Serotonergic Effects on Interoception

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Abstract

Interoception is the signaling, perception, and interpretation of internal physiological states. A causal link between serotonin and interoception was tested by a within-participant, crossover, placebo-controlled study. Forty-seven healthy human volunteers were tested on and off a 20mg oral dose of the selective serotonin reuptake inhibitor (SSRI) citalopram. For each randomly ordered session, participants made a series of judgements about the synchrony of their heartbeat to auditory tones and expressed confidence in each judgement. Citalopram enhanced insight into the likelihood that a correct interoceptive judgement occurred, driven primarily by increased confidence in correct judgements. This effect was independent of measured physiological and subjective effects of the drug and greater than a null effect on insight into exclusively exteroceptive performance on a visual task. This finding provides a foundation for considering effects of serotonin on cognition, emotion, and behavior in terms of higher order processing of interoceptive events.

Introduction

Interoception is the afferent limb of allostasis, through which health and viability are maintained by dynamic, often predictive, adaptations in physiology and behavior. By the signaling, perception and interpretation of internal physiological states, interoception influences how we feel, what we choose, how we react, what we learn, and our physiological sense of 'self' (Cameron, 2002; Craig, 2002; Seth, 2013a). Interoceptive changes also feature as a transdiagnostic feature across multiple psychiatric disorders (Avery et al., 2014; Ehlers, 1993; Herbert & Pollatos, 2019; Paulus et al., 2019), a significant majority of which are treated, with some success, by selective serotonin reuptake inhibitors (SSRIs). In this study, we tested the causal relationship between serotonin and interoceptive cognition.

Selective serotonin reuptake inhibitors (SSRIs) change the synaptic availability of serotonin. In addition to their clinical effects, even single doses affect cognition, including learning (Chamberlain et al., 2006; Michely et al., 2020; Scholl et al., 2017), social perception (Harmer & Cowen, 2013), and choice (Crockett et al., 2010). They also alter central nervous system plasticity (Castrén & Rantamäki, 2010). Given these central effects, we supposed that SSRIs on interoception, if present, may involve the central processing of interoceptive signals.

There are many reasons to suspect a relationship between serotonin and interoception. Interoception responds to both rewards and punishments, influences multiple types of affective cognition, and putatively requires regulatory orchestration of various neural signals (A. P. Owens et al., 2018). Serotonin has regulatory, orchestrating effects on the transmission of other systems, is implicated in a variety of cognitive and behavioral control processes (Cools et al., 2008; Dayan & Huys, 2009; Deakin & Graeff, 1991), and represents both rewards and punishments (Cohen et al., 2015). Like interoception, serotonin is linked to homeostasis. It has peripheral effects on the heart, metabolism, temperature control, and pain (Berger et al., 2009). In rats, central serotonin disruption results in problems of thermal and respiratory control (Ray et al., 2011). Central serotonin availability can also be altered by visceral states, potentially by peripheral regulation of tryptophan metabolism (O'Mahony et al., 2015). Anatomically,

central nuclei in the brain stem reach far and wide in the brain, reflecting influence on many other processes. These nuclei are well placed to regulate communication between the brain and the rest of the body. Already, we know serotonin receptors in the spine modulate responses to visceral pain (Danzebrink & Gebhart, 1991). In healthy human brains, reduced correlation between neural and cardiac responses to surprise occurs when tryptophan is depleted (Mueller et al., 2012). In brains of patients with serotonin-related disorders, reduced 5-HT_{1A} receptor activity has been identified in the insula, an interoception-related cortical area (Craig, 2002; Lanzenberger et al., 2007; Schulz, 2016). However, to our knowledge, no causal link between serotonin and interoception, other than pain, has been reported.

A helpful advance for interoception research was the recognition that three different dimensions of interoception can be measured in experiments and vary independently (Garfinkel et al., 2015). These are interoceptive accuracy (such as good judgements about interoceptive events), interoceptive sensibility (such as confidence in these judgements), and interoceptive awareness (such as correspondence of confidence to accuracy, denoting metacognitive insight into one's interceptive accuracy). Interoceptive awareness can also be described as insight into the uncertainty associated with an interoception-based inference. High interoceptive awareness can occur as higher confidence in good interoceptive performance and lower confidence in poor performance.

One path (of many possible) to interoceptive awareness could be awareness of the reliability of the afferent interoceptive signal. This path features in predictive coding models of interoception and related disorders (Allen & Tsakiris, 2018; A. P. Owens et al., 2018; Seth, 2013a). According to these models, the influence of interoceptive information is regulated according to a representation of the precision of the afferent signal. If this regulatory system falters, such as by an inability to distinguish precise from noisy interoceptive signals, interoceptive sensations could have too much or too little influence on mental states. This could theoretically result in problems such as heightened anxiety (Paulus et al., 2019), blunted affect (Paulus & Stein, 2010), inappropriate response to hunger (Herbert & Pollatos, 2019), poor choices (Damasio, 1996; Werner et al., 2009) and reactive aggression (Spoont, 1992). In contrast, improved ability

to distinguish between reliable and unreliable interoceptive signals could provide for better control of interoceptive influence. Even outside of predictive coding frameworks, knowing when an inference based on interoception can be relied on and when it cannot is useful for determining when to use alternative information sources for forming beliefs. Since the heart has rich and bidirectional connections with the brain, cardiac interoception is commonly tested (Tsakiris, 2017).

We formally tested causative links between serotonin and interoception, with a focus on interoceptive accuracy and interoceptive awareness. We used a within-subject, placebo-controlled, crossover study of healthy participants on and off a highly selective SSRI, citalopram. This design controlled for individual differences and effects of repeated task performance. Citalopram was chosen for its specificity to serotonin, tolerability, and common use. It binds to the serotonin transporter with 3,800 times the affinity to the norepinephrine transporter and 10,000 times the affinity to the dopamine transporter (M. J. Owens et al., 2001). Interoception was quantified using a heartbeat discrimination task (Garfinkel et al., 2015; Katkin et al., 1983). This requires a participant to attend to interoceptive sensations and report whether auditory tones are perceived as in or out of time with their heartbeat, and then self-rate confidence in that judgement. For comparison, we tested the link between serotonin and pure (visual) exteroception. For the visual task, participants repeatedly attended to two briefly presented circles with a similar numbers of dots and were asked to make a perceptual decision of which had more dots and then provide a confidence rating (Fleming et al., 2014). Both tasks allowed for measurement of accuracy, sensibility, and awareness.

Materials and Methods

Experimental Design

This study involved a double-blind, placebo-controlled repeated-measures design. Participants underwent two test sessions, at least one week apart, under medical supervision. In one session they ingested 20mg citalopram (mean mg/kg = 0.34 ($SD = .05$)) in a cellulose capsule, with extra space filled with microcrystalline cellulose which is an inactive ingredient of the citalopram tablet. In the other session they received placebo (an identical capsule containing only microcrystalline cellulose). No-one who had contact

with participants was aware of the treatment order, which was pseudo-randomized, balanced for sex, and coded by a researcher who was not present during testing. Capsules were manufactured according to good manufacturing practice.

Participants

On a separate occasion prior to testing, prospective participants undertook a screening session with a health questionnaire, heart rate and blood pressure monitoring by a medical doctor, and a structured clinical interview to determine any undiagnosed psychiatric conditions (Mini International Neuropsychiatric Interview; MINI (Sheehan et al., 1998)).

Exclusion criteria included: age under 18 or over 35 years; history of psychiatric disorder (including anxiety disorder, depression, eating disorder, psychosis and substance abuse disorder); presence of significant ongoing medical condition (including migraine, diabetes, epilepsy, glaucoma and hypertension); pregnancy or breastfeeding; currently taking any medication (excluding oral contraceptive pill); first-degree family history of bipolar disorder; Mini International Neuropsychiatric Interview (MINI) indication of: major depressive episode, manic episode, panic disorder, social phobia, OCD, PTSD, alcohol dependence, substance dependence, mood disorder with psychotic features, psychotic disorder, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, or antisocial personality disorder. Participants were instructed to abstain from alcohol or caffeine in the preceding 12 hours before the start of test sessions.

Fifty-one participants were recruited. Three were excluded for feeling their pulse in their finger and one for technical errors preventing data collection. Forty-seven participants were successfully tested (mean age 23 ($SD = 3.9$), 31 female, mean weight 64 kg ($SD = 10.9$)). Testing was conducted in two separate locations (test cubicles) and no differences in results were observed between locations. This study received ethical approval from the University of Sussex Sciences & Technology Cross-Schools Research Ethics Committee (ER/JL332/3, ER/JL332/9). Participants gave informed written consent.

Procedure

Each participant performed a battery of tests including the interoception tasks. Behavioral testing was timed to begin at 3 hours after administration, corresponding to estimated peak plasma levels (Milne & Goa, 1991).

Citalopram can exhibit side effects (typically mild at 20mg) including nausea, headache and dizziness (Ekselius et al., 1997). Visual analogue scales (VAS; from 0-100) assessed the presence of these three somatic effects. Additionally, five emotion/arousal related effects were assessed with VAS scales between pairs of antonyms: alert−drowsy, stimulated−sedated, restless−peaceful, irritable−good-humored, anxious−calm. Each measure was recorded three times: immediately following dosing, at the start behavioral testing and at the end. Mean scores for the two testing times were used in our analyses, with paired t-tests to analyze whether significant differences occurred between citalopram and placebo sessions. Cardiac measures of heart rate (HR) and heart rate variability (the standard deviation of HR across intervals) were calculated at baseline and test time. Citalopram has been reliably shown to not affect blood pressure without interaction with other drugs (Watts et al., 2012; Zhong et al., 2017) and was not measured.

Tasks

For the interoception task, participants were connected to a fingertip pulse oximeter to monitor cardiac events (Xpod with 8000SM sensor, Nonin Medical Inc., Minnesota, USA). The task was run in Matlab (version 2018a, MathWorks) using a previously developed variant (Hart et al., 2013).

Interoception task: The interoception task (Garfinkel et al., 2015; Katkin et al., 1983) is a two-alternative forced choice task, often called the heartbeat discrimination task. Participants were instructed beforehand that the computer would play a set of tones that would be in or out of sync with their heartbeat. During each trial, their heartbeat was measured in real-time, while a computer played a set of ten tones at either ~250ms or ~550ms after the R-wave (Payne et al., 2006). These timings correspond respectively to judgements of maximum and minimum simultaneity (i.e. synchronous or delayed) between stimulus presentation and heartbeat (Wiens & Palmer, 2001). Following each trial, the participant was directed to

respond whether the tones were in or out of time with their heartbeats, and how confident they were in that answer using a Likert scale ranging from 'total guess' to 'complete confidence'. Synchronous and delayed trials were presented in pseudorandomized order. Twenty trials (10 synchronous and 10 delayed) were carried out in each session.

Visual task: The visual task was taken from (Fleming et al., 2014). Participants were shown circles containing dots and instructed to indicate which contained more. Following each trial, they were asked to indicate their confidence in the previous response on a Likert scale. 200 trials were conducted in 8 blocks, with a self-timed rest every 25 trials. The difficulty was staircased over the course of the task, with the difference in numbers of dots (Δd), adjusted to target a mean rate of correct answers of 70%, in order to maintain a consistent level of difficulty between participants. One randomly selected circle always contained 50 dots. After two consecutive correct responses, Δd was decreased by one dot; after one incorrect response, Δd was increased by one dot.

Analysis

For the interoception task, accuracy scores were calculated by taking the mean number of correct responses for the session and dividing by the number of trials, resulting in a proportion correct. Confidence scores were computed as the mean of the trial-wise confidence VAS measure in each task, coded 0-10. Interoceptive awareness was calculated as the area under the receiver-operating characteristic curve (AUC) (Green & Swets, 1966; Hajian-Tilaki, 2013), measuring the correspondence of trial-by-trial relative changes in confidence to accuracy, independent from and unbiased by individual differences of confidence. This non-parametric measure has the additional advantage of not requiring distributional assumptions over type 1 (accuracy) performance, which were not met. After testing for order and gender effects (there were none), we used repeated-measures GLMs to model within-subject differences between drug and placebo. Rigorous testing of the influence of side effects was completed by mediation analysis and restricted dataset approaches.

For the visual task, we calculated Δd corresponding to the number of dots differing between the two circles necessary to maintain 70% accuracy as a measure of performance. Staircasing was successful: mean accuracy was .71 ($SD = .02$) on placebo and .72 ($SD = .02$) on citalopram. Confidence scores were recorded on each trial. Using performance and confidence ratings (1 to 6), we calculated visual metacognitive awareness (VMA) as AUC, corresponding to the interoceptive awareness measure. This common measure allowed a direct comparison of citalopram effects on cardiac interoception and visual exteroception. We could then look specifically for changes of confidence on correct and incorrect judgements.

We also calculated visual metacognitive sensitivity (meta d') and efficiency (meta d' / d') as per previous research for reference (Fleming & Lau, 2014; Green & Swets, 1966) (this was not a stable calculation for the interoception task). Correlation of VMA and meta d' in the placebo condition was $r = .92$, and correlation between VMA and meta d'/d' was $r = .86$. We used GLMs to model within-subject differences between drug and placebo. No significant order effects were observed on the effect of VMA, though order effects were observed for meta d and metacognitive efficiency (Table S4). Inclusion of order or gender as a factor did not change statistical inferences.

For comparison of VMA with interoceptive awareness controlling for the difference in accuracy between tasks, we completed a supplementary analysis on VMA. 1000 random draws of 20 samples each were taken from each participant separately for drug and placebo sessions, weighted to include correct and incorrect trials at the same proportion as that person's interoception task accuracy, in the same session. Computations on awareness for each sample were made and the average of these used in statistical comparison with interoceptive awareness at the same level of performance.

Mediation Analyses: To provide assurance that drug effects on interoception were not the result of any side effects (such as on heart rate or nausea) or a general effect on metacognition, we performed a set of post hoc mediation analyses (Fig S2). These tested for both the drug effect on interoception measures by way of effects on side effects or metacognition, as well as for the remaining direct effect of the drug on

interoception once these effects are controlled. We also interrogated subsets of data where nausea and heart rate were balanced in both conditions.

Results

Baseline performances on both tasks were consistent with previous studies (Table 1 and Table 2) (Fleming et al., 2014; Garfinkel et al., 2015). Interoceptive awareness correlated with its equivalent measure in visual perception (visual metacognitive awareness) (VMA) ($r(45) = .34, p = .02$) in the placebo condition indicating some consistency between measures, but this relationship disappeared on citalopram ($p = .85$). The change of correlation is reflected in the significant drug x task interaction effect reported later in this section. No other correlations between related measures were observed.

Table 1. Effects of Citalopram on Interoception Task Performance

	Mean, SD			
	Placebo	**Citalopram**	***t*(46)**	***p***
interoceptive accuracy	0.56 (0.13)	0.58 (0.16)	0.76	.453
confidence	5.03 (1.85)	5.46 (1.48)	1.90	.056
interoceptive awareness	0.50 (0.18)	0.57 (0.17)	2.58	.013

Interoceptive accuracy was above chance in both conditions (placebo $t(46) = 3.2$, $p = .002$, citalopram $t(46) = 3.6$, $p = .001$) but unchanged by citalopram (see Table 1). Citalopram significantly increased interoceptive awareness (Figs 1, S1). Two-thirds of individuals showed this effect. Further investigation showed awareness was selectively increased for correct interoceptive judgements. There was a significant interaction between the effect of drug and correct / incorrect judgements ($F(45,1) = 6.9, p = .012$). Confidence in correct judgements was higher on citalopram ($t(46) = 2.4, p = .021$) but confidence for incorrect judgements was unchanged ($p = .42$).

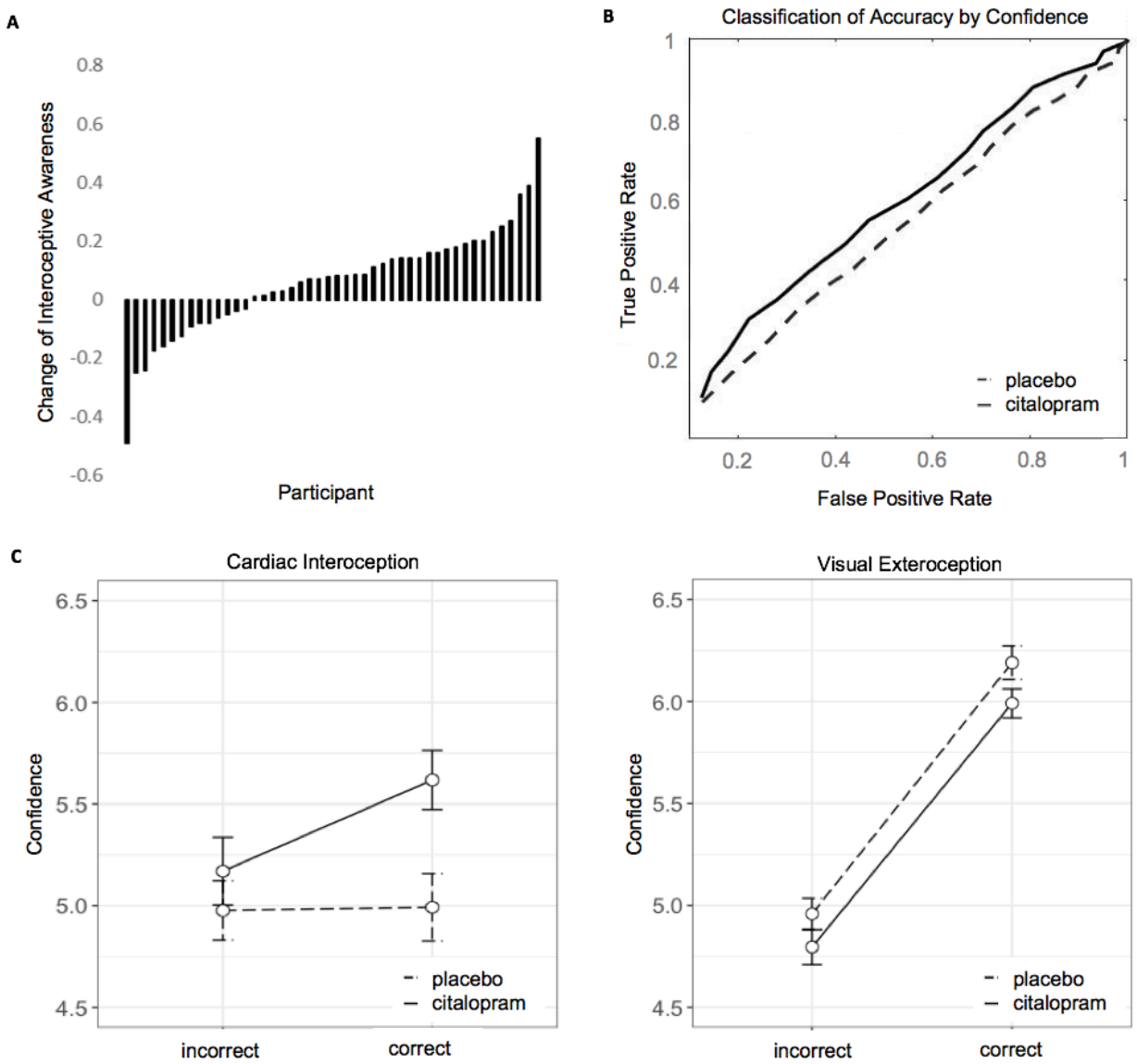

Fig 1. Effect of citalopram on interoceptive awareness. **A**. Change in interoceptive awareness by each participant. **B.** Receiver operating characteristic curve representing confidence classification of interoceptive accuracy. **C**. Confidence in each with each treatment for correct and incorrect judgements, commonly scaled from 0 to 10. Error bars are within-subject standard error.

Citalopram reduced heart rate (beats per minute (bpm): $t(46) = 3.9, p = .01$, mean diff $\Delta M = 4.0$ $(SD = 1.0))$ and increased nausea (on 100-point scale: $t(46) = 2.9, p = .01, \Delta M = 4.7$ $(SD = 1.6))$ compared with placebo. Citalopram did not change heart rate variability or any other measured physiological or subjective state (Table S1). Effects of citalopram on interoceptive awareness showed near zero correlation with cardiac effects and no significant correlation with effects on nausea (Table S2). In a

restricted dataset of participants with less than a 1-point change in nausea ($n = 38$), citalopram's effect on interoceptive awareness remained robust ($F(1,37) = 6.4,\ p = .016$). The effect of citalopram on interoceptive awareness was not mediated drug effects on accuracy, confidence, or any other measured side effect of the drug (Fig S2, Table S3). No effects of order or gender were observed.

Citalopram slightly reduced confidence in exteroceptive visual decisions (Table 2), opposite to its effect on interoception (task comparison of effect ($F(1,46) = 5.4,\ p = .025$). There was no change of visual metacognitive awareness (VMA) ($p = .95$), the exteroceptive counterpart to interoceptive awareness, or the required difficulty to maintain 70% accuracy (Δd) (Table 2). A comparison of citalopram effects between interoceptive awareness and VMA demonstrated a significant drug x task interaction ($F(1,45) = 6.16, p = .017$), with a greater effect on interoception. This effect remained for subsets of visual perception data matching interoceptive task accuracy (mean AUC of 1000 samples per participant, each with 20 visual task trials with same mean accuracy as the participant's interoceptive task performance). AUC differences of subsets and full sets near perfectly correlate (r(45) = .99), confirming the independence of AUC from task accuracy and supporting the cross-task comparison.

Table 2: Effects of Citalopram on Visual Task Performance. Δd = average dot difference to maintain 70% correct (lower number indicates better performance). See Table S4 for alternative measures. † ($p < 0.05$ when controlling for non sig effect of order).

	Mean (SD)			
	placebo	**citalopram**	***t*(46)**	***p***
staircased task difficulty (Δd)	5.49 (1.93)	5.74 (1.24)	0.94	.35
confidence	5.83 (0.08)	5.65 (1.11)	-1.96	.06
awareness (VMA)	0.65 (0.06)	0.65 (0.07)	0.08	.93

Discussion

For decisions based on interoceptive sensations, a single dose of the SSRI citalopram enhanced awareness of one's accuracy without changing accuracy itself. This effect was independent of effects on heartrate, performance on an exclusively exteroceptive task, or self-reported subjective states. This demonstrates that an acute SSRI dose is sufficient to cause a change in interoceptive metacognitive insight. Below, we consider potential mechanisms, specificity, implications for other cognition, implications for serotonin function, and implications for clinical settings.

Mechanism: The mechanism of citalopram's effect on interoceptive awareness will depend on the method or methods by which individuals increase the probability of a correct judgement. For instance, if a particular allocation of attention (between sound, cardiac interoception and other) increases the likelihood of a correct choice, then improved retrospective awareness of attentional allocation would also improve awareness of performance (Kanai et al., 2010). There are many potential routes to the effect, though any would need to account for the specificity of the effect on interoceptive awareness. One route of significant promise, is that serotonin may increase awareness of qualities of interoceptive information used to make the choice (Yeung & Summerfield, 2012). Predictive coding models have gained traction for explaining subjective feelings and allostasis as outputs of interactions between top-down predictions about the states of the body and environment, and new, bottom-up sensations (Allen & Tsakiris, 2018; Friston, 2012; A. P. Owens et al., 2018; Seth, 2013b). Within this framework, layers of processing are implemented by similarly hierarchical neural networks, through which top-down predictions suppress or explain away signals encoded at lower levels. This leaves remaining signals to be broadcast forward to adjust higher-order predictions and drive allostasis (our physiological, cognitive and behavioural responses to changes within the body) (Allen & Tsakiris, 2018; Friston, 2012; A. P. Owens et al., 2018). Central to the present study, the top down predictions are posited to represent 'confidence' in the lower-level prediction errors, which in turn, can be used to mediate post-synaptic gain (Abbott et al., 1997). This gain can facilitate the propagation of bottom-up information to influence higher levels of the network (Feldman & Friston, 2010).

If confidence in good information is increased on citalopram, then the individual is better equipped to facilitate the flow of good interoceptive information, making beliefs and feelings more accurate reflections of reality. It is currently assumed that access to information about the precision of upward interoceptive signals may be mediated by serotonin, but that precision itself is encoded by other systems on which serotonin acts (e.g. dopamine) (Friston, 2009). Clinical disorders associated with interoception have been considered within this predictive processing framework. Anxiety disorders, for instance, are proposed to arise from suboptimal interactions between lower and higher-level processes, whereby overreliance on incorrect prior expectations rather than useful lower level inputs lead to constant surprise from new information and a perpetual drive for correction (Paulus et al., 2019). Improved interoceptive awareness could help remediate such maladaptive cycles through increased reliance on reliable interoceptive inputs (Spence et al., 2016; Yeung & Summerfield, 2012).

The interoceptive task is challenging. Average accuracy was above chance in both treatment conditions, but only a minority performed above chance in both sessions. This provided a poor fit for signal detection approaches to analysis (rather than the AUC used here) that assume that metacognitive insight arises from the same information and processes as the perceptual decision, necessitating above chance accuracy to interpret above chance metacognition (Barrett et al., 2013). However, decision-making and metacognition can have different inferential goals and can be represented by different anatomy. They can therefore be receptive to different types of information or be determined by different processing of the same information. These differences can lead to situations of high metacognitive sensitivity despite low first-order accuracy (Fleming & Daw, 2017), and indeed, high metacognitive accuracy has been demonstrated to occur at robustly chance performance (Scott et al., 2014). In the current study, the effect of citalopram on interoceptive awareness fits well with a top-down regulatory role of serotonin, whereby citalopram alters top down insight into the choice process, without altering the choice itself. This specificity provides a pharmacological dissociation between choice and insight, with implications for studies of perception and consciousness.

Even targeted blockade of serotonin transporters has indirect effects on other systems (Zhou et al., 2005). So, while a shift of serotonin is sufficient to cause a change of interoceptive awareness, the mechanism can involve other neurotransmitters (e.g. dopamine as mentioned earlier). The effect could also stem from either activation or inhibition of serotonin transmission. Acute SSRI treatment can cause reductions or increases in serotonin transmission due to activation of 5-HT_{1A} autoreceptors with variation of this occurrence across brain regions (Beyer & Cremers, 2008). Effects of long term citalopram treatment on interoceptive awareness are also not yet known.

Specificity: Citalopram affected interoceptive awareness without affecting first order performance accuracy. This is a pharmacological distinction between the two processes. It also increased confidence in correct choices without reducing confidence in incorrect choices. With respect to the comparison between tasks, the 'interoception task' requires interoception, auditory exteroception, and a comparison of the two. The exteroceptive task requires processes within a single sensory (visual) domain. Similar awareness measures were obtained on both interoception and visual tasks, so we can infer that citalopram's metacognitive effect on interoceptive awareness is not a general effect of correspondence between confidence and perception. However, the effect on interoceptive task performance could be either enhanced awareness of processing interoceptive information or awareness of interoceptive-exteroceptive signal integration. Future studies will delineate these and also demonstrate whether the serotonergic effect on cardiac interoception generalizes to other interoceptive domains. In previous study, cardiac and respiratory interoceptive awareness have been positively correlated (Garfinkel et al., 2016).

Implications for Other Cognition: As suggested by the predictive coding framework, accurate higher order representations of the ability to make good interoceptive inferences could enable better top down weighting, consciously or unconsciously, of interoceptive influence on other processes. In turn, this could result in mental states that are better reflections of reality (2,64). In this study, we were limited to measuring a key ingredient of this theoretical weighting process, rather than the weighting itself. So,

whether the effect on interoceptive awareness translates to better weighting of interoceptive, prior or exteroceptive information remains an important avenue for future research.

Implications for Serotonin Function: The long pursuit of a unifying function for serotonin has been informative but unsuccessful (Dayan & Huys, 2015). However, the involvement of both interoception and serotonin in aversive and rewarding signals (perhaps weighted more toward threat) (Cohen et al., 2015), impulsive aggression (Spoont, 1992), startle (Grillon et al., 2007) and perceptual bias (Harmer & Cowen, 2013), sets the stage for more overlap of mechanism across serotonergic effects than previously thought.

Clinical Implications: The effect of citalopram on interoceptive awareness provides a new framework for the study of serotonin in interoception-associated disorders. SSRI treatments and successful interoceptive therapies in depression and anxiety (Khoury et al., 2018) may be found to overlap in mechanism as they ameliorate blunted affect (Paulus et al., 2019) or break maladaptive cognitive cycles (Roy-Byrne et al., 2006). Perceptual biases that appear before clinical effects of SSRIs are observed and are thought to predict clinical outcomes (Harmer & Cowen, 2013; Michely et al., 2020) may be discovered to have interoceptive foundations. Anxiogenic effects arising near the onset of SSRI treatment (Taylor et al., 2006) may be due interoceptive inputs suddenly being processed in a new way. If these speculative hypotheses become experimentally supported in future studies, the clinical effectiveness of SSRI treatment could potentially be predicted by early interoceptive effects.

Conclusions: Research on exteroceptive perceptual decision-making has identified dissociable processes of perception and metacognitive oversight (Fleming & Dolan, 2012) with focal metacognitive deficits present in psychiatric (Hauser et al., 2017; Rouault et al., 2018) and neurological (Fleming et al., 2014) conditions. With this study, we contribute to a growing body of work that makes similar dissociations between perception and metacognition in the interoceptive domain (Garfinkel et al., 2015; Khoury et al., 2018; A. P. Owens et al., 2018). In doing so, serotonin is shown to be a moderator of insight into one's ability to make accurate inferences from interoceptive sensations.

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Data and materials availability: All data, code, and materials used in the analysis are available any researcher for purposes of reproducing or extending the analysis. To download the data associated with this manuscript click here: https://doi.org/10.6084/m9.figshare.12520589

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Supplementary Materials for:

Serotonergic Effects on Interoception

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Supplementary Text

Figs. S1 S2

Tables S1 to S4

Supplementary Results

Somatic and psychological effects

Table S1 shows the difference between scores in drug and placebo conditions on subjective ratings at test times. There were differences in the sample on the subjective nausea rating, corresponding to a mean 4.7 difference on a 100-point scale. To determine whether this could affect the finding on interoceptive awareness for citalopram (for example, increased nausea causing participants to become more aware of their bodily sensations), we conducted a second analysis restricted to participants with less than a 10-point change in nausea (38 participants). The citalopram effect on interoceptive awareness was similarly significant in this sample ($F(1,37) = 6.4$, $p = .016$). Similarly, if data is restricted to participants where the change in heart rate was less than 8 bpm (meaning there no difference between placebo and drug, $N = 33$, $p = .529$), the effect of citalopram on interoceptive awareness remains significant ($F(1,32) = 5.7$ $p = .022$).

No changes in cardiac or self-report variables between drug and placebo showed significant correlation with discrimination awareness or tracking accuracy changes.

To test if significant interoceptive changes were mediated by changes in heart rate, visual metacognitive efficiency or subjective report measures, we additionally modeled mediation using a within-subjects approach and the MEMORE mediation model (MEMORE v2.1) (Montoya & Hayes, 2017). This was carried out for potential mediators showing significant differences in the mediating variable between drug and placebo i.e. path B in Fig S1, or significant correlations between drug-placebo differences and task variables (path C). Additionally, we tested the hypothesis of mediation of drug effects on interoceptive awareness by a possible general metacognitive process (e.g. VMA). This allowed us to statistically separate the direct (unmediated) effect of the drug from the indirect (mediated) effect which the drug might influence interoception through somatic or psychological changes.

Montoya AK, Hayes AF. Two-condition within-participant statistical mediation analysis: A path-analytic framework. Psychological Methods. 2017;22(1):6–27.

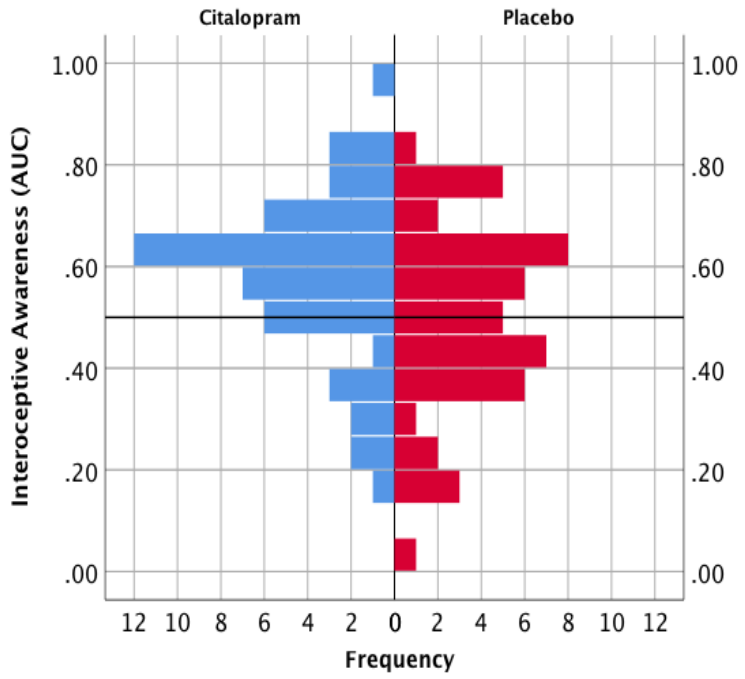
Table S1: VAS scales, mean score at test time. † full sample, ‡ restricted sample, * p < .05, ** p < .01

	scale	placebo	citalopram	*t*(46)†/ (37)‡	*p*
FULL SAMPLE	**nausea**	4.47 (7.29)	9.2 (11.8)	-2.93	.005**
	headache	12.3 (17.3)	12.2 (17.6)	0.05	.96
	dizziness	9.4 (13.0)	11.0 (12.1)	-1.22	.23
	alert − drowsy	44.0 (18.2)	47.8 (19.5)	-1.27	.21
	stimulated − sedated	46.4 (15.6)	47.7 (14.9)	-0.54	.59
	restless − peaceful	64.3 (18.6)	61.2 (18.7)	1.02	.31
	irritable − good-humoured	63.9 (17.7)	64.8 (16.1)	-0.49	.62
	anxious − calm	71.9 (15.9)	67.6 (15.7)	1.75	.086
RESTRICTED SAMPLE	**nausea**	4.7 (7.71)	5.1 (6.45)	-0.46	.65
	headache	12.5 (18.3)	10.2 (16.9)	1.46	.15
	dizziness	9.5 (11.4)	10.1 (12.1)	-0.63	.53
	alert − drowsy	43.3 (17.8)	46.6 (19.2)	-1.11	.27
	stimulated − sedated	46.6 (15.2)	47.4 (15.0)	-0.31	.76
	restless − peaceful	62.7 (19.2)	64.0 (17.8)	-0.44	.66
	irritable − good-humoured	63.5 (17.8)	66.1 (16.1)	-1.4	.17
	anxious − calm	70.7 (16.9)	70.0 (15.6)	0.27	.79

Table S2: Correlations between drug-placebo changes in cardiac/self-report variables and interoceptive awareness

	interoceptive awareness	
	***r*(45)**	**p**
heart rate	-.00	.98
heart rate variability	-.00	.98
nausea	-.14	.36
headache	-.00	.98
dizziness	.03	.82
alert−drowsy	.02	.91
stimulated – sedated	-.08	.58
restless – peaceful	.01	.95
irritable − good-humoured	-.01	.94
anxious – calm	.0	.89

Fig S1. Distribution of interoceptive awareness in both conditions.



5

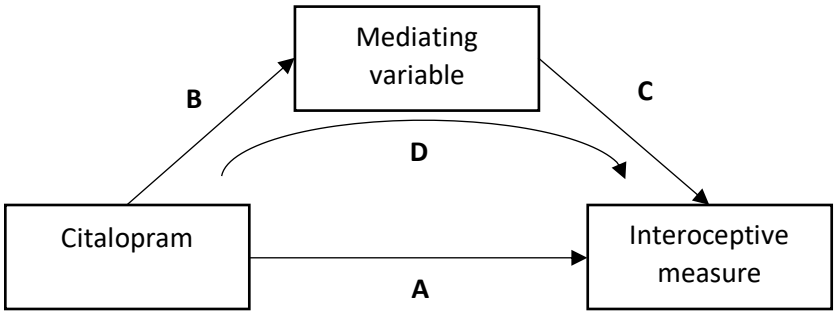


Fig S2: Mediation analysis approach

Table S3: mediation analyses on interoceptive awareness. HR – heart rate, VMA – visual metacognitive awareness, † in units of awareness scores, ‡ in units of the mediator, * p < .05, ** p < .01

	mediator		
	HR	**nausea**	**VMA**
direct citalopram effect on interoceptive awareness *†*	0.08	0.07	0.07
***t*-stat**	2.30	2.36	2.65
p	**.026***	**.023***	**.01***
effect of citalopram on mediator *‡*	-3.99	4.71	0.001
***t*-stat**	-3.91	2.93	0.08
p	**<.001****	**.005***	.93
effect of mediator on interoceptive awareness*†*	0.0013	<0.0001	0.43
***t*-stat**	0.29	0.009	1.32
p	.78	.99	.19
indirect effect of citalopram on interoceptive awareness through mediator (path D) *†*	-0.0052	0.0001	0.0004

5

Table S4: Repeated measures ANOVA results for exteroception (visual) metacognition task variables with order as a between subject factor, including signal detection theory measures.

			conditional main effect		**order interaction**	
	placebo	**citalopram**	***F*(1,45)**	***p***	***F*(1,45)**	***p***
Δd	5.49	5.74	0.846	.49	1.2	.28
confidence	3.91	3.82	4.05	.05*	2.00	.17
VMA	0.65	0.65	0.00	.96	3.05	.09
meta d'	0.96	0.96	0.00	.96	4.89	.03
meta d' / d'	0.79	0.77	0.17	.68	5.10	.03