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A single dose of lamotrigine induces a positive memory bias in healthy volunteers

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Abstract

Background. Lamotrigine has been shown to be effective in the long-term treatment and relapse prevention of depression in bipolar disorder. However, the neuropsychological mechanisms underlying these effects are unclear. We investigated the effects of lamotrigine on a battery of emotional processing tasks in healthy volunteers, previously shown to be sensitive to antidepressant drug action in similar experimental designs.

Methods. Healthy volunteers (n = 36) were randomized in a double-blind design to receive a single dose of placebo or 300 mg lamotrigine. Mood and subjective effects were monitored throughout the study period, and emotional processing was assessed using the Oxford Emotional Test Battery (ETB) 3 hours post-administration.

Results. Participants receiving lamotrigine showed increased accurate recall of positive versus negative self-descriptors, compared to those in the placebo group. There were no other significant effects on emotional processing in the ETB, and lamotrigine did not affect ratings of mood or subjective experience.

Conclusions. Lamotrigine did not induce widespread changes in emotional processing. However, there was increased positive bias in emotional memory, similar to the effects of antidepressants reported in previous studies. Further work is needed to assess whether similar effects are seen in the clinical treatment of patients with bipolar disorder and the extent to which this is associated with its clinical action in relapse prevention.

Introduction

Bipolar disorder (BD) is characterized by recurrent presentations of elevated mood episodes, in the form of either mania or hypomania and depressive episodes (APA, 2022). Affecting over 1% of the global population, this severe chronic affective illness is among the leading causes of worldwide disability (Global Burden of Disease Study, 2015; Judd et al., 2002). BD's predominant mood state is bipolar depression (Malhi, Mitchell, & Salim, 2003). However, most available treatments for BD such as mood stabilizers (i.e., lithium), antiepileptic drugs (i.e., carbamazepine and valproate sodium), or atypical antiepileptic drugs (i.e., olanzapine) exert their effects primarily on mania/hypomania and, to a lesser extent, on depression (Goldsmith, Wagstaff, Ibbotson, & Perry, 2003).

Lamotrigine is a relatively new drug that is associated with prevention of depressive episodes within the clinical presentation of BD. First licensed as an add-on treatment for epilepsy, lamotrigine was quickly seen to have beneficial effects in BD, gaining approval in 2003 as a maintenance treatment for BD by the US FDA (Goldsmith et al., 2003; Vajda, Dodd, & Horgan, 2013). The mechanisms underlying the effects of lamotrigine in BD are not fully understood but have been suggested to involve inhibition of voltage-gated sodium channels and reductions in presynaptic glutamate release (Ketter, Manji, & Post, 2003; Lee, Fu, Chen, Su, & Liou, 2008; Prica, Hascoet, & Bourin, 2008; Sills & Rogawski, 2020). Such effects would be expected to counter enhanced excitatory neurotransmission in bipolar disorder (Sanacora, Zarate, Krystal, & Manji, 2008).

BD is associated with impairments in cognition and emotional cognition (Bogie, Persaud, Smith, Kapczinski, & Frey, 2019; Fijtman et al., 2020). Generally, patients with BD depression and unipolar depression show an impairment in recall and recognition processes, which seem to be related to poor encoding rather than rapid forgetting (Bearden et al., 2006; Deckersbach et al., 2004). There is also evidence that emotional processing changes in BD may be mood-dependent. For example, Bilderbeck et al. (2016) found improved performance in categorizing positive personality adjectives as a function of increased symptoms of mania, while depression was

associated with enhanced categorization of negative personality adjectives, in a sample of patients with BD. This is in line with the idea that manic symptomatology in BD is associated with a positive bias. whereas those with depressive symptomatology show a more negative bias in emotional processing (Paykel, 1987). Interestingly, patients with BD depression showed a similar negative bias to those with unipolar depression in the categorization of ambiguous facial expressions and self-referential emotional words (Bilderbeck et al., 2016).

Despite this evidence, little research has investigated lamotrigine's effect on emotional processing and memory biases. A study involving a pediatric BD sample found that lamotrigine improved working and verbal memory performance (Stuart, Butler, Munafò, Nutt, & Robinson, 2015). Lamotrigine treatment also increased neural response associated with verbal working memory and facial expression processing in a sample of 12 adults with BD compared to pretreatment measures (Haldane et al., 2008). Interestingly, Bilderbeck et al. (2016), who also collected current medication use in their BDI and BDII sample found that the use of medication, including anticonvulsants, was associated with a greater positive bias compared to patients not taking medication. Although lamotrigine was not investigated specifically, it suggests that mood-stabilizing treatment in BD may be associated with the induction of a more positive emotional bias. However, our understanding of the direct effect of lamotrigine on cognitive processes, including emotional processes, is still incomplete. In addition, the lack of a placebo control in previous studies, together with the use of highly heterogeneous clinical populations, limits the interpretation of such results.

Experimental medicine may represent a useful approach in the investigation of lamotrigine's mechanism of action early within treatment, before changes in symptomatology are typically seen. The use of this approach in healthy volunteers has proven useful in characterizing early effects of conventional antidepressants. Accordingly, an increase in the relative processing of positive rather than negative emotional information has been observed in healthy volunteers following single or repeated antidepressant administration from a variety of pharmacological classes (e.g., selective serotonin reuptake inhibitors - SSRIs, atypical antidepressants) (see Harmer, Duman, & Cowen, 2017 for a review). For example, SSRIs have been shown to increase the recognition of positive facial expressions in a recognition task and increase recall for positive over negative information in a free recall test. Interestingly, similar effects have also been found in depressed individuals after a single dose of reboxetine compared to placebo (Harmer et al., 2009). Ultimately, these studies have highlighted that conventional antidepressants may act by reducing negative biases characteristic of depression (Godlewska & Harmer, 2021; Harmer, 2010; Harmer et al., 2009), with these effects, which are seen rapidly and in the absence of subjective mood changes, contributing to subsequent clinical changes in mood (Harmer et al., 2009; 2017).

The current study therefore aimed to use an experimental medicine approach to investigate the effects of a single dose of the novel drug lamotrigine in a healthy volunteer sample with the use of a well-validated task battery measuring emotional cognition. The use of a healthy volunteer sample can be advantageous as a translational step as it allows for the direct assessment of lamotrigine on neuropsychological mechanisms unconfounded by disorder-related factors. Additionally, the emotional test battery (ETB) has been extensively used in experimental medicine approaches to characterize different antidepressant drug classes both in healthy volunteers and clinical populations. Given that lamotrigine's predominant effects are on BD depression and that negative biases in emotional cognition have been reported when depressive symptomatology is higher, this research can aid the understanding and identification of surrogate markers for improved targets of depression in BD. It was hypothesized that lamotrigine would induce a positive bias in emotional processing and cognition, with these effects being more pronounced on those tasks including a memory component given the effect of lamotrigine reported in previous studies.

Material and methods

Study sample

Thirty-six healthy volunteers (12 women and 24 men) aged 18–40 years were recruited via print and online announcements and enrolled in this study. All participants gave written informed consent prior to participation and were reimbursed for their time and any other expenses. Participants completed a screening visit to ascertain eligibility prior to proceeding to the experimental session. This included a psychiatric interview (Structured Clinical Interview for DSM-5; SCID-5) and a general medical screening, with females testing negative on a pregnancy test. Participants were then assessed for estimated intelligence using the National Adult Reading Test (Revised Version, NART-R) (Nelson & Willison, 1991), trait anxiety using the Spielberger's State–Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), depressive symptoms using the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and personality traits using the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975). Participants were excluded if they had (a) current or past history of psychiatric disorders (as assessed using the SCID-5), (b) insufficient English language skills, (c) current or past history of drug or alcohol dependency, (d) significant medical conditions, (e) previous participation in studies using the same emotional processing tasks, (f) contraindication to MRI, (g) history of recurrent allergies and rashes, (h) consumed any psychoactive medication or folic acid supplements, (I) smoked in excess of five cigarettes a day, (j) had a high intake of caffeinated drinks (>5 cups a day), (k) were pregnant or lactating women, or (l) were taking the contraceptive pill. Ethical approval was obtained from the Central University Research Ethics Committee (CUREC). The study was registered on ClinicalTrials.gov (Identifier: NCT04396938).

Procedure

In this double-blind, placebo-controlled, randomized, parallel-group study participants were assigned to receive either a single oral dose of lamotrigine (300 mg) or placebo. All tablets were encapsulated to provide a uniform appearance and ensure a double-blinded study. The randomization code was created by another member of the lab group not involved in the experiment. Participants were asked to avoid having any alcohol for at least 12 hours and food and caffeine for at least 3 hours prior to the experimental visit. As lamotrigine peak plasma concentrations (T_{max}) occur between 1–3 hours following oral intake (Goldsmith et al., 2003), all volunteers were tested 3 hours after drug administration (T3). During the first 2 hours post-drug administration, participants stayed in a quiet clinic room, where they were free to relax or engage in any activity such as reading or using their personal electronic devices. During the next hour (T3), participants underwent a functional magnetic resonance imaging scan

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(results reported elsewhere), and were tested with the Oxford ETB (Harmer et al., 2009) (Schmidt et al., 2015).

Measures

Demographic and questionnaire measures

Self-reported questionnaires were administered to assess subjective state and side effects at three time points: prior to active drug or placebo intake (Baseline or T1), after 2 hours (T2), and after 3 hours (T3). The following measures were used: the STAI-State (Spielberger et al., 1983), Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988), and visual analogue scales (VAS) of subjectively experienced emotions. Side effects/somatic symptoms were measured on 11 symptoms (agitation, dry mouth, nausea, aggression, tremor, headache, drowsiness, dizziness, back or joint pain, vision impairments, and rashes) with the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Emotional test battery

The ETB is a validated tool of five broadly computerized behavioral tasks that allow for the assessment of emotional information processing in different cognitive domains (Harmer et al., 2009), and proved to be sensitive to the early effects of antidepressant medication (Harmer et al., 2009; Warren, Cowen, & Harmer, 2019). With a duration of 45 minutes, it was completed in the following order: facial expression recognition task (FERT), emotional categorization task (ECAT), attentional dot-probe task, emotional recall task (EREC), and emotional recognition memory task (EMEM).

In the FERT, participants were presented with pictures of facial expressions displaying one of the six basic emotions (i.e., anger, disgust, fear, happiness, sadness and surprise) or neutral. Each emotion was displayed at 10 morphed intensity levels from "neutral" (that is, 0%) to "full intensity" (that is, 100%) resulting in a total of 250 pictures (Young et al., 1997). Facial expressions were presented randomly for 500 ms each, followed by a blank black screen. Participants were instructed to identify each emotion as quickly and accurately as possible by pressing one of the seven correspondingly labelled keys on the keyboard. Main outcomes were number of misclassifications, accuracy, and reaction time (RT).

In the ECAT, participants were presented with 60 words representing personality descriptors that were either agreeable (e.g. honest, thoughtful, etc; $N = 30$) or disagreeable (e.g. untidy, bossy, etc; $N = 30$). Each word was randomly presented in the center of a computer screen for 500 ms. Participants were asked to imagine overhearing someone describing them with each word displayed and to indicate as quickly and accurately as possible whether they would like or dislike to be described as such by pressing the correspondingly labeled key on the keyboard. The main outcome measures were RT and classifications.

In the attentional dot-probe task (Schmidt et al., 2015), participants were presented with 60 positive and 60 negative words paired with neutral words (distinct from the words used in the earlier tasks). In each trial, a fixation cross was presented in the center of the screen for 500 ms, followed by two words displayed at the bottom and top of the screen. These word pairs were shown for either 500 ms in the unmasked condition or 17 ms under the masked condition and were followed by a mask for 483 ms. Masks were created from letters, non-letter symbols and digits and were matched in word length and position. A dot-probe (one or two stars) then replaced the masks or words in their location. Accordingly, the dot-probe could appear behind the emotional word (congruent trials) or the neutral word (incongruent trial). Participants were asked to identify the probe as accurately and quickly as possible by pressing the corresponding key on the keyboard. There was a total of 180 trials (30 negative-neutral, 30 positive-neutral, and 30 neutral-neutral pairs each for the unmasked and masked conditions) with emotional words displayed at equal frequency at the bottom and top of the screen. Accuracy and RT were noted. Attentional vigilance scores were then calculated by subtracting RT in congruent trials from RT in incongruent trials (Attentional vigilance = RT incongruent trials – RT congruent trials). This task was completed between the ECAT and the EREC.

The EREC took place approximately 15 minutes after the ECAT, from which participants were asked to write down as many words as they could recall from the categorization task in 4 minutes. The outcome measure was the number of correctly and incorrectly recalled words.

In the EMEM, positive and negative personality descriptors (in equal frequency) were presented in the center of the screen for 500 ms. In total, 120 words were randomly presented with 60 being familiar and having already been displayed during ECAT and 60 being novel or unfamiliar. Participants were asked to indicate as accurately and quickly as possible, whether the word displayed was familiar or novel by pressing the corresponding key on the keyboard. The main outcomes included RT, correct responses, and false positives.

Statistics

Analyses were performed using SPSS (version 25.0) with significant levels set at $p < 0.05$. One participant was excluded from the attentional dot-probe task analysis as there was a computer failure during this task. Changes in subjective ratings (STAI-State, PANAS, VAS) and side effect symptoms were analyzed using mixed analysis of variance (ANOVA), with timepoint (baseline or T1, T2, and T3) as within-subjects factor, and treatment group (lamotrigine or placebo) as between-subjects factor. ETB data were analyzed using mixed ANOVA with emotion/valence as within-subject factors and treatment group (lamotrigine or placebo) as between-subject factors. The attentional dot-probe task was analyzed using mixed ANOVA with valence and masking as within-subject factors and treatment group as between-subject factors. Significant interactions were further explored using independent sample t-tests and/or paired-sample t-tests. Whenever relevant, analyses were repeated with side effects as a covariate (averaged values for timepoint 3).

Results

Baseline measures

The baseline characteristics of our sample can be found in Table 1. Participants were well matched on age, gender distribution, proportion of university-educated participants, ethnicity, verbal IQ, the BDI, and the EPQ scales. However, the lamotrigine group displayed higher scores on the STAI-trait.

Changes in subjective ratings and side effects

Measures of subjective mood were administered to assess subjective state and somatic side effects following treatment administration.

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Table 1. Baseline characteristics of the sample

	Placebo (n = 18)	Lamotrigine (n = 18)
Demographics		
Gender, n		
Male	12	12
Female	6	6
Age, years	24.39 (4.29)	23.83 (4.67)
Education		
University	16	17
Nonuniversity	2	1
Ethnic background		
White	12	12
Asian/Asian British	5	4
Black/African/Caribbean/Black British	1	0
Mixed/multiple ethnic groups	0	2
Baseline clinical measures		
NART	118.72 (5.29)	118.67 (4.37)
STAI-trait	29.61 (5.12)	33.44 (4.95)
BDI	1.89 (1.88)	2.72 (3.10)
EPQ-neuroticism	4.82 (2.92)	7.33 (4.96)
EPQ-psychoticism	2.53 (2.4)	3.22 (1.63)
EPQ-lie/social desirability	8.65 (3.35)	9.72 (4.54)
EPQ-extraversion	16.12 (3.84)	13.61 (5.67)

Note: Data given as mean (standard deviation) unless otherwise indicated. N, sample; NART, National Adult Reading Test; BDI, Beck Depression Inventory; STAI, State–Trait Anxiety Inventory; EPQ, Eysenck Personality Questionnaire.

There were no significant effects of treatment on the PANAS, VAS, or the STAI-State (all $p > 0.05$). There was a significant main effect of the group on side effects with the lamotrigine group reporting more side effects across all time points, including more physical symptoms at baseline (F(1.34) = 6.967, $p = 0.012$). There was no significant interaction between group and time points (p = 1.19).

FERT

For the accuracy of recognizing facial expressions' emotions and number of misclassifications, there were no significant main effects of treatment nor significant interactions between treatment and emotions (all $F_s < 6$, all $p_s > 0.12$).

ECAT

For accuracy of the emotional recall and RTs, there were no significant main effects of treatment nor significant interactions between treatment and emotion (all $F_s < 1$, all $p_s > 0.31$).

Attentional Dot-Probe task

For vigilance scores during the attentional dot-probe task, there was no significant main effect or interaction with treatment (p > 0.10).

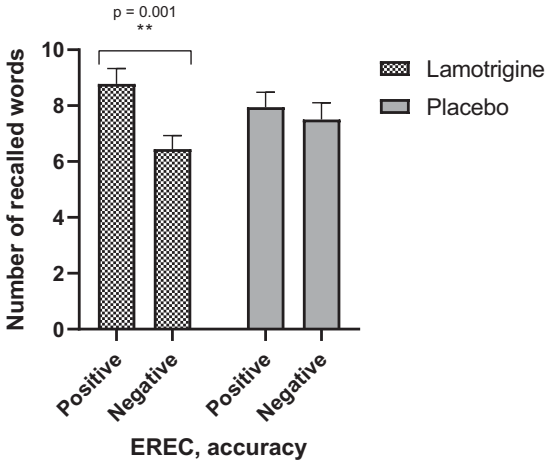

Figure 1. Accuracy of positive vs negative recalled words between treatment groups. Comparison between the number of recalled words (mean) for positively vs negatively valenced words in participants given lamotrigine vs placebo. Bars represent the standard error of the mean. Asterisks represent a statistically significant difference between positive and negative words.

EREC

For accuracy rates, there was a significant interaction between group and emotion (F(1,34) = 4.953, p = 0.03). This was driven by the lamotrigine group accurately recalling a significantly higher proportion of positive (8.78) vs negative words (6.44) compared to placebo (F(1,17) = 14.875, $p = 0.001$, Figure 1). Repeating this analysis with side effects as a covariate yielded a similar pattern of results (F(1,33) = 5.188, p = 0.03).

EMEM

For accuracy rates and RTs of correctly recalled words, there were no significant main effects of treatment and no significant interaction between group and emotion (all $F_s < 1.34$, all $p_s > 0.40$).

Discussion

The present study investigated the effects of a single oral dose of lamotrigine (300 mg) on emotional cognition in a healthy volunteer sample following a randomized double-blind, parallel placebo-controlled design. As such, this study aimed to characterize the neuropsychological mechanisms underlying lamotrigine, to ultimately help enlighten how lamotrigine is beneficial in the prevention of depressive episodes in BD. Three hours after the treatment administration, the lamotrigine group had a significantly higher accuracy for the recall of positive versus negative words compared to placebo. There were no other statistically significant effects in the analysis of the remaining ETB measures. These results are in line with a positive bias induction in emotional memory following acute lamotrigine treatment. There were significant differences between groups in subjective ratings of physical symptoms but these were also seen before the administration of lamotrigine and most likely reflect a naturally occurring difficulty of group matching via randomization. Controlling for these differences statistically did not affect the positive bias in emotional memory seen following lamotrigine.

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Lamotrigine induced a positive bias in memory recall

Participants in the lamotrigine group significantly recalled more positive than negative self-referential words in the emotional recall task, compared to those in the placebo group. This positive shift in memory has been extensively reported in experimental medicine studies of conventional antidepressant drugs using healthy volunteers. For instance, acute administration of mirtazapine or reboxetine, and 7-day treatment with citalopram or reboxetine increased positive affective memory in healthy participants (see Harmer, Cowen, & Goodwin, 2011 for a review). Preclinical models of affective bias have also revealed early changes in negative memory biases with a range of treatments used in depression including mirtazapine and reboxetine (Stuart et al., 2015). These positive shifts on emotional cognition have been proposed as a mechanism of antidepressant drug action, that is, by reversing negative biases believed to play a key role in maintenance of depression (for reviews see Harmer et al., 2017, Harmer, Cowen, & Goodwin, 2011). As such positive biases in affective memory may also be relevant to consider for the prophylactic effects of lamotrigine in depression in bipolar disorder.

It has been suggested that mood-congruent schema affect attention, interpretation, and memories about the world, oneself and the future in bipolar disorder (Paykel, 1987). Indeed in patients with BD with depressive symptomatology, negative biases are typically seen whereas in those with manic symptomatology, there is a bias toward more positive information (Bilderbeck et al., 2016). A negative cognitive style in people with BD has been reported to be a vulnerability factor that, when activated, triggers a cycle of rumination and negative self-related thoughts that feed into depression (Hitchcock et al., 2020; Van der Gucht, Morriss, Lancaster, Kinderman, & Bentall, 2009). Further emotional memory biases in BD have been observed, with patients showing enhanced memory for content that is associated with adverse emotions and for neutral content that preceded the emotional stimulus (Bogie et al., 2019; Fijtman et al., 2020). Additionally, both in BD depression and unipolar depression, patients show a worse recall for positive autobiographical memories, where these are less specific and more categorical, compared to healthy controls (Young, Bodurka, & Drevets, 2016). Understanding how these affective and cognitive biases in BD interact with both disorder stages and treatment can be helpful to determine treatment efficacy, and explore new potential treatments for BD. Consistent with previous research on conventional antidepressants (Harmer et al., 2017), lamotrigine may be shifting depressive-related negative memory biases into more positive ones. These effects may also help stabilize mood and prevent the development of depressive symptomatology in BD. However, it is crucial to investigate whether these effects seen here in healthy participants would also be seen in patients with BD and whether they would be seen across a wider body of emotional processing measures in addition to memory.

Lamotrigine has an effect on inhibition of sodium and calcium channels in presynaptic neurons and the subsequent stabilization of glutamate release. Animal models suggest that the antidepressant behavioral effects of lamotrigine are mediated via downstream increases in brain-derived neurotrophic signaling (Li et al., 2011). By which mechanism lamotrigine may have affected emotional memory here is unknown and requires further investigation. Nonetheless, animal and human studies have reported a clear effect of lamotrigine on memory. In mice, lamotrigine administration positively affected memory acquisition and spatial memory retrieval (Celikyurt et al., 2012). In humans, 14 weeks of lamotrigine treatment in a pediatric BD sample improved working and verbal memory (Pavuluri, Passarotti, Mohammed, Carbray, & Sweeney, 2010). In an adult BD sample, Haldane et al. (2008) found that 12 weeks of lamotrigine monotherapy had positive effects on working memory, with increased brain activity when performing the N-back task in regions typically activated with this task. Our results suggest that changes in emotional memory may also be seen following lamotrigine compared to placebo in a double-blind randomized design.

Strength, limitations, and future directions

The present study is the first experimental medicine study investigating the effects of a single oral dose of lamotrigine in healthy volunteers. The use of healthy volunteers allows the characterization of the effects of a drug on cognitive-emotional functions that are relevant to a disorder, avoiding potential confounding factors such as differences in disorder progression or past treatments. Prior research has highlighted lamotrigine's positive influence on memory; however, the current study explores, for the first time, its influence on the emotional memory domain, which is often affected in BD.

However, it is important to consider these results together with the study limitations. This study primarily found a significant effect on emotional memory (EREC), without widespread effects on other components of emotional processing. We had a relatively small sample (n = 36) which gave rise to reduced statistical power and we also did not correct for the multiple statistical comparisons across the ETB tasks in the current study which increases the risk for type 1 errors.

Participants in the lamotrigine group also exhibited higher trait anxiety levels, possibly causing an imbalance between groups. This might have affected their self-assessment of side effects, as the groups differed on this measure even at baseline. Nonetheless, despite this potentially negative valence experience, the lamotrigine group still displayed a positive memory bias. Finally, the sample involved in this study was comprised of healthy volunteers, and while these may provide advantages in the exploration of lamotrigine's effect on emotional cognition, it is important to consider that different underlying mechanisms may exist between healthy and patient populations. Future research should explore a similar paradigm in patients with BD to further clarify these results and assess whether they are related to the clinical effects of lamotrigine in BD.

Conclusions

This study evaluated the effects of a single oral dose of lamotrigine in healthy volunteers on a range of cognitive-emotional functions using a well-validated task battery. Lamotrigine significantly increased accurate recall of positive versus negative self-referential descriptors compared to placebo without wider effects on emotional processing. There results suggest that emotional memory may be a useful target to explore in future studies of lamotrigine's clinical action in bipolar disorder.

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Author contribution. TZ was involved in the study conception, data collection, data analysis, and manuscript preparation. PAH was involved in data analysis and data checks and prepared the first manuscript draft. LW and AK were involved in data collection and manuscript preparation. GG was involved in the study design, data interpretation, and manuscript preparation. LPC analyzed data, oversaw the study, and was involved in data interpretation and manuscript preparation. CJH was involved in the study conception, oversaw the study, and was involved in data interpretation and manuscript preparation.

Competing interests. CJH has received consultancy fees from P1 vital Ltd., Janssen Pharmaceuticals, Sage Therapeutics, Pfizer, Zogenix, Compass Pathways, and Lundbeck. CJH holds grant income from Zogenix, UCB Pharma, Pfizer, and Janssen Pharmaceuticals. GMG is Chief Medical Officer at Compass Pathways, holds shares and share options in Compass Pathways PLC and has served as a consultant, advisor, or CME speaker in the last 3 years for Beckley Psytech, Boehringer Ingelheim, Clerkenwell Health, Compass Pathways, Evapharma, Janssen, Lundbeck, Medscape, Novartis, Ocean Neuroscience, P1Vital, Servier, and Takeda.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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