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Three weeks of SSRI administration enhances the visual perceptual threshold - a randomized placebo-controlled study

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Abstract

Rationale The serotonergic system has been repeatedly linked to visual attention in general, but the effects of selective serotonin reuptake inhibitor (SSRI) on specific components of visual attention remain unknown. Changes in distinct perceptual and cognitive processes are not readily evident in most attention paradigms.

Objective In this study, we isolate basic components of visual attention to investigate potential effects of longer-term SSRI administration on non-emotional aspects of visual attention in healthy males.

Methods In a randomized double-blind placebo-controlled design, 32 young healthy males were tested on multiple attentional parameters, before and after a 3-week SSRI intervention with fluoxetine (40 mg daily) or placebo. Data were modeled with a computational theory of visual attention to derive independent estimates of five distinct components of visual attention.

Results The SSRI intervention selectively and significantly lowered the threshold for conscious visual perception. Specifically, we demonstrate that this improvement does not stem from a general increase in the speed of visual processing, as previously suggested, but specifically from a change in the perceptual threshold.

Conclusions The study provides a novel description of the attentional dynamics affected by SSRI, while supporting previous findings on attentional effects of SSRI. Furthermore, it accentuates the utility of employing accuracy-based measures of attentional performance when conducting psychopharmacological research.

Keywords SSRI · Serotonin · 5-HT · Attention · Perception · Cognition · Non-motor · Unspeeded response · Healthy · Human · TVA · Theory of visual attention

Introduction

Selective serotonin reuptake inhibitors (SSRI) range among the most prescribed drug interventions for depression. Previous experimental research has provided growing insight into potential SSRI-driven effects on emotional aspects of

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perception and affective cognition (Bar-Haim et al. 2007; Harmer et al. 2006). However, it remains to be established whether SSRIs specifically affect basic functions of visual cognition, such as early perceptual processes, in acute as well as in prolonged intervention regimes (Nathan et al. 2000; Schmitt et al. 2002).

Answers to such questions would be relevant to both pharmacological and non-pharmacological attention research. Even subtle changes in early perceptual stages of cognition might generate downstream effects, and a better understanding of the perceptual effects of SSRI may hence elaborate on or disentangle heterogeneous results in previous studies of SSRI and visual cognition. Therefore, we aimed to investigate the potential effects of prolonged SSRI administration on basic aspects of visual attention in a randomized controlled trial (RCT). To clarify previously diverse findings, we applied a theoretically founded and experimentally well-established test paradigm in the field of visual attention research, the CombiTVA paradigm (Vangkilde et al. 2011). In addition,

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we set out to probe the potential relevance of the framework offered by the theory of visual attention (TVA; Bundesen 1990) for SSRI attention studies.

Some evidence supports a relationship between serotonin (5-hydroxytryptamine, 5-HT) and visual attention. Serotonergic transmission is an integrated part of the neurochemistry of brain areas involved in attentional processing. Indeed, manipulation of the 5-HT system regulates the neuronal firing mode in structures involved in visual attention, such as the retina, the visual cortex, and the thalamus (Brunken et al. 1993; McCormick and Wang 1991; Monckton and McCormick 2002; Moreau et al. 2013). The 5-HT system projects to almost every part of the central nervous system and has been suggested to play a coordinating role between sensory and motor patterns of processing in different behavioral states (Aghajanian and Sanders-Bush 2002; McCormick and Wang 1991). Most thalamic neurons exhibit two distinct patterns of action potential generation, rhythmic burst firing, and single-spike activity, depending on the behavioral state. Rhythmic burst firing is most prevalent during periods of inattentiveness, drowsiness, and slow-wave sleep, while single-spike firing is the more prevalent mode during periods of attentiveness and vigilance (Steriade and Llinás 1988). Shifts in firing mode are determined by the status of activity in ascending serotonergic, noradrenergic, and cholinergic systems from the brainstem and descending cholinergic projections from the basal forebrain (McCormick and Wang 1991; Pape and McCormick 1989).

Animal studies show that 5-HT manipulation affects attentional processes in visual discrimination tasks and spatial learning task and can be found both after down- and upregulation of serotonergic transmission (Carli and Samanin 1992, 2000; LaRoche and Morgan 2007; Winstanley et al. 2003). Despite distinct differences in the doses that were applied, studies in humans are generally in agreement with animal-based SSRI research (Nord et al. 2013). Human neuroimaging studies suggest that 5-HT is involved in response selection or integration of external stimuli and behavioral states (Aghajanian and Sanders-Bush 2002; McCormick and Wang 1991). Acute SSRI administration has the potential to regulate the reactivity to stimuli such as emotional faces, e.g., by increasing the activity in areas such as the left posterior insula, pulvinar, and visual cortex while attenuating the activation of the amygdala (Anderson et al. 2007; Del-Ben et al. 2005). Acute SSRI administration has also been shown to affect response selection, followed by increased activity in prefrontal areas such as the orbitofrontal cortex or right BA47, as seen in, e.g., go/no-go paradigms (Del-Ben et al. 2005). The regulatory circuits between the amygdala, thalamus, hypothalamus, and prefrontal areas are considered part of a network that modulates the identification of, and response to, emotional environmental stimuli, and

hence, the 5-HT system could play a modulatory role in this integration in both perception and behavioral control (Bigos et al. 2008).

However, the specific effects of SSRIs on perceptual and cognitive processes in humans have proven difficult to disentangle when using the most commonly employed attention paradigms. Sustained and focused visual attention may be improved by SSRI, but results have been inconsistent, and only rarely have test batteries been used, that are sensitive to general CNS stimulation (Amado-Boccara et al. 1995; Dumont et al. 2005; Knorr and Kessing 2010b). One test paradigm, however, the critical flicker fusion (CFF) test, has consistently suggested improved performance following SSRI administration (Fairweather et al. 1997; Hindmarch 1987; Hindmarch and Bhatti 1988; Hindmarch and Harrison 1988; Kerr et al. 1992; Nathan et al. 2000; Schmitt et al. 2002). CFF tasks aim to measure the discriminatory ability and perceptual threshold for visual flashes of light. The CFF paradigm essentially investigates the lowest frequency of continuous flicker that is perceived as a steady source of light rather than a flicker. In healthy humans, improved performance in the CFF paradigm has been reported after interventions with different SSRIs (e.g., fluoxetine, citalopram, sertraline, paroxetine, and fluvoxamine), at different dosages, and following 1.5 h up to 15 days.

The ability to distinguish flickering glimpses of light relies partly on the responsiveness of retinal neurons, but also on occipital and cortical structures, such as the primary visual areas (Eysel and Burandt 1984; Nardella et al. 2014; Wells et al. 2001). Thus, changes in CFF performance could arise at different processing stages from the retina to cortical regions.

The cognitive ability reflected in the performance on CFF is most commonly characterized as reflecting visual processing speed or capacity; however, this very broad description is rarely elaborated or examined in more distinctive visual attentional models (Hindmarch 1995; Nardella et al. 2014; Parrott 1982). Since the CFF test only provides a single parameter (i.e., the fusion frequency), it does not afford any other description of the cognitive dynamics of the perceptual effects of SSRI. To our knowledge, no previous study has investigated the more specific cognitive mechanisms underlying the effect of SSRI that is revealed in the CFF tests. However, the ability of the CFF tests to consistently capture a cognitive effect of SSRI stimulation inspired us to try and further examine the nature of this effect.

To further examine and expand on the findings from the CFF tests, we wanted to investigate the potential beneficial effect of SSRIs on visual attention with a test paradigm, which allows for a detailed description of the timing of early perception, and that is sensitive to detect more subtle changes than the CFF test. We chose to apply the CombiTVA paradigm (Vangkilde et al. 2011), in which visual perception is investigated parametrically at a range of exposure durations,

providing a description of the temporal dynamics of different attentional processes.

The CombiTVA paradigm provides accuracy-based measures of unspeeded reports from brief exposure durations and has previously been successful in disentangling psychopharmacological effects on distinct components of visual attention, e.g., by showing specific effects of nicotine, methylphenidate, and modafinil (Finke et al. 2010; Vangkilde et al. 2011). The test is based on Bundesen's (1990) *theory of visual attention*, a formal computational theory of attentional selection and recognition. According to TVA, the selection process is described as a parallel processing *race*, in which categorizations of the objects in our visual field compete for access to visual short-term memory (vSTM). The vSTM has limited capacity, and only winners of the race are selected and encoded and become available for consciousness and action. The chance of winning the race is not equal for all objects and categories. The race is seen as a biased competition, where both the sensory evidence of certain categorizations, attentional weights, and subjective attentional biases govern the probabilities of encoding objects and categories (Desimone and Duncan 1995). Hence, using the theoretical framework offered by TVA, the CombiTVA paradigm allows for a detailed description of a range of perceptual, attentional, and mnemonic measures (see "Instruments and outcomes") derived from performance in a single task (Fig. 1). Specifically, we expected the benefits of SSRIs on the CFF tests to be reflected

in one or both of the following parameters: the threshold for conscious perception (t_0; i.e., when the race starts) and the visual processing speed (C; i.e., the speed with which the race towards vSTM progresses), since these parameters determine the visual temporal resolution according to TVA (Bundesen 1990).

Furthermore, in contrast to most computerized attention tests, the attentional functions estimated with the CombiTVA paradigm relies only on unspeeded reports of perceived items (Bundesen 1990; Vangkilde et al. 2011). This circumvents a specific criticism which has been directed towards the use of, for instance, reaction time–based paradigms in SSRI research, since serotonin has been shown to be involved in different aspects of motor function in both animal models and humans including motor output, the activation and excitability of motor neurons, and the willingness of a subject to respond (Dumont et al. 2005; Gerdelat-Mas et al. 2005; Geyer 1995; Loubinoux et al. 2002, 2005). By applying this experimental paradigm, our aim is to ensure that findings are specific to the visual perceptual system and not confounded by potential motor biases or a general speeding or slowing of reaction times.

In summary, in this study, we employed the CombiTVA paradigm, an accuracy-based test of visual attention, to investigate the effects of prolonged SSRI administration on basic visual attentional processes and in order to provide a more sensitive and detailed description of the potential changes in distinct and dissociable attentional components. Based on previous studies finding a beneficial effect of SSRI on the CFF paradigm, we hypothesized that the SSRI intervention would
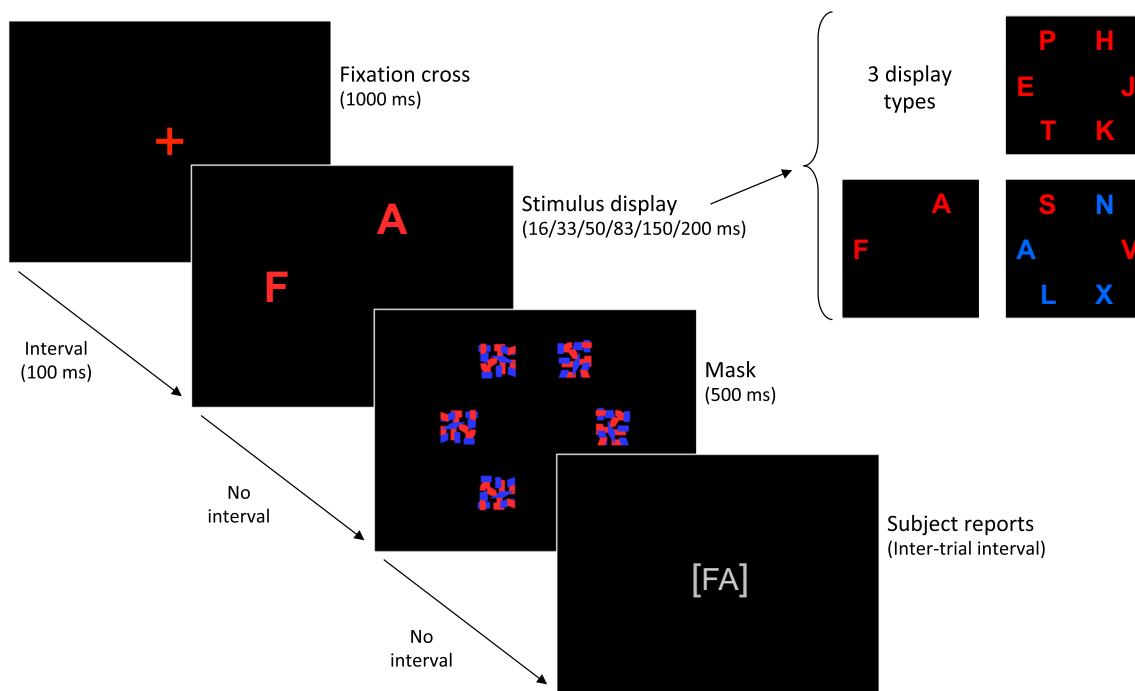
Fig. 1 Outline of a single trial in the *CombiTVA paradigm* showing the timing and the three types of letter displays: six target whole report (*red letters*), two target whole report (*red letters*), and two target and four distractor partial report (*red and blue letters*)

result in an enhanced performance at very brief exposure durations and that when modeling performance within a TVA-based framework, this would be reflected in either an improved (i.e., lower) threshold of conscious perception or an increase in visual processing speed.

Method

Study population

Participants were invited through newspaper and Internet advertisements. The study was approved by the Regional Ethical Committee of Copenhagen (Protocol no. H-KF 012006-20). Written informed consent from all participants was obtained in accordance with the Helsinki Declaration.

Eligible participants were healthy, adult males between 20 and 40 years. All included participants underwent a physical, psychological, and neurological examination, as well as blood screening and brain magnetic resonance imaging (MRI). All questionnaires were used in back-translated, approved Danish versions. The questionnaires were administered through an online system (LimeSurvey) by a project coordinator using token-generated links emailed to the participants. Exclusion criteria were any present or prior psychiatric or neurological disorder according to ICD-10 (WHO 1993) as well as any drug use within the last month or lifetime use of cocaine, heroin, amphetamine, or ecstasy more than ten times; lifetime use of cannabis > 50 times; and previous or any current pharmacological treatment. Ultimately, 32 healthy males were selected. All self-reported to have normal or corrected-to-normal vision. Demographic information is presented in Table 1.

Intervention regime

The participants in the present study also took part in a research project investigating 5-HT$_4$ receptor (5-HT$_4$R) binding (Haahr et al. 2014) and its relation to fMRI (Fisher et al. 2015; Macoveanu et al. 2014). Participants were randomly assigned to either SSRI ($N = 16$) or a placebo intervention ($N = 16$) (Table 2). Randomization was performed by an independent member of the research group, uninvolved in the contact with the participants or with data processing via a computer-generated randomization list (further detailed in Haahr et al. 2014).

The two groups underwent procedurally identical intervention regimes. Participants were tested twice: prior to any drug intervention (pretest) and again after having received the intervention for 21–23 days (retest). On the pretest day, participants received verbal and written instructions for taking the medication. Subjects self-administered identical oral capsules containing either the SSRI fluoxetine (20 mg per capsule) or a placebo pill (calcium), for 3 weeks. They were instructed to take 20 mg (one capsule) on each of the first 3 days of the intervention and to increase the dose to 40 mg (two capsules) per day, a clinically effective dose (Charlier et al. 2000), from day 4 until the day of the retest. Instructions were given to ingest the capsules at 10 p.m. or before going to bed. Upon completion of the 3-week intervention, participants were retested and then submitted to a 5-day down-titration period, where the active group would receive a dose of 20 mg/day. A medical doctor, blinded to participant group status, regularly contacted all participants to survey possible side effects during the intervention or withdrawal symptoms after the intervention and to ensure adherence to the protocol. Side effects were scored according to the UKU side effect rating scale (Lingjaerde et al. 1987).

No significant differences in reported side effects were observed between the SSRI and the placebo groups. Seven participants from the SSRI group and five participants from the placebo group reported minor discomfort such as nausea, insomnia, nervousness, and somnolence

Table 1 Demographic characteristics of the participants

Measures	Range	Placebo group		SSRI group		Group comparisons
		Mean	SD	Mean	SD	
Age	20–40	26.45	2.77	25.16	5.75	$t(30) = 0.43, p = .43$
BMI	19.9–31.3	23.07	1.74	23.36	3.15	$t(30) = -0.33, p = .75$
OS-FHAM	0–7	0.75	1.39	1.19	1.91	$t(30) = -0.74, p = .46$
Education level	12–17	15.75	1.57	15.69	1.92	$t(30) = 0.10, p = .92$
MDI	0–21	4.62	3.58	7.56	5.74	$t(30) = -1.74, p = .09$

Group comparisons were done by independent samples t tests. One participant scored 21 on the MDI but did not fulfill the International Classification of Diseases (ICD-10; World Health Organization 1993) criteria for depression and hence was not excluded

BMI body mass index (kg/m^2); *OS-FHAM* Family History Assessment Module, adopted version (http://www.nru.dk/hjerne); *MDI* Major Depression Inventory (Forsell 2005); *SSRI* selective serotonin reuptake inhibitor

Table 2 Individual blinding and compliance to intervention

Participant no.	Actual intervention	Perceived intervention	Confidence rating	Plasma fluoxetine		Plasma norfluoxetine	
				Mid	End	Mid	End
1	SSRI	–	–	45	70	107	178
2	SSRI	PLA	3	138	164	118	165
3	SSRI	PLA	5	180	210	89	115
4	SSRI	PLA	3	126	169	104	160
5	SSRI	–	–	181	216	71	115
6	SSRI	SSRI	3	74	126	68	128
7	SSRI	PLA	5	107	156	145	213
8	SSRI	PLA	4	76	150	97	207
9	SSRI	PLA	6	200	232	83	130
10	SSRI	PLA	5	180	149	154	143
11	SSRI	PLA	2	123	178	68	124
12	SSRI	PLA	5	45	95	79	131
13	SSRI	PLA	2	89	150	107	180
14	SSRI	–	–	140	241	56	95
15	SSRI	–	–	65	154	100	187
16	SSRI	SSRI	6	160	234	38	94
17	PLA	PLA	1	ND	ND	ND	ND
18	PLA	PLA	2	ND	ND	ND	ND
19	PLA	PLA	3	ND	ND	ND	ND
20	PLA	SSRI	4	ND	ND	ND	ND
21	PLA	–	–	ND	ND	ND	ND
22	PLA	–	–	ND	ND	ND	ND
23	PLA	PLA	5	ND	ND	ND	ND
24	PLA	PLA	2	ND	ND	ND	ND
25	PLA	–	–	ND	ND	ND	ND
26	PLA	PLA	3	ND	ND	ND	ND
27	PLA	PLA	5	ND	ND	ND	ND
28	PLA	PLA	1	ND	ND	ND	ND
29	PLA	–	–	ND	ND	ND	ND
30	PLA	–	–	ND	ND	ND	ND
31	PLA	PLA	1	ND	ND	ND	ND
32	PLA	PLA	6	ND	ND	ND	ND

Confidence rating (1–6): 1 = not sure; 6 = very sure; en dashes indicate those participants who could not be contacted after retest for the interview about their perceived intervention ($n = 9$). To ensure compliance, plasma fluoxetine and plasma norfluoxetine (μg/l) were measured twice: at mid-intervention (mid, approximately after 10 days of intervention) and at the time of examination (end, after 3 weeks)

ND not detectable, below detectable threshold

(UKU scores < 5). Two subjects, one in each group, showed a UKU score of > 5 and also reported sexual dysfunction and concentration problems. However, both felt able to participate in the posttest and were thus included in the present data set.

Compliance with the intervention was evaluated by a self-report questionnaire and via the measurement of plasma fluoxetine and norfluoxetine which were both performed mid-intervention and on the day of retesting (for details, see Haahr et al. 2014). Serum concentrations of fluoxetine and active metabolites were similar to those reported in patients undergoing prolonged SSRI treatment of either major depression or other neuropsychiatric conditions (Jannuzzi et al. 2002). All participants completed their interventions and adhered to the prescribed intervention, and they stayed unblinded (Table 2). A chi-square test between actual and perceived interventions indicated successful blinding ($\chi^2(1) = 0.29$, $p = .59$) (Table 2).

Instruments and outcomes

Cognitive testing for all participants was performed by the same trained tester in semi-darkened experimental test rooms, on stationary IBM computers (1.3 GHz, 1 GB RAM). Stimuli were presented using E-prime (version 1.2; Psychology Software Tools, Pittsburgh, PA), on 20-in. CRT screens at a 60 Hz refresh rate with a viewing distance of approximately 60 cm.

The CombiTVA paradigm consisted of one practice block of 24 trials and nine test blocks of 36 trials and took 40 min to complete (see Fig. 1; Vangkilde et al. 2011). Participants were instructed to fixate on a central red cross throughout each trial. After a 1000-ms delay, a stimulus display with six possible locations was presented on an imaginary circle centered on the fixation cross (radius, 7.5° of visual angle). After the stimulus exposure, the display was masked by a 500-ms red and blue letter fragment patterns at all possible stimulus locations. Each trial ended with a black screen whereupon the participant was to make an unspeeded report of the letter(s) he or she had seen. Participants respond by typing the letters in any order on a standard keyboard.

The design of the paradigm combines two different tasks: a whole report task and a partial report task. In the whole report trials, either two or six red target letters were presented, whereas the partial report trials contained two red target letters and four blue distractor letters. Displays with six target letters were shown for each of six stimulus durations (16 ms, 33 ms, 50 ms, 83 ms, 150 ms, or 200 ms), whereas all other displays were shown for 83 ms. All trial types were intermixed, and the letters in each display were chosen randomly without replacement from a set of 20 letters (ABDEFGHJKLMNOPRSTVXZ) and presented in the font Arial bold with a point size of 68. Participants were instructed to report all the red letters they were "fairly certain" of having seen (i.e., to use all available information but to refrain from pure guessing). After each block, subjects were informed about the accuracy of their responses. They were instructed to aim for a response accuracy between 80 and 90%.

Through the means of the TVA-based computational modeling, the applied CombiTVA paradigm (Vangkilde et al. 2011) provides independent measures of a range of distinct attentional functions (Duncan et al. 1999; Shibuya and Bundesen 1988). Attentional parameters are derived from the raw scores (i.e., the number of correctly reported letters in each exposure and display condition), using computational modeling based on a maximum likelihood fitting procedure (Dyrholm et al. 2011). This provides a description of performance through five different parameters (see Fig. 2)[1]: (1) t_0, the threshold of conscious perception, defined as the longest

ineffective exposure duration in milliseconds, below which the participant has neither perceived nor can report any letters; (2) C, the speed of visual processing measured in letters processed per second; (3) K, the capacity of visual short-term memory, or the maximum number of letters a participant is able to maintain in short-term memory; (4) α, a measure of top-down–controlled selectivity. The α parameter reflects the ability of the participants to disregard distractors and allocate attention only to the targets. A participant with perfect selection should be unaffected by distractors and thus report the same number of targets regardless of the number of distractors; (5) w_{index}, indicates the lateralized allocation of attention across the display, which may reveal tendencies for reporting the identity of letters in either hemifield. In addition to the estimated parameters, the error rate is also given (i.e., the probability that a reported letter was incorrect).

Human brain 5-HT$_4$ receptor binding potential was assessed with [11C]SB207145 positron emission tomography (PET). Previous studies support 5-HT$_4$ binding potential as a proxy for brain 5-HT levels (Haahr et al. 2014). A whole-brain estimate of change in 5-HT$_4$ binding potential (i.e., brain serotonin levels) that has been described previously was used in the current study (Fisher et al. 2015; Haahr et al. 2014).

Danish versions of tests for personality and demographic variables, as well as depressive symptoms and stress, were applied to determine whether participants differed at pre-test and in order to correct potential finds for interparameter correlations. Self-report scales
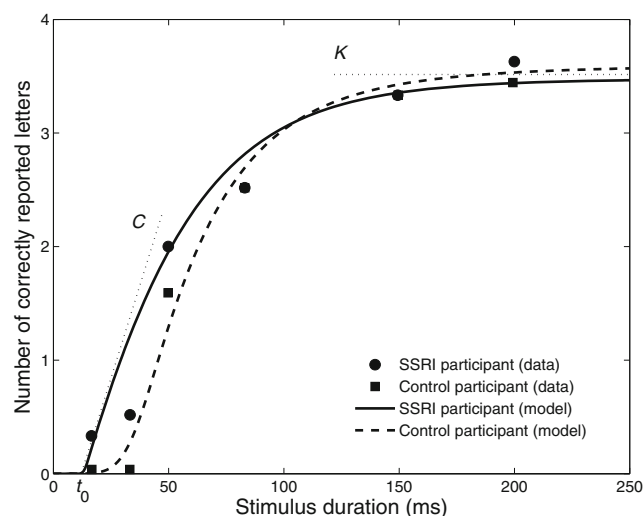
Fig. 2 Visual representation of whole report performance showing the mean number of correctly reported letters as a function of exposure duration. The lines denominate the predictions of the TVA-based fitting of the observations, with the *solid line* representing a participant in the SSRI group and the *dotted line* representing a participant in the placebo group. The estimated visual short-term memory capacity (K) is the horizontal asymptote of the fitted curve; the threshold for conscious perception (t_0) is denoted by the point, from which the curve rises from the abscissa. The slope of the curve at t_0 corresponds to the perceptual processing speed (C)

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[1] The models had 14 degrees of freedom (*df*): K, 5 *df* (the value reported is the expected K given a particular distribution of the probability that on a given trial, $K = 1, 2,…, 6$); C, 1 *df*; t_0, 2 *df* (the perceptual threshold was assumed to be drawn trial-by-trial from a normal distribution with a given mean and standard deviation); w_{index}, 5 *df* (one weight for each of the six locations under the restriction that the relative weights sum to 1); and α, 1 *df*.

measuring mental and physical health aspects included the Major Depression Inventory (MDI; Bech et al. 2001; Forsell 2005); the Revised Hopkins Symptom Checklist (SCL-90-R; Derogatis 1994); Family History Assessment Module, adopted version (FHAM; www. nru.dk/hjerne); and the International Classification of Diseases (ICD-10; World Health Organization 1993).

Data analyses

Group differences of pre- and post-test scores were examined by independent samples t tests, and post-test scores corrected for pre-test scores were examined by analyses of covariance (ANCOVAs). Our significance criterion (alpha) was .05 (two-tailed). Effect sizes were expressed as Cohen's d and η_p^2. We examined the relevance of demographic variables, compliance scores, and attentional parameters as covariates in the group comparisons, as reported when relevant. Statistical analyses were carried out in SPSS (version 23; IBM).

Results

The observed raw scores at pre-test (i.e., the number of correctly reported letters at each exposure duration) did not differ between the two treatment groups. However, as presented in Fig. 3, this pattern changed at post-test: in conditions with shorter exposure times (i.e., 16–33 ms), the SSRI group reported significantly more letters correctly than the placebo group. At longer exposure durations, the improvement was still present, but not statistically significant.

A similar pattern can be observed in the TVA-based parameter estimates. At pre-test, participants in the SSRI and the
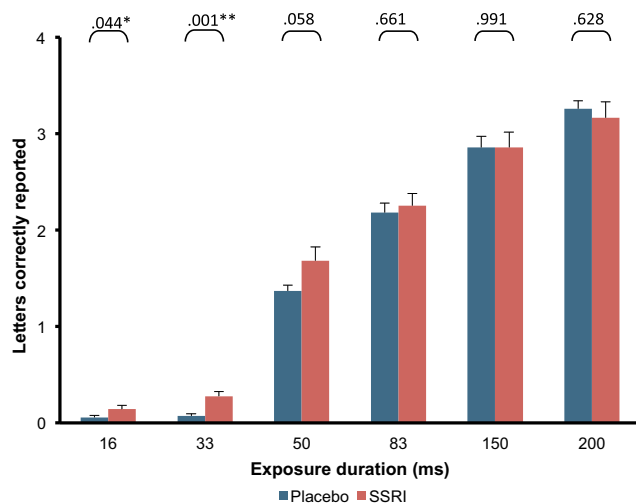
Fig. 3 Mean number of letters reported correctly at the different exposure durations, with the difference in performance between the groups being significant only in the shorter exposure durations (16 ms and 33 ms)

placebo groups performed similarly on all TVA parameters (see Table 3). However, at post-test, the visual threshold parameter (t_0) of the participants in the SSRI group showed a significantly larger improvement than that of the placebo group. An ANCOVA of post-test scores with pre-test scores as covariate revealed that participants in the SSRI group had a significantly lower t_0 compared with participants in the placebo group at post-test ($F(1,29) = 13.75$, $p = .001$, $\eta_p^2 = 0.32$). Participants in the intervention group showed a significant mean improvement of -5.0 ms (SD = 9.1 ms) from pre- to post-test ($t(15) = 2.2$, $p = .04$, $d = 0.57$). In contrast, an improvement on t_0 was not found in the placebo group ($\Delta t_0 = +2$ ms; SD = 3.7 ms). The finding was corroborated by performance at the different exposure durations at retest (Fig. 3), suggesting that the SSRI intervention decreases the amount of time required to begin processing the letters, rather than, e.g., the overall visual processing speed (C). Figure 2 shows the performance curves at post-test for a representative subject in each group. Note how the point where the curves rise from the abscissa (t_0) differs significantly between the two individuals, but the slope of the curves at t_0 (C) and the asymptote of the curves (K) do not.

Plasma levels of fluoxetine and norfluoxetine in the intervention group showed a significant correlation with performance in the early conditions (e.g., 33 ms condition) at post-testing ($b = 0.003$ [0.001; 0.005], $p = .014$). This relationship between serotonergic transmission and attention supports that the effect on t_0 was a result of the SSRI intervention. The change in t_0 could not be related to changes in global brain serotonin receptor binding as measured by in vivo PET scans. For the active group, changes in t_0 predicted by 5-HT$_4$R binding showed no evidence of an association ($b = 23.9$ [-43; 90.7], $p = .46$). Similarly, a comparison of Δt_0 predicted by SB α values of both the active and the placebo groups showed no significant association ($b = 17.7$ [-16.1; 51.5], $p = .29$). Hence, from these data, we are unable to conclude that changes in t_0 are related directly to global changes in serotonergic receptor binding.

Change scores on the visual threshold parameter (t_0) did not correlate with demographic factors or personality scores. The observed effect remained significant when including these parameters in a regression test of our model (findings available upon request).

ANCOVAs revealed no effect of the intervention on the visual *selectivity* parameter (α) ($F(1,29) = 0.85$, $p = .29$, $\eta_p^2 = 0.04$). Similarly, no effects were observed on the capacity of visual short-term memory (K) ($F(1,29) = 0.84$, $p = .37$). Processing speed (C) improved in both groups but showed no specific effect of the SSRI intervention ($F(1,29) = 0.79$, $p = .38$). Participants showed no trend towards favoring targets at specific positions or in either side of the display, and no effect of the intervention was evident for attentional laterality (w_{index}) ($F(1,29) = 0.02$, $p = .90$). Finally, participants in the

Table 3 Mean estimated attentional parameters from pre- and post-tests

	Placebo group		SSRI group		Group comparison	p value
	Mean	SD	Mean	SD		
Perceptual threshold, t_0						
Pre	26.99	7.39	25.43	9.34	$t(30) = 0.52, d = 0.19$	.61
Post	29.08	6.52	20.41	8.27	$t(30) = 3.29, d = 1.16$	.003
EMM post	28.66	–	20.84	–	$F(1,29) = 13.75, \eta_p^2 = 0.32$	.001
Processing speed, C						
Pre	59.59	19.81	60.15	23.93	$t(30) = -0.07, d = 0.03$	.94
Post	70.99	20.11	65.58	17.99	$t(30) = 0.80, d = 0.28$	.43
EMM post	71.09	–	65.49	–	$F(1,29) = 0.79, \eta_p^2 = 0.03$	.38
vSTM capacity, K						
Pre	3.38	0.48	3.07	1.11	$t(20.54) = 1.02, d = 0.36$	.31
Post	3.31	0.41	3.28	0.73	$t(23.68) = 0.09, d = 0.05$	.93
EMM post	3.23	–	3.37	–	$F(1,29) = 0.84, \eta_p^2 = 0.03$	.37
Selectivity, α						
Pre	0.67	0.35	0.67	0.42	$t(30) = -0.02, d = 0$	.98
Post	0.63	0.36	0.51	0.37	$t(30) = 0.91, d = 0.33$	.37
EMM post	0.63	–	0.51	–	$F(1,29) = 0.85, \eta_p^2 = 0.04$	.29
w_{index}						
Pre	0.51	0.07	0.52	0.12	$t(30) = -0.39, d = 0.10$	.69
Post	0.49	0.07	0.51	0.09	$t(30) = -0.40, d = 0.25$	.69
EMM post	0.50	–	0.50	–	$F(1,29) = 0.02, \eta_p^2 = 0$	.90
Error rate						
Pre	0.24	0.07	0.23	0.07	$t(30) = 0.27, d = 0.14$	.79
Post	0.21	0.06	0.21	0.06	$t(30) = 0.14, d = 0$	.89
EMM post	0.21	–	0.21	–	$F(1,29) = 0.01, \eta_p^2 = 0$	.97

Pre and post scores = independent samples t test; EMM post = estimated marginal means, ANCOVA on post scores, corrected for pre-test; units for the individual parameters: t_0 (ms), C (letters/second), K (letters), α (perfect selection at 0 to non-selectivity at 1), w_{index} (ranges from complete rightward bias at 0 to complete leftward bias at 1 with 0.5 indicating equal weighting between the two visual fields), and error rate (the probability that a given report is incorrect)

SSRI group did not differ from controls on the error rate ($F(1,29) = 0.01, p = .97$).

Discussion

The motivation for the study was to examine the nature of the improvement in attentional performance following SSRI treatment, as previously reported from CFF paradigms, in order to elaborate on our understanding of the cognitive effect on non-emotional stimuli. We employed TVA-based testing to evaluate a range of different aspects of visual attention simultaneously. A 3-week SSRI intervention resulted in a significant reduction, in the active group compared to placebo group, of the threshold for conscious visual perception (t_0) which is described as the minimal exposure time needed in order for visual processing to begin (Bundesen and Habekost 2008). In contrast, perceptual processing speed (C) was unaffected by the intervention. Hence, our results extend the findings from

CFF discrimination tests in SSRI treatment regimes, by implying that the observed enhanced temporal resolution of information processing does not stem from an increase visual processing speed, but from an earlier onset of conscious information processing.

Additionally, our study shows how this effect extends from perceiving very simple stimuli, as used in the CFF paradigms, to the processing of even relatively complex semantic visual stimuli (i.e., alphabetical letters).

This effect is expressed in the parameter estimate t_0, calculated from performance across all exposures, but it is also observable from the raw scores. As hypothesized, the group difference is most prominent in the short exposures, where a decrease in t_0 will show the biggest relative difference between the groups due to the small influence of the C parameter. The influence of the C parameter is typically reflected in the mid-range exposures whereas the K parameter is mostly reflected at longer exposures. Specifically, as time allows for more items to be

processed, the contributions from processing speed (C) and vSTM capacity (K) become more prominent, thus reducing the relative advantage of a lower perceptual threshold (t_0) (Fig. 2).

These complex dynamics could explain why some designs have been unable to capture attentional effects of SSRI (Dumont et al. 2005; Knorr and Kessing 2010). If the test does not calculate a parameter similar to t_0, the advantage afforded by a lowered perceptual threshold will only be observable when this "head-start" is enough to drive detectable group differences, i.e., in trials with brief stimulus exposures. Standard reaction time–based paradigms may not be sensitive to such subtle changes and may be obscured by reaction time variability reflecting additional factors related to, for example, decision-making processes or response selection and motor response speed.

The significant interaction between plasma levels of fluoxetine and norfluoxetine and performance in the brief exposure durations corroborates the suggestion that the effect on t_0 indeed stems from the SSRI intervention. However, our best estimate of serotonergic transmission, the 5-HT$_4$R binding potential, does not support this finding. Therefore, from these data, we are unable to conclude that changes in t_0 are related directly to global changes in serotonergic receptor binding. Interestingly, links between changes in the visual threshold as measured by TVA-based tests and the modulation of serotonergic transmission have been suggested by two previous randomized studies investigating the effects of non-pharmacological intervention (i.e., meditation-based interventions) on visual attention (Jensen et al. 2015, 2012). Both studies demonstrated a specific improvement of t_0 after participation in meditation-based stress reduction programs. Since the alleviation of depression is correlated with the modulation of serotonergic neurotransmission, one might speculate that the two stress reduction treatments could have induced similar effects to that of a prolonged SSRI intervention on the 5-HT system, and hence specifically affected the visual perceptual threshold. Standardized measures of perceptual threshold might be developed to serve as proxy measures for serotonergic function. However, future studies must elucidate the feasibility of such an approach.

The neural mechanism for the SSRI-related effect on the perceptual threshold (t_0) is unknown. However, multiple brain circuits may be relevant. The peripheral nervous system, such as facial and other cranial motor neurons, could potentially be under the influence of the SSRI. For example, the sphincter muscle of the iris is responsible for controlling the diameter and size of the pupil and thus the amount of light reaching the retina, which, in turn, determines the level of visual acuity and contrast sensitivity in a given perception (Hart and Adler 1992). SSRI intervention increases pupil size by as much as 2 mm following both single and repeated doses of SSRI

(Schmitt et al. 2002). Mydriasis, or pupil dilation, is known to increase visual sensitivity and signal detection (Campbell and Gregory 1960; Frisén 1980), which could potentially have enabled the SSRI group to detect and process stimuli at an earlier time point. Hence, in future studies, it would be relevant to include pupillometry to determine whether the source of the effect could be attributed to the dilation of the sphincter muscles of the iris.

Future studies might also investigate the contribution of the left inferior parietal lobule in relation to performance measured by the CombiTVA paradigm, since activity in this region may be causally involved in the temporal resolution and conscious perception in CFF (Gur and Snodderly 1997; Nardella et al. 2014).

The lowered threshold may also be partly explained by neural pharmacodynamic effects of SSRI. Serotonergic neuromodulation is crucial for the maintenance of the excitatory-inhibitory balance in the visual cortex and other sensory micro-circuits (Moreau et al. 2013). Maintaining an optimal interplay between excitation and inhibition is essential for fast and efficient processing of sensory information, and more finely tuned visual networks and pathways may result from prolonged SSRI administration (Mariño et al. 2005). Perceptual effects linked to the pharmacodynamics of SSRI on 5-HT neuromodulation in the visual system should be studied further.

Conclusion

This randomized placebo-controlled study investigated effects of a 3-week SSRI intervention on basic aspects of visual attention. Our data extends on previous work by demonstrating a specific SSRI-induced improvement of the perceptual threshold of conscious visual perception and not in the speed of visual processing, as previously suggested (Hindmarch 1995; Nardella et al. 2014; Parrott 1982).

Taken together, our results highlight a role for serotonergic neurotransmission in the earliest stages of visual attention and underscore the utility of research on accuracy-based aspects of attentional performance in pharmacological experimental psychology.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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