Research article

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# Subchronic treatment with St John's wort produces a positive shift in emotional processing in healthy volunteers

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## Abstract

The neurocognitive model of antidepressant treatment in depression states that antidepressants work by producing relatively immediate positive shifts in emotional processing, which translate into clinical improvement with time. St John's Wort has been shown to have antidepressant potential in RCTs. However, its pharmacological actions are broad and it is not clear whether this intervention has similar effects on emotional processing to those reported with other antidepressants such as SSRIs. In a placebo-controlled study in 48 healthy participants we found that seven days of St John's wort treatment produced similar changes to other antidepressants, for example reducing recognition of disgusted faces and attention to fearful faces, while increasing memory for positive words. We failed to find evidence for an effect of St John's wort on other aspects of cognition including working memory. These findings lend support to the theory that the production of early positive biases in emotional processing may be a common feature of all clinically effective antidepressants.

## Keywords

St John's wort, hypericum, depression, emotional processing

# Introduction

Negative biases in the processing of emotionally valenced information are believed to play a key role in maintaining the symptoms of depression. These biases have been captured in the lab using computerised measures of emotional processing. For example, depressed patients have been shown to have better memory for negative words, and worse memory for positive [1, 2]. They are also worse at recognising happy facial expressions, and interpret ambiguous expressions as sadder [1, 3].

These biases are remediated after both acute and short-term antidepressant treatment. After an acute dose of the norepinephrine reuptake inhibitor (NRI) reboxetine, patients had better memory for positive words and improved recognition of happy faces [1]. Similarly, seven days' treatment with the selective serotonergic reuptake inhibitor (SSRI) citalopram increased recognition of happy faces [4]. These early changes have also been found to predict later clinical response [5]. Importantly, similar changes have been found in non-depressed healthy volunteers, strongly suggesting that they cannot be attributed to any early clinical effects of treatment [6-10]. These findings suggest that early remediation of negative bias in depression may be a mechanism of antidepressant drug action [11](.

To date, the early neuropsychological effects of antidepressants have been demonstrated in only a few classes of antidepressants: mainly SSRIs and NRIs, with a few instances of others such as mirtazapine [12] and agomelatine [13]. It is unknown however whether similar effects underlie the effects of natural agents with purported antidepressant action, such as *Hypericum perforatum*, or St John's wort (SJW).

SJW is traditionally used to treat depression, and is one of the only "herbal remedies" with a body of research supporting its clinical use. The drug has been shown to produce greater symptomatic improvement than a placebo [14], and compares favourably with other antidepressants including sertraline [15], imipramine [16], and fluoxetine [17]. While not all studies have been supportive [18], a meta-analysis by the Cochrane Collaboration found that patients taking SJW were more likely to respond to treatment than those on a placebo, and there was no difference in clinical response between those taking SJW and those taking other antidepressants. [19].

Notably, the evidence for any broader cognitive effects of SJW is much weaker. A number of *in vivo* studies have suggested that SJW extracts could improve memory, particularly spatial working memory, in rats [20-22]. However, in humans acute doses have been found to have no beneficial effect on working memory or word or picture recognition, and perhaps even impair memory at higher doses [23]. Similarly, long-term treatment had no effect on spatial working memory [24, 25].

The compound hyperforin is the most likely candidate for producing the clinical effects of SJW. Hyperforin produces broad inhibition of neurotransmitter reuptake: both *in vivo* [26] and *in vitro* studies [27] have demonstrated inhibited reuptake of serotonin, dopamine and noradrenaline, and it also inhibits reuptake of GABA and glutamate [28]. Hyperforin does not appear to bind to any specific reuptake sites but rather increases intracellular sodium levels by binding to and activating a transient receptor potential channel (TRPC6) that is permeable to sodium on the presynaptic neuron. Because neurotransmitter reuptake transporters are reliant on the sodium gradient, reducing the difference in sodium concentration between intra- and extra-cellular fluid produces a broad-acting decline of neurotransmitter reuptake that is not limited to any particular transmitter [29, 30].

With its clear antidepressant effects and novel mechanism of action, SJW is a prime candidate to test the hypothesis that early changes in emotional bias are key features of a range of different antidepressants with diverse neurochemical mechanisms. We predicted that seven days of SJW compared to placebo would produce changes in emotional bias towards positive and away from negative information, similar to other antidepressants. We also predicted that SJW would not have any effects on working memory as assessed by an n-back task.

## Materials and Methods

Ethical permission for this study was obtained from the Central University Research Ethics Committee of the University of Oxford, and informed consent was obtained from participants at the beginning of the screening session. Healthy participants aged between 19 and 43 were screened for the study. Screening included a medical history, including questions about medication and recreational drug use, and screening for axis 1 psychiatric disorders (using the Standard Clinical Interview for DSM-IV; SCID). Exclusion criteria included concurrent use of other medications or hormonal contraception, a current or past psychological disorder, current pregnancy or breast-feeding, and use of psychotropic drugs or participation in a drug trial within the previous three months. Participants were also excluded if they had completed the emotional processing tasks before. During the screening session participants also completed a number of mood questionnaires (see below).

A total of 48 participants met criteria and agreed to take part in the study. One participant exhibited unexpected responses across a range of tasks, including reaction times that were impossibly fast or simply producing no responses; this participant was excluded from all analyses, leaving 47 participants in total (SJW = 23; placebo = 24; due to technical errors some tasks missed data from one or two participants; details are given in supplementary materials). Demographic information is reported in Table 1; t-tests found no significant differences between the groups (*p*s > .05).

Table 1. Demographic characteristics of volunteers

| | SJW (*n* = 23) | | Placebo (*n* = 24) | |
|---|---|---|---|---|
| **Gender** | **N** | **%** | **N** | **%** |
| Male | 11 | 47.83 | 12 | 50 |
| Female | 12 | 52.17 | 12 | 50 |
| | **Mean** | **SD** | **Mean** | **SD** |
| Age | 25.43 | 3.88 | 24.04 | 4.97 |
| Years of education* | 18.09 | 2.34 | 17.67 | 2.33 |

*Not available for one participant in the SJW group

Participants were randomly assigned to receive either SJW or placebo. The SJW treatment consisted of 300mg tablets (Jarsin® 300mg; Klosterfrau), containing a standard

preparation, LI 160, standardised to contain 0.3% hypericin and 3-5% hyperforin. The placebo consisted of 200mg lactose tablets (Rayotabs; RAYONEX) which were encapsulated in gelatin capsules (CapsuleDepot). The study followed a double blind design; because the SJW tablets were too large to be encapsulated, to maintain blinding, capsules were stored in opaque containers and handed to participants by another member of the lab.

Participants took three pills per day for six days, with their meals. On the seventh day, participants took a single pill two hours before the testing session. To ensure compliance, participants were asked to complete a checklist each day, in which they recorded the time that they took each dose. Throughout the week, participants also completed daily visual analogue scales and side-effects questionnaires.

In order to avoid any confounding effects of time of day, the testing session always began between 9am and 11am, with the majority of participants beginning at 10am. Testing sessions lasted approximately 2.5 hours, and testing was scheduled to avoid testing female participants in their pre-menstrual week. Participants first filled in mood questionnaires and then completed a number of computer-based tasks examining emotional processing, explained below.

## Questionnaires

Questionnaires included: the Beck Depression Inventory [BDI; 31], a standard self-report questionnaire used to measure levels of depression; the Snaith-Hamilton Pleasure Scale (SHAPS), a self-report scale that measures the ability to experience pleasure over the past few days; the State-Trait Anxiety Inventory [STAI; 32], a set of two self-report scales measuring State Anxiety and Trait Anxiety; the Positive and Negative Affect Schedule [PANAS; 33], a self-report scale in which participants have to indicate the extent to which they have felt specific positive or negative emotions that day; Visual Analogue Scales (VAS) for the emotions happy, sad, hostile, alert, anxious and calm; and the Eysenck Personality Questionnaire [EPQ; 34], a self-report measure which assesses the personality traits of extraversion, neuroticism and psychoticism. All questionnaires were completed at the screening session, and all except for the EPQ and Trait Anxiety inventory were completed at the testing session.

Each day during the treatment period, participants also completed Visual Analogue Scales, as well as side effects questionnaires measuring five potential side-effects of SJW: nausea, dizziness, dry mouth, headache or sensitivity to light. Participants could score each side-effect as absent (scored as 0), mild (1), moderate (2) or severe (3). Total side-effect scores were then calculated for each day.

## Tasks

### Facial Expression Recognition Task (FERT)

Participants were presented with facial expressions of the six basic emotions (anger, disgust, fear, happiness, sadness and surprise) taken from ten individuals from the Pictures of Facial Affect series [35]. Each photograph was morphed to provide 10 different intensities of the expression (for details on the morphing process see Murphy, Downham [36]; Young, Rowland [37]). Faces were presented in a random order for 500ms each, and participants were required to identify the facial expression as quickly and as accurately as possible by pressing the appropriate key. Participants saw forty faces for each emotion (four of each intensity) as

well as one neutral expression for each of the ten individuals, meaning 250 faces were presented in total.

## Emotional Categorisation

Participants were presented with 60 personality characteristics, 30 positive and 30 negative, and matched for length, frequency and meaningfulness. Words were presented for 500ms and participants were required to indicate whether they would like or dislike to be described in that way, as quickly and as accurately as possible.

## Emotional Recall

A reward task was conducted following emotional categorisation (see supplementary materials), which lasted approximately 15 minutes. Participants were then given a surprise recall task, in which they had two minutes to recall as many words as possible from the emotional categorisation task.

## Emotional Recognition

Participants were presented with 120 personality characteristic words: 60 from the categorisation task, and 60 new words (30 positive, 30 negative). Words were presented for 500ms and participants were required to indicate whether or not the word had been presented in the categorisation task, as quickly and as accurately as possible.

## Dot Probe

The dot probe paradigm measures attentional bias towards or away from rapidly presented stimuli. Participants are required to view two stimuli – in this case faces – and then respond to dots that appear behind one of those stimuli. If a participant responds faster when the dots appear behind a specific stimulus, for example a happy face, then that suggests they have an attentional bias towards that stimulus.

Each trial of the attentional dot probe began with a fixation cross in the centre of the screen, which was immediately followed by the presentation of two faces, one towards the top and one towards the bottom of the screen. These faces were taken from 20 individuals in the JACFEE/JACNeuF sets [38]. A pair consisted of two faces from the same individual, in of one of three combinations of expressions: neutral-neutral, neutral-happy, or neutral-fearful. In unmasked trials, these faces were presented for 100ms; in masked trials they were presented for 16ms followed by a mask, consisting of a jumbled face, for a further 84ms. There were 192 trials in total, consisting of 32 trials of each of the three combinations of faces for both the masked and unmasked conditions. These were presented in eight blocks, with masked and unmasked faces being presented in separate, alternating blocks.

Immediately after the faces had been presented, a probe appeared in the previous location of one of the faces. This probe consisted of two dots aligned vertically (:) or horizontally (. .). The participant was required to indicate the orientation of the dots as quickly and as accurately as possible.

All trials in which participants failed to correctly respond to the orientation of the dots were excluded. Median reaction times were calculated for responses to dots appearing after fearful and neutral faces in fear-neutral trials, and happy and neutral faces in happy-neutral trials. Attentional vigilance scores for happy and fearful faces were calculated for each participant by subtracting the median time taken to respond when dots were behind a neutral

face from median time taken to respond when dots were behind a happy/fearful face. A higher value represents attentional vigilance towards the emotional face; while negative scores indicate attentional bias *away* from that face.

### N-back working memory

Participants were presented with a series of upper- and lower-case letters, and were instructed to indicate whether or not each letter was the same or different from a previously presented letter: either the letter presented one, two, or three letters previously, depending on the block of the task. There was also a zero-back block, in which participants had to indicate whether or not each letter was an *X*.

A block began with instructions (e.g. "One-back"), followed by a series of 10 letters appearing sequentially, each for 500ms with an ITI of 1500ms. Reaction times and accuracy of participants' responses to each letter were recorded. The four block types each occurred four times during the experiment, resulting in a total of 16 blocks.

### Other tasks

An emotion-potentiated startle task and a reward task were also used in the study. Due to technical difficulties, data from many participants for the startle task was not usable and the task was underpowered. Both tasks did not appear to be influenced by treatment condition. For the sake of completeness the methodology and results for these tasks are described in full in the supplementary materials.

Tasks were always completed in the following order: FERT, Categorisation, Reward, Recall, Recognition, Dot probe, N-back, Startle.

### Statistical analysis

Based on our previous work[6] we calculated that a sample size of 19 per group (total n=38) would be sufficient to detect the effect of an antidepressant drug on fearful faces with 80% power ($\alpha$=0.05). This study has 24 participants per group.

The primary endpoints for the study were accuracy and reaction times on the emotion-based tasks. ANOVAs were conducted to examine group differences for each test; subsequently t-tests were conducted to examine main effects/interactions. Given our predictions that SJW's effects on word memory would be specific to positive words, in these cases t-tests were conducted in the absence of interactions (see text below). Where the assumptions of sphericity or equality of variances were violated, we report corrected results; for ease of reading we report uncorrected degrees of freedom.

# Results

## Questionnaires

Independent samples t-tests were used to investigate baseline differences between groups on measures of mood, anxiety and personality; these were all non-significant (see supplementary materials). For the questionnaires completed at both baseline and testing, 2 (timepoint) x 2 (treatment) mixed effects analyses of variance (ANOVAs) failed to find any main effects or interactions (all *p*s > .05), with the exception of a reduced 'calmness' rating

for all participants at testing, $F(1, 45)=6.11$, $p < .05$. There was therefore no evidence that SJW affected individuals' mood or other measured aspects of subjective state.

## Side-effects

Side-effect data was missing for one participant in the SJW group. Overall, SJW appeared to be well-tolerated. Only one participant reported any "severe" side-effects, and these were restricted to just one day. Ten participants (2 on placebo, 8 on SJW) reported experiencing at least one "moderate" side-effect. In order to determine whether there were any differences in side-effects between the groups, a 7 (day) x 2 (treatment) ANOVA was run on total daily side-effect scores averaged across groups. The treatment effect approached significance, $F(1, 44) = 4.07$, $p = .05$, suggesting that the SJW group did experience greater side-effects than the placebo group. The most commonly reported side-effect in this group was dry mouth, followed by headache. Nevertheless, it should be noted that the highest average daily side-effect score in the SJW group was only 1.05 (roughly equivalent to a single side-effect being rated as "mild" and the rest as "absent"), indicating that side-effects were very low overall. Additionally, a chi-square test found number no evidence for an association between the group the participants were in and the guess they made as to their treatment condition, $\chi^2(1) = .70$, $p = .53$ (see supplementary materials).

## ETB

### Facial Expression Recognition Test

Data from trials in which faces were classified as neutral were excluded from the analysis. Figure 1 shows the number of faces correctly recognised. A 6 (emotion) x 2 (treatment) mixed effects ANOVA examined whether SJW affected categorisation of emotional facial expressions. There was no significant effect of treatment, $F(1, 45) = .06$, $p = .80$. However, there was a significant interaction between treatment and emotion, $F(5, 225) = 2.90$, $p = .014$. Individual t-tests revealed that the groups differed significantly on recognition of disgust faces, with the SJW group showing reduced recognition, $t(45) = 2.38$, $p = 0.023$. For reaction times, there was no significant effect of treatment, $F(1, 45) = 2.31$, $p = .14$ and no interaction between treatment and emotion, $F(5, 255) = .54$, $p = .74$.

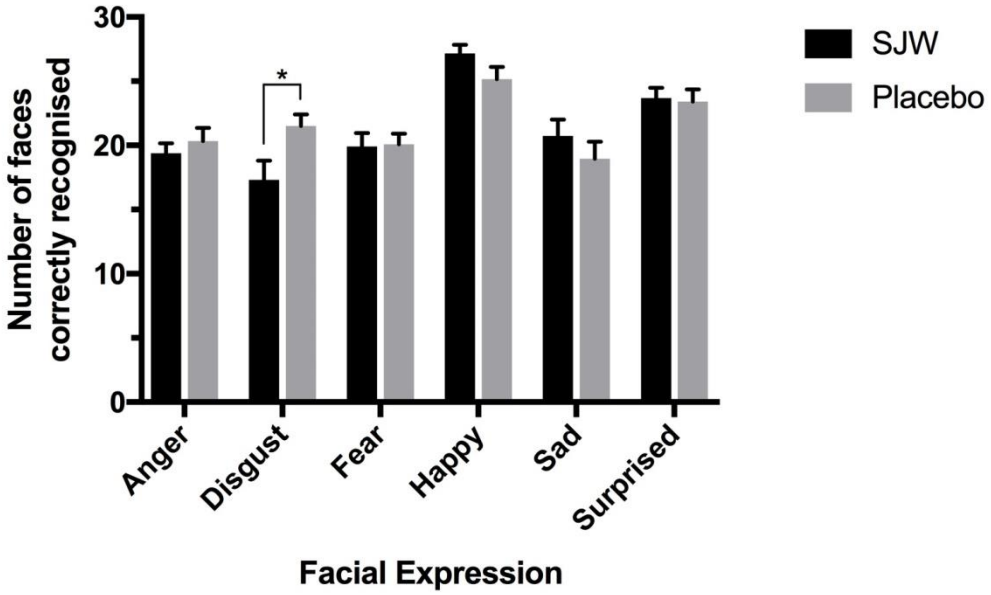
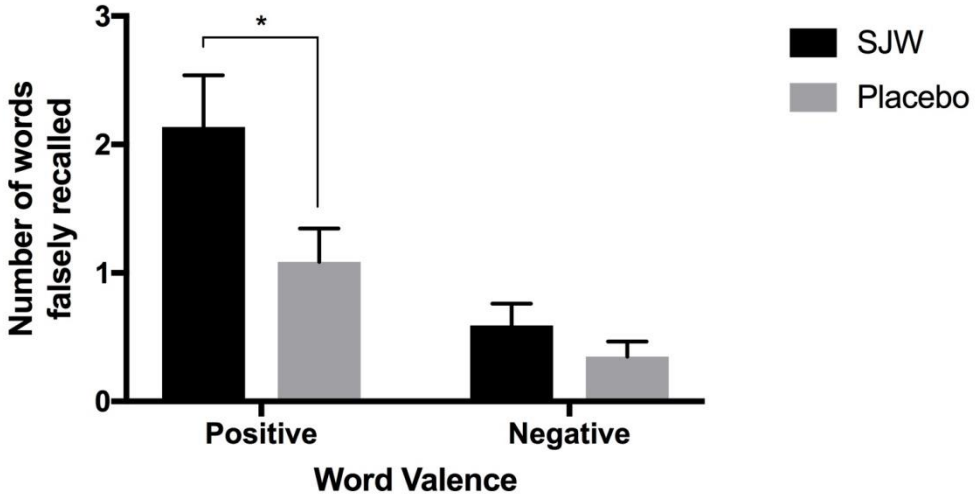


Figure 1. Mean number of faces correctly recognised (out of 30) for each facial expression in the Facial Expression Recognition Test. *p< .05;. Error bars represent standard error of the mean (SEM)

## Recall

We examined the number of positive and negative intrusion words – i.e. words that were "recalled" but which were not on the original list. A 2 (word valence) x 2 (treatment) mixed effects ANOVA was again used to investigate potential group differences. There was a significant effect of treatment, $F(1, 43) = 6.31$, $p = .016$, indicating that the SJW group recalled more words than the placebo group. There was also a main effect of stimulus, $F(1, 43) = 19.43$, $p < .001$, indicating that overall participants recalled more false positive words than false negative.

There was no significant interaction between treatment and stimulus type, $F(1, 44) = 2.42$, $p = .13$; however, given the significant main effects, coupled with the *a priori* hypothesis that St John's wort would increase recall of positive words, t-tests were conducted on each valence of stimuli to examine the specific influence of the drug on positive and negative stimuli. These revealed a significant effect of St John's wort on false positive recollections, $t(43) = 2.22$, $p < .05$, but not false negative recollections, $t(43) = 1.18$, $p = .25$.




(Figure 2).

Figure 2. Mean number of positive and negative words falsely recalled. *p < .05. Error bars represent SEM.

## Recognition

Figure 3 shows the number of positive and negatively words correctly recognised for each group. A 2 (word valence) x 2 (treatment) ANOVA was conducted to see whether there were any significant differences between group. There was a main effect of valence, $F(1,44) = 32.50$, $p < .001$, indicating that overall, subjects correctly recognised more positive than negative words. The main effect of treatment approached significance, $F(1,44) = 3.09$, $p = .09$, and there was no interaction between treatment and word valence, $F(1,44) = 1.43$, $p = .24$.

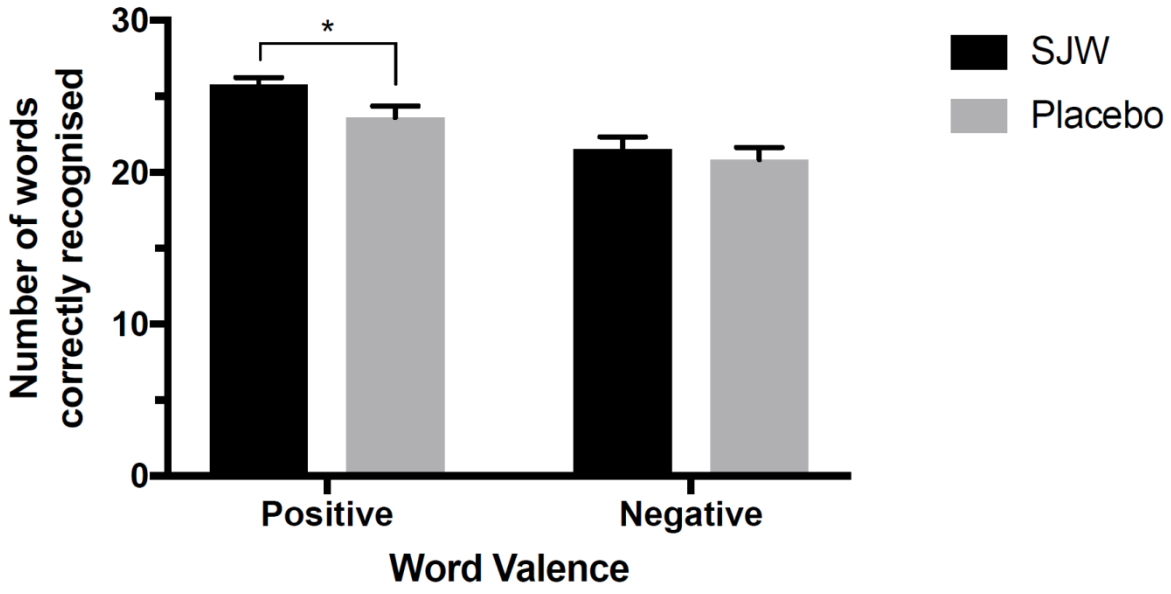



Figure 3. Mean number of words (out of 30) correctly recognised. *$p$ < .05. Error bars represent SEM.

Given the trend towards a group difference in the task, as well as the *a priori* hypothesis that St John's wort would increase recognition of positive emotional information, individual t-tests were conducted to further examine group differences in recognition. These found a significant effect of treatment on positive word recognition, $t(44) = 2.45$, $p = .018$, but not negative recognition, $t(44) = .61$, $p = .55$.

## Dot Probe

Results for the unmasked trials are presented in Figure 4. An ANOVA found no significant effect of valence, $F(1, 43) = 1.07$, $p = .31$. However, there was a significant effect of treatment, $F(1, 43) = 8.21$, $p = .006$) and an interaction between treatment and valence, $F(1, 43) = 7.73$, $p = .008$). Post-hoc t-tests found a significant difference between groups for vigilance to fearful faces, $t(43) = 3.84$, $p < .001$, but not happy faces, $t(43) = .36$, $p = .72$. Thus the placebo group showed more of a vigilance towards fearful faces than the SJW group, who appeared to show vigilance away from fearful faces.

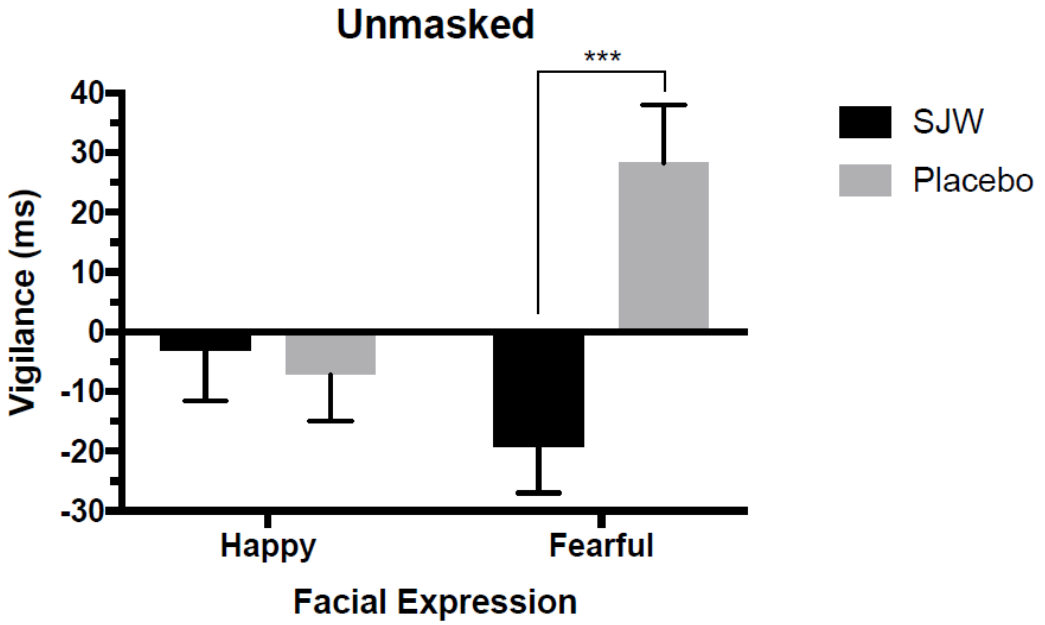



Figure 4. Group mean of individuals' median emotional vigilance towards (positive values) or away from (negative values) happy and fearful faces in unmasked trials. ***$p < .001$. Error bars represent SEM.

Individual one-sample t-tests were conducted for each group, to determine whether the mean vigilance values for fearful faces were significantly different from zero. The placebo group mean differed significantly from zero, $t(21) = 2.92$, $p = .008$, demonstrating that this group did indeed have a bias towards fearful faces. The SJW group mean also differed significantly from zero, $t(22) = 2.47$, $p = .022$, demonstrating that this group had a bias away from fearful faces.

Figure 5 displays median vigilance scores for masked trials. An ANOVA found no significant main effects of valence, $F(1,43) = 1.14$, $p = .29$, nor of treatment, $F(1,43) = .99$, $p = .33$. There was also no interaction effect, $F(1,43) = .00$, $p = .98$. Thus there was no evidence that SJW affected attentional vigilance to masked faces.

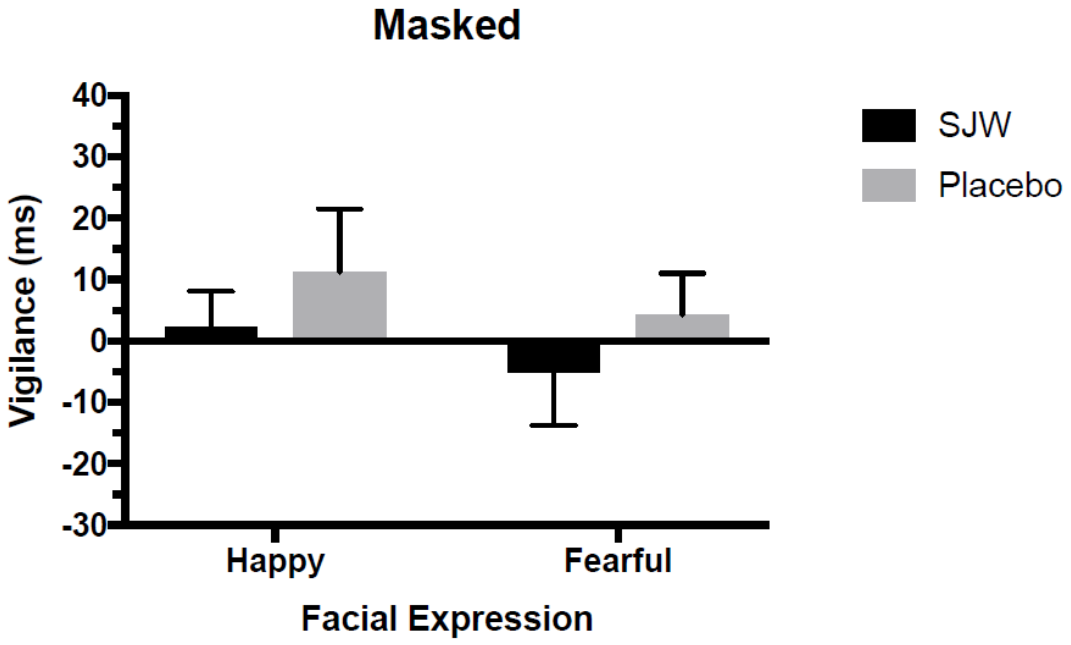


Figure 5. Group mean of individuals' median emotional vigilance towards (positive values) or away from (negative values) happy and fearful faces in masked trials. There were no significant effects. Error bars represent SEM.

## N-back

Accuracy was calculated for each block of the task for each participant. This was calculated as total number correct/total number of trials for each block. Mean accuracy for each block was then calculated for each group. A 2 (treatment) x 4 (task block) mixed effects ANOVA was used to examine whether SJW affected accuracy at responding to stimuli. There was a significant effect of task block, $F(3,135) = 71.63$, $p < .001$. Pairwise comparisons with Bonferonni correction found significant differences between all blocks ($p < .01$) except between zero-back and one-back ($p = .13$). Thus participants were most accurate for zero- and one-back, followed by two-back, and were least accurate for three-back. There was no significant effect of treatment, $F(1, 45) = 1.99$, $p = .17$, and no significant interaction between treatment and task block, $F(3, 135) = 1.30$, $p = .28$, providing no evidence that SJW had affected accuracy on the task.

A 2 (treatment) x 4 (task block) mixed effects ANOVA was used to examine whether SJW affected reaction time in correct responses to stimuli (see supplementary materials for details and graphs). There was a significant effect of block, $F(3, 135) = 63.80$, $p < .001$. Pairwise comparisons with Bonferonni correction indicated that RTs were significantly different between all conditions ($p < .001$), apart from between two- and three-back conditions ($p = 1.00$). As a group, participants were therefore fastest at the zero-back, then the one-back, and were slowest at the two- and three-back. There was no significant main effect of treatment, $F(1, 45) = .10$, $p = .76$, and no interaction between treatment and block, $F(3, 135) = .74$, $p = .53$, indicating that SJW had no effect on reaction times.

# Discussion

Our study showed that short term treatment with SJW produced changes in emotional processing similar to those found with other antidepressants. SJW decreased the perception of disgusted facial expressions, increased memory recall for positive stimuli and reduced attentional vigilance to unmasked fearful faces.

Heightened attention to threat-related information is associated with depression and anxiety, and is reduced by antidepressant treatment. Patients show greater bias towards threat-related words than controls [39], and citalopram reduces attentional bias towards unmasked fearful faces [9]. The reduction in attentional bias towards unmasked fearful faces with SJW is therefore consistent with its antidepressant effect.

SJW also reduced recognition of disgusted facial expressions. We recently reported that the pro-inflammatory agent interferon-α induced both depression and increased disgust recognition in patients undergoing treatment for hepatitis C [40]. Another study found that depressed patients had greater neural activity to disgust faces in left frontal-temporal regions including insula, and right middle/inferior temporal regions [41]. The authors suggest that increased activity to disgust faces might relate to heightened processing of cues relating to social rejection in depressed populations. Reduced recognition of disgust with SJW treatment may therefore reflect reduced processing of such cues. Consistent with this interpretation, both seven days of citalopram and 14 days of tryptophan reduced recognition of disgust in healthy volunteers [6, 42].

On the other hand, a number of studies have failed to find any effect of antidepressant treatment on disgust recognition [1, 10]. Another possibility is that the broader neurochemical changes produced by SJW have a specific effect on disgust recognition not consistently seen with other antidepressants. In particular, the dopaminergic effects of the drug may be important: disgust recognition is reduced in disorders associated with dysfunctional dopamine activity such as Parkinson's disease and Huntington's disease [43, 44]. It would be interesting to see whether other dopaminergic antidepressants such as bupropion have any specific effects on disgust recognition.

In our study, SJW affected memory for positive words. Fifteen minutes after a categorisation task, SJW increased the number of positive words incorrectly recalled in a surprise recall task, and increased the number of positive words correctly recognised amongst novel distractor words in a recognition task.

In both cases, these effects were only found in post-hoc t-tests: for neither task was there a significant interaction between treatment and valence of word. However, previous research has specifically found effects of antidepressants on positive word memory, so small effects could be obscured when negative words were also included in the analysis. For example, seven days of citalopram and reboxetine both increased recall of positive words in healthy controls [6], as did an acute dose of mirtazapine [45]. Only one study has provided any suggestion that an antidepressant (reboxetine) could reduce recall of negative words [46]. The effects of SJW on memory for positive, but not negative, words seem consistent with effects seen for other antidepressants.

In contrast to its well-documented antidepressant effect, there is currently little evidence that SJW works as an anxiolytic [47]. This may explain why there was no effect in the masked faces dot probe, despite the clear results for the unmasked faces. Attention towards stimuli presented for very short periods of time may be particularly related to anxiety-relevant processes: patients with anxiety, but not depression, showed a bias to threat-related words presented subliminally [39], and patients with panic disorder show a bias towards fearful faces in the masked but not unmasked condition [48]. Masked faces may be a better measure of the immediate, automatic processes relevant to anxiety.

Our study adds to a body of literature that has failed to find an effect of SJW on working memory in human participants, despite some positive effects in animal studies [22]. It may be that the doses used in human studies are simply too low to produce any positive effects on memory: some rodent studies used doses 20-30 times higher than those in human studies, levels that would be unacceptable to give to a human volunteer. Whatever the case, it is noteworthy that despite the lack of effects in the n-back task, SJW did affect memory for positive words. This supports the assumption that changes in emotional word memory are related to the emotional content of the words *per se*, and do not simply reflect a more general modification of memory.

Finally, it is important to note several limitations to our study that could be addressed in future research. We studied a population of healthy controls, because a healthy population would be unlikely to experience any psychological benefit from the drug. However, to demonstrate that these early changes in emotional processing are in fact clinically relevant, research now needs to be extended to depressed populations. The most robust evidence would come from studies examining the relationship between these early changes and later clinical effects in people suffering from depression. The time course of the changes in emotional processing in our population is also unclear. Hypericin has been reported to be detectable in the blood a little over an hour after administration [49], and it is

possible that changes could emerge after acute doses of the drug as with other antidepressants [1].

Taken together, our results suggest that subchronic treatment with SJW produces a positive shift in the processing of emotional information, similar to other antidepressants. Further research is now required to fully characterise the effects of SJW. It would be interesting to see whether SJW also produces changes in neural activation consistent with other antidepressants [7, 50].

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