Original Paper

Tianeptine in an experimental medicine model of antidepressant action

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Abstract

Changes in emotional processing have been shown following acute administration of a range of monoaminergic antidepressants, and may represent an important common neuropsychological mechanism underpinning their therapeutic effects. Tianeptine is an agent that challenges the traditional monoaminergic hypothesis of antidepressant action, though its exact mode of action remains controversial. Healthy volunteers were randomised to receive a single dose of tianeptine (12.5 mg) or placebo, and subsequently completed a battery of tasks measuring emotional processing, including facial expression recognition, emotional memory and attentional vigilance, as well as working and verbal memory. Tianeptine-treated subjects were less accurate at identifying facial expressions, though this was not valence specific. The tianeptine group also showed reduced positive affective memory and reduced attentional vigilance to positive stimuli. There were no effects on emotional categorization or non-emotional cognition. The negative biases in aspects of emotional processing observed following acute tianeptine administration are at variance with the positive biases generally seen after acute administration of conventional antidepressant drugs, despite tianeptine's putative antidepressant efficacy. This is an intriguing finding in the context of the lack of consensus regarding tianeptine's mechanism of action; however, it may be consistent with the reported ability of acute tianeptine to increase the re-uptake of serotonin.

Keywords

Tianeptine, atypical antidepressant, serotonin, healthy volunteers, emotional processing, experimental medicine

Introduction

The monoamine hypothesis of depression has dominated research and therapeutics in depression for many years. The theory attributes low mood to a central underactivity of monoamine neurotransmitters, most notably serotonin and noradrenaline, and was initially based upon serendipitous observations that monoaminergic drugs used for other indications had notable effects on mood (reviewed by Ramachandraih et al., 2011). As such, the vast majority of pharmacological agents licensed as antidepressants such as selective serotonin reuptake inhibitors (SSRIs) act via manipulation of the monoaminergic system and increasing the synaptic availability of these neurotransmitters.

There is increasing appreciation, however, that the pathophysiology of depression is more complex than monoamine deficit alone, and the need for more effective antidepressant agents has driven work to elucidate novel mechanisms of action. For example, aberrances in glutamatergic transmission have been extensively implicated as having a possible role in depression (Sanacora et al., 2012), and the rapid antidepressant effects of the NMDA-antagonist ketamine have generated much interest, challenging traditional models of antidepressant action (Caddy et al., 2014).

Tianeptine is a pharmacologically interesting agent which also appears to challenge these models, though its exact mechanism of action remains debated. It is licensed as an antidepressant in much of Europe, Latin America and Asia, with studies showing a broadly equivalent efficacy to more commonly used agents such as SSRIs (Kasper and Olie, 2002) and acceptable tolerability (Guelfi et al., 1992). Paradoxically, tianeptine was classified as a selective serotonin reuptake enhancer (SSRE) because in animal studies it appeared to enhance the reuptake of serotonin in certain areas of the brain and attenuate an induced serotonin-syndrome (De Simoni et al., 1992). Later work contradicted some of the early findings, with no marked alterations in extracellular serotonin found in corticolimbic structures in conscious rats (Malagie et al., 2000); technical limitations of early microdialysis techniques may explain this discrepancy. In healthy human volunteers, however, Lechin and colleagues (2006) demonstrated an acute decrease in plasma serotonin and increase in platelet serotonin following a single oral dose of tianeptine, consistent with an effect to enhance serotonin uptake. Animal work has latterly focused on several other potential mechanisms of action of tianeptine, including the potential role of normalizing deleterious effects of stress via modulation of glutamatergic tone (reviewed by McEwen et al., 2010).

One recent theory proposed as a final common pathway for the effects of different antidepressant agents suggests that clinically-effective antidepressant drugs cause early, non-conscious positive changes in the bias of processing emotional information received from the internal and external environment (Pringle

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et al., 2011). Such changes in processing are evident on computerized tasks after just a single dose of an antidepressant (Harmer et al., 2009), and over time this positive change in emotional bias is thought to contribute to the subjective lifting of mood. Given the intriguing actions of tianeptine, this study used an established battery of tests to assess the acute impact on emotional processing of a single oral dose of tianeptine (12.5 mg) in 40 healthy volunteers in a double-blind between-groups design with a view to improving understanding of its action at a neuropsychological level. Measures of working and verbal memory were also included given that tianeptine has been shown to block stress-induced memory impairments in rodents (Conrad et al., 1996; Zoladz et al., 2008) and improve neurocognitive function in depressed patients (Jeon et al., 2014).

Methods

Participants and study design

This was a double-blind, placebo-controlled parallel group study with 1:1 randomization. We studied 40 healthy volunteers (20 male; mean age 22; SD 2.5; range 18–30 years) recruited through local and online advertising. Participants were screened using the Structured Clinical Interview for DSM IV (Spitzer et al., 1995) to ensure no current or past history of any axis I psychiatric disorder. Eligible subjects were psychotropic naïve and physically fit to participate as ascertained by a physical examination and recording of an electrocardiogram. Non-pregnancy was confirmed on the morning of testing. Inclusion criteria also included fluency in English (due to the nature of the tasks), age 18–40 and body mass index (BMI) 19–30. The study was approved by the University of Oxford Medical Sciences Inter Divisional Research Ethics Committee, and all participants gave written informed consent. Participants undertook the National Adult Reading Test (NART) (Nelson, 1982) and Eysenck Personality Questionnaire (EPQ) (Eysenck et al., 1975) at screening to characterize the sample.

Subjects were randomly assigned to receive either a single dose of 12.5 mg of tianeptine or matched placebo in a double-blind manner. The standard treatment dose of tianeptine is 12.5 mg three times daily due to its short half-life of 2.5 hours (Salvadori et al., 1990).

The randomization schedule was drawn up by a member of the group not otherwise involved in the study to maintain allocation concealment. Block randomization by sex was used to ensure equal distribution. For the testing visit, participants attended the department between 08.30 hours and 09.15 hours, having fasted following an early light breakfast. They first completed a set of baseline measures of subjective mood state: Beck Depression Inventory (BDI) (Beck et al., 1961); Positive and Negative Affective Schedules (PANAS) (Watson et al., 1988); State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970); Befindlichkeits Scale (BFS) (von Zersson et al., 1974) and visual analogue scales (VAS, measuring happy, sad, hostile, alert, anxious and calm). The single dose of tianeptine or placebo was then administered by an independent group member. After 50 minutes, during which time participants remained in the department, the subjective questionnaires were repeated. Testing was then commenced 60 minutes after dose administration to coincide with peak plasma concentration (Salvadori et al., 1990). Subjects undertook a series of consecutive computer and verbal tasks of emotional and non-emotional cognition, detailed below.

Emotional test battery

Facial expression recognition. The facial expression recognition task asked participants to classify faces as one of the basic emotions (anger, fear, disgust, surprise, happy, sad, neutral) as quickly and accurately as possible by pressing a correspondingly labelled key on a keyboard. Faces were presented on screen in a random order for 500 ms before being replaced by a blank screen, at which time subjects responded. The stimuli were taken from the Picture of Affect Series (Ekman and Friesen, 1976) and morphed to portray varying intensities of each emotion (from 10% to 100% in 10% intervals) as well as neutral. Accuracy and reaction times for correct responses were recorded, as well as the number and nature of misclassifications (faces classified incorrectly as one of the other emotions). Previous studies have shown that depressed patients have enhanced recognition of faces with a negative valence (Bouhuys et al., 1999). An early effect of antidepressant drugs is to reverse this negative bias (Harmer et al., 2009); a phenomenon which has also shown to be significant and detectable in healthy volunteers (Harmer et al., 2004).

Emotional categorization and memory. Sixty words (from Anderson, 1968) denoting either positive (e.g. decisive) or negative (e.g. greedy) personality characteristics were presented on screen for 500 ms. An equal number of positive and negative words matched for length and image-ability were presented in a random order. So as to make the words self-referential, participants were asked to imagine themselves being described in such a way upon overhearing two people talking about them. They were asked to respond as quickly as possible by pressing a correspondingly labelled button according to whether they would 'like' or 'dislike' to be described as such. Data were collected on the accuracy of categorization and reaction times for correct identifications.

Following an intervening task (dot probe, see below) subjects were then given two minutes to write down as many of the personality trait words from this task as they could recall. This 'surprise' memory task assessed incidental memory for positive and negative characteristics. Participants were then presented on screen with a mixture of the 60 negative and positive target words that were presented previously, as well as 60 matched positive and negative distractor words which were not previously presented. Subjects were asked to respond as quickly as possible as to whether they recognized each word as having been presented previously or not by pressing a key marked 'old' or 'new'. Accuracy, reaction times and false alarms were recorded. Negative bias in these tasks has been shown to be present in depressed patients, and a single dose of antidepressant can reduce the time to react to positive versus negative items (Harmer et al., 2009).

Dot probe attentional task. This task addressed attention to emotional stimuli by measuring behavioural response to a probe on trials where the probe replaces emotional compared to neutral stimuli (MacLeod et al., 1986). The responses measured were the speed and accuracy of identifying the orientation of two dots, which were either vertical (:) or horizontal (..). A central fixation cross began each trial. Pairs of faces were then displayed, one at the top and one at the bottom of the screen. Three types of face pairs were used (neutral–neutral, neutral–happy and neutral–fearful) which in the unmasked condition were displayed for 100 ms. In the masked condition, face pairs were presented for

only 16 ms before being replaced by a pixelated mask for the remaining 84 ms. The horizontal or vertical dot probes were then immediately presented either at the top or the bottom of the screen (i.e. in the position where one of the two faces had been displayed). Participants were asked to identify the orientation of the probe as quickly as possible by pressing a correspondingly labelled key. There were 192 trials in total (unmasked: 32 fearful–neutral, 32 happy–neutral, 32 neutral–neutral; masked: 32 fearful–neutral, 32 happy–neutral, 32 neutral–neutral) presented in alternating blocks of masked and unmasked trials. The principle of the task is that if one were preferentially attending to the emotionally valenced stimulus (e.g. fearful face over neutral face), the response to the probe would be quicker in congruent trials (when the probe appears in the position of the emotional face) compared to incongruent trials (when the probe replaces the neutral face in an emotional–neutral face pair).

Cognitive tasks

N-back task. Working memory was studied using a letter variant of the *n*-back task (Braver et al., 1997; Harvey et. al., 2005) that used four levels of complexity: 0-, 1-, 2- and 3-back. Subjects were asked to respond to a series of stimuli (letters), indicating whether they were the same as or different to a cue by pressing a corresponding button. Stimuli consisted of the following phonologically closed characters: b, B, d, D, g, G, p, P, t, T, v and V. Participants were advised to ignore the case of the letter (i.e. treat 'b' and 'B' as the same stimulus). The response depended on the block being undertaken. In the zero-back block, subjects were asked to look out for an additional target letter 'X', pressing 'same' when this stimulus appeared and 'different' for all other stimuli. In the remaining blocks there was no specific target letter; they were asked to press 'same' when the presented stimulus was the same letter as that presented 1, 2 or 3 letters previously for the 1-, 2- and 3-back blocks, respectively. Ten stimuli were presented in a block for 500 ms each with an interval of 1500 ms between stimuli. An instruction screen (0-, 1-, 2-, 3-back) was presented for 2000 ms prior to each task, followed by a 4000 ms blank screen before the onset of the first letter. Task blocks were separated by 1000 ms of fixation cross. Four blocks of each condition matched for number of target stimuli and upper/lower case letters were presented in a fixed pseudorandom order (0-, 1-, 2-, 3-, 1-, 3-, 2-, 0-, 2-, 1-, 0-, 3-, 1-, 0-, 3- and 2-back) to give a total of 160 trials. Accuracy and latency of response were recorded.

Auditory verbal learning task. The Rey Auditory Verbal Learning Test (Rey, 1964) was used to assess declarative verbal memory. Participants were read a list of 15 words at an even pace of 1 s per word (List A) before being asked to recall as many words as possible in any order (immediate free recall). This was repeated on two further consecutive occasions with the same list of words giving a total of three presentations (an adaptation of the five presentations of the original task). A second list of words (List B) was then read and tested on just one occasion. Participants were then asked to recall words from list A again (short delay free recall). Intervening tasks were then undertaken, before participants were asked to recall words from list A (long delay free recall). As well as correct responses, intrusions and repetitions were recorded. Finally, a recognition task was undertaken with a list of words read out containing all 15 from list A, as well as 30 filler words consisting of words from list B and other distractor words. Participants were asked to indicate whether each word was in list A or not. Correctly recognized words and false alarms were recorded.

Statistical analysis

Extreme outlying data (data lying at more than three times the participants' interquartile range above their third or below their first quartile) were removed from all psychological tasks. This resulted in less than 2% of data being lost as outliers on any task. Demographic measures, subjective state ratings and emotional memory scores were analysed using one-way analysis of variance (ANOVA). Mood and energy scales completed before and after drug administration were compared between the two groups using repeated measures ANOVA, with treatment as the between-subject factor and time as the within-subject factor. Data from the facial expression recognition task, emotional categorization task, emotional recognition task and dot probe task were analysed using repeated measures ANOVA, with treatment group as the between-subject factor and valence as the within-subject factor. In the dot probe task, masking was added as an additional within-subject factor. *n*-back data were also analysed using repeated measures ANOVA, with treatment as the between-subject factor and complexity as the within-subject factor. Statistically significant interactions were followed up using simple main effects analyses. Where assumptions of equality of variances were broken, Greenhouse–Geisser procedure was used to correct the degrees of freedom.

Results

Group matching

The drug and placebo groups were well matched in terms of demographics, including verbal IQ as measured by the NART and personality traits measured by the EPQ (see Table 1).

Subjective state

The following subjective state measures were, as expected, unaffected by tianeptine administration: BDI ratings, state anxiety, BFS scores, PANAS, visual analogue scales of happiness, sadness, hostility, alertness, anxiety and calmness (all p values >0.1, see Table 2).

Facial expression recognition

There was a main effect of treatment group on accuracy in this task (see Figure 1: $F(1,38)=4.67$, $p=0.04$), with tianeptine-treated participants being generally less accurate; however there was no interaction between intervention group and emotion ($F(5, 190)=0.11$, $p=0.99$).

There were no effects of tianeptine on this task in terms of misclassifications or reaction times (all p values >0.4).

Emotional categorization task

There were no between-group differences in reaction times to categorize self-referent personality characteristics in terms of an

Table 1. Demographic, mood and personality measures at baseline. Means (standard deviations).

	Placebo (n=20)	Tianeptine 12.5 mg (n=20)	Statistical significance
Age	22.1 (2.7)	21.9 (2.2)	p = 0.77
Gender	10M:10F	10M:10F	N/A
BMI	23.0 (2.1)	23.3 (1.8)	p = 0.60
Verbal IQ	114.6 (5.4)	114.8 (5.3)	p = 0.93
Trait anxiety	29.8 (6.0)	31.2 (7.0)	p = 0.49
BDI	1.1 (1.7)	2.0 (2.7)	p = 0.21
EPQ: E	13.0 (1.6)	12.3 (1.6)	p = 0.14
EPQ: N	14.5 (1.9)	14.8 (2.6)	p = 0.67
EPQ: P	19.6 (1.9)	19.6 (1.7)	p = 0.93
EPQ: L	14.7 (2.0)	13.8 (1.9)	p = 0.13

BMI: body mass index; BDI: Beck Depression Inventory; EPQ: Eysenck Personality Questionnaire, where E: extroversion, N: neuroticism, P: psychoticism, L: lie.

Table 2. Subjective state changes over time. Values are ratings at 50 minutes after treatment minus baseline ratings. Means (standard deviations).

	Placebo (n=20)	Tianeptine 12.5 mg (n=20)	Statistical significance
BDI	−0.3 (0.7)	−0.3 (1.4)	p = 1.0
State anxiety	−1.0 (3.2)	−0.2 (3.1)	p = 0.40
BFS: Mood	1.4 (4.0)	0.2 (4.4)	p = 0.37
BFS: Energy	1.3 (3.8)	1.3 (4.0)	p = 0.97
BFS: Total	2.7 (6.8)	1.4 (7.0)	p = 0.56
PANAS: Positive	−1.7 (3.9)	−1.5 (4.6)	p = 0.85
PANAS: Negative	−0.4 (0.8)	−0.4 (1.2)	p = 1.0
VAS: Happy	0.6 (6.2)	−0.7 (8.3)	p = 0.59
VAS: Sad	−0.7 (3.1)	−2.5 (7.8)	p = 0.34
VAS: Hostile	−0.6 (4.0)	−1.3 (3.0)	p = 0.53
VAS: Alert	−1.8 (13.4)	−1.4 (24.0)	p = 0.94
VAS: Anxious	−3.4 (6.2)	−4.8 (12.3)	p = 0.65
VAS: Calm	2.2 (8.9)	−4.4 (16.4)	p = 0.12

BDI: Beck Depression Inventory; BFS: Befindlichkeits Scale; PANAS: Positive and Negative Affective Schedules; VAS: Visual Analogue Scales.

effect of group (F(1,38)=0.24, p=0.63) or emotion × group interaction (F(1,38)=0.47, p=0.50).

Emotional recall task

The total number of correct words recalled did not differ significantly between the groups and there were no differences in false intrusions (all p values >0.1). However, there was a significant between-group difference in the percentage of positive words correctly recalled in this task; the tianeptine group recalled a significantly lower proportion of positive words compared to the placebo group (one-way ANOVA F(1,38)=4.97, p=0.03; see Figure 2).

Emotional recognition task

There was a marginal main effect of treatment group on accuracy in the emotional recognition memory task as deduced by the discriminability index d', whereby the tianeptine group correctly recognised more positive and negative items overall compared to the placebo group (see Figure 3: F(1,38)=4.69, p=0.04), although this effect was not valence specific (group × valence interaction (F(1,38)=0.30, p=0.59). No difference was found between groups when positive words (one-way ANOVA F(1,38)=1.56, p=0.22) and negative words (one-way ANOVA F(1,38)=2.97, p=0.09) were considered separately. Tianeptine did not affect performance in terms of reaction times or false alarms in this task (all p values >0.1).

Dot probe attentional vigilance

There was an interaction between emotion and treatment group (F(1,38)=5.34, p=0.03), including mask as a within-subject factor. When masked and unmasked trials were considered separately, there was a trend towards an emotion × group interaction in the unmasked (F(1,38)=3.89, p=0.056; see Figure 4), but not masked (F(1,38)=0.09, p=0.77) condition. Simple main effects analysis revealed that this was driven by a significant reduction in vigilance scores for happy faces in the tianeptine-treated group compared to the placebo group (one-way ANOVA F(1,38)=4.12, p=0.05; Figure 4).

Cognitive tasks

n-back. There were no between-groups differences in accuracy (F(1,37)=0.30, p=0.59) or latency (F(1,37)=0.33, p=0.57) on the

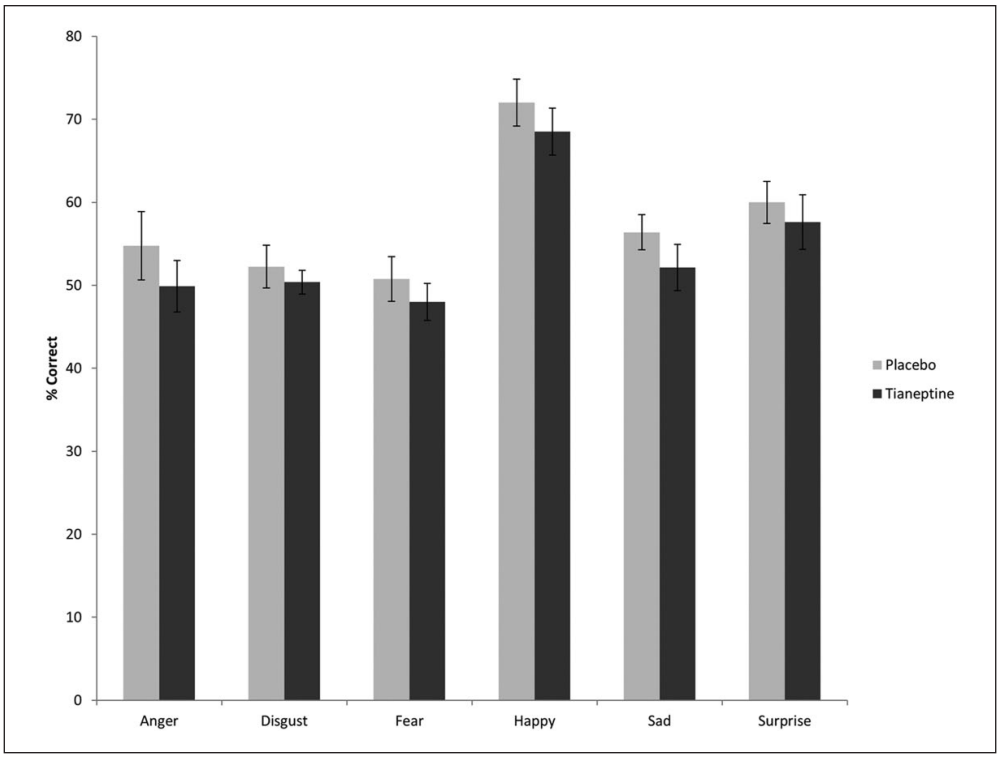

Figure 1. Performance in the facial expression recognition task following placebo (light bars) or tianeptine (dark bars). Values represent the mean percentage correct for each of the six basic emotions summed over the different intensity levels used in this task, with error bars representing standard error of the mean. A main effect of treatment group (p <0.05) was found, however this was not valence specific and there was no emotion x group interaction (p >0.05).

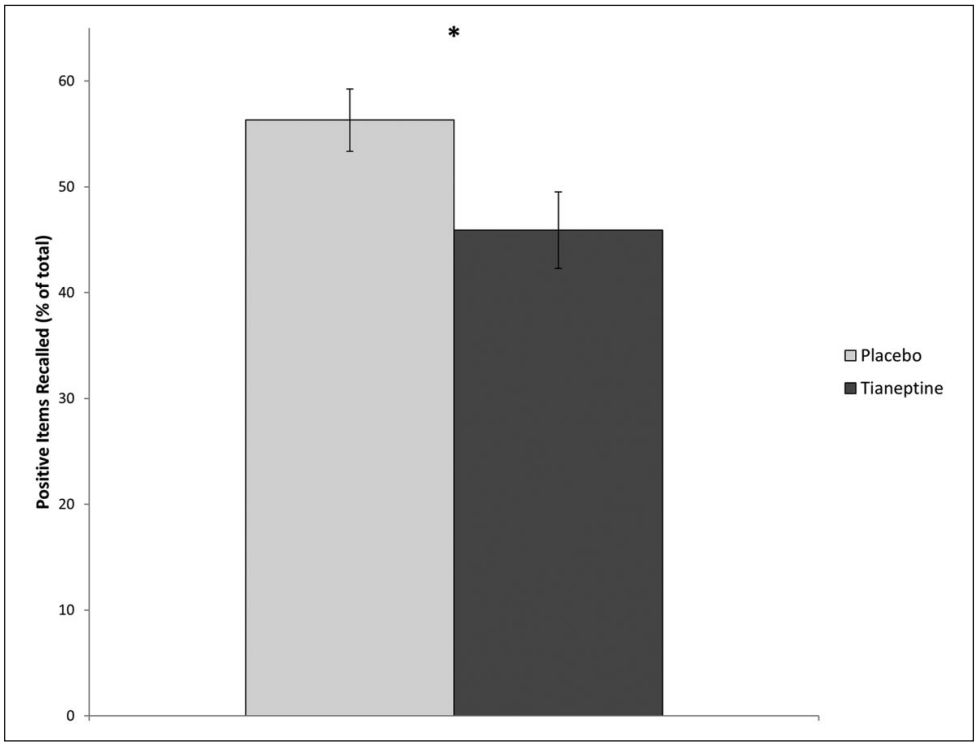

Figure 2. Recall of positive personality characteristics following a single dose of placebo (light bar) or tianeptine (dark bar). Values represent the mean percentage of positive words recalled from the total (positive and negative characteristic words). Error bars show standard error. *p <0.05.

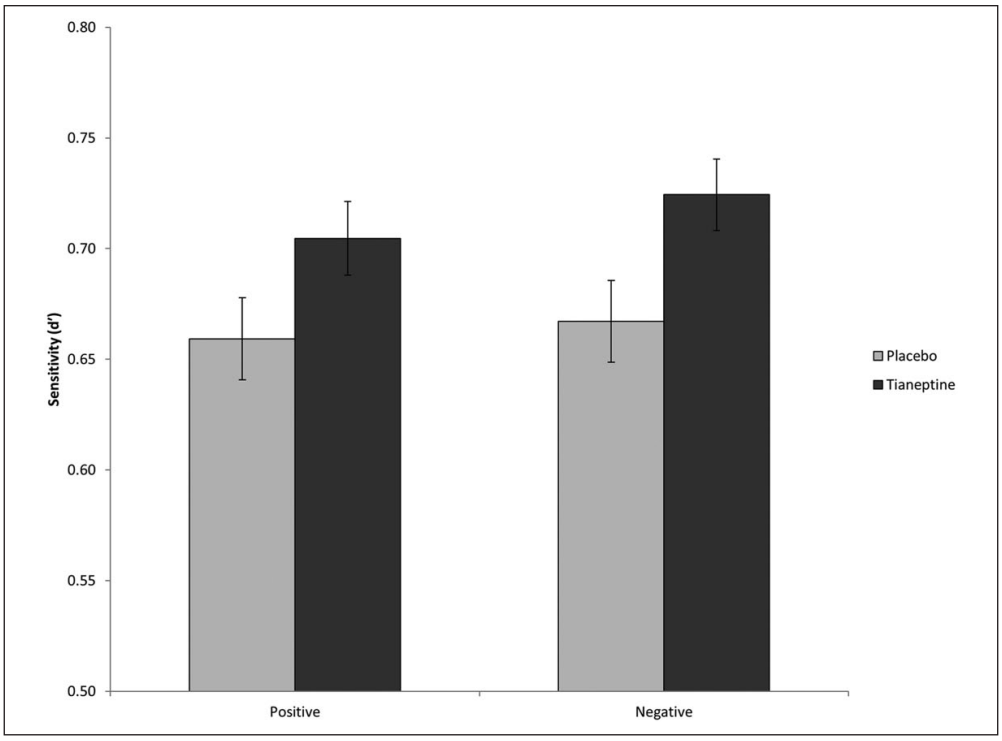

Figure 3. Discriminability index (d′) for accuracy in the emotional recognition task. d′ ranges from 0 to 1, with higher numbers indicating higher accuracy. Figure shows accuracy for correctly recognised positive and negative personality characteristic words for placebo (light bars) and tianeptine (dark bars) treated groups. The tianeptine group correctly recognised more positive and negative items overall compared to the placebo group (p<0.05). Error bars show standard error of the mean.

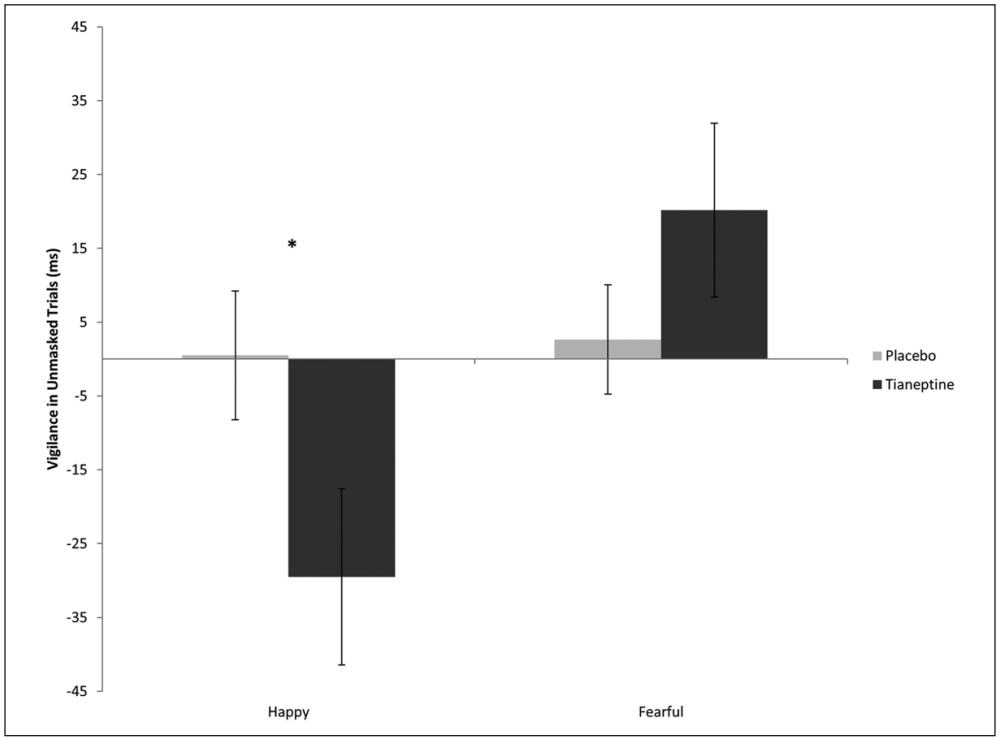

Figure 4. Effect of tianeptine on attentional vigilance for happy and fearful facial expressions in the unmasked condition of the dot probe task. Values are attentional vigilance scores in the placebo (light bars) and tianeptine (dark bars) treated groups. Attentional vigilance scores were calculated by subtracting the median reaction time from congruent trials (when the probe appeared in the same position as the emotional face) from incongruent trials (when the probe appeared in the opposite position to the emotional face, i.e. in the position of the neutral face). A positive score indicates vigilance towards the emotional face, whereas a negative score reflects avoidance of the emotional face. *p =0.05. Error bars show the standard error of the mean.

control task. One volunteer's data belonging to the placebo group was removed from the zero-back dataset due to anomalous responses that met criteria for an extreme outlier. As expected, there was a significant main effect of complexity ($F(2, 76)=37.50$, $p\leqslant 0.001$) on accuracy, however there was no main effect of treatment group, or a treatment group x complexity interaction for either accuracy or latency (all p values >0.1).

AVLT. Tianeptine did not affect declarative verbal memory performance as assessed using the Auditory Verbal Learning Test (AVLT; all p values >0.2).

Discussion

The current data indicate that a single dose of tianeptine does not produce the expected acute positive effects on emotional processing seen with other clinically effective antidepressants, including citalopram (Harmer et al., 2004), reboxetine (Harmer et al., 2003a), duloxetine (Harmer et al., 2008) and mirtazapine (Arnone et al., 2009). This is despite the ability of the test battery to detect such changes with both conventional and more novel antidepressant strategies such as agomelatine (Harmer et al., 2011) and high-density negative ion treatment (Harmer et al., 2012; Malcolm et al., 2009), a non-pharmacological environmental manipulation involving negative air ionization which, in small-scale randomized clinical trials, has shown antidepressant effects in winter depression (Terman et al., 1998; Terman and Terman, 2006) and chronic depression (Goel et al., 2005). In contrast, subjects in the tianeptine group were generally less accurate in the identification of facial expressions, though this was not valence-specific. Tianeptine-treated subjects also recalled a significantly lower proportion of positive words in the emotional recall task and diverted attention away from the happy face in the dot probe task – effects in opposition to previously tested antidepressant agents. These effects were seen without any significant differences in baseline characteristics or mood between the groups, and without significant acute effects of drug administration on mood state.

Although tianeptine is regarded as a clinically-effective antidepressant (Kasper and Olie, 2002) the effects in the present single dose study are more in keeping with the negative bias seen in depressed patients than with the positive bias induced by a range of antidepressants in healthy volunteers (reviewed by Harmer, 2013). Of relevance, the test battery used has been sensitive to manipulation of serotonergic transmission both by monoaminergic antidepressants and through tryptophan depletion. Acute tryptophan depletion has been shown to decrease the recognition of facial expressions of fear in healthy female volunteers (Harmer et al., 2003b), and specifically reduce the recognition of happy faces in recovered depressed patients (Hayward et al., 2005). In remitted depressed patients tryptophan depletion led to a decreased consistency in positive trait ratings and decreased memory for positive words in a self-referential adjectives task, though only in those exhibiting a depressive response (Booij et al., 2005). In healthy volunteers tryptophan depletion also showed impaired recall of neutral and positive words, but not of negative words (Klaassen et al., 2002) and in the present study tianeptine decreased recall of positive words. The current data therefore suggest that the acute effects of tianeptine may have some similarities to those of reduced serotonin function in these tasks, though it is important to note that we found a general reduction in accuracy of facial expression recognition rather than a valence-specific effect. In addition, tryptophan depletion is known to impair memory consolidation (Mendelsohn et al., 2009), but we saw no effect of tianeptine on the AVLT.

This is the first study to analyse the effects of acute tianeptine administration on emotional processing. The finding of a negative early effect is intriguing in the context of tianeptine's possible mechanism of action – a consensus for which has remained elusive. Investigation of the possible role of serotonin reuptake enhancement has produced contradictory results. Tianeptine had been shown to increase serotonin reuptake in ex-vivo rat platelets (Kato and Weitsch, 1988), produce opposite effects to sertraline on serotonin metabolite levels, and reduce symptoms of an induced serotonin syndrome (De Simoni et al., 1992). Further investigation by Malagie et al. (2000) challenged this, showing no marked alterations in extracellular serotonin following tianeptine administration in conscious rats. Technical limitations of early microdialysis techniques, such as the presence in solution of citalopram, may have elicited some autoreceptor effects to explain this discrepancy. Additional findings such as the lack of effect on the firing rates of serotonergic neurons have cast further doubt on the role of serotonin in tianeptine's mechanism of action (reviewed by McEwen et al., 2010). Of note, tianeptine shows no affinity for known neurotransmitter receptors (Kato and Weitsch, 1988). Much work has, therefore, diverged from serotonergic manipulation as being central to tianeptine's action. For example, downstream effects on neuroplasticity have been implicated with tianeptine preventing or reversing stress-induced changes such as in hippocampal volume and cell proliferation in tree-shrews (Czeh et al., 2001). Such effects may be mediated via modulations of glutamatergic neurotransmission; tianeptine reduced stress-induced amygdalar glutamate efflux in rats (Piroli et al., 2013) and affects signaling cascades such as potentiating AMPA receptors via phosphorylation of the GluA1 subunit (Szegedi et al., 2011). One recent study representative of a diverse literature surrounding tianeptine's action shows tianeptine to be a μ-opioid receptor agonist, proposing this as the initial molecular target to trigger downstream effects (Gassaway et al., 2014).

In a single dose study of healthy volunteers similar to our own, however, it has been shown that tianeptine induces significant acute effects on serotonin levels (Lechin et al., 2006). Following a single 12.5 mg oral dose of tianeptine, plasma free serotonin levels were reduced when compared to placebo administration in a within-subjects design; significantly so from 45 minutes following the dose. There was a parallel significant increase in platelet serotonin, suggested therefore to represent enhanced platelet uptake of serotonin.

The present results are in keeping with current understanding of tianeptine's actions in that it appears distinct from traditional monoaminergic antidepressants. Specifically, given the alignment of dosing and timing of our own study with that of Lechin and colleagues (2005), we suggest that the negative emotional biases seen would be in keeping with an acute serotonin reuptake enhancement; a mechanism which though controversial has been repeatedly proposed for tianeptine. A limitation of the current study is the lack of serotonin assays to replicate the previous findings of Lechin et al. (2005). Any serotonin reuptake enhancement effect is of course counter-intuitive to tianeptine's purported antidepressant effects. However, it is consistent with the differences between

acute tianeptine and SSRI treatment on threat processing. For example, a single dose of citalopram (alongside increasing attentional bias to positive words) increased the recognition of fearful faces (Browning et al., 2007), which is in line with the clinical phenomenon of an initial anxiogenic effect on commencing SSRIs which subsides with chronic treatment (reviewed by Bauer, 2014).

It has been proposed that tianeptine lacks this early anxiogenic effect, for example reversing anxiogenic effects in an animal model of alcohol withdrawal (File et al., 1993). Effects on fear acquisition of citalopram and tianeptine have been directly compared in an animal model, where citalopram but not tianeptine enhanced fear conditioning acutely, and both agents reduced conditioning on chronic administration (Burghardt et al., 2004). Whatever the initial action of tianeptine, it seems likely that the mechanisms through which it exerts its therapeutic effects lie in downstream adaptive changes (McEwan et al., 2010) which are likely to become apparent over time. Further work is therefore needed to elucidate effects at time-points further along the treatment pathway if greater consensus as to the nature of the therapeutic mechanism of tianeptine is to be reached.

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