

The effect of Escitalopram on tonic and phasic alertness in healthy volunteers

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1 Summary

1.1 Abstract

Attentional processes are modulated by different neurotransmitters. There is accumulating evidence of functional involvement of serotonin (5-HT) in attentional processes, especially regarding vigilance and psychomotoric speed. As demonstrated by earlier studies the statements concerning the influence of 5-HT on attentional processes remains somewhat inconsistent. Therefore, the current placebo-controlled, double-blind, cross-over study was designed to compare tonic and phasic alertness effects of acute and subchronic treatment with the most selective serotonin reuptake inhibitor available, Escitalopram, in healthy volunteers. Forty healthy volunteers, aged 18 - 39 years, underwent two treatment periods in which they were given Escitalopram 10 mg or placebo. The treatment was conducted one day or seven days. Tonic and phasic alertness were assessed at the time of the plasma peak through the Attention Network Test (ANT) during two sessions. It was found that Escitalopram did not influence tonic alertness after acute or subchronic administration. Measures of phasic alertness showed a tendency towards a reduction in phasic alertness under Escitalopram. The difference in intake-length of either one or seven days did not affect alertness. Our study indicates that Escitalopram neither facilitates nor reduces alertness of healthy volunteers in a fundamental way.

Keywords:

attention; alertness; serotonin; selective serotonin reuptake inhibitors (SSRIs); Escitalopram; Attention Network Test (ANT)

1.2 Zusammenfassung

Aufmerksamkeitsprozesse werden durch verschiedene Neurotransmitter beeinflusst. Mehrere Studien zeigen einen Zusammenhang zwischen Aufmerksamkeitsprozessen und dem Neurotransmitter Serotonin (5-HT), insbesondere hinsichtlich Vigilanz und psycho-motorischer Geschwindigkeit. Diese Studien weisen jedoch Unstimmigkeiten auf bezüglich des Einflusses von 5-HT auf Aufmerksamkeit. Die vorliegende Placebo kontrollierte, doppelblinde, cross-over Studie wurde durchgeführt, um die Effekte von Escitalopram, dem selektivsten Serotonin-Wiederaufnahmehemmer im Handel, auf tonische und phasische Alertness in einem akuten und subchronischen Verabreichungsparadigma zu untersuchen. Zu diesem Zweck wurden 40 gesunde Probanden im Alter von 18 - 39 Jahren erfasst, die 10 mg Escitalopram oder Placebo entweder einmalig oder über einen Zeitraum von sieben Tagen erhielten. Tonische und phasische Alertness wurden zum Zeitpunkt des Plasma Peaks in zwei Sitzungen anhand des Aufmerksamkeits-Netzwerk-Tests (ANT) erhoben. Es zeigte sich, dass Escitalopram bei den Probanden weder nach akuter noch nach einwöchiger Einnahme einen messbaren Einfluss auf die tonische Alertness hatte. Es zeichnete sich eine Tendenz zur Reduktion der phasischen Alertness ab. Die unterschiedliche Länge der Einnahme hatte keinen Einfluss auf die Alertness.

Unsere Studie deutet darauf hin, dass Escitalopram weder einen unterstützenden, noch einen wesentlichen hemmenden Einfluss auf die Alertness hat.

Schlüsselwörter:

Aufmerksamkeit, Alertness, Serotonin, Selektive-Serotonin-Wiederaufnahmehemmer (SSRIs), Escitalopram, Aufmerksamkeits-Netzwerk-Test (ANT)

2 Introduction

2.1 Attention

Attention is an important requirement with regard to cognitive functioning. Although knowledge of the precise neural mechanisms responsible for attentional processes is still incomplete, many of the involved brain areas and networks have been identified. According to Posner and Petersen (1990) attention can be divided into three major components: orienting to sensory events, executive control as well as achieving and maintaining an alert state.

Orienting stands for the selection of information from sensory output. It is the orientation to an occurring stimulus. The orienting system consists of circuits connecting the superior parietal lobe, the temporal parietal lobe, the frontal eye fields and the superior colliculus (Corbetta & Shulmann, 2002).

Executive control of attention is defined as the ability to resolve conflict among responses. It is involved in planning and decision-making processes in the response to novel situations (Fan & Posner, 2004). The executive control is associated with the brain area of the anterior cingulate as well as lateral prefrontal regions and parts of the basal ganglia (Fan et al., 2005; Posner & Rothbart, 2007).

Alertness is defined as achieving and maintaining a state of high sensitivity to incoming stimuli. It can be described as the activation of attention and is thought to be the most fundamental function in the hierarchy of attention (Fernandez-Duque & Posner, 2001). Alertness can be subdivided into tonic (intrinsic) and phasic (extrinsic) alertness. Tonic alertness is defined as the cognitive control of wakefulness and arousal. It represents a general responsiveness which is subject to circadian variations and situation-related requirements (Niemann & Gauggel, 2005). The term “tonic alertness” is often used synonymously with the term “vigilance”. Indeed, the difference is subtle and not presented clearly in the literature (Parasuraman et al., 1998; Robbins, 1998). According to Parasuraman et al. (1998), Posner proposed in 1978 that the mechanisms underlying alerting in short-duration reaction time tasks are not essentially different from those operating in long-term vigilance tasks. Phasic alertness represents the ability to increase response readiness if a preceding external warning stimulus is presented in reaction time tasks (Fan & Posner, 2004). The alerting system relies on a circuitry of the frontal and parietal lobes mainly of the right hemisphere as well as the thalamus with efferent conjunctions from the Locus Coeruleus (LC), located in the rostral pontine tegmentum (Fan et al., 2005; Murphy & Alexopoulos, 2006).

Figure 1 shows the anatomy of the three networks described above.

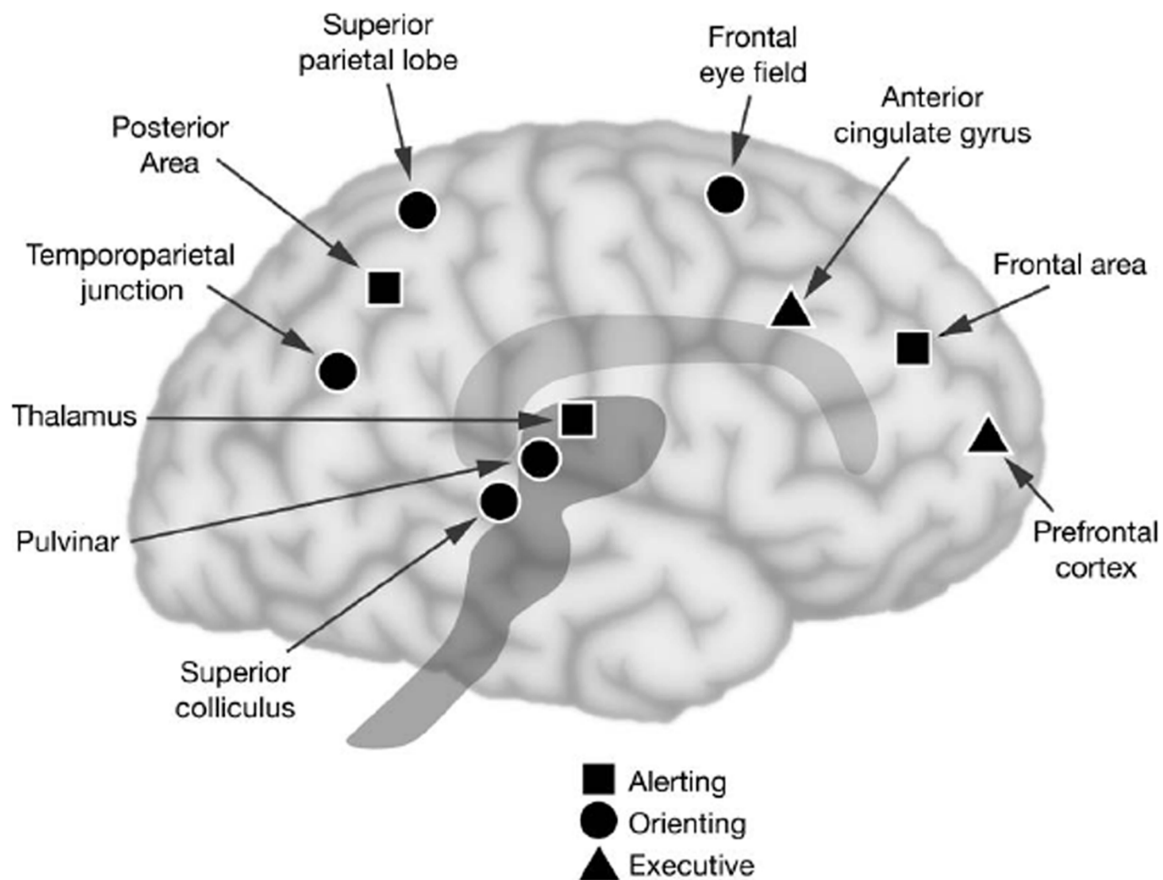


Figure 1: Anatomy of three attentional networks: alerting, orienting and executive control (from Posner & Rothbart, 2007).

To assess those major functions of attention, orienting, executive control and alerting as well as the overall mean reaction time, Fan et al. (2002) developed the Attention Network Test (ANT). The ANT is based on an advanced and specified choice-reaction-time test and measures how response times are influenced by alerting cues, spatial cues and flankers. The difference between those trials with a presentation of a warning condition and those without is called “alerting effect” (after Fan et al., 2005) and can be described by the following equation: $\text{Alerting effect} = RT_{\text{double cue}} - RT_{\text{no cue}}$ (Posner & Fan, 2007). The “alerting effect” of the ANT can be an appropriate measure for phasic alertness as it tests how fast a person can obtain maximum alertness. The overall mean reaction time can be a measure for tonic alertness. A detailed description of the ANT can be read in chapter 3.4.

2.2 Neurotransmitters involved in attention

Different neurotransmitters appear to be responsible for accomplishing operations of individual networks: cholinergic systems arising in the basal forebrain interfere with orienting attention. Anticholinergic drugs like scopolamin affect the ability of shifting attention since they impair the orienting system (Davidson & Marrocco, 2000).

The anterior cingulate and lateral frontal cortex, associated with executive control, are targets of the ventral tegmental dopamine system (Posner & Fan, 2007). Therefore it is suggested that the executive control is modulated by the neurotransmitter dopamine (Fan et al., 2002). The dopamine agonist bromocriptine has shown to improve executive tasks such as the Stroop task when administered to patients with traumatic brain injury, who had lesions in prefrontal areas (McDowell et al., 1998).

Several studies suggest that the cortical distribution of the brain's norepinephrine (NE) system is involved in the alerting process by showing that the effect of warning signals is reduced or eliminated by norepinephrine antagonists (Coull et al., 1995, 1996, 2001; Marrocco & Davidson, 1998), furthermore LC neurons as the largest nucleus of NE neurons in the brain are selectively activated during vigilance tasks in monkeys (Aston-Jones et al., 1994; Dahlstroem & Fuxe, 1964; Moore & Bloom, 1979).

Table 1 shows a summary of anatomy and neurotransmitters involved in attention.

Table 1: Summary of the anatomy and neurotransmitters involved in orienting, executive control and alertness networks.

Function	Structure	Modulator
Orienting	superior parietal lobe temporal parietal lobe the frontal eye fields superior colliculus	Acetylcholine
Executive control	anterior cingulate lateral prefrontal regions basal ganglia	Dopamine
Alertness	right frontal parietal lobe thalamus Locus Coeruleus	Norepinephrine

2.3 Serotonin and cognition

Serotonin (5-HT) seems to be another neurotransmitter involved in different cognitive processes. Interest has focused upon this neurotransmitter primarily because of its ascribed role in physiological neurocognitive functioning. There is accumulating evidence that 5-HT plays an important role in learning and memory (Riedel et al. 1999). Also, the central serotonergic system provides a functional involvement in emotional regulation, impulsivity, aggression, motor control, arousal, attention, and vigilance (Buhot, 1997; Meythaler et al., 2001; Nakamura & Kurasawa, 2000; Schmitt et al., 2006).

Additional interest focused on the 5-HT system is due to the implication that 5-HT systems may be compromised in many psychiatric disorders (Sandyk, 1992) including schizophrenia (Lee & Meltzer, 2001), bipolar disorder (Mahmood & Silverstone, 2001) and major depression (Arango et al., 2002). It has been recognized that neurocognitive impairment is a major attribute of these disorders (Bearden et al., 2001; Elvevag & Goldberg, 2000; Porter et al., 2003) and this may, in part, be a consequence of serotonergic dysfunction (Gallagher et al., 2003).

A way to study the effects of serotonin on cognition in humans, is to enhance central 5-HT through the administration of selective serotonin reuptake inhibitors (SSRIs), which increase serotonergic transmission.

2.4 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a relatively new group of antidepressants binding at the serotonin transporter and inhibiting the reuptake of 5-HT comparatively selectively. Reuptake is the major inactivating mechanism for serotonin after its release into the synaptic cleft. By enhancing serotonergic transmission, the SSRIs provide effective antidepressant activity without sedating, anticholinergic or cardiotoxic reactions as seen with the older antidepressant drugs (Kerr et al., 1992). During a depressive stage serotonin neurons are assumed to have an absolute or relative deficiency of this neurotransmitter (van Praag, 1982). This leads to an up-regulation of the number of serotonin receptors (the postsynaptic receptors as well as autoreceptors). SSRIs have been shown to enhance 5-HT neurotransmission by increasing 5-HT as a result of a progressive desensitization of somatodendritic 5-HT_{1A} and other terminal 5-HT autoreceptors (El Mansari et al., 2005), which usually exert a negative feedback influence on the function of 5-HT neurons. Additional adaptive events are processed by performing changes in multiple other 5-HT receptors, signal transducing mechanisms, expression of genes for these receptors or other components of the system (5-HT synthetic enzymes, 5-HT transporters), thereby allowing 5-HT firing rate to recover in the presence of the drug over time. These adaptive events rather than the reuptake inhi-

bition per se may be associated with the delay to onset of action of SSRIs (Artigas et al., 1996; Blier & de Montigny, 1994). The precise regulatory mechanism of SSRIs increasing 5-HT neurotransmission is still to be determined (El Mansari et al., 2005). Figure 2 shows a simplified image of the mechanism of action of SSRIs after acute and subchronic administration.

Some SSRIs like Escitalopram even show symptom improvement as well as steady-state plasma levels within seven days (Aronson & Delgado, 2004; Burke, 2002; Waugh & Goa, 2003).

Marketed SSRIs frequently used include fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram and Escitalopram. Those drugs differ with respect to their 5-HT transporter affinity, pharmacokinetic properties (including absorption, duration of action, presence of active metabolites and interactions via drug metabolizing enzymes with other drugs) as well as additional effects on other neurotransmitter systems that may have implications for their clinical profile.

Treatment with SSRIs often results in improvement of cognitive performance. However, since this improvement coincides with the relief of depression, it is not apparent whether these cognitive changes are directly due to altered 5-HT function or are a result of the improvement of the depression itself (Schmitt et al., 2000).

2.5 Serotonin and attention in healthy volunteers

In healthy volunteers there is evidence that 5-HT stimulation influences measures of vigilance by using oral administration of SSRI to enhance levels of central 5-HT. A common measurement for vigilance is the Mackworth Clock Test (MCT), a task that demands continuous alertness for rare events (Mackworth, 1948). Acute and subchronic administration of the SSRIs citalopram 20 and 40 mg (Riedel et al., 2005), fluoxetine 20 mg (Ramaekers et al., 1995) and paroxetine 20 and 40 mg (Schmitt et al., 2002a), showed impairment of performance on the Mackworth Clock vigilance paradigm in healthy volunteers. Sertraline 50 and 100 mg (Riedel et al., 2005; Schmitt et al., 2002a) did not show any effect on vigilance. In contrast to that, it is claimed that SSRIs in general increase central arousal and alertness. These findings are mainly based on the notion that SSRIs can increase the results of the Critical Flicker Fusion Threshold (CFFT) in healthy volunteers. It is a task requiring subjects to discriminate flicker from fusion in a set of light diodes held in foveal fixation (Schmitt et al., 2006). The CFFT has been widely used as a non specific assessment of alertness, (Mattilla et al., 1988) vigilance and visual arousal (Hindmarch, 1995; Kerr et al., 1992; Rammsayer & Netter, 1988) as well as an index of the overall information processing capacity of the central nervous system (Fairweather et al., 1997). Acute and subchronic administration of citalopram 20 mg (Nathan et al., 2000), fluoxetine 60 mg (Rammsayer & Netter, 1988), paroxetine 20 mg (Kerr et al., 1992; Ridout et al., 2003) and sertraline 100 mg (Hindmarch & Bhatti, 1988; Mattila et al., 1988) improved the results of CFFT. Only the group of Ramaekers et al. (1995) found a reduction of CFFT after administration of 20 mg fluoxetine. The apparent contradiction between his findings and other studies may lie in the fact that subjects participating in his study viewed flickering light through an artificial pupil. This is important, because drugs that affect serotonergic neurotransmission can cause pupillary mydriasis (Danjou et al., 1992; Schmitt et al., 2002b) which can raise the results of the CFFT (Lawrence et al., 1982). Without the control of pupil size, the CFFT under the influence of serotonergic drugs might not be a valid index for central effects (Ramaekers et al., 1995; Schmitt et al., 2002b). Global attention has often been assessed by tests charging a rapid elementary motor response to a simple stimulus. The Choice Reaction Time (CRT) is an attentional measurement consisting of a simple motor response to visual stimuli (Amado-Boccaro et al., 1995). It has often been used as an indicator for sensorimotoric performance and psychomotoric speed (Hindmarch, 1995; Kerr et al., 1992; Ridout et al., 2003). Results on the CRT remain contradictory for different SSRIs: Single and subchronic administration of fluoxetine 60 mg (Rammsayer & Netter, 1988) and fluvoxamine 50 and 100 mg (Fairweather et al., 1996) as well as subchronic administration of 50 mg sertraline (Siepmann et al., 2003) did not influence the results of the CRT. In contrast to that, single doses of sertraline showed an improvement in reaction time (Hindmarch & Bhatti, 1988). For the SSRIs citalopram and paroxetine there is contradictory data concerning their effect on CRT.

To sum it up, the results concerning the influence of SSRIs on different aspects of attention remain rather inconsistent.

2.6 Aim of this study

The aim of this study is to further examine the relationship between serotonin and alertness. As an enhancer of central 5-HT the SSRI Escitalopram was administered, as it is the most selective SSRI available and possesses no affinity for additional receptor systems instead for the serotonin transporter (Aronson & Delgado, 2004).

Statements in the literature concerning the acute and subchronic influence of SSRIs on different aspects of attention are not always pointing in the same direction and even are conflicting in some cases. Therefore we assumed an undirected hypotheses of Escitalopram on attention: alertness could be either facilitated or it could be reduced after intake of Escitalopram. The first objective was to determine the influence of Escitalopram on phasic alertness and to determine whether the length of intake (challenge = single dose versus steady-state = 7 day intake) influences the results. The second objective was to determine the effect of Escitalopram on tonic alertness and again whether the length of intake influences the results.

3 Methods

3.1 Participants

A total number of 40 healthy, nondepressed male volunteers aged between 18 and 39 ($M = 24$, $SD = 4$) participated in the study. Participants were recruited via poster advertisement/-e-mail. Most of them were students of different disciplines. Means and standard deviations for body weight (kg) and height (cm) are $M = 86$ kg, $SD = 16$ kg and $M = 183$ cm, $SD = 7$ cm. All participants declared to be non-smokers and drug-free. Participants were interviewed concerning their medical and psychiatric history. The interview was based on health questionnaires prepared by medical staff. To establish physical health blood samples of each subject were analyzed. Any kind of acute or chronic physical or mental disorder led to rejection from the study. All participants had no current or past history of major medical illness, especially psychiatric disorders. No concomitant drug therapy was allowed during the study period. The participants were not allowed to smoke, eat chocolate, nuts or bananas nor drink any alcoholic or caffeine-containing beverages throughout the days of the trials.

There was written informed consent signed by the participants after being informed about the objectives of the study, the substance and possible adverse effects of the drug. The participants were subsequently paid for their time with approximately 10 Euros per hour.

Approval from the Ethics Committee of the RWTH Aachen University and the National Institute for BfArM was obtained. Participants were allowed to quit the experiment any time they wished. All participants finished the study.

3.2 Design

The participants chose to join the challenge or the steady-state group. 20 participants who assigned to the challenge paradigm, received a single oral dose of either 10 mg Escitalopram or placebo in a randomised double-blind cross-over design at a time interval of 7 days. The other 20 participants who assigned to a steady-state treatment, received either 10 mg Escitalopram or placebo every day for one week. After a leaching-out period of one week participants started their second week of intake of either 10 mg Escitalopram or placebo.

During the time of investigation participants completed different personality questionnaires (Freiburger Persönlichkeitsinventar, german versions of the Sensation Seeking Scale, Wender Utah Rating Scale, Tridimensional Personality Questionnaire, Behavioral Inhibition System and Behavioral Approach System Questionnaire) and accomplished the Attention Network Test as well as another computer-based reaction time task, the Stop Signal Task. The personality questionnaires as well as the Stop Signal Task will not be focus of the current

study. Information towards the drug Escitalopram, the ANT as well as the general procedure will be explained in the following chapter.

3.3 Escitalopram

Escitalopram (see figure 3), the therapeutically active s-enantiomer of citalopram, is a highly selective serotonin reuptake inhibitor, licensed for the indication of major depression, anxiety disorder and social phobia (Burke, 2002). Escitalopram shows no or only small affinity to other receptors than the serotonin transporter and is therefore much more selective than other selective serotonin reuptake inhibitors. This results in less autonomic disturbances. Nevertheless, autonomic signs, e.g. nausea, insomnia, reduced appetite, ejaculation disorder, dry mouth and somnolence have been observed. The common dose constitutes 10 - 20 mg per day. The mean peak for plasma levels occurs at 3 ± 1.5 hours. The half life of Escitalopram is 27 - 32 hours. Steady-state levels are achieved in approximately 7 days with one-daily intake (Aronson & Delgado, 2004). For the study we used the drug called Cipralex[®] manufactured by Lundbeck.

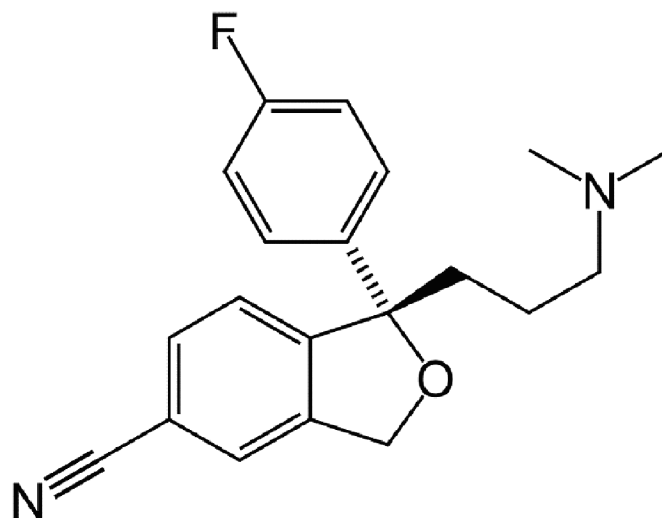


Figure 3: Structure of Escitalopram (www.lexapro.com).

3.4 Attentional Network Test

The Attentional Network Test (ANT) is a computer based choice reaction time task, designed to evaluate alerting, orienting and executive functions of attention within a single task (Fan et al., 2002), that only takes 30 minutes. It requires subjects to determine whether a central arrow presented on a computer screen points left or right by pressing the equivalent button on the keyboard (across all conditions participants should response with one hand only). The central arrow is flanked on each side either by lines (neutral condition), by two arrows pointing in the opposite direction (incongruent condition) or two arrows pointing in the same direction (congruent condition). The three target conditions are pictured in figure 4. The target and flankers are presented until the subject responds, but for no longer than 1700 ms. During each trial a fixation cross appears in the centre of the screen. The stimuli (one central arrow accompanied by four flankers) appear either above or below the fixation cross. The task varies in presenting a warning cue appearing on the screen for 200 ms.

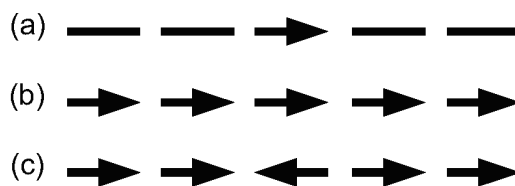


Figure 4: The three ANT target conditions: (a) neutral, (b) congruent, (c) incongruent.

There are four warning conditions indicating the imminent appearance and/or possible location of the target: (a) no cue, (b) centre cue, (c) double cue and (d) spatial cue as illustrated in figure 5.

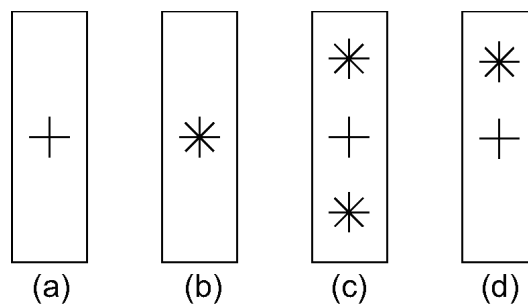


Figure 5: The four ANT warning conditions: (a) no cue, (b) centre cue, (c) double cue, (d) spatial cue.

The practice-block includes 24-full-feedback trials. The three experimental blocks contain 96 trials each of them without feedback. Each trial lasts exactly 4000 ms and consists of five different periods. In the first period, a fixation cross is presented for 400 - 1600 ms. An additional cue is then shown for 100 ms in the second period followed by the fixation cross for 400 ms in the third period. In the fourth period, the target arrow with flankers is shown for

at most 1700 ms. The duration of the last period depends on the duration of the first fixation period and the reaction time ($3500 \text{ ms} - \text{first fixation period} - \text{reaction time}$). The procedure of one trial is illustrated in figure 6.

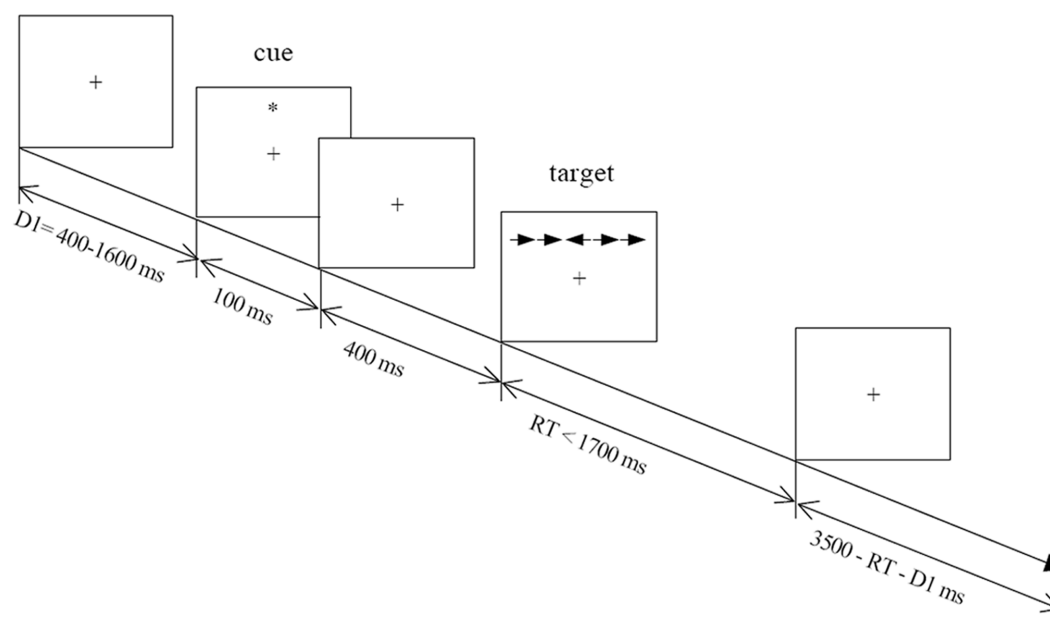


Figure 6: Trial event in the ANT (from Posner & Fan, 2007): The cue provides information of when and where the target will occur. The target is a central arrow that indicated a left or right response surrounded by congruent or incongruent flankers.

The trials are presented in a random order. For data analysis, only valid trials and trials with reaction times between 200 ms and 2000 ms were considered. Trials with a reaction time of two standard deviations above or below the condition means were not considered. Participants were asked to focus on the fixation cross in the centre of the screen and to answer as quickly and accurately as possible. Additional to the condition means, the overall mean reaction time as well as the accuracy (percentage of correct responses) were recorded. For this study, we analyzed the no cue and double cue conditions as well as the overall mean reaction time. Neither of those two cue conditions provided information about the following position of the target. When the double cue is presented as well as when no warning cue is presented, attention tends to remain diffused across the two potential locations the target could appear, whilst the double cue alerts the participant to the upcoming appearance of the target.

The difference of $RT_{\text{double cue}} - RT_{\text{no cue}}$ could be seen as a measure for phasic alertness, whilst the mean reaction time could be seen as a measure for tonic alertness.

3.5 Procedure

The present study was part of a larger research project. Analyses of blood samples, personality questionnaires and results of the Stop Signal Test will be analysed separately. For reasons of completeness the full procedure of one session will be described.

Figure 7 shows an illustration of the procedure of one testing day: Participants arrived at our institute at 1.30 p.m. They were weighed, measured, blood pressure and heart rate were taken, an aditus was set and the first blood sample was taken. At 2.00 p.m. drug-intake (Escitalopram or placebo) was accomplished. After that participants were asked to fill out personality questionnaires. After a certain time another two blood samples were taken (see figure 7). The short-term-treatment group performed the ANT three hours after verum-intake, one time after taking Escitalopram and one week later after taking placebo respectively vice versa. Then another neuropsychological test, the Stop Signal Test was performed.

The steady-state group performed the ANT as well as the Stop Signal Test at the seventh day of drug/placebo intake, three hours after the last intake, since this is the time of the mean peak of plasma (Aaronson & Delgado, 2004). There was a period of at least 7 days washout between experimental sessions. At the end of each session heart rate and blood pressure were measured again. The participants stayed at our institute during the time of the testing, which lasted about 4.5 hours. Throughout the experiment participants were asked if they had undergone any side effects. All participants completed the study.

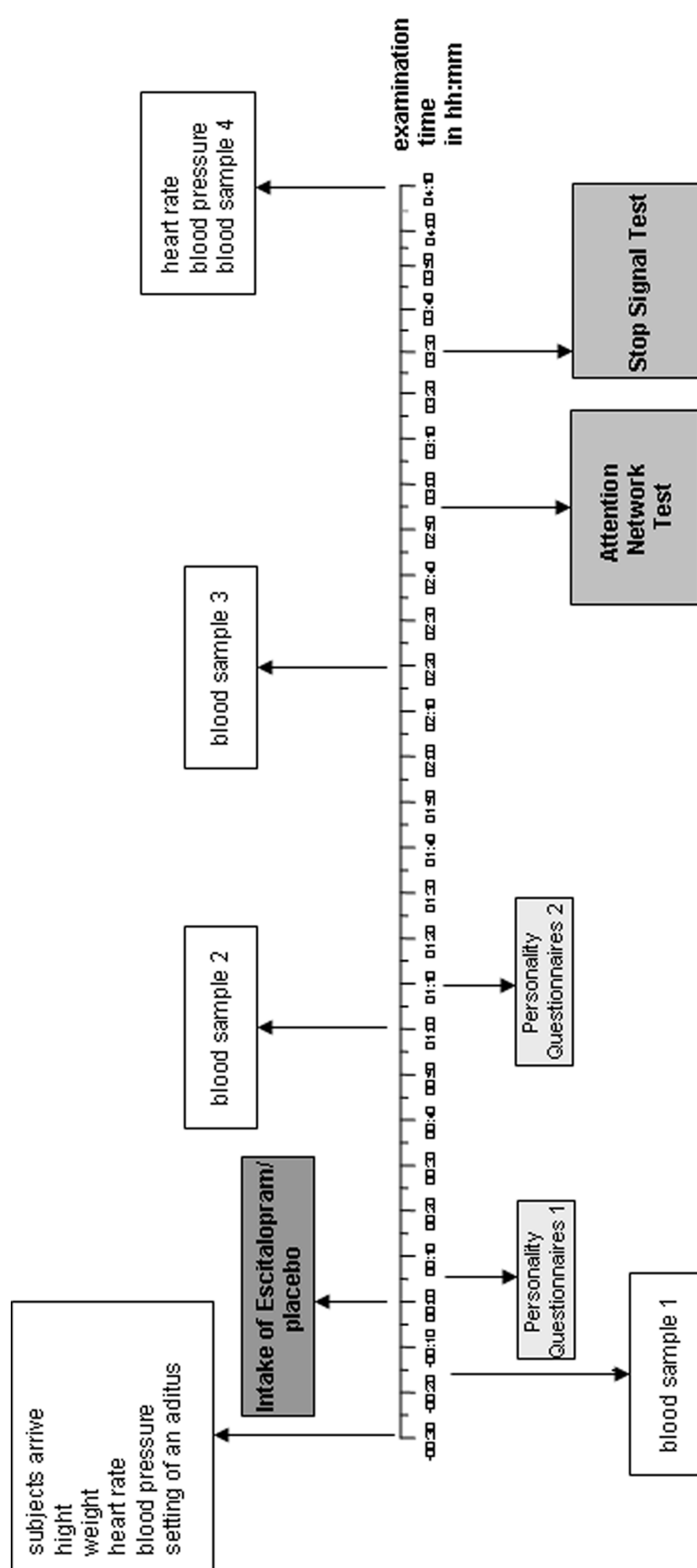


Figure 7: Procedure of one session.

3.6 Statistics

The first objective of the present study is to find out if and how Escitalopram influences phasic alertness (measured by the no cue and the double cue condition of the ANT) and if the length of the intake (challenge = single dose versus steady-state = 7 day intake) has an influence on the results. The second objective is to determine the effect of Escitalopram on tonic alertness (measured by the mean reaction time (mean RT) of the ANT) and whether the length of the intake influences the results.

The independent variables for the first objective are “substance” (intake of Escitalopram versus placebo), “cue condition” (no cue versus double cue) and “length of the intake” (challenge = single dose versus steady-state = 7 day intake). The dependent variables are the reaction times for the no cue and the double cue conditions. For the second objective the independent variables are “substance” and “length of the intake” and the dependent variable is the overall mean reaction time of the ANT.

The experimental data was analyzed using the Statistical Package for the Social Sciences (SPSS) Version 14.0.

We conducted an analysis of variance (ANOVA) for repeated measures with the three factors “substance”, “cue condition” and “length of intake” for the first objective. In case of significance of interaction for any of the main factors, we calculated t-tests for paired samples on the mean values of median reaction times. Additionally in case of a significant interaction of “cue” and “substance” we conducted a t-test with the paired samples:

$RT_{\text{double cue}} - RT_{\text{no cue}}$ under Escitalopram ($\Delta E_{\text{Alerting}}$) and $RT_{\text{double cue}} - RT_{\text{no cue}}$ under placebo ($\Delta P_{\text{Alerting}}$). By comparing these two differences we will receive information about the influence of Escitalopram on the ability to increase response readiness after a preceding stimulus. For the t-tests the results were compared based on a corrected $\alpha < .0125$.

For the second objective we conducted another ANOVA for repeated measures for the factors “substance” and “length of intake”. Due to small and different sample sizes neuropsychological results were compared using effect sizes that were calculated and interpreted according to Cohen (1988). As effect size estimates are slightly biased they are corrected using a factor provided by Hedges and Olkin (1985).

4 Results

4.1 Results for the no cue and double cue condition

We carried out a 2 (cue condition) $\times$ 2 (substance) $\times$ 2 (length of intake) ANOVA of reaction times data. The arithmetic mean of the individual reaction times and standard deviations are found in table 2.

Table 2: Arithmetic mean (M) of individual mean reaction times and standard deviations (SD) of the no cue and double cue conditions in ms for participants joining the challenge group (single dose) (C) and the steady-state group (7 day intake) (S), taking Escitalopram (E) versus placebo (P).

		Challenge	Steady-State	Total (C+S)
		$N = 20$	$N = 20$	$N = 40$
		$M (SD)$	$M (SD)$	$M (SD)$
Escitalopram	no cue	492 (74)	480 (37)	486 (58)
	double cue	465 (72)	448 (38)	457 (58)
	total	479 (73)	464 (37)	471 (58)
Placebo	no cue	489 (54)	487 (32)	488 (43)
	double cue	458 (56)	448 (35)	453 (46)
	total	474 (55)	468 (33)	471 (44)
Total (E+P)	no cue	491 (64)	483 (34)	487 (51)
	double cue	462 (64)	448 (36)	455 (52)
	total	476 (64)	466 (35)	471 (51)

There were no significant effects found for the main factors “substance” ($F(1, 38) = .02, p = \text{n.s.}$) and “length of intake” ($F(1, 38) = .45, p = \text{n.s.}$). Findings indicate that neither the intake of Escitalopram nor the length of the intake affected the participants’ overall mean reaction time for the no cue and double cue condition in a significant way. The calculated effect sizes confirmed these results with $ES = .00$ for the factor “substance” and an effect size of $ES = .19$ for the factor “length of intake”.

The graphs figure 8 and figure 9 depict the reaction times of ANT data under Escitalopram and placebo as well as the difference in length of intake.

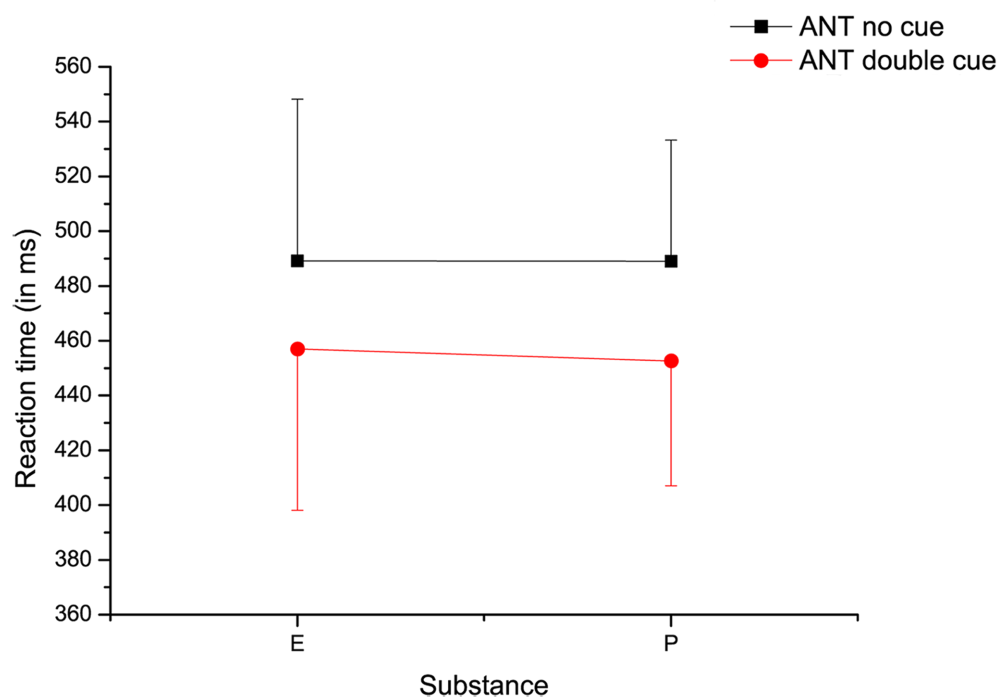


Figure 8: No cue and double cue reaction times (ANT) under administration of Escitalopram (E) or placebo (P).

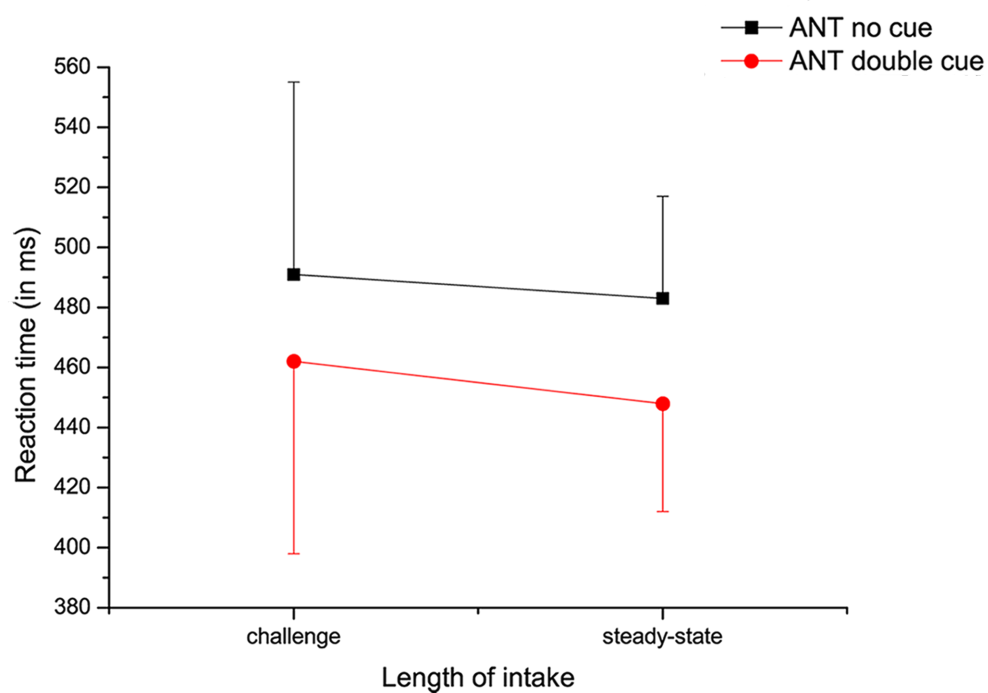


Figure 9: No cue and double cue mean reaction times (ANT) for the challenge as well as the steady-state group.

There was a highly significant effect for the main factor cue condition ($F(1, 38) = 159.72, p = .00$). As can be seen in figure 8, participants show a faster reaction time under the double cue condition than under the no cue condition, which means that they profit from a warning task. These findings were endorsed by a calculated effect size of $ES = .62$, which can be interpreted as a medium effect (after Cohen, 1988).

There was no significant interaction between “substance” and “length of intake” ($F(1, 38) = 1.00, p = \text{n.s.}$). The same was true for the interaction of “cue condition” and “length of intake” ($F(1, 38) = 1.55, p = \text{n.s.}$). The interaction of “cue condition” and “substance” revealed a significant effect with $F(1, 38) = 6.48$ and $p = .02$. Post hoc we calculated t-tests for paired samples to further investigate the significant interaction of “cue condition” and “substance”. The results of the t-tests can be seen in table 3.

Table 3: Results of the post-hoc t-tests for paired samples of mean reaction times of the no cue and double cue condition under the influence of Escitalopram and placebo as well as the results of a t-test for the paired samples of double cue under Escitalopram minus no cue under Escitalopram ($\Delta E_{\text{Alerting}}$) and double cue under placebo minus no cue under placebo ($\Delta P_{\text{Alerting}}$) and effect sizes of mean values involved in the interaction of “cue condition” $\times$ “substance”, $N = 40$.

Pair	T	df	p	ES
$M_{\text{noEscitalopram}} / M_{\text{noPlacebo}}$	-.52	39	.60	.04
$M_{\text{noEscitalopram}} / M_{\text{doubleEscitalopram}}$	10.39	39	.00*	.50
$M_{\text{noEscitalopram}} / M_{\text{doublePlacebo}}$	6.27	39	.00	.62
$M_{\text{noPlacebo}} / M_{\text{doubleEscitalopram}}$	5.96	39	.00	.60
$M_{\text{noPlacebo}} / M_{\text{doublePlacebo}}$	12.37	39	.00	.63
$M_{\text{doubleEscitalopram}} / M_{\text{doublePlacebo}}$	.76	39	.45	.08
$M \Delta E_{\text{Alerting}} / M \Delta P_{\text{Alerting}}$	-2.37	39	.02	.29

As table 3 shows (and as you can see at the arithmetic means in table 2), the reaction times under the no cue and double cue condition differ from each other significantly ($p < .0125$). Similar to the results of the ANOVA for the main factor “cue” these results show that participants provide a faster reaction time under the double cue condition than under the no cue condition. This shows that they profit from a warning cue. The t-tests for paired samples for the factors no cue Escitalopram, no cue placebo and double cue Escitalopram, double cue placebo did not show a significant difference, similar to the results of the ANOVA for the main factor “substance”. There was no significant interaction between the three main factors “cue condition” “length of intake” and “substance” ($F(1, 38) = .23, p = \text{n.s.}$).

Calculated effect sizes validate the results of the t-tests. Medium effects can be seen comparing no cue and double cue, almost no effects comparing no cue Escitalopram, no cue placebo ($M_{\text{noEscitalopram}} / M_{\text{noPlacebo}}$) and double cue Escitalopram, double cue placebo ($M_{\text{doubleEscitalopram}} / M_{\text{doublePlacebo}}$) as seen in table 3.

Another conducted t-test revealed results for the difference of double cue under Escitalopram minus no cue under Escitalopram ($\Delta E_{\text{Alerting}}$) and double cue under placebo minus no cue under placebo ($\Delta P_{\text{Alerting}}$) (see table 3). The results of the t-test are not significant, but show a tendency in difference of $\Delta E_{\text{Alerting}}$ and $\Delta P_{\text{Alerting}}$. Subjects under the influence of Escitalopram tend to profit less from warning cues than under the influence of placebo. A calculated effect size shows that the effect is only a small one with $ES = .29$.

4.2 Results for the mean reaction time

We carried out a 2 (substance) $\times$ 2 (length of intake) ANOVA of the mean reaction time data of the ANT. The arithmetic mean of the individual mean reaction times and standard deviations are found in table 4.

Table 4: Arithmetic mean (M) of individual mean reaction times (mRT) and standard deviations (SD) of ANT variables in ms for participants joining the challenge group (C) and the steady-state group (S), taking Escitalopram (E) versus placebo (P).

	Challenge	Steady-state	Total (C+S)
	$N = 20$	$N = 20$	$N = 40$
	$M (SD)$	$M (SD)$	$M (SD)$
mRT Escitalopram	467 (70)	453 (37)	460 (56)
mRT Placebo	462 (52)	453 (30)	458 (42)
Total (E+P)	465 (61)	453 (34)	459 (49)

No significant main effect was found for the factor “substance” ($F(1, 38) = .16, p = \text{n.s.}$) nor for the factor “length of intake” ($F(1, 38) = .62$ and $p = \text{n.s.}$). This means that the intake of Escitalopram/placebo and the length of intake did not influence participants’ overall mean reaction time significantly. There was also no significant interaction found for the two main factors ($F(1, 38) = .19, p = \text{n.s.}$).

The results of the first factor “substance” were endorsed by calculating an effect size of $ES = .04$. The effect size for the second factor “length of the intake” demonstrated a very small effect of $ES = .24$. The following two graphs present the reaction times of ANT data under Escitalopram and placebo as well as the difference in length of intake.

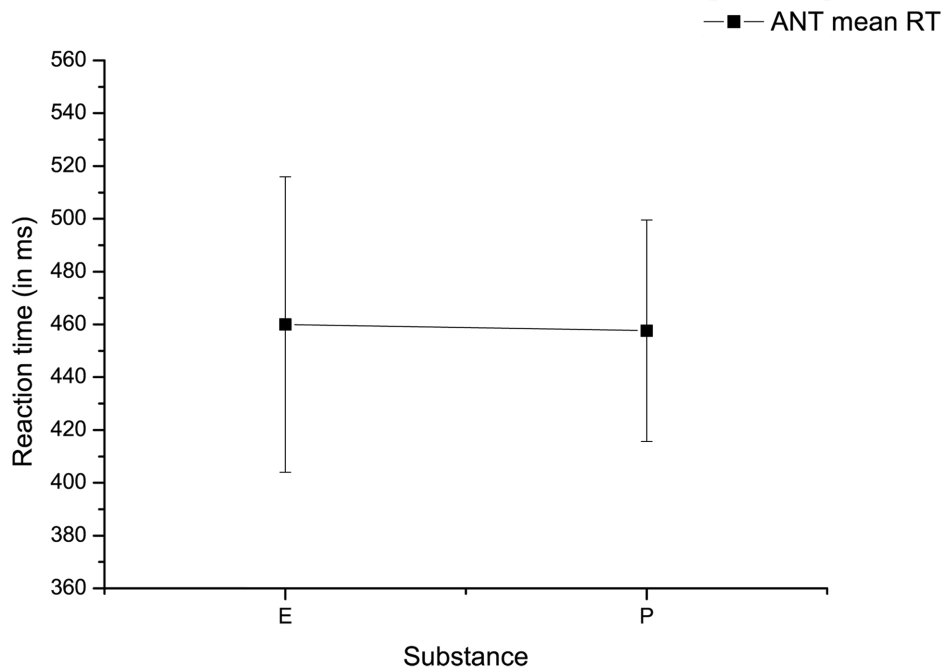


Figure 10: Mean reaction time under administration of Escitalopram (E) or placebo (P).

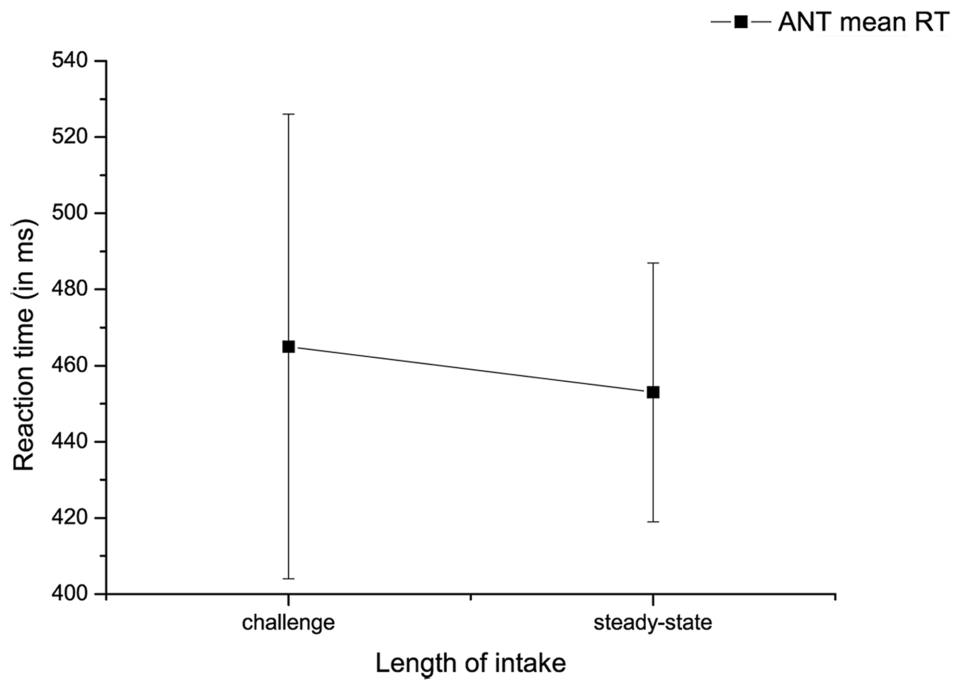


Figure 11: Mean reaction time for the challenge as well as steady-state group.

5 Discussion

5.1 Summary of major results

The primary aim of the study was to investigate the effects of Escitalopram 10 mg in a challenge as well as steady-state paradigm on phasic and tonic alertness. Our results demonstrate that single and repeated doses of Escitalopram 10 mg neither affected the phasic nor the tonic alertness of young healthy volunteers.

The results from calculations for phasic alertness show that in both groups (challenge as well as steady-state) responses were faster when the target was preceded by presenting a cue before the target stimulus (double cue) than when it was not (no cue), but those results are not related to an influence of Escitalopram. There was also a significance concerning the interaction of the two factors “cue” and “substance”. Probably the largest part of this significance can be explained by the fact that the no cue and double cue condition differed from each other to a major extent after intake of Escitalopram as well as placebo. Additionally to that, we looked at the difference of “double cue Escitalopram” and “no cue Escitalopram” ($\Delta E_{\text{Alerting}}$) compared with the difference of “double cue placebo” and “no cue placebo” ($\Delta P_{\text{Alerting}}$). These differences, $\Delta E_{\text{Alerting}}$ and $\Delta P_{\text{Alerting}}$ are measures for what we call “phasic alertness”. It describes the participants’ ability to increase response readiness when a usual target (no cue) is preceded by a warning stimulus (double cue). Results of the calculated t-test revealed the tendency that participants under the influence of Escitalopram did not profit as much from a warning condition as participants under the influence of placebo, as the alerting effect under Escitalopram is smaller than under placebo. However, as a matter of fact, the difference between $\Delta E_{\text{Alerting}}$ and $\Delta P_{\text{Alerting}}$ is really small and only has a value of 6 ms. Calculated effect sizes additionally showed a minor effect for this difference. Furthermore the results for the no cue and double cue condition of participants under Escitalopram are quite inhomogenous. The variance of the results under Escitalopram are of larger diversity than those of the results under placebo. This can play an accessory role when interpreting the significance of interaction of the two main factors “cue” and “substance”. All these conditions still make it doubtful whether Escitalopram really has an influence on phasic alertness. For the second object it can be stated that Escitalopram has no influence on the mean reaction time of the ANT. Therewith it can be interpreted that tonic alertness is not influenced by Escitalopram.

The results of the present study are in accordance with the results of Wingen et al. (2005, 2007) who did not find an effect of Escitalopram (10 - 20 mg) on two different reaction time tasks in an acute and steady-state treatment phase as well as on the Mackworth Clock vigilance paradigm (MCT). Additionally, there are several other studies that used a Choice Reaction Time test (CRT) as a measure of sensorimotoric performance and psychomotoric

speed with equal results for other SSRIs than Escitalopram namely for citalopram, paroxetine, fluoxetine, fluvoxamine and sertraline either (Fairweather et al., 1996; 1997; Loubinoux et al., 2005; Rammsayer & Netter, 1988; Siepmann et al., 2003).

5.2 Neuropsychological tests of vigilance and alertness

In contrast to our study, several results of the vigilance-paradigm MCT showed impairments of the latter after administration of citalopram, fluoxetine and paroxetine (Ramaekers et al., 1995; Riedel et al., 2005; Schmitt et al., 2002a).

The MCT has been widely used to study human vigilance performance (Schmitt et al., 2006; Wingen et al., 2007). 30 signals are presented during the length of the task comprising of 45 minutes, with intervals ranging from 8 seconds to 7.2 minutes, which means that the event rate is quite low. In contrast to this assessment, the ANT provides a precise measure of tonic alertness by measuring the overall mean reaction time over all cue conditions (no cue, double cue, centre cue, spatial cue). The ANT also assesses the phasic alertness by measuring the reaction time with presentation of a warning cue (double cue condition) minus the reaction time without a warning cue (no cue condition) by providing a very high event rate. So even though the term tonic alertness is sometimes used synonymously with vigilance, alertness and vigilance are assessed differently in this example. The difference between an alertness task and a vigilance task is seen in the frequency with which targets are presented. Under vigilance conditions, targets have a low frequency of occurrence, thus resulting in extremely monotonous situations, which demand mental effort and conscious volition over a period of at least 30 minutes (Sturm & Willmes, 2001). MCT and ANT differ from each other in too many aspects to be directly compared to each other. In this regard it is not surprising that our results of the ANT differ from those of the MCT.

In the past, it has been argued that short-term, high demanding cognitive assessment may not be as sensitive to subtle drug effects as vigilance assessments, as subjects may enhance or reduce compensatory effort, depending on the conditions the drug provides (Clark et al., 1986; Kahnemann, 1973; Oken et al., 1995). Those compensatory mechanisms are unlikely to be maintained during long lasting vigilance tasks (Schmitt et al., 2006). Therefore, we cannot be sure how sensitive the results of the ANT are to subtle drug effects produced by such a selective enhancer of 5-HT as we used in this paradigm.

5.3 Pharmacological properties of diverse SSRIs

The discrepancy between previous studies addressing the relationship between SSRIs and attention and the present study may be related to the relative potencies of the SSRIs for reuptake inhibition. Paroxetine and sertraline seem to be the most potent 5-HT reuptake

inhibitors (Hyttel, 1994). It has been suggested that subtle, but significant affinities in selective serotonin reuptake inhibitors for other receptor systems than the 5-HT reuptake transporter do exist: citalopram shows moderate, additional affinity to histaminergic H_1 receptors (Burke, 2002), paroxetine to norepinephrine reuptake receptors and muscarinic cholinergic receptors (Sanchez & Hyttel, 1999), fluvoxamine and fluoxetine to norepinephrine reuptake receptors and sertraline to dopamine and norepinephrine reuptake receptors (Hyttel, 1994). Those additional affinities have to be taken into account when interpreting the results of previous studies. The affinity to H_1 receptors for example may be associated with mild sedation, which could reflect the results of Riedel et al. (2005), who found an impairment of citalopram on the MCT. The absence of an impaired vigilance performance (MCT) after sertraline could be explained by the affinity of sertraline to block dopamine reuptake (Bolden-Watson & Richelson, 1993) for dopamine is an excitatory neurotransmitter in attentional processes. Escitalopram is the most selective SSRI available and possesses no or only very little affinity for serotonin 5-HT₁₋₇, dopamine D₁₋₅, alpha- and beta-adrenergic, histamine H₁₋₃, muscarinic M₁₋₅ and benzodiazepine receptors, nor on various ion channels including Na⁺, K⁺, Cl⁻, Ca²⁺ channels (Aronson & Delgado, 2004; Waugh & Goa, 2003).

5.4 Modulation of the norepinephrine system by serotonin

Even though Escitalopram is such a selective enhancer of central 5-HT, it may also influence other transmitter systems through indirect actions involving other neurotransmitter. Serotonin (5-HT) is thought to be a modulatory neurotransmitter, which has inhibitory influences over cortical norepinephrine (NE) (Robbins, 1997; Schmitt et al., 2002a); NE is able to alter alerting functions. As early as 1977, Pickel et al. found out that the activity of noradrenergic neurons may be modulated by a direct action of 5-HT neurons. The Locus Coeruleus (LC) receives dense 5-HT projections coming from dorsal raphe and pericoerulear 5-HT neurons (Kaehler et al., 1999). In accordance with several electrophysiological and biochemical studies, the existence of a tonic inhibition LC NE neurons by 5-HT afferents has been suggested (Blier & Szabo, 2005; Haddjeri et al., 1997; Leger & Descarries, 1978; Segal, 1979), partially due to an increased activation of the inhibitory input of GABA to the LC (Chiang & Aston-Jones, 1993). This is supported by the observation that neurotoxic lesioned 5-HT neurons produced a marked elevation of firing rate of NE neurons (Haddjeri et al., 1997). The tonic inhibitory effects on norepinephrinergic neurons are mediated mainly via 5-HT_{2C} inhibitory receptors (Millan et al., 1998).

Subchronic augmentation of serotonergic activity by SSRI administration inhibits norepinephrinergic transmission as demonstrated in rodents (Grant & Weiss, 2001; Szabo et al., 1999; 2000; Szabo & Blier, 2002), which could subsequently result in diminished performances in alertness and vigilance task. However, the present study did only reveal a ten-

dency of inhibitory activity of serotonin on NE neurons for measures of phasic alertness, for a major decrement in tonic and phasic alertness could not be demonstrated. The degree of decrements in NE might not be strong enough in the present study to reveal a significant effect on the results of the ANT.

5.5 Route of administration, dosage, length of intake

To enhance central 5-HT we used an oral dose of 10 mg/day Escitalopram, which is the recommended starting dosage for treatment of major depression disorder. Depending on the individual patient response, it may be titrated to a maximum dosage of 20 mg/day. The dosage of 10 mg or 20 mg a day showed similar efficacy to citalopram 40 mg/day (Waugh & Goa, 2003). It is possible that a higher dosage of 20 mg would have shown greater effects. On the other hand, it was shown that 20 mg of Escitalopram were associated with higher rates of adverse effects (Aronson & Delgado, 2004). In the present study, we did not want to risk a drop out of participants owing to adverse side effects. Wingen et al. (2007) used oral doses of 20 mg of Escitalopram to enhance central 5-HT, but nevertheless did not find any effect on vigilance.

Another problem for human psychopharmacology is that oral administration of a drug proceeds necessarily via the peripheral or systemic route, which means that it is almost impossible to define its kind of action in the brain or to untie its many different effects both centrally and peripherally at different groups of receptors (Robbins, 1997). Specific action on attentional and cognitive functions is likely to be masked or confounded by other actions of the drug, that we do not know of yet.

Enumerated studies and the present also differ in the length of subchronic administration. Other studies like the one of Wingen et al. (2005) had their participants take Escitalopram for 15 days. In our study the subchronic administration included 7 days of intake. It was previously shown that Escitalopram caused reductions in the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impressions-Improvement (CGI-I) as early as one week of treatment (Lepola et al., 2003). Therefore we used a 7 day treatment period for the steady-state paradigm. Maybe a longer time range of intake would have shown greater effects compared to a single intake. Yet, there should be an ethic limit of the intake period which is reasonable for healthy volunteers.

Taken together, the discrepancies in outcome possibly result from inconsistencies in type of the used test, selectivity of the serotonergic manipulation in dosage, route of administration (e.g. oral versus i.v.) and length of intake. This makes it extremely difficult to reach a uniform conclusion about the role of 5-HT in alertness.

5.6 Limitations

There are a number of potential limitations to consider when interpreting the study outcomes: A potential limitation of the present study is the selective sample of participants: All participants were of male gender and were restricted to an age range of 18 - 39 years. It can generally be assumed that elderly people are more vulnerable to side effects from pharmacological treatment than younger participants. Generalization of results from experimental studies in young volunteers to the elderly population has to be done with caution.

According to Schmitt et al. (2006) there is increasing evidence that low 5-HT is at least partially related to cognitive problems. Those populations lacking a certain level of central 5-HT may specifically profit from pro-serotonergic pharmacological therapies that shift central 5-HT neurotransmission to a more optimal level, thereby normalizing cognitive function. The present study was limited to healthy volunteers. In contrast to patients, in healthy volunteers there should be no performance deficits due to a compromised 5-HT system. It is apparent that a balanced transmitter system might be difficult to alter. As healthy volunteers already operate close to their optimal cognitive performance level, cognitive enhancement is generally difficult to achieve. Additionally, healthy volunteers might be able to develop redeeming strategies and compensating interventions to repel the potential effects of Escitalopram intentionally. As such, assessing cognitive changes of altered central 5-HT levels in healthy volunteers is a valuable method to identify the fundamental role of 5-HT in cognition, thereby providing a path to investigate possible serotonergic mechanisms underlying impaired cognition in patients suffering from certain pathologies. It should be an interesting prospect to test cognitive effects of Escitalopram on patients that already suffer from an unbalanced central 5-HT system.

The present study was conducted as a placebo-controlled double blind design. Still there are further limitations due to methodological reasons: Fan et al. (2002) developed the Attention Network Test (ANT) to assess the three major functions of attention: orienting, executive control and alerting as well as the overall mean reaction time within a single task. With a test-retest correlation of $r = .52$, the alerting network is the least reliable among the four, whereas the raw reaction time highly correlated between two sessions ($r = .87$) (Fan et al., 2002). Besides the ANT there are other psychometric tests to assess alertness, for example the subtest "alertness" from the "Testbatterie zur Aufmerksamkeitsüberprüfung" (TAP), provided by Zimmermann and Fimm in 2002. For future studies measuring the alertness, it could be interesting to additionally use the "alerting" subtest of the TAP to validate the results of the ANT.

Another methodological consideration concerns the timing of administration of tests. Conducted after a 3-hour period, the timing of sessions in the present study was based on the pharmacokinetic profile of Escitalopram, where testing sessions were to coincide with the

approximate time at which plasma concentrations of the drug peaked. According to Aronson and Delgado (2004), the mean peak level following 20 mg Escitalopram occur at 3 ± 1.5 hours. Burke (2002) described maximal plasma concentrations of Escitalopram approximately 4 hours after administration and Waugh and Goa (2003) even stated maximal peak concentrations 4 - 5 hours after administration. Nevertheless, it has been recognized that plasma levels may not necessarily correlate with the behavioural effects (Lader et al., 1986). Therefore, a clear conclusion about the role of the plasma peak is not possible at this point. When considering methodological limitations, it has to be stated that no control of drug intake of the steady-state group was performed. Participants received Escitalopram as well as placebo at the beginning of the week and took the drugs home. In advance participants received particular intake-information and assured to take the drugs as demanded. Still we can not be definite on the compliance of each participant.

Plasma concentration levels were also not taken into account. In the review of Waugh and Goa (2003) it was shown that there is a response rate for patients to treatment of 50 - 63.7 %. Even if all participants were compliant, we can not line out that some of the participants were non-responders and therefore did not establish an adequate plasma concentration of Escitalopram.

5.7 Training effect

By looking at the present data more precisely, we found out that there was an obvious training effect in the ANT-data: Three 2×2 ANOVAs were calculated with the main factors: a) mean reaction time (first session, second session) and length of intake (1 day, 7 days); b) no cue condition (first session, second session) and length of intake (1 day, 7 days) and c) double cue condition (first session, second session) and length of intake (1 day, 7 days) of ANT-data. Arithmetic means are pictured in table 5.

Table 5: Arithmetic mean (M) and standard deviations (SD) of individual mean reaction time (mRT), no cue and double cue condition in ms for participants joining the challenge group (single dose) (C) and the steady-state group (7 day intake) (S), on their first and second session of measurement.

	Challenge	Steady-State	Total (C+S)
	$N = 20$	$N = 20$	$N = 20$
	$M (SD)$	$M (SD)$	$M (SD)$
mRT			
1. session	473 (65)	460 (38)	467 (53)
2. session	456 (56)	446 (27)	451 (44)
no cue			
1. session	496 (69)	489 (38)	493 (55)
2. session	485 (59)	477 (30)	481 (46)
double cue			
1. session	471 (68)	455 (41)	463 (56)
2. session	452 (59)	442 (29)	447 (46)

In the first ANOVA a statistical significant main effect was found for the factor “mean reaction time” ($F(1, 38) = 8.98, p = .01$), in the second ANOVA for the factor “no cue condition” ($F(1, 38) = 6.83, p = .01$) reached significance and in the third ANOVA for the factor “double cue condition” ($F(1, 38) = 15.57, p = .00$) became significant. This demonstrates that participants provided significantly faster reaction times in all three conditions (mean RT, no cue condition, double cue condition) on the second time they performed the ANT. Comparing the challenge and the steady-state group, larger effects were seen on the steady-state group, presumably mainly because of smaller standard deviations (demonstrated in table 5).

The main factor “length of intake” did not achieve significance in any of the three ANOVAs. Also, there was no interaction found for “mean reaction time” and “length of intake”, “no cue condition” and “length of intake” as well as “double cue condition” and “length of intake”. Calculated effect sizes after Cohen (1988) revealed small effects and are demonstrated in table 6.

Table 6: Effect sizes (*ES*) of mean values (mean reaction time (mRT), no cue condition (no) and double cue condition (double) in first (s1) and second (s2) session in the challenge group ($N = 20$), steady-state group ($N = 20$) as well as altogether ($N = 40$)).

effect	<i>ES</i>
$M_{mRT_{s1}} / M_{mRT_{s2}} N = 40$	.33
$M_{no_{s1}} / M_{no_{s2}} N = 40$	.23
$M_{double_{s1}} / M_{double_{s2}} N = 40$	.31
$M_{mRT_{s1}} / M_{mRT_{s2}} \text{ challenge}$	.27
$M_{no_{s1}} / M_{no_{s2}} \text{ challenge}$	.17
$M_{double_{s1}} / M_{double_{s2}} \text{ challenge}$	.29
$M_{mRT_{s1}} / M_{mRT_{s2}} \text{ steady-state}$	.42
$M_{no_{s1}} / M_{no_{s2}} \text{ steady-state}$	.34
$M_{double_{s1}} / M_{double_{s2}} \text{ steady-state}$	.36

A graphic demonstration of the training effect can be seen in figure 12.

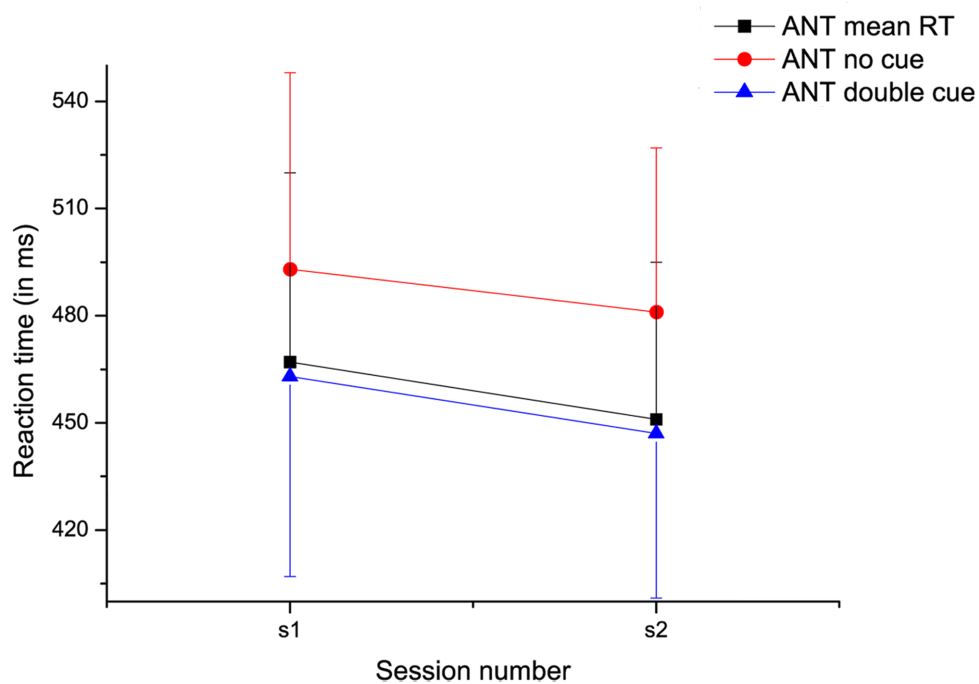


Figure 12: Training effect comparing results of the ANT from session 1 (s1) and session 2 (s2).

Fan et al. (2002) stated that there is little evidence for major practice effects in the ANT since the different scores did not change significantly between sessions, although the overall reaction times of the second session were faster than those of the first session in the study of Fan et al. (2002). Indeed, effect sizes of the present study only show small and not major effects comparing the sessions, but still there is evidence that participants profit from knowing the test at the second session and providing shorter reaction times in all three conditions. For methodical reasons, drug effects on the ANT could be interpreted more precisely, if participants were trained on the ANT prior to the study, thereby eliminating a training effect to some extent.

5.8 Conclusion

Cognitive impairment, psychomotor retardation and autonomic disturbances are among the characteristic features of clinical depression (Siepmann et al., 2003). Impairment of attention and reaction times may interfere with the performance of every day tasks. The sedative effect induced by antidepressants like tricyclic antidepressants may be counter therapeutic, since they can hinder improvement in some of the cognitive manifestations of depression (Kerr et al., 1991). Antidepressants without sedative adverse effects and associated cognitive impairment are essential for maintaining a maximum therapeutic response in patients with depression.

In summary, current findings suggest that single and subchronic administration of Escitalopram do not affect tonic and phasic alertness in young, healthy volunteers. We could not demonstrate any obvious facilitating nor reducing effects of Escitalopram on tonic alertness and only found a tendency towards a reduction of phasic alertness. This indicates the conclusion that Escitalopram may represent a therapeutic advance in antidepressant therapy, especially when compared with the considerable sedative effects of existing therapies. Further research should try to reply the results after eliminating some of the limitations discussed above. It would be interesting to investigate the effect of different doses of Escitalopram on other measures of attention as well as on different cognitive processes in healthy volunteers, but also in patients suffering from depression.

6 References

- Amado-Boccaro, I., Gougoulis, N., Poirier Littré, M.F., Galinowski, A., Loo, H. (1995). Effects of antidepressants on cognitive functions: a review. *Neuroscience and Biobehavioral Reviews*, 19 (3), 479-493.
- Arango, V., Underwood, M.D., Mann, J.J. (2002). Serotonin brain circuits involved in major depression and suicide. *Progress in Brain Research*, 136, 443-453.
- Aronson, S., Delgado, P. (2004). Escitalopram. *Drugs Today (Barc)*, 40 (2), 121-131.
- Artigas, F., Bel, N., Casanovas, J.M., Romero, L. (1996). Adaptive changes of the serotonergic system after antidepressant treatments. *Advances in Experimental Medicine and Biology*, 398, 51-59.
- Aston-Jones, G., Rajkowski, J., Kubiak, P., Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience*, 14 (7), 4467-4480.
- Bearden, C.E., Hoffmann, K.M., Cannon, T.D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disorders*, 3, 106-150.
- Blier, P., de Montigny, C. (1994). Current advances and trends in the treatment of depression. *Trends in Pharmacological Sciences*, 15 (7), 220-226.
- Blier, P., Szabo, S.T. (2005). Potential mechanism of action of atypical antipsychotic medications in treatment-resistant depression and anxiety. *Journal of Clinical Psychiatry*, 66 (suppl 8), 30-40.
- Bolden-Watson, C., Richelson, E. (1993). Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sciences*, 52, 1023-1029.
- Buhot, M.-C. (1997). Serotonin receptors in cognitive behaviours. *Current Opinion in Neurobiology*, 7, 243-254.
- Burke, W.J. (2002). Escitalopram. *Expert Opinion on Investigational Drugs*, 11 (10), 1477-1486.
- Chiang, C., Aston-Jones, G. (1993) A 5-hydroxytryptamine₂ agonist augments gamma-aminobutyric acid and excitatory amino acid inputs to noradrenergic locus coeruleus neurons. *Neuroscience*, 54 (2), 409-420.
- Clark, C.R., Geffen, G.M., Geffen, L.M. (1986). Role of monoamine pathways in attention and effort: effects of clonidine and methylphenidate in normal adult humans. *Psychopharmacology*, 90 (1), 35-39.

-
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.
- Corbetta, M., Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3 (3), 201-215.
- Coull, J.T., Middleton, H.C., Robbins, T.W., Sahakian, B.J. (1995). Clonidine and diazepam have differential effects on tests of attention and learning. *Psychopharmacology*, 120 (3), 322-332.
- Coull, J.T., Nobre, A.C., Frith, C.D. (2001). The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cerebral Cortex*, 11 (1), 73-84.
- Coull, J.T., Sahakian, B.J., Hodges, J.R. (1996). The alpha(2) antagonist idazoxan remedies certain attentional and executive dysfunction in patients with dementia of frontal type. *Psychopharmacology*, 123 (3), 239-249.
- Dahlstroem, A., Fuxe, K. (1964). Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiologica Scandinavica*, 62 (Suppl. 232), 1-55.
- Danjou, P., Warot, D., Hergueta, T., Lacomblez, L., Bouhours, P., Puech, A.J. (1992). Comparative study of the psychomotor and antistress effects of ritanserin, alprazolam and diazepam in healthy subjects: some trait anxiety-independent responses. *International Clinical Psychopharmacology*, 7, 73-79.
- Davidson, M.C., Marrocco, R.T. (2000). Local infusion of scopolamine into intraparietal cortex slows covert orienting in rhesus monkeys. *Journal of Neurophysiology*, 83 (3), 1536-1549.
- El Mansari, M.E., Sánchez, C., Chouvet, G., Renaud, B., Haddjeri, N. (2005). Effects of acute and long-term administration of escitalopram and citalopram on serotonin neurotransmission : an in vivo electrophysiological study in rat brain. *Neuropsychopharmacology*, 30 (7), 1269-77.
- Elvevag, B., Goldberg, T.E. (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Critical Reviews in Neurobiology*, 14, 1-21.
- Fairweather, D.B., Ashford, J., Hindmarch, I. (1996). Effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers. *Pharmacology, Biochemistry and Behavior*, 53 (2), 265-269.
- Fairweather, D.B., Dal Pozzo, C., Kerr, J.S., Lafferty, S.V., Hindmarch, I. (1997). Citalopram compared to dothiepin and placebo: effects on cognitive function and psychomotor performance. *Human Psychopharmacology*, 12, 119-126.

- Fan, J., McCandliss, B.D., Fossella, J., Flombaum, J.I., Posner, M.I. (2005). The activation of attentional networks. *Neuroimage*, 26 (2), 471-479.
- Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, 14 (3), 340-347.
- Fan, J., Posner, M.I. (2004). Human Attentional Networks. *Psychiatrische Praxis*, 31 (Suppl. 2), 210-214.
- Fernandez-Duque, D., Posner, M.I. (2001). Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology*, 23 (1), 74-93.
- Gallagher, P., Massey A.E., Young, A.H., McAllister-Williams R.H. (2003). Effects of acute tryptophan depletion on executive function in healthy male volunteers. *BMC Psychiatry*, 3 (10), Epub 2003 Aug 4.
- Grant, M.M., Weiss, J.M. (2001). Effects of chronic antidepressant drug administration and electroconvulsive shock on locus coeruleus electrophysiology activity. *Biological Psychiatry*, 49, 117-129.
- Haddjeri, N., de Montigny, C., Blier, P. (1997). Modulation of the firing activity of noradrenergic neurones in the rat locus coeruleus by the 5-hydroxytryptamine system. *British Journal of Pharmacology*, 120 (5), 865-875.
- Hedges, L.V., Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando: Academic Press.
- Hindmarch, I. (1995). The behavioural toxicity of the selective serotonin reuptake inhibitors. *International Clinical Psychopharmacology*, 9 (Suppl 4), 13-17.
- Hindmarch, I., Bhatti, J. (1988). Psychopharmacological effects of sertraline in normal, healthy volunteers. *European Journal of Clinical Pharmacology*, 35, 221-223.
- Hyttel, J. (1994). Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *International Clinical Psychopharmacology*, 9 (Suppl. 1), 19-26.
- Internetresource: www.lexapro.com
- Kaehler, S.T., Singewald, N., Philippu, A. (1999). Release of serotonin in the locus coeruleus of normosensitive and spontaneously hypertensive rats (SHR). *Naunyn-Schmiedeberg's Archives of Pharmacology*, 359 (6), 460-465.
- Kahnemann, D. (1973). *Attention and Effort*. Englewood Cliffs, NJ: Prentice-Hall.

- Kerr, J.S., Fairweather, D.B., Mahendran, R., Hindmarch, I. (1992). The effects of paroxetine, alone and in combination with alcohol on psychomotor performance and cognitive function in the elderly. *International Clinical Psychopharmacology*, 7, 101-108.
- Kerr, J.S., Sherwood, N., Hindmarch, I. (1991). The comparative psychopharmacology of 5-HT reuptake inhibitors. *Human Psychopharmacology*, 6, 313-317.
- Lader, M., Melhuish, A., Frcka, G., Fredricson Overo, K., Christensen, V. (1986). The effects of citalopram in single and repeated doses and with alcohol on physiological and psychological measures in healthy subjects. *European Journal of Clinical Pharmacology*, 31, 183-190.
- Lawrence, J.R., McEwen, J., Stonier, P.D., Pidgen, A.W. (1982). Pupil size and critical flicker fusion threshold: a reevaluation. *Drug Development Research*, 2 (Suppl 1), 67-75.
- Lee, M.A., Meltzer H.Y., (2001). 5-HT(1A) receptor dysfunction in female patienta with schizophrenia. *Biological Psychiatry*, 50 (10), 758-766.
- Leger, L., Descarries, L. (1978). Serotonin nerve terminals in the locus coeruleus of adult rat: a radioautographic study. *Brain Research*, 145 (1), 1-13.
- Lepola, U.M., Loft, H., Reines, E.H. (2003). Escitalopram (10-20 mg /day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *International Clinical Psychopharmacology*, 18 (4), 211-217.
- Loubinoux, I., Tombari, D., Pariente, J., Gerdelat-Mas, A., Franceries, X., Cassol, E., Rascol, O., Pastor, J., Chollet, F. (2005). Modulation of behaviour and cortical motor activity in healthy subjects by a chronic administration of a serotonin enhancer. *Neuroimage*, 27 (2), 299-313.
- Mackworth, N.H. (1948). The breakdown of vigilance during prolonged visual search. *The Quarterly Journal of Experimental Psychology*, 1, 6-21.
- Mahmood, T., Silverstone T. (2001). Serotonin and bipolar disorder. *Journal of Affective Disorders*, 66, 1-11.
- Marrocco, R.T., Davidson, M.C., (1998). Neurochemistry of attention. In: Parasuraman, R. (Ed.), *The Attentive Brain* (pp. 35-50). Cambridge, MA: Massachusetts Institute of Technology Press.
- Mattila, M.J., Saarialho-Kere, U., Mattila, M. (1988). Acute effects of sertraline, amitriptyline, and placebo on the psychomotor performance of healthy subjects over 50 years of age. *Journal of Clinical Psychiatry*, 49 (Suppl 8), 52-58.
- McDowell, S., Whyte, J., D'Esposito, M. (1998). Differential effect of dopaminergic agonist on prefrontal function in traumatic brain injury patients. *Brain*, 121, 1155-1164.

- Meythaler, J.M., Depalma, L., Devivo, M.J., Guin-Renfroe, S., Novack, T.A. (2001). Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. *Brain Injury*, 15 (4), 321-331.
- Millan, M.J., Dekeyne, A., Gobert, A. (1998). Serotonin (5-HT)_{2C} receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. *Neuropharmacology*, 37, 953-955.
- Moore, R.Y., Bloom, F.E. (1979) Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annual Review of Neuroscience*, 2, 113-168.
- Murphy, C.F., Alexopoulos, G.S. (2006). Attention network dysfunction and treatment response of geriatric depression. *Journal of Clinical and Experimental Neuropsychology*, 28, 96-100.
- Nakamura, K., Kurasawa, M. (2000). Serotonergic mechanisms involved in the attentional and vigilance task performance of rats and the palliative action of aniracetam. *Naunyn-Schmiedelberg's Archives of Pharmacology*, 361, 521-528.
- Nathan, P.J., Sitaram, G., Stough, C., Silberstein, R.B., Sali, A. (2000). Serotonin, noradrenaline and cognitive function: a preliminary investigation of the acute pharmacodynamic effects of a serotonin versus a serotonin and noradrenaline reuptake inhibitor. *Behavioural Pharmacology*, 11, 639-642.
- Niemann, H., Gauggel, S. (2005). Störungen der Aufmerksamkeit. In: Karnath, H.-O., Hartje, W., Ziegler, W. (Ed.) *Kognitive Neurologie* (pp. 110-125). Stuttgart: Georg Thieme Verlag.
- Oken, B.S., Kishiyama, S.S., Salinsky, M.C. (1995). Pharmacologically induced changes in arousal: effects on behavioral and electrophysiologic measures of alertness and attention. *Electroencephalography and Clinical Neurophysiology*, 5, 359-71.
- Parasuraman, R., Warm, J.S., See, J.E. (1998). Brain System of Vigilance. In: Parasuraman, R. (Ed.), *The Attentive Brain* (pp. 221-256). Cambridge, MA: Massachusetts Institute of Technology Press.
- Pickel, V.M., Hyub Joh, T.H., Reis, D.J. (1977). A serotonergic innervation of noradrenergic neurons in nucleus locus coeruleus: demonstration by immunocytochemical localization of the transmitter specific enzymes tyrosine and tryptophan hydroxylase. *Brain Research*, 131(2), 197-214.
- Porter, R.J., Gallagher P., Thompson, J.M., Young, A.H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *British Journal of Psychiatry*, 182, 214-220.

-
- Posner, M.I. (1978). *Chronometric Explorations of Mind*. Hillsdale, New York: Lawrence Erlbaum.
- Posner, M.I., Fan, J. (2007). Attention as an organ system. In: Pomerantz, J. (Ed.), *Neurobiology of Perception and Communication: from Synapse to Society*. London: Cambridge University Press. In press.
- Posner, M.I., Peterson, S.E. (1990). The attention system of the human brain. *Annual Reviews of Neuroscience*, 13, 25-42.
- Posner, M.I., Rothbart, M.K. (2007). Research on attention networks as a model for the integration of psychological science. *Annual Review of Psychology*, 58, 1-23.
- Ramaekers, J.G., Muntjewerff, N.D., O'Hanlon, J.F. (1995). A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *British Journal of Clinical Pharmacology*, 39, 397-404.
- Rammsayer, T., Netter, P. (1988). Effects of changes in brain 5-HT activity on indicators of cortical arousal. *International Clinical Psychopharmacology*, 3 (3), 231-237.
- Ridout, F., Meadows, R., Johnsen, S., Hindmarch, I. (2003). A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance. *Human Psychopharmacology: Clinical and Experimental*, 18, 261-269.
- Riedel, W.J., Eikmans, K., Heldens, A., Schmitt, J.A.J. (2005). Specific serotonergic reuptake inhibition impairs vigilance performance acutely and after subchronic treatment. *Journal of Psychopharmacology*, 19 (1), 12-20.
- Riedel, W.J., Klaassen, T., Deutz, N.E.P., Van Someren, A., Van Praag, H.M. (1999). Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. *Psychopharmacology*, 141, 362-369.
- Robbins, T.W. (1998). Arousal and Attention: Psychopharmacological and neuropsychological studies in experimental animals. In: Parasuraman, R. (Ed.), *The Attentive Brain* (pp. 189-220). Cambridge, MA: Massachusetts Institute of Technology Press.
- Robbins, T.W., (1997). Arousal systems and attentional processes. *Biological Psychology*, 45, 57-71.
- Sanchez, C., Hyttel, J. (1999). Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. *Cellular and Molecular Neurobiology*, 19 (4), 467-489.
- Sandyk, R., (1992). L-tryptophan in neuropsychiatric disorders: a review. *The International Journal of Neuroscience*, 67, 127-144.

- Schmitt, J.A.J., Jorissen, B.L., Sobczak S., van Boxtel, M.P.J., Hogervorst, E., Deutz, N.E.P., Riedel, W.J. (2000). Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. *Journal of Psychopharmacology*, 14 (1), 21-29.
- Schmitt, J.A.J., Ramaekers, J.G., Kruizinga, M.J., van Boxtel, M.P.J., Vuurman, E.F.P.M., Riedel, W.J. (2002a). Additional dopamine reuptake inhibition attenuates vigilance decrement induced by serotonergic reuptake inhibition in man. *Journal of Psychopharmacology*, 16 (3), 207-214.
- Schmitt, J.A.J., Riedel, W.J., Vuurman, E.F.P.M., Kruizinga, M., Ramaekers, J.G. (2002b). Modulation of the critical flicker fusion effects of serotonin reuptake inhibitors by concomitant pupillary changes. *Psychopharmacology*, 160 (4), 381-386.
- Schmitt, J.A.J., Wingen, M., Ramaekers, J.G., Evers, E.A.T., Riedel, W.J. (2006). Serotonin and human cognitive performances. *Current Pharmaceutical Design*, 12, 2473-2486.
- Segal, M. (1979). Serotonergic innervation of the locus coeruleus from the dorsal raphe and its action on the responses to noxious stimuli. *Journal of Physiology*, 286, 401-415.
- Siepmann, M., Grossmann, J., Mück-Weymann, M., Kirch, W. (2003). Effects of sertraline on autonomic and cognitive functions in healthy volunteers. *Psychopharmacology*, 168, 293-298.
- Sturm, W., Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage*, 14, 76-84.
- Szabo, S.T., Blier, P. (2002). Effects of serotonin (5-Hydroxytryptamine, 5-HT) reuptake inhibition plus 5-HT_{2A} receptor antagonism on the firing activity of norepinephrine neurons. *Journal of Pharmacology and Experimental Therapeutics*, 302 (3), 983-991.
- Szabo, S.T., de Montigny, C., Blier, P. (1999). Modulation of noradrenergic neuronal firing by selective serotonin reuptake blockers. *British Journal of Pharmacology*, 126, 568-571.
- Szabo, S.T., de Montigny, C., Blier, P. (2000). Progressive attenuation of the firing activity of locus coeruleus noradrenergic neurons by sustained administration of selective serotonin reuptake inhibitors. *International Journal of Neuropsychopharmacology*, 3(1), 1-11.
- Van Praag, H.M. (1982). Serotonin precursor in the treatment of depression. In: Ho, B. T., Schoolar, J.C., Usdin, E. (Eds.), *Serotonin in biological psychiatry* (pp. 259-286). New York: Raven press.
- Waugh, J., Goa, K.L. (2003). Escitalopram: a review of its use in the management of major depressive and anxiety disorders. *CNS Drugs*, 17 (5), 343-362.

- Wingen, M., Bothmer, J., Langer, S., Ramaekers, J.G. (2005). Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: A crossover trial. *Journal of Clinical Psychiatry*, 66, 436-443.
- Wingen, M., Kuypers, K.P.C., Ramaekers, J.G. (2007). The role of 5-HT1a and 5-HT2a receptors in attention and motor control: a mechanistic study in healthy volunteers. *Psychopharmacology*, 190, 391-400.
- Zimmermann, P., Fimm, B. (2002). *Testbatterie zur Aufmerksamkeitsprüfung (TAP): Handbuch Teil 1 und 2, Version 1.7*. Herzogenrath: Psychologische Testsysteme Vera Fimm.

A Abbreviations

5-HT	serotonin
ANT	Attentional Network Test
LC	Locus Coeruleus
NE	Norepinephrine
SSRI	Selective serotonin reuptake inhibitor
MCT	Mackworth Clock Test
CFFT	Critical Flicker Fusion Threshold
CRT	Choice Reaction Time
GABA	Gamma-aminobutyric acid
TAP	Testbatterie zur Aufmerksamkeitsprüfung

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C Affix

Selbstständigkeitserklärung

Hiermit erkläre ich, dass die vorliegende Arbeit ohne unzulässige Hilfe und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt wurde und dass die aus fremden Quellen direkt oder indirekt übernommenen Gedanken in der Arbeit als solche gekennzeichnet sind.

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