The OFC has been implicated in mediation of inhibitory control (Rubia et al. 2005). Eagle et al. (2008) also suggested that the OFC is involved in the stopping process by mediating stopping via an orbitofrontal-DMStr-pathway. However, there are also differences to results of Del-Ben et al. (2005) who found increased activation of right lateral OFC (BA 47) and dorsolateral PFC (BA 9), whereas attenuations were seen in OFC (BA 11), an area which showed increased activation in our study. Nevertheless, Del-Ben et al. saw medial OFC activation related to response inhibition though not enhanced by citalopram. This might be due to task- and design related differences. Del-Ben et al. used a go/no-go task while we used a stop signal paradigm. The go/no-go task does not consist of a stop signal delay and measures prepotent responses, i.e. action restraint, consequently. The stop signal task is more precise in measuring response inhibition of ongoing processes, i.e. action cancellation. Because of the different paradigms used in both studies there were also designed different contrasts. Consequently, one can expect differing results. Del-Ben et al. only reported a more complex *no-go minus go* contrast, whereas the contrast $StopInhibit_{escitalopram} > StopInhibit_{placebo}$ that we generated was not investigated in their study. We only saw increased activations in right medial OFC in this condition. However, in our similar contrast $StopInhibit\ minus\ Go_{escitalopram} > StopInhibit\ minus\ Go_{placebo}$ we found activation patterns particularly in subcortical regions which is consistent with previous findings relating subcortical regions to response inhibition (Aron and Poldrack 2006; Li et al. 2008; Del-Ben et al. 2005; Kelly et al. 2004). The OFC is strongly connected to subcortical regions (Alexander et al. 1990; Cools et al. 2008). The study of Del-Ben et al. (2005) and our study also differ in the substance used for pharmacological modulation and its admisitration route: Intravenous administration of SSRI citalopram used by Del-Ben at al. versus the oral administration of escitalopram we used. Although both citalopram and escitalopram belong to the same group of pharmaceutical substance, escitalopram still owns more selectivity for the human 5-HT transporter. The different way of drug administration also could be a reason for the differing results. We decided to investigate acute administration of SSRI escitalopram which produces extended 5-HT availability in the synaptic cleft by blocking the human 5-HT transporter. However, Rubia et al. (2005) found a similar activation

pattern like Del-Ben et al. (2005). Rubia et al. likewise used a go/no-go task but ATD procedure for 5-HT modulation. This method interferes in the serotonergic system by producing a decrease of central 5-HT via decreased tryptophan availability in the brain. According to Cools et al. (2008) this reduction is mild and only transient though. Actually, Evers et al. (2006) did not see any effect of ATD on brain activation in a go/no-go task ascribing this matter of fact likewise to differences in the paradigma and design. However, our findings are partly consistent with a study by Anderson et al. (2002) using m- chlorophenylpiperazine (mCPP) for modulation. They demonstrated increased brain activations associated with mCPP in a *no-go minus go* contrast in right ventral lateral PFC, but also in the caudate, a region showing activation enhancement in our study in the corresponding condition *StopInhibit minus* $Go_{escitalopram}$ > *StopInhibit minus* $Go_{placebo}$ as well. The caudate is reached by ascending sertonergic projections from the raphe nuclei (Feldman et al. 1997) which could be a reason for increased activations in this region with escitalopram. However, recent findings suggested the caudate playing a role in the controlled execution of movement. Li et al. (2008) found greater activity in the caudate in association with short SSRT compared to long SSRT and this activity also correlated with medial prefrontal activity. Just like Li et al. we would suppose that more research is needed to specify the definite role of the caudate. Consistent with findings in previous literature we found activations in insula and thalamus (Aron and Poldrack 2006; Del-Ben et al. 2005; Kelly et al. 2004). The thalamus as component of the fronto-striato-thalamic-pathway is supposed to gate and facilitate cortically initiated movements (Alexander et al. 1990). However, Li et al. (2008) supposed amongst others that thalamus and basal ganglia might delay SSRT. The insula has been implicated in response selection processes under conditions of reduced preparation (Kelly et al. 2004). But then, Anderson et al. (2002) found attenuations in right insula and thalamus whereas we located increased activations in right thalamus and left insula. This might be likewise due to task- and substance-related differences as discussed before. mCPP is a non-selective 5-HT ligand binding to diverse 5-HT receptors, even α2-adrenoceptors, with greatest affinity for 5-HT_{2C} and possibly 5-HT_{1B}. It is therefore an unspecific substance for modulation of 5-HT, most notably in comparison to escitalopram with greatest selectivity for the serotonin transporter and for 5-HT_{1A} receptors, too. For comparison of both substances one also has to keep in mind that mCPP is an agonist whereas escitalopram has antagonistic property. Whereas agonists bind a certain receptor and alter the receptors´ activity, antagonists simply bind the receptor without producing a response itself though blocking agonist-mediated

responses. Nevertheless, Völlm et al. (2006) found enhanced activations in right lateral OFC and left insula as well though the latter region did not remain significant after small volume correction. Völlm et al. used mirtazapine, an antidepressant substance blocking presynaptic α2-adrenic autoreceptors which leads to increased noradrenaline (NA) release and enhances serotonergic transmission again. Since mirtazapine blocks 5-HT_{2C} receptors as well, its main effects on 5-HT are mediated via postsynaptic agonistic action on 5-HT_{1A} receptors. Although the authors related alterations of brain activations to the serotonergic effects of mirtazapine, most likely adrenergic receptor effects also influenced the results. Another interesting aspect is that we found enhanced activations in BA 24 and BA 8, areas that have been related to error detection and conflict monitoring and therefore they have been suggested to reflect response conflict in a go/no-go task (Kelly et al. 2004; Rubia et al. 2003). This might implicate a serotonergic influence not only on pure inhibitory control but also on other components belonging to response inhibition. To sum up, several studies provide evidence for 5-HT mediated alterations of brain activations associated with response inhibition. Mainly enhancement of activation in right lateral OFC was found across substances in contrast to our own results. These studies commonly used a go/no-go task investigating action restraint, though. However, all studies including our findings support a 5-HT related enhancement in right PFC, particularly in right OFC in general. It remains unclear why our results implicate an involvement of medial OFC. The medial PFC is strongly innervated by serotonergic projections from the rostral raphe nuclei (for review Hornung 2003; Feldman et al. 1997). As escitalopram is more selective than other substances used so far its effects might be responsible for dislocation from lateral to medial regions in the OFC. Our findings of increased activations of subcortical regions confirm suggestions of their involvement in response inhibition. The basal ganglia have been implicated in response inhibition in previous research (Rieger et al. 2003; Gauggel et al. 2004; Eagle et al. 2008; Aron and Poldrack 2006). Our results are consistent with an orbitofrontal-striatal-circuitry that has been discussed for stopping before (Eagle et al. 2008; Chamberlain et al. 2006). Furthermore, we found a serotonin related modulation, most likely because of the numerous serotonergic projections ascending from the raphe nuclei to the basal ganglia (Feldman et al. 1997). Altogether, our results clearly support an influence of serotonin on response inhibition. We found 5-HT modulated activations of brain regions that have been associated consistently with response inhibition providing first evidence for an influence of 5-HT on action cancellation.

Our results of brain activation patterns during failed stopping are in line with Rubia et al. (2003) who found activations in mesial frontopolar cortex (BA 10) and anterior cingulate cortex (ACC) (BA 24/32). Rubia et al. likewise used a stop signal task though the study was not designed to investigate any kind of modulation of neurotransmission. We found increased activation in BA 24/32 in our study as well. Rubia et al. supposed that this region might be implicated in error detection. This is consistent with observations made in two go/no-go studies, both implicating that the rostral anterior cingulate is involved in error processing (Kiehl et al. 2000; Menon et al. 2001). However, since the ACC has also been related to successful response inhibition and even to go-trials the region has been suggested to reflect generic attention or conflict and decision monitoring functions (Liddle et al. 2001; Rubia et al. 2003). Furthermore, we detected increased activation in medial frontopolar cortex (BA 25) which is consistent with Rubia´s assumption of an involvement of mesial prefrontal cortex in error detection in the context of failed inhibition. Kelly et al. (2004) also found activations in medial frontal lobe during a go/no-go task which they related to the response conflict inherent in a no-go trial. Thus, our findings might support the suggestion of a neural network of mesial prefrontal cortex, including ACC for error detection. 5-HT might even lead to activation enhancement possibly by reason of the serotonergic projections reaching this area. However, bearing in mind that our results only represent enhanced activations with escitalopram they cannot be discussed in that way without considering the modulating effects of the drug. Aron and Poldrack (2006) found activations in right lateral IFC and STN similar to activation patterns during successful response inhibition but also they did not investigate effects of manipulation of any neurotransmission. According to the horse race model (Logan, 1994) stop-process and failed stopping should function similar but with different results, i.e. either successful or postponed and therefore unsuccessful inhibition. The regions Aron and Poldrack found did not show enhanced activations in our study. However, we found increased activations in medial prefrontal cortex and cingulate as well as in subcortical regions in both, successful and failed inhibition. This matter of fact would confirm a similar network for successful and failed inhibition. Our pharmacological modulation might have produced activation patterns deviating from the regions Aron and Poldrack (2006) detected. Whereas we found increased activation in right putamen associated with escitalopram, Aron and Poldrack found by substracting *StopInhibit minus StopRespond* that there was significantly more activation within putamen for StopInhibit than StopRespond which they related to a slower go-process. Increased activation in putamen associated with escitalopram could otherwise implicate

a fronto-striato-pallidal-STN pathway for response inhibition which they discussed in the context of putamen-activation as well. The putamen is one of the input structures of the basal ganglia and it is reached by serotonergic projections (Alexander et al. 1990; Mink 1996; Cools et al. 2008; Feldman et al. 1997) By taking both, results of successful and failed inhibition, into consideration a fronto-striato-circuitry might be suggested possibly in conjunction with serotonin. However, since there is no literature of failed inhibition combined with serotonergic modulation results are difficult to frame. Clearly, more research is needed not only to investigate an involvement of 5-HT in failed inhibition, but also to find out if unsuccessful inhibition is associated with a similar activation pattern like response inhibition or if the mesial frontal cortex and anterior cingulate are particularly responsible for failed inhibitory performance in terms of error detection.

During the go-process we located enhanced activations mainly right-lateralized in insula, anterior and posterior cingulate, somatosensory, temporal and frontal cortex. Our results are contrary to Aron and Poldrack (2006) who found activations of motor areas contralateral to the response hand, including primary motor cortex, SMA, putamen and pallidum. The only accordance is activation of left STN which Aron and Poldrack related to a hyperdirect discharge before voluntary movement (Mink, 1996) but they decided not to go into detail. To discuss these results, again, one has to consider that our results only represent activations which were enhanced by escitalopram compared to placebo while Aron and Poldrack did not undertake any pharmacology intervention. However, our results are partly consistent with brain activations Liddle et al. (2001) found during a go/no-go task. They as well detected brain activations of anterior cingulate, superior temporal gyrus and in parietal lobe as well as in SMA although we only found activations in the latter region with placebo. In previous studies investigating serotonergic modulation activation patterns during the go-process were not published, so there is no literature to compare with. As we were able to demonstrate in our placebo condition of stopping that our study produced activation patterns in accordance with the literature, this might lead to the assumption that the differences of activations during the go-process are caused by our manipulation in the serotonergic system. Consistent with this assumption activations were seen in regions reached by the serotonergic projections which implicates thereby a modulating effect also in the go-process. However, for further considerations more research of the go-process is needed. Since our main focus lies on response inhibition we decided likewise not to discuss this further.

The contrasts vice versa with enhanced activations under placebo compared to escitalopram did not reveal many results. As the focus of our study was on effects of serotonin we listed them just for reasons of completeness. Yet, we decided not to go into detail since our contrasts with *escitalopram* > *placebo* compete with more interesting questions in the context of our study.

In comparison to serotonin results of studies using pharmacological manipulation of the noradrenergic system showed promising effects of noradrenaline even on task performance in response inhibition (Chamberlain et al. 2006). The results of Völlm et al. (2006) who investigated the effects of mirtazapine on response inhibition also could be considered against the background of possibly mediated effects through the substance´s noradrenergic actions. Further research is clearly needed to find out if other central neurotransmitters influence response inhibition, perhaps even more than 5-HT.

Limitations

A relative small sample size was used for the present study which is limiting factor particularly for analysis of performance data. However, compared to other studies with even less participants (Anderson et al. 2002; Del-Ben et al. 2005) our number of participants seems suitable. It is definitely necessary to replicate the acute effects of oral administration of escitalopram on brain activation in following studies using at best more significant sample sizes. Although the stop signal task is a very specific paradigm for measuring response inhibition, estimation of SSRT still deals with a conclusion as response inhibition is not measured directly but estimated via mathematical formula. We anticipate that response inhibition performance is measured by SSRT which is based on an assumption, though. Inhibiting highly selective the 5-HT transporter, escitalopram still holds affinity for other neurotransmitter receptors, including 5-HT_{1A} and 5-$HT_{2\ A}$ even though this affinity has been proven to be little (Burke, 2002). However, to our opinion escitalopram is the drug of first choice to investigate the serotonergic system by reason of its highest selectivity. Whenever comparing results of studies using different substances for pharmacological modulation one has to think about the various affinities drugs may exhibit. Being rapidly and nearly completely absorbed after oral single-dose administration escitalopram achieves maximal plasma concentrations (C_{max}) after approximately 3 $\pm$ 1.5 hours (Rao, 2007). Based on this fact we started fMRI scanning and likewise performance of the stop signal task at the moment we expected to reach most likely C_{max}. For reasons of control we determined plasma hormone concentrations

(data not presented here) to document an increase of plasma prolactin e.g. as SSRIs are known to elevate plasma prolactin concentrations in humans (Attenburrow et al. 2001). Nevertheless, to be sure that task performance and fMRI scanning were starting exactly at time of C_{max} continuous monitoring of prolactin plasma level would have been desirable and should be done in future studies. We used a dose of 10 mg escitalopram consistent with the commonly used dose of 10-20 mg in clinical treatment (Rao, 2007). Yet, the dose we administered was lower limit and a higher dose possibly might produce effects to a greater extent, resulting in wider or different modulation of brain activation patterns or even in effects on task performance. Moreover, there is evidence that 5-HT increase following acute administration of SSRIs not only stimulates postsynaptic 5-HT receptors but also activates inhibitory $5\text{-}HT_{1A}$ autoreceptors producing a reduction of activity in the 5-HT system (Cools et al. 2008). In contrast, during long-term treatment autoreceptors are desensitized and 5-HT system activity increases. Therefore it is necessary to differ between acute and chronic administration of SSRIs. To achieve steady plasma concentrations of escitalopram approximately 7-10 days of administration are required (Rao, 2007). This is in line with findings from the treatment of major depression where escitalopram shows first positive effects on symptoms not before 1-2 weeks of continuous administration (Burke, 2002). To secure an increase of activity in the 5-HT system chronic administration of escitalopram for at least this time period should be used. More research using chronic drug administration hence aiming for steady plasma concentrations would provide more definite evidence. Although fMRI technique provides a good possibility for investigation of cerebral structures and functions it still leaves some uncertainties. For instance, the influence of drug administration on general blood flow has to be considered. Activations measured in fMRI are direct reflection of the difference between the magnetic properties of oxygenated and desoxygenated hemoglobin or BOLD response. But they are considered to measure also neural activity indirectly. However, it cannot be eliminated that ecsitalopram could produce non-specific effects on blood flow in the brain and therefore on BOLD response. We found activations in brain areas that have been associated with response inhibition previously in similar studies and also in studies using no pharmacological modulation. So we would argue that activations measured in our study are not caused by general effects of escitalopram on blood flow. Another uncertainty in interpretation of fMRI data is the fact that increase of activity is believed to be an indirect measurement of increased neural metabolism. Nevertheless, it has to be questioned whether this activity increase reflects neurons being more activated because

of better performance. This activity could likewise reflect the recruitment of more cells needed to achieve same capacity. Also, fMRI just allows a conclusion on activations. To investigate actual activations it would be superior to use PET. However, this method is more invasive and as it is connected with radiation it holds more risk for physical health of participants consequently.

Conclusions

In the present study we investigated the effects of SSRI escitalopram on brain activations associated with response inhibition. We did not find differences in behavioral measures of response inhibition with escitalopram and placebo. Yet, we found modulation of brain activation patterns after acute administration of escitalopram during a stop signal task. Escitalopram enhanced activations of brain regions that have been consistently related to response inhibition, including right OFC and subcortical regions. Our results support suggestions of an involvement of 5-HT in neural regulation of response inhibition. So far, 5-HT involvement was predominantly discussed for action restraint. However, this study shows that 5-HT also influences action cancellation through modulation of brain activations. In addition, we found modulating effects of serotonin on activations during failed inhibition. In fact, escitalopram enhanced brain activations in anterior cingulate supporting its assumed role in error-detection. Our results also implicate a fronto-striatal-circuitry for response inhibition in conjunction with serotonin. To draw stronger conclusions clearly more research is needed in the field of serotonergic modulation and its influence on response inhibition, most notably in consideration of the distinction between action restraint and action cancellation.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten im Institut für Medizinische Psychologie und Medizinische Soziologie des Universitätsklinikums Aachen, Pauwelsstraße 30, 52074 Aachen hinterlegt sind.