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Combined NK_1 antagonism and serotonin reuptake inhibition: effects on emotional processing in humans

Catherine J Harmer[1], Gerry R Dawson[2], Colin T Dourish[2], Elisa Favaron[1], Elizabeth Parsons[1], Monica Fiore[3], Mauro Zucchetto[3], Angelo Bifone[3], Italo Poggesi[3], Sofia Fernandes[3], Robert C Alexander[3] and Guy M Goodwin[1]

Abstract

Background: Synergistic effects of NK_1 receptor antagonism combined with serotonin reuptake inhibition have been reported in preclinical models. GSK424887 is a selective competitive antagonist of the human NK_1 receptor and inhibitor of the serotonin transporter. However, its actions in human models of depression have not been assessed.

Methods: This study explored the effects of acute administration of GSK424887 compared to placebo in healthy male volunteers. The selective serotonin reuptake inhibitor (SSRI) citalopram was used as a positive control. A battery of emotional processing tasks was given at the peak time of drug effect.

Results: GSK424887 enhanced attentional vigilance in the dot-probe task to both positive and negative stimuli. By contrast, citalopram enhanced perception of angry, sad and happy facial expressions and increased positive bias in the facial expression recognition task. Neither drug significantly affected emotion potentiated startle responses or emotional memory.

Conclusions: These results suggest that acute administration of GSK424887 modulated some aspects of emotional processing but these effects were not similar to those seen previously with antidepressant agents. This was the first use of the battery of emotional processing tasks in a Phase 1 study. Repeated administration of the test and active control drugs may be needed to reliably characterise their effects.

Keywords

Antidepressants, emotional processing, biomarker models, depression, serotonin, NK1 receptors

Introduction

Most antidepressants in current clinical use potentiate the activity of serotonin (5-HT) and/or noradrenaline (NA), usually through blockade of the relevant neurotransmitter re-uptake site in the presynaptic nerve terminal (see Nutt, 2002). However, levels of disability from major depression are high and conventional drug treatments have a modest clinical efficacy/tolerability balance as well as a delayed clinical onset of action. Consequently, there is a continuing need for innovation in the pharmacological treatment of depression to address these unmet needs.

Current interest in the role of substance P and its preferred NK_1 receptors in stress, pain and anxiety in animal models has highlighted a potential application of NK_1 receptor antagonists in the treatment of depression and anxiety (Ebner and Singewald, 2006; Ebner et al., 2009). However, while initial phase II studies of NK_1 receptor antagonists reported a higher rate of symptom remission than for active comparators or placebo (Kramer et al., 1998, 2004), subsequent larger scale studies have failed to replicate positive effects of NK_1 antagonism in depression (Keller et al., 2006).

Experimental medicine models may be a useful method to characterise novel drug targets in humans and provide early markers of efficacy which allow refinement of subsequent clinical trial design and application (see Harmer et al., 2011). One model focuses on negative affective biases in information processing seen in depression, where patients are more likely to attend to, interpret and remember negative compared to positive affective information (Roiser et al., 2012). Recent research suggests that antidepressants can target these processes early in treatment, before therapeutic effects are seen, and may be involved in the later evolution of clinical change (see Harmer et al., 2009a). For example, antidepressants such as the selective serotonin reuptake inhibitor (SSRI) citalopram or the noradrenaline reuptake inhibitor reboxetine increase the ability to recognise facial expressions of happiness and memory for positive compared to negative affective information in healthy volunteer models (Harmer et al., 2003a, 2003b, 2004). However, acute administration of SSRIs like citalopram also appears to increase the recognition of threat relevant facial expressions and reactivity in the emotion potentiated startle task (a human analogue of the fear potentiated startle

[1]Department of Psychiatry, University of Oxford, Oxford, UK
[2]P1vital Ltd, University of Oxford, Oxford, UK
[3]Glaxosmithkline (GSK), Verona, Italy

Corresponding author:
Catherine J Harmer, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JX, UK.
Email: Catherine.harmer@psych.ox.ac.uk

task used for preclinical screening of anxiolytic drugs) which may be relevant to early unwanted anxiogenic effects of drug treatment.

Studies exploring the effects of aprepitant on these experimental medicine measures have revealed that blockade of NK_1 receptors does affect emotional processing in humans but that this is less consistent than typically observed with conventional antidepressant agents. In particular, while a single dose of aprepitant improved the recognition of positive facial expressions of happiness and increased attention to positive stimuli in a visual-probe task, it also led to overall reductions in emotional memory and a slowing of responses during facial expression recognition compared to double blind administration of placebo (Chandra et al., 2010). With repeated seven day dosing, there was a clear reduction in the emotion potentiated startle response and an improvement in positive affective memory performance without any effect on facial expression recognition (Pringle et al., 2011). These results suggest that there may be some effect of NK_1 blockade on key aspects of psychological function associated with depression, but that this may not be sufficient to work in isolation as an antidepressant agent. More recent evidence from animal studies suggests that NK_1 receptor antagonists and SSRIs have synergistic actions at relatively low levels of NK_1 receptor and serotonin transporter (SERT) occupancy. For example, microdialysis studies suggest that although administration of an NK_1 receptor antagonist alone has no effect on serotonin efflux, it is able to potentiate cortical serotonin levels in response to an SSRI (Guiard et al., 2004). Behavioural studies have also revealed that NK_1 receptor antagonism selectively potentiates the activity of subthreshold doses of citalopram and paroxetine in the mouse forced swim test (Chenu et al., 2006). Such results suggest that co-administration of a NK_1 receptor antagonist with an antidepressant drug such as a SSRI, may have a therapeutic potential to improve the treatment of major depressive episodes compared to treatment with a SSRI alone.

GSK424887 is a high affinity NK_1 receptor antagonist and SERT inhibitor (chemical name: N-[(1S)-1-(3-chloro-1-naphthalenyl)ethyl]-2-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-N-methylacetamide). In a panel of 84 enzyme, receptor, ion channel and transporter targets, GSK424887 only showed binding to rat non-selective sigma receptors (GSK, on file). In healthy volunteers a 100 mg dose of GSK424887 results in an estimated receptor occupancy of up to 50% and 40% of NK_1 receptors and SERT respectively (see Supplementary Information). These levels of occupancy are in line with those that have been shown to induce acute anxiolytic effects in animal models. However, prediction of therapeutic efficacy from preclinical animal models alone represents a major challenge for the pharmacological development of new agents, where up to 90% of new agents fail at relatively late stages of development because of lack of efficacy in man (Dawson and Goodwin, 2005).

The current study therefore explored the effects of GSK424887 on emotion in humans to assess the possibility that NK_1 antagonism combined with serotonin reuptake inhibition would have synergistic actions compared to SSRI administration alone. Acute administration of citalopram would be expected to facilitate the recognition of both positive and threat relevant facial expressions and increase startle responses in the emotion potentiated startle paradigm, similar to previous studies (Browning et al., 2007; Grillon et al., 2007; Harmer et al., 2003a). Given the synergistic properties of GSK424887 seen in pre-clinical neurochemical and behavioural models, it was predicted that this drug would have greater effects on the processing of emotional stimuli in humans following acute administration. Such actions would highlight GSK424887 as an intriguing candidate for further clinical development.

Methods

Study design

This study (GSK Protocol 105012) was a randomised double-blind, placebo-controlled, single centre study with three parallel groups conducted in the UK. The study was approved by the local ethics committee and by the Medicines and Healthcare products Regulatory Agency (MHRA) who regulate clinical trials in the UK. The study took place on an in-patient basis. Based on a power analysis of male volunteers given citalopram versus placebo in a previous study (Browning et al., 2007), this study had a statistical power of 95% to detect a difference between groups in the facial expression recognition of fear (mean difference between groups of five with a standard deviation (SD) of 4.1).

Subjects

Fifty-four healthy male volunteers, between the ages of 18–45 years old who provided written informed consent were included in the study. Participants meeting criteria for the study were confirmed to be healthy based on physical examination, ECG, medical and surgical history and blood test. They were also screened using a structured clinical interview for DSM-IV-TR axis 1 disorder and excluded if they met criterion for any current or past axis 1 disorder or if they scored >7 for anxiety and depression scores on the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983). Participants were required to be nonsmokers or light smokers (<5 cigarettes a day, confirmed with cotinine urine levels <200 ng/mL) and to not take illicit drugs (screened for cannabinoids, amphetamines, cocaine, barbituates, methamphetamines, benzodiazepines, opiates). Additional exclusion criteria were a body mass index (BMI) outside the range of 18–33 kg/m^2, consumption of more than 21 units of alcohol weekly, concomitant medication that would interfere with the study tasks or drug or experience with any of the cognitive tasks used in the study.

Study procedures

The questionnaires and the emotional test battery (ETB) measures were given in the order detailed below. To monitor group matching, the Eysenck Personality Questionnaire (EPQ) was measured at screening. To assess change following drug administration, the following questionnaire measurements were taken at baseline and after cognitive testing: the Befindlichkeit Scale, (BFS, Von Zerrsen et al., 1974), and Positive and Negative affective schedules (Watson et al., 1998). The Bond and Lader Visual analogue scales, (VAS, Bond and Lader, 1974). VAS scores were combined into the three factors alertness, calmness and mood as suggested by Bond and Lader (1974) and change scores were computed for each mood variable.

The study was run with a double placebo procedure since citalopram and GSK424887 have different absorption times. Participants randomised to the GSK424887 arm therefore received GSK424887 at approximately 09:00 and placebo to match citalopram at approximately 13:00. Participants randomised to the citalopram arm received placebo to match GSK424887 at approximately 09:00 on the test day and citalopram at approximately 13:00. Participants randomised to the placebo arm received placebo at both time points. At approximately 15:00 participants completed the ETB followed by subjective rating scales.

Plasma drug level analysis

Blood samples were taken via an indwelling cannula (or by direct venepuncture), collected into ethylene diamine tetraacetic acid (EDTA) before and immediately after emotional processing assessment (at approximately six hours and eight hours). Human plasma samples were analysed for GSK424887 and its metabolite GSK419301 using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography and mass spectrometry (HPLC-MS/MS) analysis. The lower limit of quantification (LLQ) for GSK424887 and its metabolite GSK419301 was 0.300 ng/mL using a 50 uL aliquot of human EDTA plasma with a higher limit of quantification (HLQ) of 300 ng/mL (GSK Document Number VD2006/00238/00).

Emotional processing tasks

Facial expression recognition. The facial expression recognition task featured six basic emotions (happiness, surprise, sadness, fear, anger and disgust) taken from the Pictures of Affect Series (Ekman and Friesen, 1976), which had been morphed between each prototype and neutral (Young et al., 1997). Briefly, this procedure involved taking a variable percentage of the shape and texture differences between the two standard images 0% (neutral) and 100% (full emotion) in 10% steps. Four examples of each emotion at each intensity were given (total of 10 individuals). Each face was also given in a neutral expression, giving a total of 250 stimuli presentations. The facial stimuli were presented on a computer screen (random order) for 500 ms and replaced by a blank screen. Volunteers classified the expression on the face by pressing labelled keys corresponding to each of the six emotions and neutral on the keyboard. Each participant was asked to respond as quickly and as accurately as possible. Accuracy, false alarms (misclassifications) and reaction times were measured in this task.

Emotional categorisation and memory. *Self-referent*: Sixty personality characteristics selected to be extremely disagreeable (n=30 e.g. domineering, untidy, hostile) or agreeable (n=30 e.g. cheerful, honest, optimistic) (taken from Anderson, 1968) were presented on the computer screen for 500 ms. These words were matched in terms of word length, ratings of frequency and meaningfulness. Participants were asked to categorise these personality traits as to whether they would like or dislike to be referred to as this characteristic as quickly and as accurately as possible. Classifications and reaction times for correct identifications were computed for this task. Approximately five minutes after completion of the categorisation task, participants were asked to recall, and write down, as many of the personality trait words as possible within a two minute limit. Correct recall for positive and negative word stimuli was recorded. Recognition memory was then assessed by asking participants to respond with a 'familiar' or 'novel' to each item presented on the computer screen containing the 60 targets plus 60 matched distracters (30 positive, 30 negative). Correct responses and false alarms for each of the positive and negative conditions were recorded and combined to give a measure of sensitivity using the following equation:

$$A' = (0.5 + ((y–x)(1 + y–x))/4y(1–x))$$

where y = number of correct responses/30 for each emotion and x = number of false alarms/30 for each emotion.

Visual probe task

This task measures attention to emotional stimuli by comparing the behavioural response to a probe on trials when the probe replaces emotional compared to neutral stimuli (see Macleod et al., 1986). Two types of emotional words were used in this task: 60 negative words and 60 positive words. Each emotional word was paired with a neutral word matched for length. On each trial, one of the words appeared above, and the other below a central fixation position. In the unmasked condition, the word pair was presented for 500 ms and followed by a probe in the location of one of the preceding words. The probe was either one or two stars and participants were asked to press one of two labelled buttons to indicate the number of stars present. Participants were asked to respond as quickly and as accurately as possible. The sequence of events was the same in the masked condition, except the duration of the word pair was 14 ms and the display of the word pair was immediately followed by a mask which was displayed for 186 ms. The mask was constructed from digits, letters and other non-letter symbols and was matched for word position and length. There were 180 trials in total (masked: 30 positive-neutral, 30 negative-neutral, 30 neutral-neutral; unmasked: 30 positive-neutral, 30 negative-neutral, 30 neutral-neutral) and masked and unmasked trials were presented in a random order.

Reaction time and accuracy scores were recorded. In keeping with our standard practice, reaction time data lying at more than two SDs above or below each participant's mean score was removed. To simplify these results, attentional vigilance scores were calculated for each participant by subtracting the reaction time from trials when probes appeared in the same position as the emotional word (congruent trials) from trials when probes appeared in the opposite position to the emotional word (incongruent trials). The premise behind this task is that if you were attending to the emotional word you would be slower to respond to the probe if it was in the opposite compared to same location as that word.

Emotion potentiated startle task (EPST). Picture stimuli from the International Affective Picture System, designed to elicit positive, negative or neutral emotions were used (Lang et al., 1999). Stimuli were presented for 13 s (inter-trial interval of 11–15 s) on a 43 cm computer screen approximately 1 m away from the

volunteer. Pictures were presented in three blocks each containing seven pictures of each category in a fixed random order with the constraint that no two of the same type (neutral, positive or negative) were presented successively. The eye-blink component of the startle response was recorded from the orbicularis oculi using electromyography (EMG Startle Response System, San Diego Instruments Inc., USA). Acoustic probes were 50 ms, 95 dB bursts of white noise with a nearly instantaneous rise time and were delivered binaurally through headphones (delivered at 1.5, 4.5 or 7.5 s following picture onset). Within each block of 21 pictures, probes were delivered on 5 out of every 7 trials of each valence (neutral, positive or negative). To limit expectation of the noise, two trials per valence did not contain any startle probes and three probes per block were given within the inter-trial interval. To habituate participants to the startle probes and to orient them to the procedure, participants viewed an introductory set of nine neutral pictures and received nine startle probes.

EMG signals were filtered (low cut off: 1 Hz; high cut off: 300 Hz) and rectified. Eye blink reflex magnitudes in mV were calculated by subtracting the amount of integrated EMG at baseline (average of 0–20 ms after probe onset) from the peak amplitude maximum amount of integrated EMG between 20 and 120 ms following probe onset. Eye blink reflexes with excessive noise during the 20 ms, prestartle baseline period were excluded. This task provides a measure of the relative acoustic startle response during unpleasant, pleasant and neutral pictorial stimuli presentation. Therefore, eye blink reflex magnitudes were *z*-transformed within subjects to allow comparison between these different conditions and minimise inter-subject variability. Of the 54 volunteers, three volunteers (one per group) were not included in the analysis because of electrode interference (n=2) or because they displayed fewer than 25% satisfactory blink responses in the paradigm (n=1).

Statistical analysis

As the study was exploratory, each drug was compared to placebo in a separate analysis. Demographic characteristics were analysed with one way analysis of variance with group as the factor. For the emotional processing and subjective state data, split-plot analyses of variance were applied with group as the between-subjects factor (placebo vs drug) and emotion as the within-subjects factor. For the visual probe task, presentation time (masked vs unmasked) was added as an additional within-subjects factor and for the facial expression recognition task emotion intensity (five levels, 20% blocks) was included as an additional within-subjects factor. Significant interactions in this analysis were completed with simple main effect analyses (one way analysis of variance), comparing the two groups for each emotion.

Results

Plasma drug concentration

Volunteers receiving GSK42887 had a mean plasma drug concentration of 171.1 ng/mL (SD 72.2) and 179.7 ng/mL (73.1) pre and post-administration of the psychological test battery. Concentrations of the metabolite GSK419301 were 42.1 (14.2) and 45.4 (15.1) respectively. Pharmacokinetic modelling based on the results from a recent positron emission tomography (PET) study suggests that these concentrations correspond to around 50% receptor occupancy of NK_1 receptors and 40% occupancy of serotonin transporter receptors (see supplementary information).

Table 1. Baseline characteristics of the three groups (mean and standard deviation (SD)).

	Citalopram		424887		Placebo	
	Mean	SD	Mean	SD	Mean	SD
Age	24.3	(7.1)	27.1[a]	(7.5)	23.1	(3.1)
EPQ: Neuroticism	7.4[a]	(4.1)	5.7	(4.1)	4.9	(3.1)
EPQ: Psychoticism	3.6	(2.3)	3.2	(2.3)	3.7	(2.5)
EPQ: Lie scale	6.7	(3.4)	7.4	(3.2)	7.2	(4.0)
EPQ: Extraversion	15.7	(2.1)	13.6	(4.2)	15.7	(3.1)
PANAS: Positive	32.8	(6.3)	31.1	(6.9)	32.9	(7.4)
PANAS: Negative	13.6	(3.4)	12.1	(1.5)	11.6	(1.7)
BFS: Energy	6.0	(5.6)	5.0	(5.9)	4.5	(4.8)
BFS: Mood	9.2	(8.0)	7.8	(6.6)	8.8	(7.7)

BFS: Befindlichkeit Scale; EPQ: Eysenck Personality Questionnaire; PANAS: positive and negative affect schedules.
[a]p<0.05 between drug and placebo treatment.
Values represent mean change from baseline with standard deviation (SD). There were no significant differences between groups on these measures.

Table 2. Subjective measures of state in each group.

Rating scale	Citalopram		424887		Placebo	
	Mean	SD	Mean	SD	Mean	SD
Alert	−0.15	(4.3)	−0.24	(4.1)	−0.88	(5.1)
Mood	−0.01	(7.8)	0.19	(7.7)	0.30	(3.6)
Calmness	−0.06	(13.0)	−3.7	(9.6)	−3.72	(11.0)
PANAS: Positive	−2.2	(3.6)	−0.2	(3.9)	−1.72	(4.9)
PANAS: Negative	−1.8	(2.8)	−0.8	(2.0)	−0.33	(1.4)
BFS: Energy	0.4	(7.6)	3.6	(7.1)	2.78	(4.9)
BFS: Mood	1.9	(8.1)	1.7	(9.2)	1.17	(12.)

BFS: Befindlichkeit Scale; PANAS: positive and negative affect schedules.
Values represent mean change from baseline with standard deviation (SD). There were no significant differences between groups on these measures.

Group details

The three groups scored comparably on baseline mood and EPQ scores on the psychoticism and extraversion subscales (see Table 1). However, those randomised to receive GSK424887 were slightly older on average and those randomised to the citalopram treatment group had higher neuroticism scores relative to placebo. These variables were therefore entered as co-variates in subsequent analyses.

Subjective state

As expected, there was no effect of either GSK424887 or citalopram on subjective ratings of mood and subjective state measured with the VAS scales, positive and negative affect schedules (PANAS) or BFS (see Table 2).

Facial expression recognition

Accuracy: There was a trend for an interaction between group×emotion×intensity in the overall analysis of variance for the

citalopram treated group ($F(20,660)=1.4$, $p=0.1$, see Figure 1). This was driven by increased recognition of anger (group × intensity $F(4,132)=2.8$, $p=0.03$; main effect of group ($F(1,33)=4.3$, $p=0.046$), sadness (group × emotion $F(4,132)=2.1$, $p=0.1$; main effect of group ($F(1,33)=5.7$, $p=0.02$) and happy facial expressions (group *x* emotion $F(4,132)=2.9$, $p=0.02$); main effect of group $F(1,33)=0.0$, $p>0.9$) following citalopram treatment (see Figure 1). There was no effect of citalopram administration on the recognition of disgusted, surprised or fearful faces (all *p*-values >0.2). GSK 424887 did not affect facial expression recognition in this task for any emotion (all *p*-values >0.4).

Reaction time: Neither citalopram nor GSK424887 affected reaction time in this task (all *p*-values >0.4)

Misclassifications: Citalopram specifically increased misclassification of other facial expressions as happy in this task (group × emotion $F(6,198)=2.2$, $p=0.044$; happy: $F(1,33)=5.1$, $p=0.03$). By contrast, there was no significant effect of GSK442887 on the number of misclassifications in this task ($F(6,198)=0.4$, $p=0.9$; $F(1,33)=0.03$, $p=0.9$). The mean number of faces misclassified as happy was 2.3 (SD 2.5), 5.2 (SD 5.1) and 4.2 (SD 4.3) following placebo, citalopram and GSK442887 respectively.

Emotional categorisation and memory

Neither citalopram nor GSK424887 modulated reaction time to classify self-referent stimuli in this task (all *p*-values >0.4). There was also no effect of citalopram on emotional memory recall ($F(1,33)=1.9$, $p=0.2$). However, there was a trend for GSK424887 to decrease the relative recall of positive vs negative affective information ($F(1,33)=3.0$, $p=0.09$). Recognition memory, was unaffected by either drug manipulation (all *p*-values >0.3).

Visual probe task

Citalopram did not affect attentional vigilance in this task (all analyses involving group $p>0.3$). However, there was a main effect of group following GSK424887 ($F(1,33)=7.3$, $p=0.011$). This was driven by increased attentional vigilance to emotional stimuli irrespective of stimuli valence in the unmasked condition (main effect of group: $F(1,33)=9.7$, $p=0.004$, see Figure 2).

EPST

There was no effect of either GSK442887 or citalopram on startle reactivity in this task, either analysed as raw amplitudes or as *Z*-converted data (all *p*-values >0.2).

Discussion

The results from this study suggest that a drug which combines NK_1 antagonism and selective serotonin reuptake inhibition modulates some aspects of emotional processing in healthy volunteers. In particular, volunteers receiving GSK424887 showed increased vigilance to emotional stimuli in the attentional probe task and also a trend for increased negative vs positive affective memory performance. By contrast, administration of acute citalopram increased the recognition of negative (sad and angry) and positive (happy) facial expressions. These effects are similar to those observed previously with SSRI administration and may help us understand early effects of antidepressants which are important in their therapeutic action (Harmer et al., 2009a). However, the results do not support the hypothesis that acute administration of a compound with combined NK_1 and SERT activity, at least at the occupancies achieved, would have actions superior to an SSRI on relevant measures of emotional cognition.

Acute administration of antidepressants such as citalopram, duloxetine or reboxetine has previously been reported to enhance recognition of happy facial expressions (Harmer et al., 2003a, 2003b, 2008, 2009b; Murphy et al., 2009) and a similar effect was seen here following acute administration of the positive control antidepressant. Hence, those volunteers receiving citalopram showed increased perception of low intensity happy facial expressions and were more likely to misclassify other facial expressions as happy in this task. Such an increase in 'positive bias' may target the negative focus of emotional processing seen in depression which is believed to play a key role in aetiology and maintenance of this illness (Beck et al., 1979). Indeed, early increases in happy recognition in depressed patients with citalopram treatment were predictive of later therapeutic responses to this drug seen after six weeks of treatment (Tranter et al., 2009), suggesting that increased positive processing may be relevant to antidepressant drug action. NK_1 receptor antagonism with aprepitant was also previously found to have weak effects on happy facial expression recognition (Chandra et al., 2010) and it therefore noteworthy that GSK424887 which has combined NK_1 antagonism and serotonin reuptake inhibition at lower occupancies had no effect on positive affective processing in this task.

A human PET study conducted with GSK442887 revealed that the levels of NK_1 antagonism and SERT inhibition are lower than those normally achieved with conventional drug treatments targeting these processes separately (see supplementary information Figure 1). The observed receptor occupancies achieved by GSK442887, approximately 50% of NK_1 receptors and 40% of the serotonin transporter at the dose administered, are well below those required for efficacy, >90% for NK_1 (Hargreaves, 2002) and >75% for citalopram (Meyer et al., 2001). It was hypothesised that although the receptor occupancies achieved would be below clinically efficacious levels, a synergistic effect might be induced. However, the evidence from the emotional processing battery suggests that such synergistic effects are not apparent functionally in human models relevant to depression, at least with acute administration. Interestingly, GSK442887 was not completely without effect at these receptor occupancies in the current study, but it tended to impair positive affective memory rather than to enhance it: an effect opposite to that seen with conventional antidepressants such as reboxetine, mirtazapine and duloxetine (Arnone et al., 2009; Harmer et al., 2004, 2008, 2009b). Future studies would be needed to evaluate the effects of longer term administration of GSK442887 on emotional processing as some relevant actions of antidepressants emerge later in the treatment cascade. For example, acute administration of citalopram does not typically affect emotional memory (Browning et al., 2007; current study) though increased positive memory recall is seen after seven days administration (Harmer et al., 2004).

Acute administration of GSK442887 did, however, increase attentional vigilance in the dot-probe task to both positive and negative stimuli in the current study. A similar effect was seen

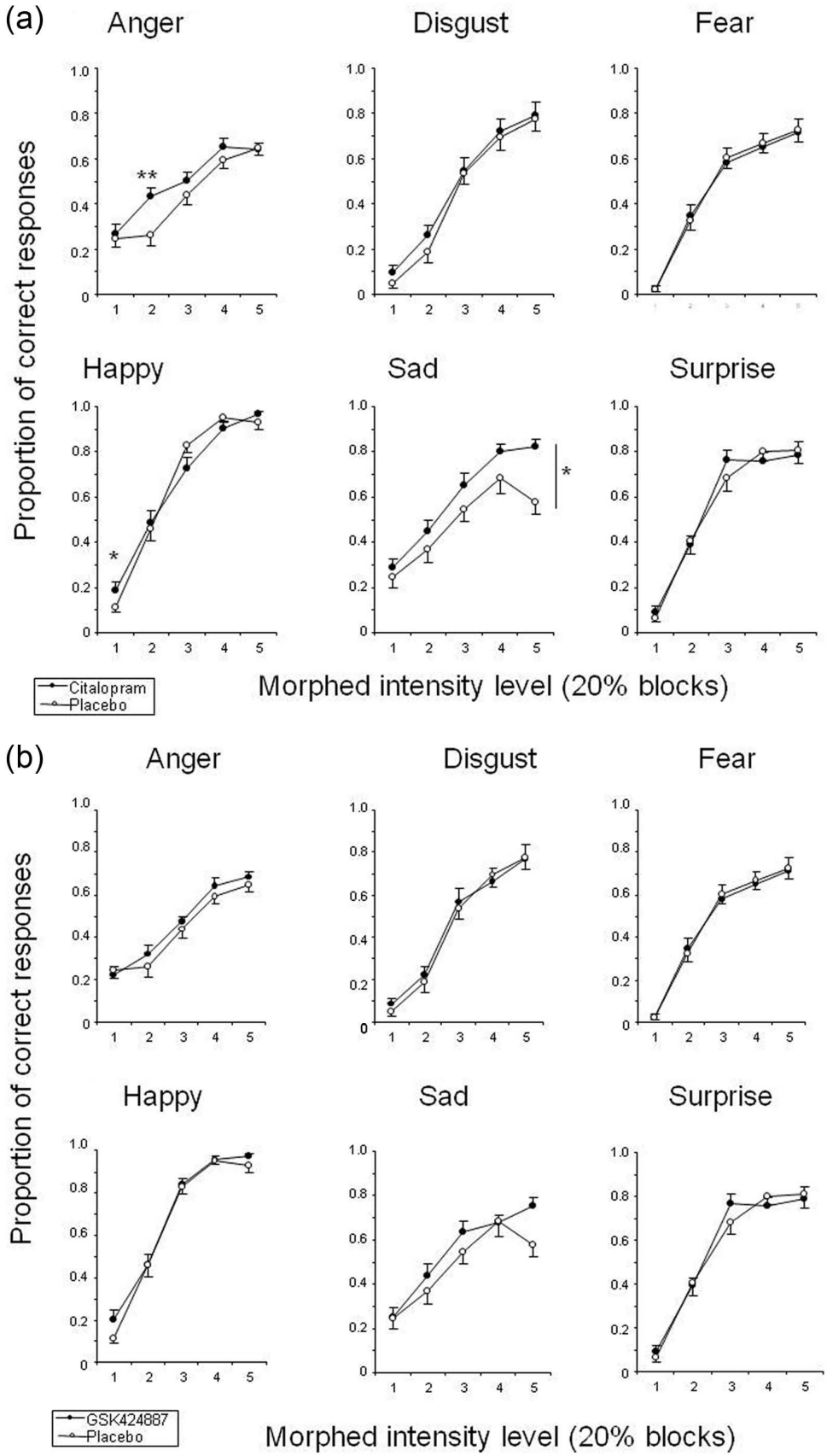

Figure 1. Facial expression recognition following (a) citalopram or (b) GSK424887. Values represent mean accuracy across five binned intensity levels for each emotion, with 1 standard error of the mean (SEM). *p<0.05 between drug and placebo treatment; ** p<.01.

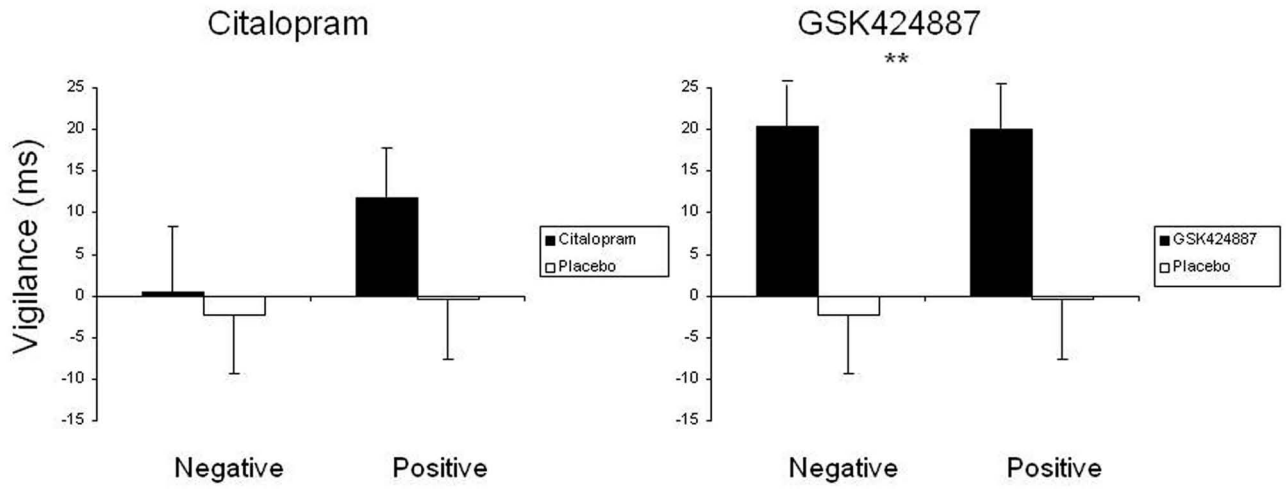

Figure 2. Attentional vigilance in the dot-probe paradigm under the unmasked condition. Values represent means with 1 standard error of the mean (SEM). Asterisks show significant difference at $^{**}p<0.01$ between drug and placebo treatment.

with acute administration of aprepitant (Chandra et al., 2010) suggesting that such actions may be related to antagonism of NK_1 receptors. This pattern may represent increased engagement and/or attention to emotional stimuli in general following NK_1 blockade. Anxiety has been associated with increased vigilance to threatening stimuli at similar stimuli durations used in the current study (Mogg and Bradely, 1998) and anxiolytic agents such as diazepam typically decrease vigilance to threat in this task (Murphy et al., 2008). While increased attention to positive stimuli with GSK442887 may therefore be relevant to antidepressant drug action, the effects on threat stimuli are reminiscent of early anxiety-like orienting. Such effects underscore the necessity of investigating the effects of repeated administration of GSK442887 on these outcome measures to assess longer term outcomes (see Harmer et al., 2009a, 2011).

Previous studies have found increased perception of fearful facial expressions with acute administration of citalopram (Browning et al., 2007; Harmer et al., 2003a though not in Murphy et al., 2009) which was not seen here: citalopram did enhance the recognition of anger and sadness in the current study which may represent similar underlying processes because fear and anger are both important threat-relevant emotional stimuli. Pharmacological manipulations have often been reported to affect one or both of these emotions. For example, citalopram decreased the perception of fear and anger following seven days administration in healthy volunteers (Harmer et al., 2004) and 15 mg of diazepam had a similar effect in one study (Zangara et al., 2002) but specifically impaired anger in another study by the same group (Blair and Curran, 1999). Both fear and anger are used in emotion paradigms in functional magnetic resonance imaging (fMRI) to reliably activate the amygdala complex (e.g. Hariri et al., 2002) and meta-analyses suggest that the amygdala may particularly respond to meaningful stimuli which are important for further processing (Phan et al., 2002). Related to this, gender may also be relevant: the effects of citalopram on fear processing have been characterised in either all-female or largely female samples (Browning et al., 2007; Harmer et al., 2003a) and it is interesting to speculate whether a similar effect may be expressed as greater anger perception in males. However, it is also important to note that differences between groups were small in this task and were only noted at a trend level in the overall omnibus analysis of variance test used to evaluate statistical significance.

There was also no effect of citalopram on the EPST or on attentional vigilance in the present sample, which contrasts with a number of previous reports exploring the effects of this drug on emotional processing (Browning et al., 2007; Grillon et al., 2007). Reduced sensitivity to these effects may relate to the male sample used in the present study, or to the enhanced medical setting that an experimental study with a drug early in development necessitated. In particular, the study required additional medical exclusion criteria and medical procedures during the test day, involved greater risk assessment and the use of an in-patient setting in a hospital. Hence, participants who were prepared to take part in this study may have been more resistant to anxiogenic-like effects of SSRI administration. Indeed, anxiogenic effects are only observed in a subset of patients following SSRI administration and such effects may be expected to interact with the trait characteristics of the sample (see Murphy et al., 2009). It is also worth noting that the emotional processing assessment here was performed two hours following citalopram administration. This is slightly earlier than in our previous studies where testing began three hours post administration (Browning et al., 2007; Murphy et al., 2009). The time to peak plasma concentrations of citalopram tend to be in the region of 3–4 hours (Al-Ghazawi et al., 2007), so it is possible that drug levels were not sufficiently high in this study to detect reliable effects.

Drug discovery and screening of agents for depression is limited by the availability of good models to predict efficacy. Emotional processing measures represent a possible solution and allow assessment of those processes closer to the human experience of depression, whilst still allowing tight experimental control over confounding variables. GSK442887 had negligible effects on emotional processing in the current study. Hence, the synergistic action of combined selective SERT inhibition and NK_1 receptor antagonism observed in single administration preclinical studies has not been confirmed in this healthy volunteer model.

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Conflict of interest

CJH is on the advisory panel of P1vital and holds shares in the company. She is a company director of Oxford Psychologists Ltd and has received consultancy fees from P1vital Ltd, Lundbeck, Eli-Lilly and Servier.
MF, MZ, AB, IP, SF and RCA are current or former employees of GSK.
GRD and CTD are employed by and are company directors and shareholders of P1vital Ltd and are company directors and shareholders of P1vital Products Ltd.
In the past three years, GMG has received compensation from AstraZeneca, Boehringer-Ingelheim, BMS, Cephalon, Eisai, Janssen-Cilag, Eli Lilly, LA-SER, Lundbeck, Ono Pharma, Roche, Servier and Schering Plough and holds shares in P1vital.
EF declares that, except for income received from her primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest

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