An experimental medicine investigation of the effects of potential novel antidepressant interventions on emotion and reward related information processing

Alexander Kaltenboeck

Department of Psychiatry
University of Oxford
Oxford, UK

Somerville College

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Supervisors:

Prof. Catherine Harmer

Prof. Philip Cowen

Prof. Michael Browning

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Declaration

I declare that this thesis has been composed solely by myself and that I have not submitted it — in whole or in part — in any previous application for an academic degree. For all three empirical studies that contributed to this thesis I have acted as the primary researcher. Under the guidance of my DPhil supervisors, I have conceived each study, have developed appropriate research protocols, have obtained approval from the local ethics committee to conduct each study, have undertaken day-to-day study management (including recruitment of study volunteers and communication with participants), have collected the majority of empirical data myself (using questionnaires, cognitive tasks, and saliva sampling, respectively), have undertaken all statistical analyses reported in the thesis (including computational modelling), and have written up all obtained results as separate thesis chapters.

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Abstract

Recent attempts to reconcile neuropharmacological and cognitive accounts of depression have led to the development of a cognitive neuropsychological model of antidepressant treatment action. This model suggests that antidepressant drugs exert their clinical effects by acutely inducing positive biases in "hot" (i.e. emotion-related) cognitive processes which can counteract the negative biases in affective information processing that are inherent to depression. The validity of this model is well supported by a multitude of empirical studies investigating the effects of different established antidepressant drugs which, taken together, suggest that the induction of positive biases is a common and crucial causal mechanism of antidepressant action.

The aim of this thesis is to investigate whether potential novel antidepressant treatments could have similar effects. Taking an experimental medicine approach, three different interventions were studied in healthy volunteers: bright light treatment, practising positive psychology, and administration of the dopamine D2/D3 receptor-preferring agonist pramipexole. In addition to their effects on hot cognitive processes, for each of these interventions, potential effects on subjective state and, where of interest, also effects on other relevant measures (e.g. HPA axis activity for practising positive psychology, gustatory processing for pramipexole treatment) were tested.

Contrary to our predictions, we did not find conclusive evidence for an antidepressant-like effect on emotional information processing for any of the three treatments we studied. However, several interesting patterns in other measures were observed: First, an early memory practice that has previously been used as a supposedly inert control intervention in positive psychology studies showed a blunting effect on cortisol awakening responses and potentially also a general

improvement of hot cognitive processes. Second, subacute pramipexole treatment showed a potential effect on exploration-exploitation strategies in an information bias learning task, maintaining random exploration after repeated-testing as compared to placebo. Furthermore, pramipexole also showed a potential effect on gustatory processing, enhancing taste recognition but blunting subjective evaluation of appetitive and aversive taste samples.

In conclusion, previously reported antidepressant effects of the putative novel treatments that were studied in this thesis seem not to be explainable by the induction of positive biases in emotion-related information processing. Further studies on the mechanisms behind their efficacy are warranted. The observed effects of the mental practice and of subacute pramipexole treatment deserve further attention and should be interrogated in closer detail in future research.

Chapter 1: Introduction

Motivation, objective, and outline of thesis

Depression is a common mental disorder that affects more than 300 million people globally and has an estimated life time risk of 10% to 20% (Friedrich, 2017; Harrison et al., 2018). It frequently presents with a recurrent or chronic course (American Psychiatric Association, 2013; Harrison et al., 2018) and constitutes one of the leading causes of disability worldwide (Friedrich, 2017) — putting an enormous burden on the individual patient, their immediate environment, and on society at large. Current standard treatment approaches for depression include antidepressant pharmacotherapy (such as selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors) and psychotherapy (such as cognitive behavioural therapy), either as stand-alone treatments or in combination (Harrison et al., 2018; NICE, 2009).

Depressive disorders are often regarded as having a comparatively favourable prognosis, with many patients supposedly experiencing symptom relief following standard treatment strategies (Cowen, 2017a). However, both clinical experience and empirical research suggest that full recovery occurs less frequently than is commonly assumed and that, as a matter of fact, a significant number of patients do not experience significant improvement under standard therapies (Cowen, 2017a).

To give one example, a large US study that analysed data from more than 1800 individuals found that only about a third of depressed patients actually reached remission (i.e. a satisfyingly low symptom score) after three months of typical community-practice treatment with antidepressant medication and/or psychotherapy (Cowen, 2017a; Simon et al., 2006). Similar results were found in the STAR*D study, a large-scale pragmatic investigation of sequenced antidepressant

therapies in patients with major depression (Cowen, 2017a; Rush et al., 2006). Here the data showed that when undergoing first-line treatment with the selective serotonin reuptake inhibitor citalopram, less than 40% of patients reached remission after twelve weeks (Cowen, 2017a; Rush et al., 2006). In fact, even after four treatment steps of systematic and tailored pharmacotherapy or psychotherapy administered over a year, only about two thirds of patients reached remission, and if a patient did not experience symptom remission after two treatment steps, the chance of remitting with a subsequent therapy was only about 15% (Cowen, 2017a; Morriss et al., 2016; Rush et al., 2006). In a similar vein, in a recent study in the United Kingdom, patients with persistent depression that had not responded to six months of secondary care treatment were randomly allocated to either a specialist depression service or treatment as usual directed by a consultant psychiatrist (Cowen, 2017a; Morriss et al., 2016). Surprisingly, the study found that there was little added benefit of the specialist depression service, despite the fact that it offered long-term Beckian cognitive behavioural therapy for depression (Cowen, 2017a; Morriss et al., 2016).

Taken together, the foregoing findings thus provide evidence that current standard treatment approaches for depression have limited efficacy and that there is a considerable number of patients who do not benefit sufficiently from these therapies. Therefore, in addition to developing improved treatment algorithms and better strategies for matching individual patients to current therapies (along the ideas of "precision psychiatry" (Bzdok and Meyer-Lindenberg, 2018; Fernandes et al., 2017)), it is also vital for psychiatric research to continue exploring potential new antidepressant interventions.

The last decades have indeed seen the development and description of a considerable number of such potential novel[1] treatments. Although several of these interventions have demonstrated promising clinical effects in pilot empirical investigations (and sometimes even small meta-analyses), they have often received little to no attention from the clinical neurosciences. As a result, for many of these treatments little is currently known about the potential mechanisms through which they could bring about antidepressant effects. The aim of this thesis is to provide a first attempt in filling this gap in the literature.

To this end, three potential novel antidepressant interventions were assessed through the lens of the so-called "**cognitive neuropsychological model of antidepressant treatment action**" (from here on referred to as the "**CONEMATA**"). The CONEMATA is a promising new theoretical framework that explains antidepressant effects mechanistically via an influence of a given treatment on emotional/affective information processing (Harmer et al., 2009a, 2017; Roiser and Sahakian, 2017; Roiser et al., 2012; Warren et al., 2015) — for further information see below.

Using an established healthy volunteer assay, we assessed the effects of three distinct treatments, each representing a different therapeutic modality. First, we studied **bright light treatment,** a non-pharmacological physiological treatment (Pail et al., 2011). Second, we assessed the effects of a **positive psychology practice**, which constitutes a simple self-administered psychological intervention (Seligman et al., 2005). Finally, we explored the cognitive effects of **pramipexole**, a selective

[1] Note that the term "novel" in the context of this thesis is used for treatments that are not yet considered to be part of to the standard armamentarium of a modern psychiatrist. The term is not meant to imply that a treatment has only recently been discovered. As a matter of fact, many "novel" antidepressant treatments have been known and used by clinicians for decades — either as treatments for other disorders or sometimes even as non-conventional/experimental/alternative interventions for depression.

agonist at the dopamine D2 receptor subfamily, and a potential novel pharmacological treatment option for depression (Tundo et al., 2019). Whilst being different in many regards, these three treatments have two things in common: First, they have all shown preliminary but promising beneficial effects in patients with depression and therefore can be regarded as potential candidates for the inclusion in the therapeutic armamentarium of future psychiatry. Second, and more importantly, none of these treatments have been assessed through the lens of the CONEMATA and whether they can influence emotional/affective information processing is not known to date.

The thesis presented here consists of seven chapters in total. **Chapter 1** introduces the reader to the basic idea of the CONEMATA.[2] It describes how this theoretical framework conceptualises the development of depressive symptoms mechanistically, how it explains the clinical effects of antidepressant interventions, and what empirical evidence there is to support the validity of model. Chapter 1 also gives background information on the three interventions that were studied as part of the thesis (i.e. bright light treatment, a positive psychology practice, and pramipexole administration). This provides the context for the subsequent chapters, in which we assess our interventions of interest with regards to effects on emotional information processing (as well as some other neurobiological measures relevant to depression).

In **Chapter 2**, we probe potential effects of a single dose of bright light treatment on emotional information processing and subjective state.

In **Chapter 3**, we study whether a positive mental exercise can influence affective information processing, HPA axis activity, or subjective state.

[2] Please note that small parts of the discussion in Chapter 1 have previously been published in Kaltenboeck and Harmer (2019).

In **Chapter 4,** we explore the influence of subacute treatment with the dopamine D2/D3 receptor-preferring agonist pramipexole on emotional information processing and subjective state.

In **Chapter 5**, we take a computational modelling approach to probe whether subacute pramipexole treatment might show differential impact on learning and decision-making based on positive and negative outcomes.

In **Chapter 6**, we further extend the assessment of neurocognitive effects of pramipexole to the domain of gustatory processing and probe a potential influence of dopaminergic manipulation on taste recognition as well as hedonic experience of appetitive and aversive taste samples.

Finally, **Chapter 7** brings together all findings from this thesis, discusses their implications and relevance in a broader context, and outlines potential avenues for future research.

Theoretical background: The cognitive neuropsychological model of antidepressant treatment action

Antidepressant drug treatments are widely used today, yet the mechanisms through which they exert their clinical effects are still not well understood. When the first clinically useful antidepressant agents were discovered serendipitously approximately 60 years ago, laboratory studies showed that they were able to increase the synaptic availability of the monoamines serotonin and/or noradrenaline (Harmer et al., 2009a, 2017). Therefore, it was hypothesised that these neurochemical changes might underlie the clinical effects of efficacious antidepressant drugs (Harmer et al., 2009a, 2017; Mulinari, 2012). This assumption has had a major influence on the formulation of theories about the pathophysiology of depression as well as antidepressant drug development (Cowen, 2017b; Harmer et al., 2009a, 2017; Mulinari, 2012) and, to this date, practically all licensed

antidepressant drugs target the serotonergic and/or the noradrenergic system in one way or another (Harmer et al., 2017).

However, already in the early days of the monoaminergic theories of depression and antidepressant drug action it was recognised that the time scales with which neurochemical and clinical effects become apparent under treatment do not match up: While synaptic monoamine potentiation occurs within hours of drug administration, clinical improvements take weeks to emerge (Harmer et al., 2009a, 2017; Vetulani and Sulser, 1975). This has led scholars to develop alternative theories of antidepressant treatment action that can identify a mechanism of action while at the same time also explain the time lag of clinical efficacy. Most such theories that have been proposed to date focus on a neurophysiological level of description, including for example the autoreceptor desensitisation theory or the neurotrophic theory (Harmer et al., 2017; Sharp and Cowen, 2011).

An alternative (or complementary) contemporary framework that has gained considerable momentum in the past two decades is the so-called "cognitive neuropsychological model of antidepressant treatment action" (CONEMATA) (Harmer and Pringle, 2017; Harmer et al., 2009a; Pringle et al., 2011; Roiser and Sahakian, 2017, 2013; Roiser et al., 2012; Warren et al., 2015). This theoretical framework focuses on the quality of information processing — specifically information with emotional tone/valence — in order to explain both, how antidepressants exert their effects, and why they take so long to show clinical effects.

When the healthy human brain processes information with emotional valence, it generally does so in a positively biased way; that is, it shows a tendency to process positive (as opposed to negative) affective input preferentially (Roiser and Sahakian, 2017, 2013). Such positive biases can be objectively measured using

neuropsychological tests and are observable in different cognitive domains (Roiser and Sahakian, 2017). In the depressed brain, in contrast, "hot" (i.e. emotion-related) cognitive processes are frequently disturbed: positive biases are either less pronounced or even completely replaced by a tendency to prioritize negative emotional information (Roiser and Sahakian, 2017, 2013; Roiser et al., 2012). In other words, compared to the healthy state, the depressed brain processes emotion-related information in a negatively biased way (Elliott et al., 2011; Harmer et al., 2009a; Miskowiak and Carvalho, 2014; Roiser and Sahakian, 2017, 2013; Roiser et al., 2012; Warren et al., 2015).

For example, in facial expression recognition tasks, patients with depression, as compared to healthy controls, have been reported to show reduced recognition of positive facial expressions, enhanced recognition of negative facial expressions, and a tendency to interpret ambiguous faces as negative (Elliott et al., 2011; Miskowiak and Carvalho, 2014). Similarly, in emotional memory tasks, depressed individuals (as compared to healthy controls) demonstrate preferential memory for negatively valenced (relative to positively valenced) emotional material (Bradley et al., 1995; Dillon and Pizzagalli, 2018; Gilboa-Schechtman et al., 2002; Hamilton and Gotlib, 2008; Miskowiak and Carvalho, 2014; Ridout et al., 2003; Watkins et al., 1992). Moreover, in affective go/no-go and categorisation tasks (where study participants have to quickly react to emotional target stimuli) depressed patients, compared to non-depressed controls, show relatively faster responses to negative as opposed to positive stimuli (Clark et al., 2009; Miskowiak and Carvalho, 2014; Warren et al., 2015).

In contrast to the negative biases observed in depression, a considerable body of literature now shows that antidepressant drugs share the ability to acutely push hot cognitive processes towards a preference for positive relative to negative stimuli in

both healthy participants and depressed patients (Harmer et al., 2009a, 2017; Roiser et al., 2012; Warren et al., 2015), and this insight has led to the development of the CONEMATA. The CONEMATA suggests that the negative biases in emotional information processing that are observable in patients with depression are not just a mere epiphenomenon of low mood, but rather play a crucial causal role in its development in the first place as well as its subsequent maintenance (Harmer et al., 2009a, 2017; Pringle et al., 2011; Roiser and Sahakian, 2017, 2013; Roiser et al., 2012; Warren et al., 2015). The clinical effects of antidepressant drugs, according to the model, can be explained by their ability to push hot cognitive processes back to a more normal state, thus allowing the depressed brain to harvest (i.e. notice, perceive, and remember) an increased amount of positively valenced information again. If this happens over a prolonged period of time, according to the model, subjective mood will also improve (Harmer et al., 2009a, 2017; Roiser and Sahakian, 2017; Roiser et al., 2012; Warren et al., 2015).

The CONEMATA is well-supported by empirical evidence. As already mentioned above, negative emotional biases have been described in acutely depressed non-medicated patients in different cognitive domains, including perception, attention, memory, and reward processing (Elliott et al., 2011; Miskowiak and Carvalho, 2014; Roiser and Sahakian, 2017; Tavares et al., 2003). Moreover, negative biases have also been observed in never-depressed individuals who are at increased risk to develop depression, such as those who score high in neuroticism (Chan et al., 2007) or those with a first-degree relative with the disorder (Masurier et al., 2007). These findings indicate that negative biases are not just the result of depressed mood but rather precede it and may constitute a risk factor for developing a depressive disorder. Importantly, experimental induction of negative biases in healthy volunteers has been shown to increase anxiety when new emotionally significant information is

processed, providing direct evidence that biased emotional information processing can causally influence subjective state (Mathews and MacLeod, 2002).

The ability of antidepressant drugs to shift emotional information processing towards positivity has also been documented consistently in the literature (Harmer et al., 2009a, 2017; Roiser et al., 2012; Warren et al., 2015). Such effects have been reported for various antidepressant agents acting on different neurochemical targets, e.g. citalopram (Harmer et al., 2004), reboxetine (Harmer et al., 2003a, 2004), mirtazapine (Arnone et al., 2008), duloxetine (Harmer et al., 2008), agomelatine (Harmer et al., 2011) or bupropion (Walsh et al., 2018b, 2018a). This suggests that effects on affective information processing might represent a common target or final pathway of action that is shared between different antidepressant drugs (Harmer et al., 2009a, 2017; Warren et al., 2015).

It is important to point out that effects of antidepressant drugs on emotional information processing have not only been documented in patients with depression but also in healthy volunteers (see Warren et al. (2015) for a comprehensive overview). This is relevant insofar as it demonstrates that the induction of a positive bias is an effect that can be brought about by an antidepressant drug even in the absence of psychopathology (Harmer et al., 2004). Thus, the ability to shift emotional information processing seems to be a direct effect of antidepressant drug treatment and not just a subtle sign of clinical improvement in patients (Harmer et al., 2004).

The shift towards positivity that antidepressants induce in emotional information processing typically occurs early on in treatment, in some cases even after single-dose challenges, i.e. long before clinical effects are to be expected in patients (Harmer et al., 2009a; Warren et al., 2015). In addition, preliminary evidence now exists that shows that changes in emotional information processing occurring early

on in treatment can be predictive of later-emerging clinical improvements in patients with depression (Browning et al., 2019; Shiroma et al., 2014).

In recent years, some authors have extended the CONEMATA to also incorporate "cold" (i.e. emotion-independent) cognitive processes. For example, Roiser and colleagues (2017, 2013; 2012) have put forward a cognitive neuropsychological model that distinguishes between low-level negative biases in emotional information processing and high-level negative beliefs about the world. The basic idea of their model is that negative biases in affective processing lead to the adoption of negative beliefs about the world in a bottom-up manner. Negative beliefs, in turn, can exert top-down influence on cognitive processes, thereby biasing them (even further) towards negativity. This, in turn, provides further support for the negative beliefs, and so on. The result is a vicious cycle of negatively biased information processing and negative beliefs, each feeding into the other. In addition to these two factors, the model also attributes a key role to executive functioning, which is thought to mediate the influence high-level beliefs can exert on low-level cognitive processes (Roiser et al., 2012). Impaired executive functioning, which is also frequently observed in depression, is thought to allow negative beliefs to exert their undue top-down influence on cognitive processes to a stronger degree (Roiser et al., 2012). According to this model, different forms of cognitive enhancement might thus also constitute a viable strategy for breaking the vicious cycle and alleviating symptoms of depression (Roiser et al., 2012).

Interestingly, relatively little is currently known about whether non-drug treatments for depression can also influence emotional information processing and only a few such treatments have been studied with respect to effects on emotional processing such as those predicted by the CONEMATA. Nevertheless, there is some evidence showing that non-drug antidepressant treatments can have effects on hot

cognitive processes that parallel those of conventional drug treatments (see Kaltenboeck and Harmer (2019) for a longer discussion). For example, patient studies show that cognitive behavioural therapy (CBT) can improve free recall of positive stimuli while attenuating recall of negative stimuli (Docteur et al., 2013). Furthermore, CBT has also been reported to decrease abnormal vigilance to negative cues (Reinecke et al., 2013) and to remediate abnormal brain activation in response to emotional stimuli (Fu et al., 2008; Ritchey et al., 2011; Yoshimura et al., 2014). In a similar vein, high-density negative ion treatment, which has shown antidepressant effects in randomised controlled trials, has also been demonstrated to increase the recognition of positive compared to negative facial expressions and to enhance recognition and recall memory for positive stimuli (Harmer et al., 2012; Malcolm et al., 2009). Qualitatively similar results have also been obtained for electroconvulsive therapy (Bai et al., 2017; Miskowiak et al., 2018; Redlich et al., 2017) and transcranial direct current stimulation (Boggio et al., 2007; Brunoni et al., 2014). These findings thus support the idea that emotional information processing might be a mutual target, or a common final pathway of action, that is not just shared by conventional antidepressant drugs, but potentially also across different treatment modalities.

Study intervention 1: Bright light treatment

The use of light as a treatment for depression has a long history in medicine and can be traced back to the ancient world where, for example, the Greek physician Aretaeus of Cappadocia stated that "Lethargics be laid in the light, and exposed to the rays of the sun, for the disease is gloom" (Geoffroy et al., 2018). The origins of bright light treatment (BLT) in modern psychiatry can be found more than three decades ago when it was introduced as a specialised treatment for seasonal affective disorder (SAD), a condition characterised by episodes of depression that occur

repeatedly at the same time of the year, usually in autumn or winter (Geoffroy et al., 2018; Harrison et al., 2018; Rosenthal et al., 1984).

Originally, BLT was developed as a means of mimicking conditions of increased sunlight exposure, a lack of which is considered to be an important pathophysiological factor in SAD (Lam and Levitan, 2000; Rosenthal et al., 1984). BLT is often described as the treatment of choice for SAD and its efficacy for this condition has been well-documented in the literature (Golden et al., 2005; Pail et al., 2011; Pjrek et al., 2020). In addition, there is a growing body of evidence indicating that bright light treatment also shows efficacy in non-seasonal major depression (Al-Karawi and Jubair, 2016; Golden et al., 2005; Lam et al., 2016; Lieverse et al., 2011; Tuunainen et al., 2004; Zhao et al., 2018), with clinical effect sizes potentially comparable to those of conventional antidepressant drug treatments (Golden et al., 2005). Potential beneficial effects have also been described for a range of other neuropsychiatric conditions, including disruptions of the sleep-wake cycle (e.g. jet lag, shift work), eating disorders, attention-deficit hyperactivity disorder, and neurodegenerative conditions (Wirz-Justice et al., 2013).

BLT shows several advantages compared to antidepressant drug treatment (also see Table 1), including a more favourable side effect profile and faster clinical responses (Maruani and Geoffroy, 2019; Terman and Terman, 1999; Tuunainen et al., 2004). Efficacy as well as side effects of BLT depend on light dose (determined by irradiance, duration of exposure, distance to the light source and angle of light exposure), colour spectrum of light, and timing of exposure (Geoffroy et al., 2018; Terman and Terman, 2005). Possible side effects include jumpiness/jitteriness, headache, and nausea (Terman and Terman, 1999). However, these are generally mild and rare and tend to remit spontaneously or after dose reduction (Pail et al., 2011). Hence, BLT might also be a useful therapeutic option for peripartum

depression and depression in the elderly (Crowley and Youngstedt, 2012; Lieverse et al., 2011; Maruani and Geoffroy, 2019; Zhao et al., 2018).

BLT is typically self-administered at home using a special light box that contains fluorescent lamps, a reflector, and a diffusing screen and emits full-spectrum visible light (Pail et al., 2011). A widely cited standard daily dose for SAD treatment is 5000 lux-hours and generally morning light exposure seems to show superior efficacy compared to evening exposure (Pail et al., 2011).

Despite its excellent efficacy and side effect profile as an antidepressant intervention, BLT has received surprisingly little attention in the clinical neuroscience community. To date, relatively little is understood about how BLT might exert beneficial effects on mood. Extraocular administration has failed to show antidepressant efficacy (Pail et al., 2011), which suggests that the antidepressant effects of BLT is mediated through the eyes — possibly through melanopsin-containing intrinsic photosensitive retinal ganglion cells and the non-image forming visual system (Güler et al., 2008; Schwartz and Olds, 2015; Stephenson et al., 2012). Different effects of light on the brain have been proposed as potential mechanisms of treatment action of BLT, including effects on circadian rhythms (e.g. phase-shifting, entrainment of the biological clock) and effects on serotonin function and melatonin secretion (Boyce and Hopwood, 2013; Geoffroy et al., 2018; Maruani and Geoffroy, 2019; Oldham and Ciraulo, 2014; Stephenson et al., 2012). More recently, discussions of the impact of light on sleep and sleep homeostasis, alertness, as well as the autonomic nervous system have highlighted other potential causal factors in the effects of BLT on mood (Boyce and Hopwood, 2013; Geoffroy et al., 2018; Maruani and Geoffroy, 2019; Oldham and Ciraulo, 2014; Stephenson et al., 2012).

With regards to effects on hot cognition, to the author's knowledge, there are currently no published studies that directly assess whether BLT can exert differential effects on the processing of positive versus negative cues. However, there are at least two studies available that suggest that light exposure can in principle influence emotional information processing. For example, Fisher and colleagues (2014) studied the impact of repeated BLT, with varying individual dosages, on neural correlates of threat processing. Using functional magnetic resonance imaging, they measured neural activity in the cortico-limbic circuit before and after the intervention while participants were viewing fearful, angry, and neutral faces. The study found that higher bright light dosages were associated with decreased neural activity in response to angry and fearful faces in the amygdala and medial prefrontal cortex, and increased left amygdala-prefrontal and intra-prefrontal functional coupling. This led the authors to conclude that bright light treatment might dampen amygdala reactivity to negative affective input — an effect that has also been observed for antidepressant drug treatments (Murphy et al., 2009) — whilst also enhancing top-down regulation of the prefrontal cortex on threat-induced amygdala reactivity. The specific interpretation of these observations notwithstanding, the findings certainly lend support to the idea that bright light treatment can have direct and dose-dependent effects on emotional information processing.

This idea is further corroborated by Vandewalle and colleagues (2010) who also explored whether light can affect emotional information-processing in healthy volunteers, although they focused on the effects of different wavelengths rather than full-spectrum white light, as is used for clinical purposes. In their study, the authors measured neural responses to angry and neutral vocal stimuli while participants were exposed to pulses of green or blue light. This experiment showed

that exposure to blue light (as compared to green light) was associated with increased activity of the voice area (temporal cortex) and hippocampus in response to angry vocal stimuli. Furthermore, the authors also observed increased functional connectivity between the voice area, the amygdala, and the hypothalamus during processing of emotional stimuli. These results thus provide further evidence that light can directly influence neural measures of affective information-processing and these effects seem to depend on specific light spectra used.

Indirect evidence for a potential effect of bright light on emotional information processing also comes from studies using nutritional depletion methods. For example, aan het Rot et al. (2010) studied effects of acute tryptophan depletion (which produces a transient decrease in serotonin transmission) on facial expression recognition in healthy volunteers. They found that acute tryptophan depletion lead to measurable changes in facial expression recognition, but that these effects were blocked when bright light was applied concomitantly. This suggests that bright light and tryptophan depletion had opposing effects in terms of emotional processing. However, it is worth noting in this context that the effects of acute tryptophan depletion that were observed in this study (impaired accuracy for disgust and surprise) were at odds with several other studies in the literature and therefore should be interpreted with caution (Harmer et al., 2003b; aan het Rot et al., 2010). A similar study in women with subsyndromal seasonal affective disorder found that acute phenylalanine/tyrosine depletion (which produces a transient decrease in dopamine transmission) also led to changes in emotional information processing (increased recognition performance for sad faces) but, again, this effect was alleviated by bright light exposure (Cawley et al., 2017).

Table 1: Advantages of bright light treatment compared to conventional antidepressant drug treatment (adopted from Oldham et al. (2014)).

Greater effect size in patients with SAD and comparable effect size in non-seasonal depression relative to psychotropic medication
More rapid antidepressant response in SAD and non-seasonal depression responses within a week
Near absence of systemic adverse events (e.g. sexual dysfunction, weight gain)
Non-dependence on absorptive capacity of the gastrointestinal system
Non-dependence on metabolic or elimination processes
Absence of medication interactions
No conceivable means of overdose
No documented discontinuation syndrome
Absence of recurring monthly costs
Absence of teratogenic effects
Clinical acceleration of treatment response in non-seasonal depression when employed as adjunct to conventional antidepressant medication

Study intervention 2: Positive psychology practice

Since its beginnings about two decades ago, the field of "Positive Psychology" has produced an ever-growing body of research. As a scientific discipline, its broad aim is to study the factors that enable human beings to live a happy and positive life, fulfil their individual potential, and to flourish and thrive (Seligman, 2011; Seligman and Csikszentmihalyi, 2000; Seligman et al., 2005; Sheldon and King, 2001). Positive psychology concerns itself not only with positive subjective experience (e.g. wellbeing, optimism, flow, and happiness) and positive personality traits (e.g. capacity for love, interpersonal skills, courage, wisdom, perseverance) pertaining to the individual human being, but also with the civic virtues, institutions, and characteristics of communities that support good citizenship (e.g. responsibility, altruism, tolerance) (Seligman, 2005, 2011; Seligman and Csikszentmihalyi, 2000). Such an approach is intended to complement traditional academic psychology which has long focused primarily on a disease model of human functioning and mostly studied pathological conditions and the means to alleviate the suffering they cause (Seligman, 2005, 2011; Seligman and Csikszentmihalyi, 2000).

An active area of research in positive psychology is the development and empirical testing of interventions that can increase subjective wellbeing (Bolier et al., 2013; Seligman et al., 2005; Sin and Lyubomirsky, 2009; White et al., 2019). This approach is based on the idea that personal happiness and thriving are influenced by modifiable factors (e.g. positive feelings, positive behaviours, positive cognitions) that can be deliberately cultivated and introduced in an individual's life through targeted practice (Lyubomirsky and Layous, 2013; Sin and Lyubomirsky, 2009).

Such positive interventions can be used within a clinical context, e.g. as a treatment for patients suffering from depression (Rashid, 2015; Seligman et al., 2006;

Taghvaienia and Alamdari, 2020), but they can also be distributed more widely to the general public (e.g. through online programmes) as a simple means for people to proactively improve their personal quality of life (Mitchell et al., 2010). The efficacy of positive psychology interventions in general is supported by several meta-analyses (Bolier et al., 2013; Chakhssi et al., 2018; Sin and Lyubomirsky, 2009; White et al., 2019).

The positive psychology exercise that is studied in detail in this thesis is the so-called "Three good things in life exercise" (TGT exercise), which, according to previous studies, shows relatively strong and lasting effects compared to other interventions (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Proyer et al., 2014; Seligman et al., 2005). It was originally introduced in the literature by Seligman and colleagues (2005).

In this practice, people are asked to set up a simple diary where they keep track of positive events that occur in their life on an everyday basis (Seligman, 2011). They are asked to reflect every evening on the past day and to identify three things that they think went well for them on that day. These can be relatively trivial events (e.g. having had some nice food, having been able to answer a hard question in class), or very important ones (e.g. a birth in the family). People are asked to write down each event in the diary and in addition provide a brief explanation as to why they think this event had occurred (e.g. "I had some nice food: Because my friend came over and we cooked together"). The idea behind this exercise is to gradually build a habit of becoming aware and focusing to a greater extent on the positive aspects of one's own life (Seligman, 2011).

In a large-scale landmark study, Seligman and colleagues (2005) tested the efficacy of the TGT exercise (and a range of other positive psychology interventions) in an online setting using a randomised placebo-controlled study design. They found

that a seven-day long practice of the TGT exercise led to significantly increased happiness and decreased depressive symptoms for up to 6-months. Since then, several studies have provided further evidence for beneficial effects of the TGT exercise in different populations. For example, in people aged 50 and above, Proyer and colleagues (2014) report effects of the TGT, compared to a placebo control, on both happiness and depressive symptoms (although this effect was only detectable immediately after the week-long practice period and not in any of the subsequent assessments). In a similar vein, in schoolchildren aged eight to eleven years, Carter et al. (2018) also found an increase in happiness and a decrease in depression after practicing the TGT, and in this study the effect was also detectable at a three month follow-up. Interestingly, the authors also found that the least happy children benefitted most from the intervention, whilst the most happy children actually showed a reduction in happiness scores — which raises questions about the universal value of the exercise (Carter et al., 2018). In a pilot study without a control group, Sexton and Adair (2019) demonstrated that the TGT exercise can improve happiness, depression, exhaustion, and problems with work-life balance in health care workers. In a small-scale clinical setting with patients suffering from depression, a positive psychotherapy intervention that contained the TGT exercise as part of a larger program, also showed beneficial effects, with the program outperforming treatment as usual (including medication) in terms of remission rates (Seligman et al., 2006).

However, not all studies were able to replicate all the effects originally reported by Seligman et al. (2005). Gander and colleagues (2013), for example, could replicate the positive effect of the TGT exercise on happiness in a German-speaking sample, but not the effect on depressive symptoms. A similar pattern was observed by Mongrain and Anselmo-Matthews (2012). In contrast to this, another replication

effort found that effects of the TGT exercise on happiness and depressive symptoms were indistinguishable from those of a placebo control (Woodworth et al., 2017). In addition, a different study by the same authors explored effects on affect in an N-of-1 study design and found no evidence for a relevant intra-individual beneficial impact of the TGT exercise on affect over time (Woodworth et al., 2016).

Taken together, the studies discussed above generally suggest that the TGT exercise can exert positive effects on wellbeing. However, as shown, these effects might be more modest than originally thought and it may be that not every person benefits from the TGT exercise in the same way. This of course also raises the question of what mechanisms might bring the beneficial effects of this practice about.

Whilst there is a growing body of research that evaluates the efficacy of positive psychology interventions, much less is currently known about potential mechanisms through which these practices might exert their effects on wellbeing. In the clinical neurosciences, positive psychology interventions have received almost no attention to date, and, to the author's knowledge, there is currently no neurobiologically-informed mechanistic framework for positive psychology practices like the TGT exercise. Current theories of how positive psychology practices might work mechanistically are therefore mostly restricted to an abstract psychological level of description.

One dominant mechanistic theory can be derived, for example, from the "broaden-and-build" framework of positive emotion (Fredrickson, 2004; Gander et al., 2013). This theory suggests that positive emotions are not just simple indicators of human wellbeing but can themselves exert long-lasting effects on a person's mental health (Fredrickson, 2001, 2004). The core idea of the broaden-and-build theory is that the experience of a positive emotion (e.g. joy, contentment, interest) momentarily broadens a person's cognition-action repertoires, that is, the array of potential

thoughts and actions that come to mind becomes larger (Fredrickson, 2001, 2004). This effect, according to the theory, then allows a person to gradually build enduring personal, physical, psychological, and social resources, which can ultimately produce an upward spiral towards enhanced wellbeing (Fredrickson, 2001, 2004; Fredrickson and Joiner, 2002). For example, joy might broaden the thought-action repertoire by sparking urges to play, push limits, or be creative, which then might lead to bonding with other humans, physical exercise, or a sense of mastery, which in turn might make it more likely to experience joy in the future (Fredrickson, 2001). Thus, a plausible working mechanism of positive interventions like the TGT exercise might be the strategic and regular "harvesting" (or "savouring") of the effects of positive emotions that are deliberately elicited through targeted practice.

Another plausible mechanism of action for positive psychology interventions is a subjective shift towards positivity (Seligman et al., 2006). Whilst people with low mood, especially patients with depression, tend to be pre-occupied with the negative experiences of their life, positive psychology practices have been suggested to push this bias more towards positivity (Seligman et al., 2006). For example, rather than ruminating about what went wrong during their day, an individual engaging in the TGT exercise might cultivate the habit of ending their day by focusing on the positive events in their life and their daily achievements (Seligman et al., 2006).

The two mechanisms discussed above are also captured in a more broad mechanistic model suggested by Quoidbach et al. (2015). These authors propose that positive psychology exercises work by engaging different emotion regulation strategies (namely, situation selection, situation modification, attentional deployment, cognitive change, and response modulation) that, although

representing distinct psychological processes, all lead to an increase in positive emotions.

Wellenzohn and colleagues (2016) add to these mechanistic accounts by suggesting that the specific working mechanism of a given positive psychology intervention might depend on the time focus of that intervention, i.e. whether a practice involves thinking about past, present, or future events. They suggest, for example, that exercises that involve reflecting on positive events that lie in the past might work via the re-experience (or "savouring") of positive emotions associated with these events. On the other hand, exercises that elicit thinking about positive events that lie in the future might work by biasing attention towards these events. Finally, exercises that focus on the immediate present might engage both mechanisms.

In addition to this, Lyubomirsky et al. (2013) postulate that a person-activity fit might moderate the effectiveness of positive psychology interventions. In other words, how much benefit a person derives from a given positive psychology intervention might be determined, at least in part, by how well the intervention resonates with their personal interests and values. There is indeed some empirical support for this latter idea. For example, it has been shown that extroverted and introverted individuals benefit differently from different exercises (Schueller, 2012). In addition, Proyer and colleagues (2015) found that indicators of the person-activity fit can predict depression and wellbeing more than three years after the completion of a positive intervention.

Study intervention 3: Pramipexole treatment

Historically, neurochemical theories of depression have been built around the core idea of disturbed serotonin and/or norepinephrine function as the crucial causal factor in the development of depressive disorders (Bunney, 1965; Coppen, 1967; Mulinari, 2012; Schildkraut et al., 1965). However, converging lines of evidence suggest that the dopaminergic system could also play an important pathophysiological role in this context (Belujon and Grace, 2017; Dunlop and Nemeroff, 2007).

For example, several signs and symptoms of depression (e.g. anhedonia, lack of energy, psychomotor retardation, diminished ability to concentrate) represent abnormalities of cognitive processes (e.g. reward processing, motivation, attention) that are known to be influenced by the dopaminergic system (Cowen, 2017a; Dunlop and Nemeroff, 2007). In turn, patients with Parkinson's disease, in whom a dysfunction of dopaminergic signalling is well established, frequently experience depressive symptoms (van der Hoek et al., 2011; Tandberg et al., 1996). Furthermore, neuroscientific studies in humans have associated depression with reduced reward-related neural responses in dopamine-rich brain regions such as the ventral and dorsal striatum (Forbes et al., 2009; Pizzagalli et al., 2009, 2019) and decreased dopamine transporter binding (Meyer et al., 2001; Pizzagalli et al., 2019; Sarchiapone et al., 2006). Additionally, it has been demonstrated that experimental depletion of catecholamines in patients with currently remitted depression can lead to a rapid increase in depressive symptoms (Hasler et al., 2008, 2009; Homan et al., 2015; Pizzagalli et al., 2019). In experimental animal models of depression, such as the learned helplessness model or the chronic mild stress model, abnormalities in the mesolimbic dopamine system have also been reported (Belujon and Grace, 2017), including altered dopamine receptor expression within limbic structures

(Dziedzicka-Wasylewska et al., 1997; Kram et al., 2002) and altered dopamine release in the nucleus accumbens (Di Chiara and Tanda, 1997). Moreover, genetic animal models of depression have been found to show abnormal burst firing patterns of neurons in the ventral tegmental area and, reversely, chemical destruction of these neurons in otherwise healthy rats has been demonstrated to lead to depression-like behavioural changes (Belujon and Grace, 2017; Friedman et al., 2008; Winter et al., 2007).

Taken together, the foregoing observations suggest that altered dopaminergic signalling activity might be implicated in the development of depressive symptoms, at least in a subset of patients. Nevertheless, with the exception of the monoamine oxidase inhibitors and the norepinephrine and dopamine reuptake inhibitor bupropion, currently used antidepressant drugs do not directly target dopamine transmission (Cowen, 2017a). This had led some researchers to explore the utility of dopamine agonists, which are commonly used in the treatment of Parkinson's disease and restless legs syndrome, as a pharmacotherapeutic option in the treatment of depression (Hori and Kunugi, 2013).

One dopamine agonist that has received particular attention in this context is the non-ergoline pramipexole (Cowen, 2017a). This drug is characterised by several important pharmacological qualities. First, it shows selective affinity for the dopamine D2 receptor subfamily (which includes the D2, D3, and D4 receptor) without affinity for dopamine D1 and D5 receptors (Piercey, 1998). It also shows low affinity for α_2 adrenoreceptors but no affinity for any other receptors (e.g. adrenergic, serotonergic, cholinergic, glutaminergic, histaminergic, adenosine and benzodiazepine receptors) (Piercey, 1998). Second, within the dopamine D2 receptor subfamily it shows highest affinity for the D3 receptor (Aiken, 2007; Piercey, 1998), which is found at a particularly high concentration in mesolimbic

dopaminergic regions (Bouthenet et al., 1991; Piercey, 1998). Finally, pramipexole has full intrinsic activity at all of the dopamine D2-like receptors (i.e. D2, D3, and D4) (Piercey, 1998). In particular, pramipexole's preferential binding to the dopamine D3 receptor, which is present in mesolimbic areas implicated in emotion and mood, has been invoked as a theoretical indicator for its potential utility as an antidepressant agent (Piercey, 1998).

To date, only a relatively small number of studies have assessed the efficacy of pramipexole for treating major depressive disorder in humans. A recent meta-analysis summarising the current state of knowledge included 504 participants in total and found a short-term response rate of 52.2% and short-term remission rate of 36.1% and a long-term response rate of 62.1% and long-term remission rate of 39.6% (Tundo et al., 2019). The meta-analysis also showed that in randomised controlled trials, pramipexole treatment was associated with a superior response rate compared to placebo and a similar response rate compared to SSRIs (Tundo et al., 2019).

However, the mean maximum dose used across the studies included in the meta-analysis was 1.62 mg (range 0.69 mg to 2.18 mg) with all except for two studies using doses below 2 mg. This is relevant insofar as a recent case series used relatively high doses of pramipexole (mean > 2.0 mg per day, maximum 5.0 mg per day) in patients with treatment-resistant depression and demonstrated striking clinical results (Fawcett et al., 2016). The series included 24 patients with major depression and 18 with bipolar depression. All included patients were severely treatment-refractory at baseline and each person had failed a minimum of four different treatment steps (eight patients had also shown no response to electroconvulsive therapy). The results of the series were highly impressive, especially given the degree of treatment-resistance in the patients: Out of 42

depressed patients, 20 achieved remission and a further 12 showed a response to pramipexole treatment. Additionally, out of the 10 remaining patients who did not respond, eight had simply been unable to tolerate pramipexole treatment. In those patients where treatment was maintained, only two relapsed (mean time of follow-up was 15 months), which again is highly impressive from a clinical perspective. Whilst it is important to keep in mind that these findings have to be independently replicated in large randomised controlled trials, the series does raise an important point, namely that higher doses than those used in previous studies of pramipexole might be necessary to achieve a considerable antidepressant effect (Cowen, 2017a). This conclusion is also supported by preliminary data from an earlier study, where high-dose pramipexole in patients with depression was associated with the most obvious improvement (but also a significant dropout rate) compared to lower doses of pramipexole or fluoxetine (Corrigan et al., 2000).

Because current research on the use of pramipexole for depression is still in its early days, little is known to date about potential cognitive mechanisms through which the drug could exert antidepressant effects. With particular relevance to this thesis, to the author's knowledge there are currently no data available about the effects of pramipexole treatment on emotional information processing in healthy volunteers or patients with depression. However, because pramipexole treatment has been associated with impulse control problems in patient populations, such as gambling or hypersexuality (Etminan et al., 2017), several studies have explored the drug's effects on reward-related information processing in healthy participants in order to better understand potential mechanisms behind this effect (also see Table 2 for an overview).

On a behavioural level, acute pramipexole treatment has been found to enhance punishment-driven learning (Kanen et al., 2019), decrease biased responding

towards more frequently rewarded stimuli (Pizzagalli et al., 2008), increase the probability of making risky choices in a gambling task following an unexpected high win (Riba et al., 2008), and decrease the preferential consolidation of high-reward memories during sleep (Feld et al., 2014). Furthermore, single-dose pramipexole treatment has been shown to enhance the perceived attractiveness of human faces (Bellucci et al., 2019), decrease decision and motor impulsivity (Ersche et al., 2011a; Yang et al., 2016), increase the tendency to chase large losses in a gambling paradigm (Campbell-Meiklejohn et al., 2011), and more broadly impair cold cognitive performance such as associative learning (Gallant et al., 2016; Hamidovic et al., 2008; Morein-Zamir et al., 2010). In smokers, acute pramipexole challenge also increased reward responsivity (i.e. the tendency to put more effort into rewarded as compared to non-rewarded task conditions) (Freeman et al., 2013). On the neural level, effects of pramipexole treatment have also been reported in healthy volunteers. For example, during the passive receipt of appetitive and aversive taste and visual stimuli, pramipexole-treatment was observed to blunt neural responses (McCabe et al., 2013). Specifically, pramipexole decreased neural activity in response to rewarding stimuli in the ventromedial prefrontal cortex, the orbitofrontal cortex, striatum, thalamus, and dorsal anterior cingulate cortex (McCabe et al., 2013). In addition, the drug also reduced activation to aversive stimuli in the dorsal anterior cingulate cortex (McCabe et al., 2013). However, these neural changes were not associated with behavioural effects (McCabe et al., 2013). A single dose of pramipexole has also been reported to lead to increased activity of the nucleus accumbens, enhanced interaction between the nucleus accumbens and the anterior insula, and weakened interaction between the nucleus accumbens and the prefrontal cortex during the anticipation of rewards (Ye et al., 2011) and to

decreased activation in the rostral basal ganglia and midbrain in response to unexpected high rewards (Riba et al., 2008).

As with clinical effects, when assessing cognitive effects of pramipexole in humans it is crucial to take into consideration both the length of treatment and the specific dose used. This is because neurochemical effects might vary depending on these parameters. For example, due to presence of pre-synaptic dopamine D2 autoreceptors, relatively low doses of pramipexole might decrease dopamine transmission whilst higher doses might enhance it (Martins et al., 2017). In addition, short-term and long-term treatment might give rise to different cognitive changes due to secondary adaptive effects on receptors (e.g. changes in receptor sensitivity and expression) (Chernoloz et al., 2009, 2012; Martins et al., 2017; Newton et al., 2015; Tokunaga et al., 2012). To the author's knowledge, all current studies assessing cognitive effects of pramipexole in healthy volunteers have only used acute pramipexole challenges employing comparatively low doses (also see Table 2). Unfortunately, this means that their results are of limited relevance when it comes to understanding potential working mechanisms through which pramipexole could decrease depressive symptoms, since such clinical effects are generally observed at higher doses (and after longer treatment) (Fawcett et al., 2016; Tundo et al., 2019).

However, there are also a few studies available that have assessed cognitive effects following longer treatment with pramipexole at higher doses in psychiatric patients.[3] For example, one study in patients with cocaine use disorder found that subacute pramipexole treatment with doses titrated up to 3.0 mg significantly

[3] Such cognitive studies have also been conducted in patients with Parkinson's disease or restless legs syndrome, (see e.g. Costa et al. (2009), Nagy et al. (2012), Bayard et al. (2013), Shepherd et al. (2013), Galbiati et al. (2015)). However, since these populations have pronounced dopaminergic abnormalities, the observed effects of pramipexole are not informative for our purposes and therefore are not reported here.

increased the positive subjective effects of cocaine consumption (Newton et al., 2015). This effect might thus indicate that pramipexole treatment can increase the hedonic experience of rewards — a potential cognitive mechanism that could explain its clinical effects in depression. Furthermore, in euthymic bipolar patients, 8-week long pramipexole treatment led to impaired performance in the Iowa Gambling Task (Burdick et al., 2014). Specifically, patients exhibited a tendency to make high-risk, high-reward choices and to attend more readily to feedback related to gains than to losses, which might also reflect a positive (albeit maladaptive) bias when navigating the task (Burdick et al., 2014).

Summary of Chapter 1

This chapter provided the necessary theoretical background for the individual studies that will be presented in the remainder of this thesis. First, a structured overview of the work that will be discussed was given. Next, the cognitive neuropsychological model of antidepressant treatment action (CONEMATA) was introduced as a contemporary mechanistic framework to explain how antidepressant treatments bring about their clinical effects and why they show a time lag before alleviating depressive symptoms. It was shown how the CONEMATA conceptualises the development and maintenance of depressive symptoms, how it explains the clinical effects of antidepressant interventions, and what empirical evidence there is to support its core ideas. Finally, three potential novel antidepressant interventions — namely, bright light treatment, practising positive psychology, and administration of the dopamine D2/D3 receptor-preferring agonist pramipexole — were introduced. It was highlighted that, for each of these treatments, there is preliminary and promising evidence that supports their clinical efficacy. However, it was also discussed that there is currently scant

data on potential mechanisms through which these interventions might bring about their effects — especially with regards to potential effects on hot cognition.

The remainder of this thesis will now be dedicated to exploring such potential cognitive mechanisms for each of the three treatments through the lens of the CONEMATA.

Table 2: Overview of reported cognitive effects of pramipexole treatment in healthy volunteers.

Study	Cognitive process	Effects of pramipexole in healthy volunteers	Treatment duration (dose)	Comments
Kanen et al. (2019)	Probabilistic reversal learning	↑ punishment-driven learning	Single dose (0.5 mg)	Additional use of domperidone
Bellucci et al. (2019)	Face evaluation	↑ perceived facial attractiveness	Single dose (0.5 mg)	Additional use of domperidone; only female participants
Murray et al. (2019)	Probabilistic outcome learning	↓ reaction time in reward trials	Single dose (0.5 mg)	Additional use of domperidone
Yang et al. (2016)	Motor impulsivity	↑ motor impulse control	Single dose (0.5 mg)	-
Gallant et al. (2016)	Learning of stimulus-response associations Subjective alertness	↓ stimulus-response learning ↓ subjective alertness	Single dose (0.5 mg)	-
Feld et al. (2014)	Reward-related memory consolidation	↓ preferential consolidation of high-reward contingencies ↑ time spent in sleep stages 1 and 2 ↓ time spent in sleep stages 3 and 4	Single dose (0.5 mg)	Additional use of domperidone; only male participants
McCabe et al. (2009)	Neural processing of rewarding and aversive taste stimuli	↓ neural activation in response to rewarding stimuli in ventromedial prefrontal cortex, orbitofrontal cortex, striatum, thalamus, and dorsal anterior cingulate cortex ↓ neural activation in response to aversive stimuli in dorsal anterior cingulate cortex	Single dose (0.25 mg)	-
Drijgers et al. (2012)	Subjective state	↑ anger, fatigue, tension, vigor	Single dose (0.5 mg)	-
Ersche et al. (2011a)	Probabilistic reversal learning	↓ neural activation during a probabilistic reversal learning task in right superior parietal gyrus	Single dose (0.5 mg)	Additional use of domperidone
Ye et al. (2011)	Reward anticipation	↑ neural activity of the nucleus accumbens during anticipation of reward	Single dose (0.5 mg)	Additional use of domperidone

		↑ functional interaction between the nucleus accumbens and the anterior insula during anticipation of reward ↓ functional interaction between nucleus accumbens and prefrontal cortex		
Ersche et al. (2011b)	Decision-making	↓ impulsivity in an information sampling task	Single dose (0.5 mg)	Additional use of domperidone
Campbell-Meiklejohn et al. (2011)	Decision-making (loss chasing) Affect	↑ value of losses chased ↓ value of losses surrendered ↓ positive affect	Single dose (0.25 mg)	-
Morein-Zamir et al. (2010)	Paired-associates learning Rapid visual information processing Subjective alertness	↓ association learning ↓ sustained attention ↓ alertness	Single dose (0.5 mg)	Additional use of domperidone
Santesso et al. (2008)	Probabilistic reward learning	↑ feedback-related negativity ↓ activity in response to reward-feedback in dorsal anterior cingulate regions ↑ activity in response to reward-feedback in medial prefrontal cortex regions	Single dose (0.5 mg)	-
Riba et al. (2008)	Decision-making	↑ probability of risky choices following unexpected high wins ↓ neural activation of the rostral basal ganglia and midbrain in response to unexpected high wins	Single dose (0.5 mg)	Additional use of domperidone
Hamidovic et al. (2008)	Cold cognitive performance Subjective state	↑ simple reaction times and procedural reaction times (= ↓ cognitive performance)	Single dose (two conditions: 0.25 mg and 0.5 mg)	-

		↑ euphoria, intellectual efficiency, energy, vigor, positive mood ↑ subjective sedation		
Pizzagalli et al. (2008)	Probabilistic reward learning	↓ response bias towards more frequently rewarded stimulus ↓ probability of using a "win-stay" strategy ↓ accuracy for the more frequently rewarded stimulus ↑ accuracy for less frequently rewarded stimulus ↓ motor speed	Single dose (0.5 mg)	-
Samuels et al. (2007)	Subjective alertness Subjective state	↓ subjective alertness ↓ subjective contentedness	Single dose (0.5 mg)	Pramipexole alone and in combination with domperidone assessed
Samuels et al. (2006a)	Behavioural sleepiness Subjective alertness Subjective state	↑ behavioural sleepiness ↓ subjective alertness ↓ subjective contentedness	Single dose (0.5 mg)	-
Samuels et al. (2006b)	Behavioural sleepiness Subjective alertness Subjective state	↑ behavioural sleepiness ↓ subjective alertness ↓ subjective contentedness	Single dose (0.5 mg)	-

Chapter 2: Assessing potential effects of acute bright light treatment on emotional information processing

Introduction

The first intervention studied in this thesis is bright light treatment (BLT). As described in greater detail in Chapter 1, BLT is a non-pharmacological therapeutic modality whereby a patient is exposed to white light at a relatively high intensity in order to mimic conditions of increased sunlight exposure. Although BLT was originally developed as a means for treating seasonal affective disorder (Rosenthal et al., 1984), it has more recently also been reported to be efficacious in non-seasonal depression (Al-Karawi and Jubair, 2016; Golden et al., 2005; Lam et al., 2016; Lieverse et al., 2011; Tuunainen et al., 2004; Zhao et al., 2018).

Despite having considerable advantages compared to conventional antidepressant drugs (e.g. a more favourable side effect profile, more rapid clinical responses, no means of overdosing (Oldham and Ciraulo, 2014); also see Table 1), BLT has received relatively little attention in the neuroscientific community. As a result, the mechanisms through which it exerts it clinical effects are not well understood to date.

Both human and rodent studies suggest that different forms of light exposure can directly and immediately influence cognitive processes, including neural activity during the processing of negative emotional cues (Fisher et al., 2014; LeGates et al., 2014; Vandewalle et al., 2009, 2010, 2011). However, no study to date has explored the effects of BLT on positive *versus* negative emotional stimuli and therefore it is currently not known whether bright light treatment could have valence-specific effects such as those described by the CONEMATA.

The aim of the study reported in this chapter, was to test this hypothesis. Drawing on an established experimental medicine assay (Browning et al., 2007; Cooper et al.,

2015, 2018; Harmer et al., 2003a, 2004, 2009b; Murphy et al., 2008; Pringle et al., 2012; Schmidt et al., 2015; Warren et al., 2019), we explored the effects of a single dose of BLT on the processing of positive and negative stimuli across different cognitive domains. We hypothesised that BLT would parallel the effects of common antidepressant drugs, that is, induce a positive bias in behavioural measures of emotional information processing across different cognitive domains but without necessarily affecting self-reported subjective state.

Material and methods

Study sample

Fifty healthy volunteers were recruited via online and print announcements. The sample size was based on previous experimental medicine studies using a comparable design and the same outcome measures (Browning et al., 2007, 2011; Cooper et al., 2015, 2018; Harmer et al., 2003a, 2004, 2009b, 2012; Murphy et al., 2008; Pringle et al., 2012; Schmidt et al., 2015; Warren et al., 2019) and in addition was increased to the maximum number of participants that could be feasibly recruited within the dedicated study period. One participant was excluded from the final analysis because of prior experience with the Oxford Emotional Test Battery. Thus, the final sample consisted of 49 participants (26 female, 23 male), aged 18 to 65 years (see Table 4 for basic demographic and psychological characteristics). All participants were mentally and physically healthy as assessed by a structured psychiatric interview (SCID-5) (First et al., 2015) and a general medical interview conducted during a screening visit prior to the experimental session. Basic psychological characteristics that were assessed included personality (using the Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975)), estimated intelligence (using the Spot-the-Word Test (Baddeley and Crawford, 2012)), trait anxiety (using the State-Trait Anxiety Inventory (Spielberger et al., 1983)), and

depressive symptoms (using the Beck Depression Inventory (Beck et al., 1996)). Only volunteers who did not fulfil any of the pre-specified exclusion criteria (see Table 3) were included in the study. The study was approved by the local ethics board and all participants gave written informed consent prior to inclusion.

Table 3: Exclusion criteria for the bright light study.

Exclusion criteria
1. Any current or past major psychiatric disorder
2. Any first-degree relative with a diagnosis of schizophrenia-spectrum or other psychotic disorder, bipolar disorder, or depressive disorder
3. Any severe medical condition not stabilized at the time of the experiment (e.g. cardiac disease)
4. Any condition precluding treatment with bright light (e.g. retinal disorder)
5. Any current or past major physical illness that has the potential to significantly affect mental functioning (e.g. Parkinson's disease)
6. Pregnant, lactating, or sexually active female who does not use a medically accepted method of contraception
7. Any history of seizures or any condition with the potential to manifest with seizures
8. Diagnosis of diabetes (risk of retinal disorder)
9. Current intake of medication that has a significant potential to affect mental functioning, or intake of such medication in the previous 3 months (e.g. antidepressants, neuroleptics, sedatives)
10. Any intake of recreational drugs in the last 3 months prior to the experiment
11. Excessive alcohol consumption up to 3 days before the experiment
12. Previous use of bright light treatment or negative ion treatment
13. Participant usually (more than 5 days a week) wakes up later than 10.00 a.m.
14. Necessity to wear tinted glasses
15. Any kind of sun exposure in the last month that would be expected to be unusually high compared to local conditions (e.g. beach vacation, skiing holidays)
16. Researcher's decision to exclude a participant for any other reason (e.g. participation could be harmful to a participant, participant does not properly interact with the researchers at screening, participant has previous experience with Oxford Emotional Test Battery)

Table 4: Basic demographic and psychological characteristics of 49 healthy volunteers randomly allocated to 60-minute long double-blind treatment with either bright light or sham-placebo. Values represent group means with standard deviations in parenthesis.

	Bright light (n = 25, 14 female)	**Sham-placebo (n = 24, 12 female)**
Age in years	24.7 (8.1)	28.6 (12.0)
Years in full-time education	17.2 (2.1)	17.8 (1.9)
IQ estimate (Spot-the-word Test)	107.8 (8.9)	113.8 (7.6)
Self-reported estimate of hours outside on a typical day	2.6 (1.1)	3.0 (1.7)
Neuroticism (Eysenck Personality Questionnaire)	6.0 (4.8)	6.0 (4.5)
Psychoticism (Eysenck Personality Questionnaire)	2.4 (1.7)	2.5 (2.0)
Extraversion (Eysenck Personality Questionnaire)	15.2 (4.3)	13.2 (4.6)
Lie (Eysenck Personality Questionnaire)	9.6 (4.2)	9.4 (4.5)
Depressive symptoms (Beck Depression Inventory)	4.2 (4.5)	3.7 (3.8)
Trait Anxiety (State-Trait Anxiety Inventory)	34.1 (8.6)	36.4 (10.0)

Experimental session

Testing took place in Oxford (United Kingdom) between November and March, when sunlight exposure is typically low, and symptoms of seasonal affective disorder would become apparent in susceptible patients. All participants were instructed to arrive for the experimental session no later than one hour after their usual wake-up time. For female participants, testing during the pre-menstrual week was avoided, as is common practice when using this assay for the assessment of acute interventions (Browning et al., 2011; Murphy et al., 2008, 2019). Participants completed a range of questionnaires to assess subjective state prior to treatment. Following that, they were randomly allocated to 60-minute long treatment with either bright light or sham-placebo in a double-blind design. Immediately following treatment, participants completed the same subjective state questionnaires that had been administered prior to treatment and were also asked about their expectations regarding the effects of the treatment they had received. Subsequently, they completed the Oxford Emotional Test Battery to assess emotional information processing.

Treatments

Bright light treatment was applied using a Litepod Company Diamond 5 SAD Light which emits full-spectrum white light with a rated output of 10,000 lux at 55 cm distance. Sham-placebo treatment was based on a previously established protocol in which participants are told at the outset of the study that the aim of the trial is to compare two effective antidepressant interventions — bright light treatment and negative ion treatment — but that half of all participants would receive inactive placebo treatment (Lam et al., 2016). In reality, BLT always served as the active treatment and the alleged negative ion treatment always served as the placebo. Our sham negative ion treatment device was a Bionaire air purifier that produced an

audible hum and very mild air blow but that was deactivated so that it did not emit negative ions.

Subjective state assessment

Subjective state was assessed before treatment and immediately thereafter using the following questionnaires: Befindlichkeitsskala (BFS) (van Zerssen et al., 1974), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), and visual analogue scales (VAS) of subjectively experienced emotions (for two participants no suitable visual analogue scale measurements are available).

Assessment of emotional information processing: The Oxford Emotional Test Battery

The Oxford Emotional Test Battery (ETB) is a validated and widely used set of five largely computerised behavioural tasks that allow researchers to assess the processing of emotional information in different cognitive domains. The tasks it includes have been shown repeatedly to be sensitive to acute challenge with conventional antidepressant medications as well as some non-pharmacological biological treatments (Warren et al., 2015). Participants complete the tasks in the order described below.

Facial expression recognition task (FERT)

Participants are presented with pictures of human facial expressions of emotions. Each face displays one of six basic emotions (anger, disgust, fear, happiness, sadness, or surprise). Each emotional expression is presented at different levels of intensity (10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%), which have been created by combining shape and texture features of the two extremes "neutral" (i.e. 0%) and "full prototypical emotion" (i.e. 100%) to varying degrees (based on a previously described procedure by Young et al. (1997)). In total, 4 examples of each

emotion at each intensity level are presented. Emotions are displayed by 10 different individuals overall and for each of the 10 individuals a neutral facial expression is presented as well. Thus, 250 stimulus presentations (6 emotions × 10 intensities × 4 examples + 10 neutral faces) are used in total. Facial expressions are presented in random order on a computer screen for approximately 500 milliseconds each, followed by a blank black screen. Participants are instructed to correctly classify each facial expression as quickly and as accurately as possible. Responses are made by pushing one out of seven labelled buttons on a button box. Main outcomes of interest are hit rate, false alarm rate, non-identification rate, and median reaction time for correct classifications.

Emotional categorisation task (ECAT)

Participants are presented with positive and negative personality descriptors and are asked to correctly classify the valence of each word. In total, 60 words describing either extremely agreeable/positive characteristics (e.g. "cheerful", "honest", "optimistic") or extremely disagreeable/negative characteristics (e.g. "domineering", "untidy", "hostile") are presented individually in the centre of the screen for approximately 500 milliseconds each. Positive and negative words have been chosen to be comparable with regards to frequency, length, and meaningfulness (Harmer et al., 2004) and are presented in the task in random order. Participants are instructed to imagine themselves overhearing someone describing them with each of the words and to indicate as quickly and accurately as possible whether they would like or dislike to be described with each of the words. Responses are made by pressing correspondingly labelled buttons on a button box. The main outcome of interest is the median reaction time for correct classifications.

Emotional faces dot probe task (FDOT)

Vigilance to emotional stimuli is assessed by comparing behavioural responses to a probe replacing a positive, negative, or neutral emotional cue. Each trial starts with the presentation of a fixation cross in the centre of the screen. This is followed by the presentation of a pair of pictures of facial expressions (neutral & neutral, neutral & fearful, or neutral & happy). One face appears above and the other one below the fixation cross. After approximately 100 milliseconds, both faces disappear and two dots in either vertical (:) or horizontal (..) orientation appear behind one of the faces. Participants are asked to indicate as quickly and as accurately as possible which orientation the dots are in. Half of all trials are masked, i.e. faces are presented on the screen for approximately 16 milliseconds and are then replaced by a jumbled face for approximately 84 milliseconds. The other half of trials are unmasked with faces simply being presented on the screen for approximately 100 milliseconds. For neutral-emotional pairs, the emotional expression appears equally often on top and below the fixation cross, and the probe appears equally often behind the emotional and behind the neutral face. In total, the task consists of 192 trials (32 happy & neutral, 32 fearful & neutral, 32 neutral & neutral, once masked and once unmasked). The main outcome of interest is the vigilance score for emotional stimuli. Vigilance scores are calculated for emotional pairs by subtracting median reaction times in congruent trials (i.e. the probe appears behind the emotional expression) from those in incongruent trials (i.e. the probe appears behind the neutral expression). If a participant shows for example an attentional bias *towards* positive emotional information, one would expect that, when presented with a happy & neutral face pair, they will identify the probe in congruent trials (probe in position of the positive face) faster than in incongruent trials (probe in position of

the neutral expression), thus resulting in a vigilance score for positive information greater than 0.

Emotional recall task (EREC)

Following a distraction period (approximately 15 minutes of engagement in the FDOT), subjects are asked to recall as many words as possible from the emotional categorisation task. They are given 4 minutes to write down as many words as they can. Main outcomes of interest are numbers of correctly and incorrectly recalled words.

Emotional recognition task (EMEM)

Following the EREC, participants are presented with positive and negative personality descriptors on the computer screen and are asked to indicate for each word whether they have encountered it in the ECAT completed previously. All 60 personality characteristics featured in the categorisation task as well as 60 novel distractor words (equal frequency of positive and negative words) are presented in random order in the centre of the screen, each for approximately 500 milliseconds. Participants are asked to indicate as quickly and as accurately as possible for each word whether they have encountered it in the previous task. Main outcomes of interest are hit rate, false alarm rate and median reaction time for correct classifications.

Assessment of subjective expectations with regards to treatment effects

Due to the nature of treatment administration, creating a suitable placebo condition for light treatment is challenging and this problem constitutes one of the biggest limitations in the BLT literature (Pail et al., 2011). The sham-placebo protocol we employed here has previously been established as a suitable placebo condition in patients with depressive disorders (Desan et al., 2007; Eastman et al., 1998; Lam et

al., 2016). In addition to that, the ETB has been shown to be robust to acute placebo effects in healthy volunteers (Huneke et al., 2017). Nevertheless, due to the ready availability of the information we chose to also explicitly assess and compare participants' expectations of their respective treatment. To do so, participants were presented with three separate statements about possible treatment effects: (1) "*I believe that the treatment I have just undergone will influence my mood or emotions in a positive way or make me feel happier*", (2) "*I believe that the treatment I have just undergone will influence my mood or emotions in a negative way or make me feel less happy*", and (3) "*I believe that the treatment I have just undergone can in general influence a person's emotions or mood (either positively or negatively)*". Participants were asked to indicate how much they agree with each of the statements on a 5-level Likert scale ranging from "Strongly Disagree" (-2) to "Strongly Agree" (2).

Statistical analysis

Analyses were conducted in IBM SPSS (version 25.0) and R (version 3.5.3) using RStudio and the "tidyverse" package as well as "afex", "WRS2", and "coin".

Subjective state measures were compared between treatment groups using one-way ANCOVAs with post-treatment score as dependent variable, group as independent variable, and pre-treatment score as covariate. Performance of treatment groups in the ETB was compared using two-way mixed ANOVAs. Treatment group served as between-subjects factor and emotion/valence served as within-subjects factor. Where the assumption of sphericity was broken, Greenhouse-Geisser correction was used. In order to corroborate findings, a robust mixed-design ANOVA based on the 20% trimmed mean was conducted as well (Field and Wilcox, 2017; Field et al., 2012). In cases where conclusions from the standard ANOVA and the robust ANOVA differed, another robust mixed-design comparison based on an M-estimator (modified one-step estimator of location

based on Huber's Psi) in combination with a bootstrap (2000 bootstrap samples) was used for clarification (Field and Wilcox, 2017; Field et al., 2012). For the analysis of the neutral face condition in the FERT, groups were compared using standard independent t-tests and a robust equivalent based on the 20% trimmed mean (Field and Wilcox, 2017; Field et al., 2012). Beliefs about treatment effects were compared between treatment groups using exact Wilcoxon-Mann-Whitney tests.

Table 5: Subjective state before and after bright light or sham-placebo treatment. Values represent means with standard deviations in parentheses.

	Bright light		**Sham-placebo**		
	Baseline	**After treatment**	**Baseline**	**After treatment**	**ANCOVA results**
BFS	17.5 (13.7)	12.1 (16.2)	24.5 (18.9)	18.5 (16.0)	$F(1,46) = 0.2$, $p = 0.67$
STAI state	31.2 (8.1)	29.6 (7.4)	34.8 (11.2)	31.9 (7.4)	$F(1,46) = 0.1$, $p = 0.82$
PANAS positive	32.6 (8.6)	33.1 (8.5)	27.6 (9.8)	27.9 (9.3)	$F(1,46) = 0.6$, $p = 0.44$
PANAS negative	12.5 (2.5)	12.3 (2.6)	12.9 (4.0)	12.0 (2.6)	$F(1,46) = 1.0$, $p = 0.33$
VAS anxious	18.2 (20.3)	17.4 (21.7)	16.5 (23.5)	9.4 (16.5)	$F(1,44) = 2.0$, $p = 0.16$
VAS alert	61.8 (22.6)	62.1 (26.5)	53.8 (24.5)	47.5 (29.7)	$F(1,44) = 1.3$, $p = 0.26$
VAS happy	70.0 (18.3)	72.6 (18.1)	58.8 (20.7)	65.5 (16.4)	$F(1,44) < 0.001$, $p = 0.98$
VAS sad	16.9 (20.7)	10.2 (11.6)	15.7 (22.0)	11.1 (13.9)	$F(1,44) = 0.3$, $p = 0.60$
VAS angry	7.2 (6.1)	5.4 (4.4)	9.0 (17.8)	4.8 (4.2)	$F(1,44) = 0.4$, $p = 0.53$
VAS disgusted	4.5 (5.9)	3.6 (3.9)	6.0 (11.3)	2.4 (2.0)	$F(1,43) = 1.6$, $p = 0.21$ (excluding one outlier)
VAS afraid	8.9 (10.5)	5.5 (7.5)	9.9 (18.7)	6.2 (13.3)	$F(1,44) < 0.001$, $p = 0.98$

Results

Did bright light treatment affect subjective state?

As expected, when adjusted for pre-treatment scores, subjective state measures did not differ between groups after treatment ($p > 0.05$ for all measures). Details on subjective state before and after treatment can be found in Table 5.

Did bright light treatment affect emotional information processing?

Facial expression recognition task (FERT)

Analysis of FERT hit rates (= pre-specified primary outcome) suggested that there was no significant main effect of treatment ($F(1,47) = 0.8$, $p = 0.37$) and no significant treatment × emotion interaction ($F(3.1,144.8) = 0.4$, $p = 0.73$) (also see Figure 1). Likewise, for FERT false alarm rates there was no significant main effect of treatment ($F(1,47) = 0.1$, $p = 0.81$) and no significant treatment × emotion interaction ($F(3.9,180.9) = 1.0$, $p = 0.42$). For FERT non-identification rates, there was also no significant main effect of treatment ($F(1,47) = 0.9$, $p = 0.35$) but there was a significant treatment × emotion interaction ($F(3.8,178.1) = 3.1$, $p = 0.02$). However, this interaction was not significant in either of the robust analyses ($p = 0.30$ and $p = 0.81$, respectively) and was likely a false positive due to violation of distributional assumptions. For FERT reaction times, there was no significant main effect of treatment ($F(1,47) = 0.9$, $p = 0.36$) and no significant treatment × emotion interaction ($F(1.9,90.5) = 0.6$, $p = 0.52$). Hit rates ($t(47) = -0.9$, $p = 0.37$) and reaction times ($t(47) = -0.3$, $p = 0.76$) for neutral faces also did not differ between treatment groups. Except for the aforementioned discrepancy in the non-identification rate, standard and robust analyses led to the same conclusion.[4] Also see Table 6.

[4] As an alternative approach, we also compared groups on signal detection theory measures (target sensitivity and response bias, calculated following Grier (1971)). This analysis also did not find a significant main effect of treatment or a treatment × emotion interaction.

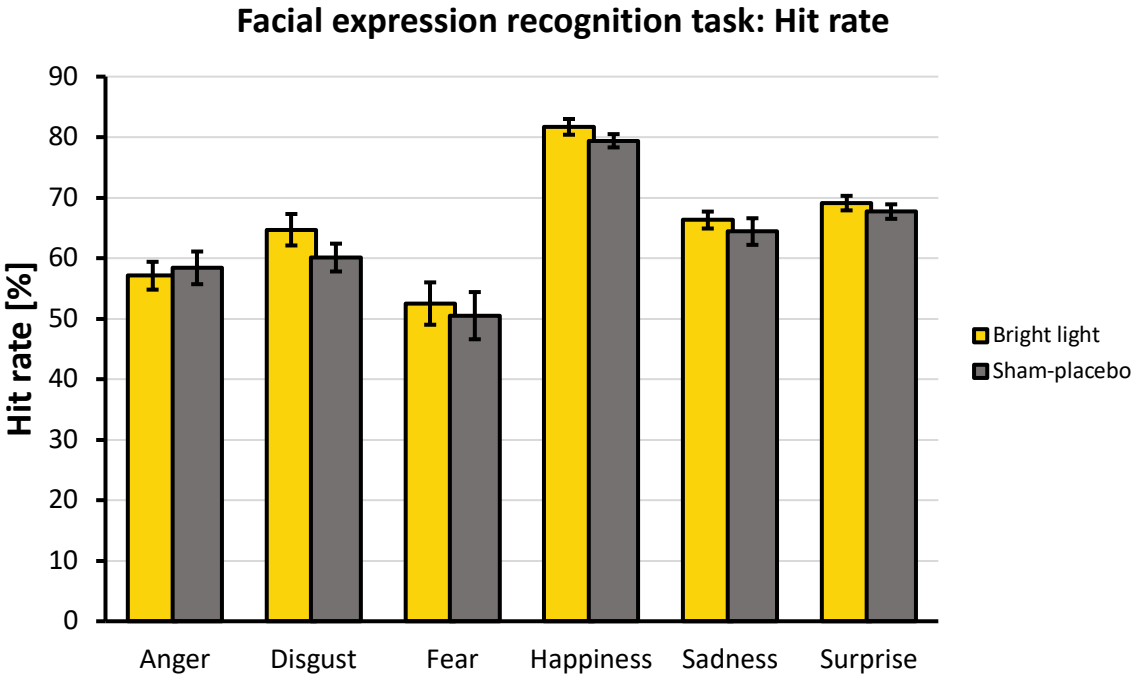


Figure 1: Comparison of hit rates for different emotions in the facial expression recognition task. Bars represent means, error bars represent standard errors.

Emotional categorisation task (ECAT)

Engagement in the task was appropriate, as indicated by median hit rates > 90% in both treatment groups. Analysis of ECAT reaction times suggested that there was no significant main effect of treatment ($F(1,47) = 0.4$, $p = 0.54$) and no significant treatment × valence interaction ($F(1,47) = 0.7$, $p = 0.39$). Standard and robust analyses led to the same conclusion. Also see Table 6.

Faces dot probe task (FDOT)

Engagement in the task was appropriate, as indicated by median hit rates > 90% in both treatment groups. Analyses of FDOT vigilance scores were performed separately for the masked and unmasked condition. In the masked condition, there was no main effect of treatment ($F(1,47) = 0.1$, $p = 0.80$) and no treatment × valence interaction ($F(1,47) = 0.03$, $p = 0.86$). Likewise, in the unmasked condition, there was also no main effect of treatment ($F(1,47) = 2.6$, $p = 0.12$) and no treatment × valence interaction ($F(1,47) = 2.0$, $p = 0.16$). Standard and robust analyses led to the same conclusion. Also see Table 6.

Emotional recall task (EREC)

With regards to the number of words correctly recalled, there was no main effect of treatment ($F(1,47) = 1.1$, $p = 0.30$) and no significant treatment × valence interaction ($F(1,47) = 0.04$, $p = 0.84$). With regards to the number of words incorrectly recalled, there was also no main effect of treatment ($F(1,47) = 0.001$, $p = 0.97$) and no treatment × valence interaction ($F(1,47) = 0.03$, $p = 0.85$). Standard and robust analyses led to the same conclusion. Also see Table 6.

Table 6: Performance in the Oxford Emotional Test Battery. Values represent means with standard deviations in parentheses.

	Bright light	**Sham-placebo**
Facial expression recognition task		
Hit rate [%]		
Anger	57.1 (11.3)	58.4 (13.2)
Disgust	64.7 (12.9)	60.1 (11.0)
Fear	52.5 (17.6)	50.5 (19.3)
Happiness	81.7 (6.7)	79.4 (5.6)
Sadness	66.3 (6.9)	64.4 (10.7)
Surprise	69.1 (5.8)	67.7 (5.9)
Neutral	80.0 (12.9)	83.3 (13.1)
False alarm rate [%]		
Anger	2.1 (2.0)	2.2 (1.9)
Disgust	2.0 (1.8)	3.1 (2.9)
Fear	1.3 (1.3)	1.3 (1.7)
Happiness	0.6 (0.7)	0.5 (0.7)
Sadness	3.1 (2.2)	2.6 (3.1)
Surprise	3.0 (2.6)	2.9 (2.6)
Non-identification rate [%]		
Anger	34.2 (7.7)	31.5 (9.0)
Disgust	21.7 (5.3)	25.3 (6.4)
Fear	22.0 (4.2)	22.6 (5.1)
Happiness	15.1 (5.8)	17.8 (3.3)
Sadness	31.5 (7.0)	32.1 (8.3)
Surprise	25.4 (4.9)	28.2 (6.1)
Reaction time [ms]		
Anger	1422.1 (309.4)	1495.3 (338.6)
Disgust	1480.6 (405.8)	1526.6 (276.3)
Fear	1877.3 (467.0)	2071.7 (835.3)
Happiness	1177.5 (234.9)	1181.7 (168.2)
Sadness	1220.6 (232.4)	1275.3 (154.8)
Surprise	1260.3 (243.9)	1289.5 (185.7)
Neutral	1204.8 (310.9)	1230.0 (250.3)
Emotional categorisation task		
Reaction time [ms]		
Positive	843.1 (169.6)	828.8 (133.3)
Negative	943.6 (191.4)	902.3 (170.5)
Faces dot probe task		
Vigilance bias score [ms]		
Masked positive	-9.7 (41.3)	-6.0 (32.9)
Masked negative	1.3 (48.3)	2.1 (46.6)
Unmasked positive	-4.3 (39.0)	19.6 (40.1)
Unmasked negative	6.1 (38.1)	8.2 (39.2)
Emotional recall task		
Hits [n correct]		
Positive	6.0 (3.1)	5.2 (3.1)
Negative	5.5 (3.3)	4.6 (2.6)
Intrusions [n wrong]		
Positive	2.3 (1.8)	2.3 (2.0)
Negative	1.5 (1.9)	1.5 (2.3)
Emotional recognition task		
Hit rate [%]		
Positive	83.6 (9.4)	85.8 (13.8)
Negative	72.1 (14.8)	73.1 (16.0)
False alarm rate [%]		
Positive	26.5 (14.9)	23.5 (16.5)
Negative	14.1 (8.9)	16.5 (11.7)
Reaction time [ms]		
Positive	904.7 (190.1)	938.0 (175.3)
Negative	1025.8 (195.7)	1072.5 (221.5)

Emotional recognition task (EMEM)

Analysis of EMEM hit rates suggested there was no significant main effect of treatment ($F(1,47) = 0.2$, $p = 0.65$) and no significant treatment × valence interaction ($F(1,47) = 0.1$, $p = 0.72$). Analysis of EMEM false alarm rates also showed no main effect of treatment ($F(1,47) = 0.01$, $p = 0.92$) and no treatment × valence interaction ($F(1,47) = 2.2$, $p = 0.15$). The same pattern was also observed for reaction times for correctly recalled words: no main effect of treatment ($F(1,47) = 0.6$, $p = 0.46$), and no treatment × valence interaction ($F(1,47) = 0.2$, $p = 0.68$). Standard and robust analyses led to the same conclusion. Also see Table 6.

Did the sham-placebo treatment elicit similar beliefs about treatment effects as BLT in healthy volunteers?

Comparisons of participants' expectations yielded a significant difference between treatment groups for expectations of a general treatment effect ("*I believe that the treatment I have just undergone can in general influence a person's emotions or mood (either positively or negatively*"), $Z = 2.4$, $p = 0.02$). However, there were no significant differences between treatment groups when the direction of expected effects was explicitly specified as positive ($Z = 1.5$, $p = 0.12$) or negative ($Z = 0.6$, $p = 0.57$). Participants in the bright light group showed stronger expectations of a general effect on mood/emotion than participants in the sham-placebo group (see Figure 2).[5]

[5] Although the Oxford ETB has previously been shown to be robust against placebo effects (Huneke et al., 2017), all standard analyses were repeated with expectations of a general effect included as a covariate in order to rule out any confounding effects. This led to the same overall conclusions as reported above.

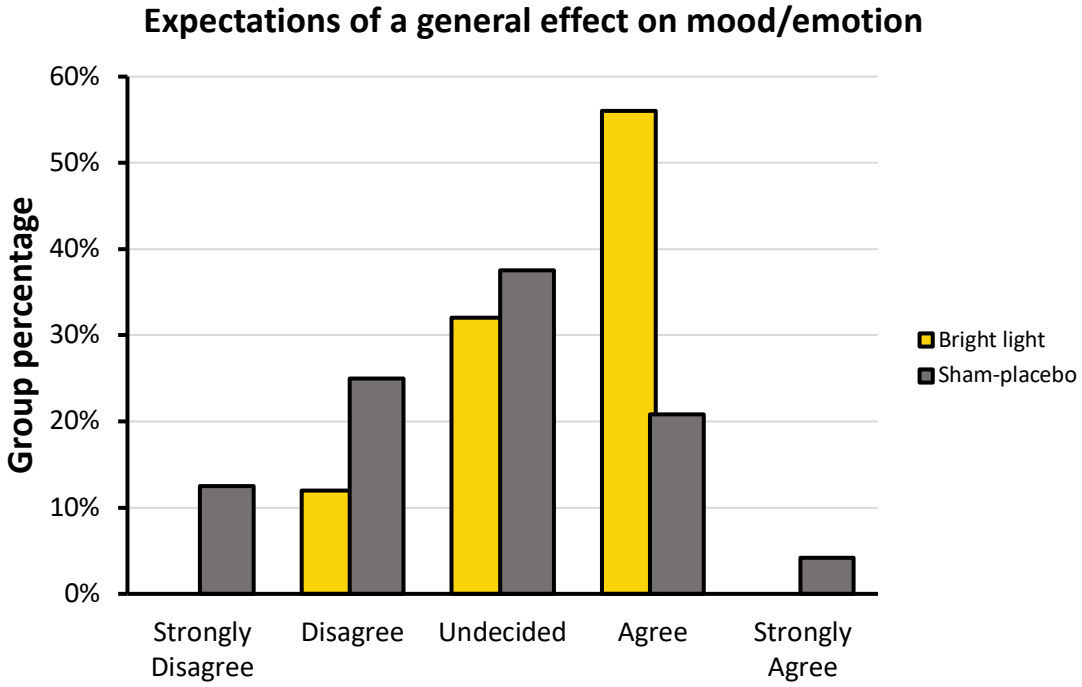


Figure 2: Comparison of participants' expectations concerning a general (i.e. unspecified) effect of the assigned treatment on mood/emotion ("I believe that the treatment I have just undergone can in general influence a person's emotions or mood (either positively or negatively)").

Discussion

In this chapter, we used an established experimental medicine assay to explore whether acute treatment with bright light can influence emotional information processing in line with the predictions of the CONEMATA. In brief, we did not find any conclusive evidence for such an effect.

Finding 1: BLT showed no acute effect on subjective state

As predicted, changes in self-reported subjective state did not differ between treatment groups. This is consistent with previous similar studies using conventional antidepressant drugs and comparable sample sizes, which generally also do not show clear-cut acute effects on subjective state in healthy volunteers (Browning et al., 2007; Capitão et al., 2019; Harmer et al., 2003c, 2003a; Murphy et al., 2009; Walsh et al., 2018b). However, in contrast to antidepressant drugs, BLT devices are frequently marketed to the general population as exerting various positive effects on mood and well-being, a claim resonating well with the common intuition that being exposed to sunlight makes one feel good. At least with regards to *acute effects,* our results provide reason to evaluate these claims critically and suggest that the utility of BLT for healthy people should be properly evaluated in large randomised placebo-controlled trials.

Finding 2: Acute BLT had no effect on emotional information processing

In contrast to our predictions, and to what has been previously observed for different antidepressant drugs as well as some non-drug treatments, there was no conclusive evidence for an immediate valence-specific effect of BLT on emotional information processing in any cognitive domain. Whilst this result is preliminary and has to be replicated by future research, it might suggest that, at least on the cognitive level, BLT exerts its clinical effects via a different mechanism than many antidepressant drugs and that its clinical effects might therefore not be explainable

within the theoretical framework of the CONEMATA. Of note, this idea might also be supported by the fact that BLT and common antidepressant drugs differ significantly in their side effect profiles and speed of clinical effect (Maruani and Geoffroy, 2019; Oldham and Ciraulo, 2014), which could also point to a divergent mechanisms of treatment action.

Finding 3: Participants receiving BLT showed stronger expectations for a general effect on mood/emotion than those receiving sham-placebo

Paralleling previous findings, we found that participants receiving sham negative ion treatment held expectations about treatment effects that were comparable to those receiving BLT — but only when the direction was explicitly mentioned. In other words, responses did not differ between treatment groups when participants were asked whether they believed their treatment would induce a specific positive/negative change in mood or emotion. However, groups did differ when they were asked whether they believed that their treatment had *any* effects on mood or emotion at all (i.e. no specified direction). In this case, the BLT group showed stronger expectations for an effect than the sham-placebo group. This could suggest that, at least for healthy volunteers, sham negative ion treatment in conjunction with a cover story might not be as good a placebo control as previously suggested for patients with depression (or, alternatively, it might have become less so with the increasing popularity and public awareness of bright light as an antidepressant treatment modality). Given that the ETB is relatively robust to placebo effects (Huneke et al., 2017), this should not pose a significant problem in the context of our study (and this was confirmed by re-running all analyses with expectations of a general effect as a covariate). However, we do recommend that future studies using sham negative ion treatment as a placebo control also explicitly assess

treatment expectations to confirm their placebo control treatment is credible and serves its purpose.

Study strengths and limitations

This study was based on a clear pre-specified hypothesis that was driven by a large corpus of literature describing valence-specific effects of antidepressant interventions on emotional information processing (Harmer and Cowen, 2013; Harmer et al., 2009a; Warren et al., 2015). The experimental medicine assay we employed is widely used, well-validated, and has been shown to be *sensitive* and *specific* for antidepressant drug manipulations (Warren et al., 2015). In contrast to many other studies investigating mechanisms of light treatment, we also explicitly refrained from preparing our participants with low- or no-light exposure prior to the experiment in order to keep the treatment as ecologically valid as possible. Finally, we employed an established sham-placebo protocol in order to create a credible control condition. Because this protocol has been used largely in a clinical context, we also aimed to validate its usefulness in healthy volunteers by explicitly assessing participants' treatment expectations.

Whilst our study provides a first answer to the question of whether BLT might act through an acute influence on emotional information processing as proposed by the CONEMATA, its findings must be viewed in the context of several potential limitations. First, BLT might have a weaker acute effect on emotional information processing than common antidepressant drugs. Although the study design was properly powered to detect large effect sizes (as are typically observed for single-dose treatments with antidepressant drugs (Huneke et al., 2017; Rock et al., 2016)), it was under-powered to reliably capture small effects. However, the clinical effects of BLT have previously been estimated to be of a magnitude comparable to common antidepressant drugs (Golden et al., 2005; Lam et al., 2016). Hence, it is not

clear why smaller effect sizes on emotional information processing (compared to antidepressants) would be expected and — perhaps even more important — whether they would be clinically relevant.

Second, we employed only a single-dose design (although we applied ≥ 10,000 lux for 1 hour, which is a relatively high dose). Given that light can also influence cognition through the indirect pathway of sleep and circadian phase changes (LeGates et al., 2014), it is possible that potential effects on emotional information processing might only become apparent after a prolonged period of time and hence would not have been captured in this study. Fisher et al. (2014) for example treated healthy volunteers with bright light over a period of 3 weeks and found effects on amygdala and prefrontal neural activity in response to threat-related stimuli. In addition, in the context of antidepressant drug therapies, subacute (as opposed to acute) treatment has generally also yielded clearer and more consistent effects (Roiser et al., 2012). It would thus be desirable to assess emotional information processing after a longer BLT regime and to explicitly take into account potential chronobiological influences.

Finally, we tested healthy volunteers without any personal or family history of mental health problems. While this population allows for a clearer assessment of potential treatment mechanisms unconfounded by psychopathological changes, it might be less sensitive to treatment effects. The absence of valence-specific effects of BLT on emotional information processing thus also has to be replicated in clinical populations, such as in patients with seasonal affective disorder or non-seasonal depression.

Conclusion of Chapter 2

In conclusion, we found no conclusive evidence for an acute effect of BLT on subjective state or emotional information processing in an established experimental

medicine assay of antidepressant treatment action. While this finding might indicate that BLT has a different mechanism of action than common antidepressant drugs, it has to be considered preliminary and should be replicated by further research. Future studies should also include clinical populations, employ longer treatment regimes, and take into account potential chronobiological and sleep-mediated effects. Furthermore, sham negative ion treatment in conjunction with a plausible cover story needs to be properly validated as a credible sham-placebo control in healthy volunteers.

Chapter 3: Assessing potential effects of a positive psychology exercise on emotional information processing and HPA axis activity

Introduction

After bright light treatment, the next intervention that was studied for this thesis was a positive psychology practice. As reviewed in more detail in Chapter 1, the field of "positive psychology" (Seligman and Csikszentmihalyi, 2000) (including its branches "positive psychiatry" (Jeste et al., 2015), "positive psychotherapy" (Seligman et al., 2006), and "positive clinical psychology" (Wood and Tarrier, 2010)) has described a range of simple behavioural and mental exercises that aim to enhance subjective wellbeing and/or alleviate depressive symptoms (Bolier et al., 2013; Seligman et al., 2005; Sin and Lyubomirsky, 2009). These practices are typically designed to be simple enough so that people can conduct them at home on a regular basis in order to cultivate positive feelings, cognitions and behaviours that can support psychological functioning and "flourishing" (Layous et al., 2014; Lyubomirsky and Layous, 2013; Seligman, 2011; Seligman et al., 2005).

One widely-cited positive psychology exercise is the "Three good things in life" (TGT) practice, first described and empirically validated in a randomised controlled trial by Seligman and colleagues (2005). In their landmark study, these authors found that a seven-day-long practice of the TGT exercise significantly increased happiness and decreased depressive symptoms for up to six months. Subsequent studies supported the notion that the TGT exercise (or variants of it) can improve well-being, although probably with more modest effects than originally reported (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012) — also see Woodworth and colleagues (2016, 2017) for a more critical perspective.

Positive psychology exercises are cheap, easy-to-do, self-maintaining, require little instruction, can be done without a therapist, and have no known significant side

effects (Layous et al., 2014; Lyubomirsky and Layous, 2013; Seligman et al., 2005). Despite these advantages they have received almost no attention in the clinical neurosciences, which is surprising, especially given that they could not only provide an elegant and simple way of increasing wellbeing in the general public but could also potentially be combined with antidepressant pharmacotherapy to improve outcomes in clinical populations.

As a result of the paucity of neuroscientific research in this area, to date very little is understood about the neurobiological mechanisms through which practices such as the TGT exercise might bring about their effects on wellbeing. Current mechanistic accounts of positive psychology exercises are thus restricted to a psychological level of description and invoke, for example, the deliberate activation of positive self-relevant information, the strategic harvesting and savouring of positive emotions (broaden-and-build theory), attentional shifts to the positive aspects of life, or enhanced emotion regulation (Fredrickson, 2004; Lyubomirsky and Layous, 2013; Mongrain and Anselmo-Matthews, 2012; Wellenzohn et al., 2016; Xu et al., 2018).

The aim of this chapter is to explore whether simple positive exercises can influence depression-relevant neurobiological processes — similar to the effects of many antidepressant drugs and also some non-drug treatments. To this end, a comparison was made of the effects of the widely cited TGT exercise with those of a previously described control exercise (EM exercise, see below for further details) on two key neurobiological processes, namely emotional information processing and hypothalamic pituitary adrenal (HPA) axis activity.

With regards to emotional information processing, and in line with the primary research question of this thesis, we hypothesised that the TGT but not the EM

exercise would induce a positive bias in line with the CONEMATA without necessarily affecting subjective state.

HPA axis activity constitutes another neurobiological process relevant to depression that can be elegantly studied in a healthy volunteer assay. It can be assessed via the cortisol awakening response (Pruessner et al., 1997; Wüst et al., 2000). Dysregulated functioning of the HPA axis in depression has been described as one of the most consistent findings in psychiatric research and is believed to play an important role in the pathophysiology of depressive disorders (Pariante and Lightman, 2008). Elevated cortisol awakening responses have not only been observed in depressed patients (Vreeburg et al., 2009) but also in individuals at risk for the disorder (Mannie et al., 2007; Portella et al., 2005; Vreeburg et al., 2010) and even in those recovered from it (Bhagwagar et al., 2003; Vreeburg et al., 2009), suggesting that it could be a trait-like risk factor for depression. In addition, several interventions have been shown to potentially decrease salivary cortisol on awakening, including for example prebiotic intake in healthy volunteers (Schmidt et al., 2015) and attentional bias modification in patients with remitted depression (Browning et al., 2012). Thus, putative effects of positive mental exercises on the HPA axis are also of interest for a better understanding of their potential neurobiological effects. We hypothesised that the TGT but not the EM practice would lower cortisol on awakening.

Material and methods

Study sample

We recruited 100 never-depressed healthy volunteers (70 female, 30 male), aged 18 to 62 years, using online and print advertisements (see Table 8 for demographic and psychological characteristics). As in the previous study, the sample size was based on previously published experimental medicine trials using a comparable design

and the same outcome measures (Browning et al., 2007, 2011; Cooper et al., 2015, 2018; Harmer et al., 2003d, 2003a, 2004, 2009b, 2012; Murphy et al., 2008; Pringle et al., 2012; Schmidt et al., 2015, 2015; Warren et al., 2019) and in addition the sample size was increased to the maximum number of participants that could be feasibly recruited within the dedicated study period. All participants were deemed mentally and physically healthy as assessed by a structured psychiatric interview (SCID-5) (First et al., 2015) and a general medical interview carried out prior to inclusion in the study. None of the included study participants fulfilled any of the pre-specified exclusion criteria (see Table 7). The study was approved by the local ethics board and all participants gave written informed consent prior to their inclusion.

Table 7: Exclusion criteria for the positive mental exercise study.

Exclusion criteria for the positive mental exercise study
1. Any current or past psychiatric disorder
2. Any first-degree relative with a diagnosis of schizophrenia-spectrum or other psychotic disorder, bipolar disorder, or depressive disorder
3. Any severe medical condition not stabilized at the time of study participation (e.g. cardiac disease)
4. Any current or past physical illness that has the potential to significantly affect mental functioning (e.g. Parkinson's disease)
5. Current intake of medication that has a significant potential to affect mental functioning, or intake of such medication in the previous 3 months (e.g. antidepressants, neuroleptics, sedatives)
6. Any intake of recreational drugs in the last 3 months before the experiment
7. Regular consumption of higher doses of alcohol (more than 2 pints of beer or equivalent on more than 3 days a week within the last month)
8. Regular engagement in mental exercises specifically aimed at improving cognitive abilities (e.g. concentration, attention, memory), mood, or general well-being, such as (online) cognitive training, positive psychology exercises, regular meditation or mindfulness practice, yoga practice, or psychotherapy
9. Regular engagement in any of the practices outlined above within the last 6 months
10. Researcher's decision to exclude a participant for any other reason (e.g. participation could be harmful to a participant, participant does not properly interact with the researchers at screening, participant has previous experience with the test battery)

Table 8: Basic demographic and psychological characteristics of 100 healthy volunteers who were randomly allocated to a seven-day-long practice period doing either the three good things exercise or an early memories exercise (means with standard deviations in parentheses).

	Three good things (n = 50; 15 male)	**Early memories (n = 50; 15 male)**
Age in years	26.7 (9.2)	26.4 (9.3)
Years in full-time education	17.7 (2.9)	17.0 (2.4)
IQ estimate (Spot-the-word Test)	110.2 (6.8)	109.3 (7.0)
Neuroticism (Eysenck Personality Questionnaire)	5.3 (4.2)	5.0 (3.7)
Psychoticism (Eysenck Personality Questionnaire)	2.4 (2.1)	2.4 (2.3)
Extraversion (Eysenck Personality Questionnaire)	13.7 (4.5)	14.5 (4.9)
Lie (Eysenck Personality Questionnaire)	9.8 (3.3)	9.8 (4.1)
Trait Anxiety (State-Trait Anxiety Inventory)	32.5 (6.6)	31.9 (7.0)

General procedure

Participation in the study started with an initial screening visit during which a participant's eligibility to take part was assessed and basic demographic and psychological information was collected. If a participant was deemed eligible, they were then asked to complete a range of different questionnaires to assess subjective state at baseline. Following that, every participant was randomly allocated to one of two possible mental exercises (see below) which they subsequently conducted at home for seven consecutive days. Each participant received a standardised instruction letter and a practice journal in which they were asked to document their regular engagement in the mental exercise. In order to verify engagement, participants also had to electronically submit a picture of their notes every day. To increase compliance, the total study reimbursement (£50) was reduced by £4 for every missing submission and if a participant submitted less than five entries in total they were excluded from the study.

Prior to and upon completion of the seven-day practice period a subset of participants (n = 62)[6] also collected saliva samples in the morning in order to assess the cortisol awakening response. After seven days of practicing their allocated exercise, all participants returned to the lab for a testing visit. This visit started with the participant reading through their exercise journal again. Subsequently, they completed the same set of questionnaires administered at baseline and then underwent testing with the Oxford Emotional Test Battery (ETB). The investigator remained blinded about the exercise allocation until a participant had completed all assessments.

[6] Saliva could not be collected for all participants for logistical reasons. Hence the sample size is smaller for this measure.

Interventions

We compared two different mental exercises, a three good things (TGT) exercise and an unspecific early memories (EM) exercise. The TGT practice has previously been reported to have beneficial effects on happiness and to potentially decrease depressive symptoms (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Seligman et al., 2005). Study participants assigned to this practice were asked to recall three things every evening that had gone well for them in the last 24 hours. They were instructed to list them in their exercise journal, including a brief explanation of why they thought each event had happened.

Versions of the early memories exercise have previously been used as control interventions in positive psychology studies (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Seligman et al., 2005). If allocated to this exercise, participants were asked to recall every evening an event from their childhood and to write it down in their exercise journal, including a brief explanation of why they thought it had occurred. Importantly, no prompt about the valence of the memory to be recalled was given (that is, it could be positive, negative, or neutral).

Assessment of subjective state

Subjective state was assessed at baseline as well as after the seven-day-long exercise period using the following questionnaires: Befindlichkeits-Skala (BFS) (van Zerssen et al., 1974), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), Beck Depression Inventory (BDI) (Beck et al., 1996), Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), Center for Epidemiological Studies Depression Scale Revised (CESD-R) (Eaton et al., 2004), Authentic Happiness Inventory (AHI) (Shepherd et al., 2015), and visual analogue scales (VAS) of different subjectively experienced emotions.

Assessment of HPA axis activity

The cortisol awakening response was assessed before and after the seven-day-long exercise period. Participants were asked to collect five saliva samples (using a Sarstedt Salivette system) at home immediately upon awakening and thereafter every 15 minutes until 60 minutes post-awakening. Saliva samples were delivered on the same day as they were collected, rendered acellular, and then frozen at -20°C. Salivary cortisol was measured in batches using a commercial ELISA kit (Salimetrics Salivary Cortisol ELISA Kit, assay #1-3002 — special thanks to Ms. Kalina Naidoo and Prof. Philip Burnet for their friendly help with measuring cortisol concentration in saliva).

Assessment of emotional information processing

The processing of emotional information was assessed in different cognitive domains using the Oxford Emotional Test Battery (ETB). A detailed description of the ETB can be found in Chapter 2 of this thesis.

Statistical analysis

Analyses were conducted in SPSS (version 25.0) and R (version 3.6.1.) using RStudio and the "tidyverse" package as well as the packages "afex", "WRS2", and "pracma".

Subjective state measures and ETB outcomes were compared between groups using two-way mixed-design ANOVAs. Group served as the between-subjects factor and visit (for subjective state outcomes) or emotion/valence (for ETB outcomes) served as within-subjects factors, respectively. Where the assumption of sphericity was broken, Greenhouse-Geisser correction was used. In order to corroborate results, a robust mixed-design ANOVA based on the 20% trimmed mean was conducted as well (Field and Wilcox, 2017; Field et al., 2012). In cases where conclusions from the standard ANOVA and the robust ANOVA differed, another robust mixed-design

comparison based on an M-estimator (modified one-step estimator of location based on Huber's Psi) in combination with a bootstrap (2000 bootstrap samples) was used for further clarification (Field and Wilcox, 2017; Field et al., 2012). For subjective state measures, effects of interest were main effects of visit and treatment group × visit interactions. For ETB outcomes, effects of interest were main effects of treatment group and treatment group × emotion interactions.

For the analysis of the neutral face condition in the FERT, groups were compared using standard independent t-tests and a robust equivalent based on the 20% trimmed mean (Field and Wilcox, 2017; Field et al., 2012).

Salivary cortisol responses were first analysed using a three-way mixed ANOVA with group as the between-subjects factor and visit and collection time as within-subject variables. This was followed-up using two-way ANOVAs comparing groups separately for each visit as well as analysing each group individually across visits. In addition, the area under the curve (AUC) of the salivary cortisol response was calculated for each participant and visit using trapezoidal integration. AUCs were then analysed using the same approach as for the subjective state measures.

All reported values below are from standard ANOVAs and t-tests, unless explicitly stated otherwise. Where it was deemed of interest, correlations between outcome measures were calculated using Spearman's correlation.

Results

Subjective state measures

The practices did not show significant differential impact on any subjective state measure, except for negative affect in the PANAS where there was a significant treatment group × visit interaction ($F(1,96) = 5.9$, $p = 0.02$) (same conclusion in the robust ANOVA and after exclusion of outliers). The PANAS negative sub-score increased significantly in the TGT group ($t(48) = 2.5$, $p = 0.02$, $d = 0.4$) but not the

EM group ($t(48) = -0.6$, $p = 0.56$, $d = 0.1$) following the intervention and this was not due to a baseline difference ($t(97) = 0.01$, $p = 0.99$). For VAS anxious scores, the standard ANOVA showed a trend-wise main effect of visit ($F(1,98) = 2.8$, $p = 0.10$) and this was significant after outliers were excluded ($p = 0.03$) as well as in the robust ANOVA ($p = 0.02$).[7] VAS anxious scores decreased in both groups following the intervention. There were no significant main effects of visit and no treatment group × visit interactions in any of the other subjective state measures ($p > 0.05$ in all standard and robust analyses). Also see Table 9.

Cortisol awakening response

A standard three-way mixed ANOVA (group × visit × sampling time) showed a significant main effect of sampling time ($F(2.4,144.0) = 15.7$, $p < 0.001$) and a significant group × visit interaction ($F(1,60) = 8.3$, $p = 0.01$), but no other significant main or interaction effects ($p > 0.05$ for all other effects). In other words, salivary cortisol differed between treatment groups depending on visit but independent of sampling time. When groups were compared individually for each visit, there was no difference prior to practice (no main effect of group ($F(1,60) = 0.001$, $p = 0.97$) and no group × sampling time interaction ($F(2.1,125.1) = 0.3$, $p = 0.74$) in either analysis approach). After practice, however, there was a significant difference between groups with the EM group showing lower cortisol levels independent of sampling times (main effect of group ($F(1,60) = 6.1$, $p = 0.02$), but no group × sampling time interaction ($F(2.7,159.8) = 0.8$, $p = 0.49$); same conclusion in the robust analysis). As can be seen in Figure 3, salivary cortisol decreased in the EM group but did not change significantly in the TGT group. This result was also

[7] Note that there was also a trend-wise group × visit interaction ($F(1,98,) = 3.1$, $p = 0.08$) in the standard ANOVA, however, this depended on the presence of outliers and was not significant in the robust ANOVA.

confirmed by running repeated-measures ANOVAs (visit × sampling time) separately for each group, which yielded a significant main effect of visit in the EM group ($F(1,27) = 6.8$, $p = 0.01$) but not in the TGT group ($F(1,33) = 2.0$, $p = 0.17$). There was no significant visit × sampling time interaction in either group ($p > 0.05$ in both analyses).

When AUCs were analysed, the same overall pattern was observed. A two-way mixed ANOVA suggested a significant group × visit interaction ($F(1,60) = 9.0$, $p = 0.004$) (same conclusion in the robust analysis). As can be seen in Figure 4, the AUC decreased in the EM group but not in the TGT group. This was also confirmed by running dependent t-tests separately for each group, which suggested that the AUC decreased significantly from pre-intervention to post-intervention in the EM group ($t(27) = -2.8$, $p = 0.01$, $d = 0.5$), but not the TGT group ($t(33) = 1.3$, $p = 0.19$, $d = 0.2$) in the absence of baseline differences between groups.

Table 9: Comparison of groups' subjective state measures before and after the intervention. Values represent means with standard deviations in parentheses for each group and study visit.

	Three good things (n = 50)		**Early memories (n = 50)**	
	Before	**After**	**Before**	**After**
BFS	12.4 (9.6)	13.1 (13.4)	11.3 (10.5)	13.7 (12.9)
STAI state	28.5 (5.5)	30.5 (9.0)	29.1 (5.8)	28.8 (7.3)
BDI	2.4 (2.8)	3.1 (4.2)	2.8 (3.2)	2.5 (2.7)
PANAS positive	33.2 (7.0)	33.6 (7.8)	33.1 (5.4)	34.5 (7.2)
PANAS negative	11.7 (2.4)	12.9 (3.6)	11.7 (1.9)	11.6 (2.2)
CESD-R	4.1 (4.1)	4.1 (4.2)	4.0 (4.5)	3.3 (2.9)
AHI	76.3 (8.1)	76.6 (9.9)	76.6 (8.3)	76.7 (9.9)
VAS anxious	11.5 (14.6)	11.7 (17.6)	14.1 (20.2)	8.0 (11.5)
VAS alert	67.3 (17.9)	63.9 (24.0)	70.5 (15.1)	67.0 (20.5)
VAS happy	71.9 (13.2)	71.8 (17.7)	72.3 (13.2)	70.4 (16.1)
VAS sad	9.0 (10.5)	11.0 (14.7)	9.5 (13.4)	9.7 (15.5)
VAS angry	4.9 (9.1)	5.3 (11.8)	2.7 (4.7)	3.9 (7.7)
VAS disgusted	3.4 (5.4)	4.4 (11.0)	2.3 (3.9)	2.3 (3.8)
VAS afraid	6.4 (8.1)	8.1 (12.1)	5.1 (10.1)	3.7 (5.4)

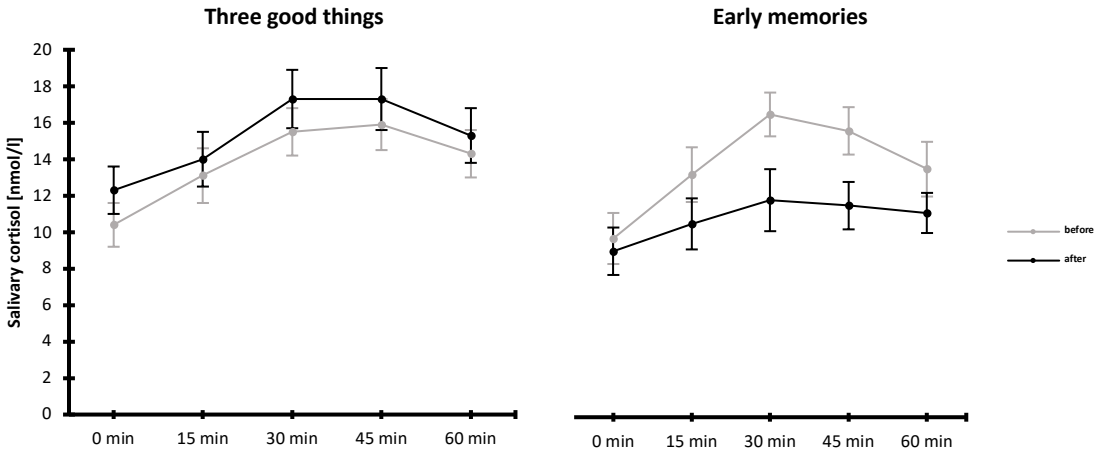


Figure 3: Cortisol awakening response before and after the intervention. Mean (± 1 S.E.) salivary cortisol for each group against sampling time after awakening. The early memories group (F(1,27) = 6.8, p = 0.01), but not the three good things group (F(1,33) = 2.0, p = 0.17), showed a blunted CAR following the intervention.

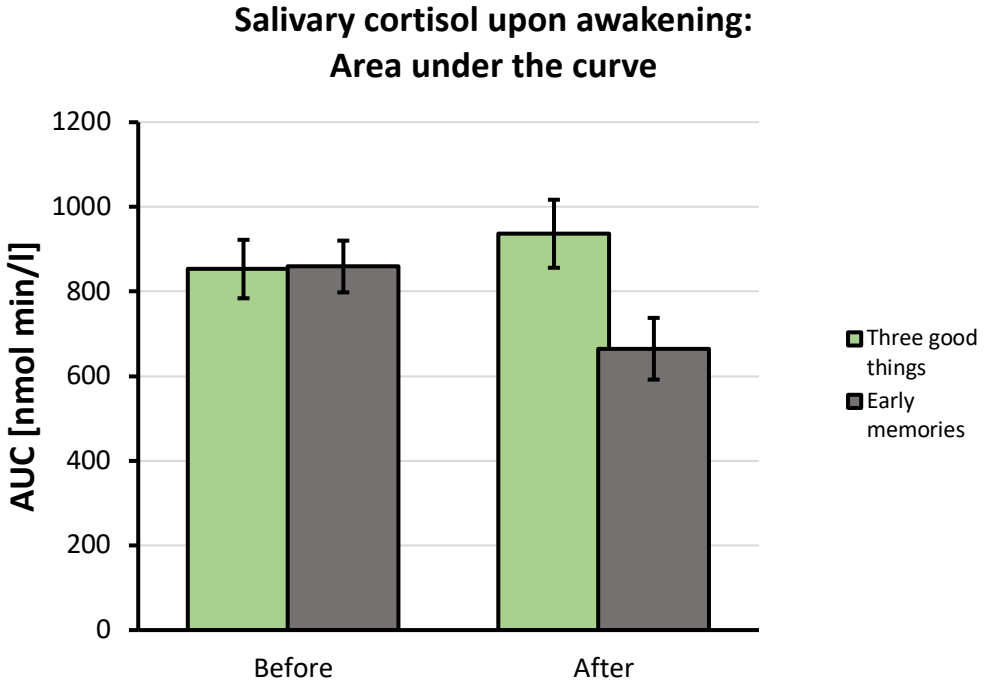


Figure 4: Area under the curve (AUC) of salivary cortisol after awakening, prior to and following the interventions (Mean ± 1 S.E.). The early memories group (t(27) = -2.8, p = 0.01, d = 0.5) but not the three good things group (t(33) = 1.3, p = 0.19, d = 0.2), showed a significant decrease after the intervention.

Emotional information processing

Facial expression recognition task (FERT)

Three participants (one from the TGT group and two from the EM group) were excluded from the analysis because they did not classify any of the fearful faces correctly, which suggests that they might have misunderstood the instructions of the task or that they were not properly engaged in it. Thus, data from a total of 97 participants was analysed.

Analysis of FERT hit rates (pre-specified as the primary outcome) showed a significant main effect of group ($F(1,95) = 4.3$, $p = 0.04$) but no significant group × emotion interaction ($F(3.4,320.1) = 2.0$, $p = 0.11$) (same conclusion in the robust analysis). As can be seen in Figure 5, compared to the TGT group, overall the EM group showed higher hit rates independent of the specific emotion that was displayed.

Analysis of FERT false alarm rates showed no significant main effect of group in the standard ANOVA ($F(1,95) = 2.6$, $p = 0.11$). However, the robust ANOVA did show a main effect of group ($p = 0.04$) and this was corroborated by an alternative robust mixed-design analysis based on an M-estimator ($p = 0.03$). Further inspection suggested that the disparity in analyses was due to the presence of extreme values which bias the standard ANOVA more than the robust equivalents. Once these outliers were removed, the standard ANOVA also showed a significant main effect of group ($p = 0.02$). Compared to the TGT group, the EM group showed lower false alarm rates independent of the displayed emotion. There was no significant group × emotion interaction ($F(4.2,397.2) = 1.8$, $p = 0.13$) in either analysis.

Analysis of FERT non-identification rates indicated no significant main effect of group ($F(1,95) = 1.0$, $p = 0.32$) and no significant group × emotion interaction ($F(4.1,391.8) = 0.6$, $p = 0.64$) in either analysis.

For FERT reaction times, there was again a significant main effect of group ($F(1,95) = 4.5$, $p = 0.04$) (same conclusion in the robust ANOVA). Overall, reaction times were lower in the EM group independent of the displayed emotion. In the standard ANOVA, there was also a significant group × emotion interaction ($F(2.9,276.5) = 3.4$, $p = 0.02$), however, this was neither significant in the robust ANOVA based on trimmed means ($p = 0.16$) nor the alternative robust mixed-design analysis based on an M-estimator ($p = 0.51$) and thus deemed a false positive, likely due to violation of distributional assumptions.

Hit rates ($t(95) = 1.6$, $p = 0.11$) and reaction times ($t(95) = -0.8$, $p = 0.44$) for neutral faces did not differ between treatment groups (same conclusion in the robust analysis). See Table 10 for detailed results in the FERT.

Emotional categorisation task (ECAT)

Median hit rates greater than 90% in either group suggested appropriate engagement in the task. Analysis of reaction times showed no significant main effect of group ($F(1,98) = 0.1$, $p = 0.77$) and no significant group × valence interaction ($F(1,98) = 0.2$, $p = 0.70$). The robust analysis led to the same conclusion. See Table 10 for detailed results in the ECAT.

Faces dot probe task (FDOT)

Median hit rates greater than 90% in either treatment group suggested again appropriate engagement in the task. Vigilance scores were analysed separately for the masked and the unmasked condition. Analysis of the masked condition showed no significant main effect of group ($F(1,98) = 0.1$, $p = 0.78$) and no group × valence

interaction ($F(1,98) = 0.8$, $p = 0.37$). The same pattern was observed in the unmasked condition: no main effect of group ($F(1,98) = 0.1$, $p = 0.74$) and no group × valence interaction ($F(1,98) = 1.2$, $p = 0.27$). The robust analysis led to the same conclusions. See Table 10 for detailed results in the FDOT.

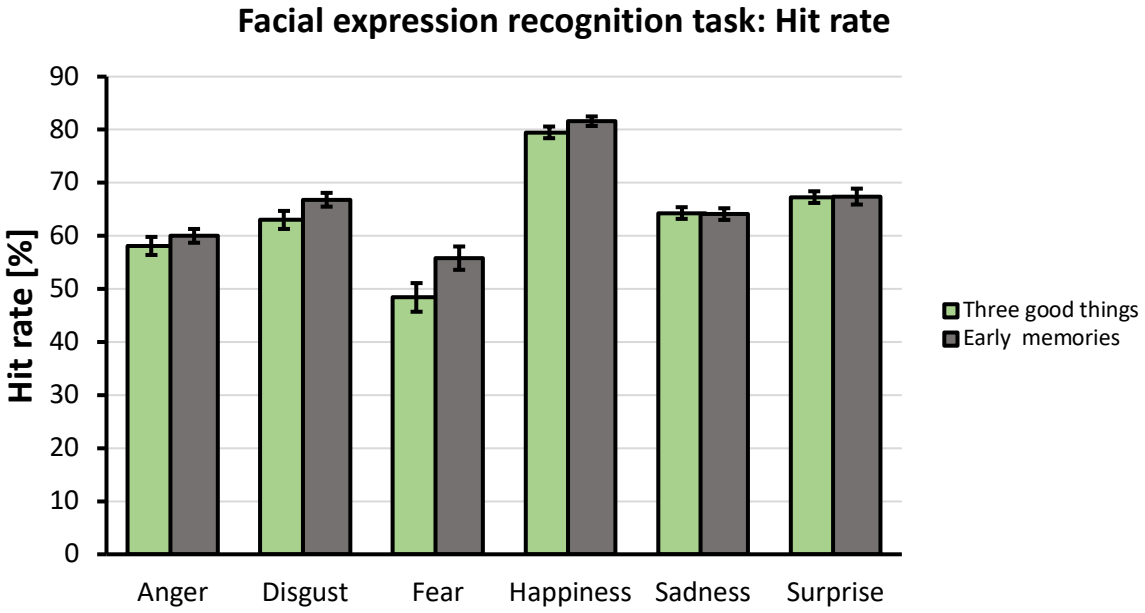


Figure 5: Hit rates (Mean ± 1 S.E.) for different emotions in the facial expression recognition task. The early memories group, as compared to the three good things group, showed significantly higher hit rates independent of the specific emotion that was presented (main effect of group ($F(1,95) = 4.3$, $p = 0.04$)).

Emotional recall task (EREC)

Analysis of hits showed no main effect of group in the standard ANOVA ($F(1,98) = 2.6$, $p = 0.11$). However, there was a trend-wise main effect of group in the robust ANOVA ($p = 0.05$) and this trend was also present in the alternative robust mixed-design analysis based on an M-estimator ($p = 0.06$). Compared to the TGT group, the EM group recalled more words correctly regardless of valence. There was no group × valence interaction ($F(1,98) = 0.03$, $p = 0.85$) in either analysis approach. Also see Figure 6.

Analysis of intrusions showed no main effect of group ($F(1,98) = 0.4$, $p = 0.55$) and no group × valence interaction ($F(1,98) = 0.02$, $p = 0.90$). The robust analysis led to the same conclusion. See Table 10 for detailed results in the EREC.

Emotional recognition task (EMEM)

Analysis of EMEM hit rates showed no significant main effect of group ($F(1,98) = 0.2$, $p = 0.64$) and no significant group × valence interaction ($F(1,98) = 2.3$, $p = 0.14$). Analysis of EMEM false alarm rates also showed no main effect of group ($F(1,98) = 1.7$, $p = 0.19$) and no group × valence interaction ($F(1,98) = 0.1$, $p = 0.74$). For reaction times, there was also no main effect of group ($F(1,98) = 0.4$, $p = 0.51$) and no group × valence interaction ($F(1,98) = 0.003$, $p = 0.96$). The robust analysis led to the same conclusions. See Table 10 for detailed results in the EMEM.

Correlations between salivary cortisol and emotional information processing measures

In order to probe a potential relationship between the changes in salivary cortisol and the treatment group differences in emotional information processing that were observed, we correlated these measures using Spearman's correlation. However, for both groups, there was no significant correlation between change in cortisol AUC and FERT total hit rate (TGT group: $\rho = -0.3$, $p = 0.08$, EM group: $\rho = -0.1$,

p = 0.59), FERT reaction time (TGT group: ρ = 0.1, p = 0.43, EM group: ρ = -0.2, p = 0.35), or EREC hits (TGT group: ρ = -0.1, p = 0.58, EM group: ρ = -0.05, p = 0.80).

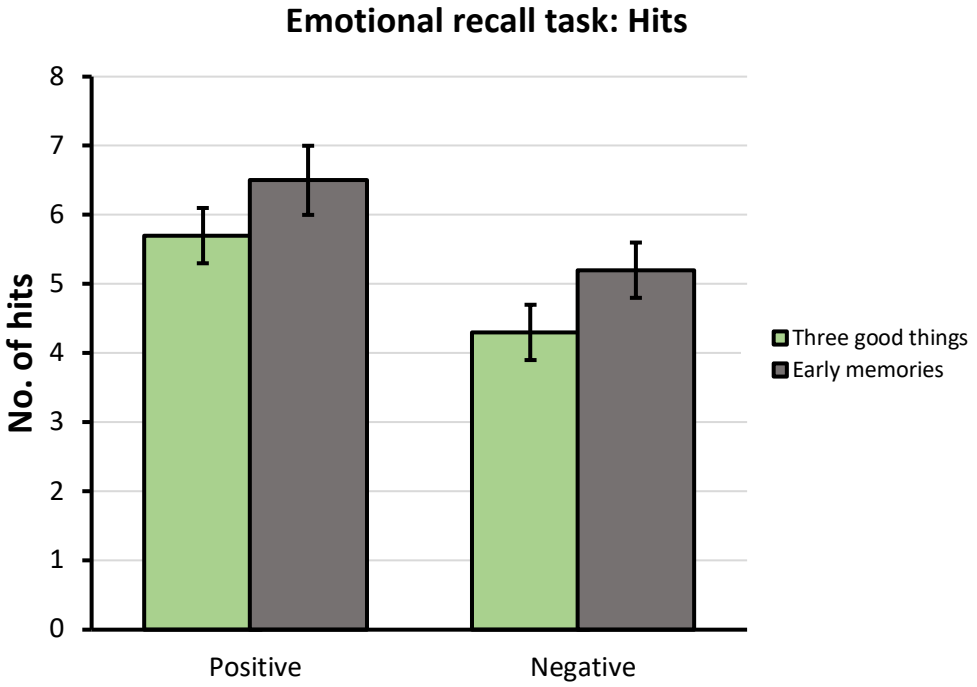


Figure 6: Number of correctly recalled words (Mean ± 1 S.E.) in the emotional recall task. The early memories group, as compared to the three good things group recalled more emotional words independent of valence (trend-wise significance in robust analyses only).

Table 10: Performance in the Oxford Emotional Test Battery. Values represent means with standard deviations in parentheses.

	Three good things (n = 50)	**Early memories (n = 50)**
Facial expression recognition task		
Hit rate [%]		
Anger	58.1 (11.8)	60.0 (8.8)
Disgust	63.0 (11.7)	66.8 (8.9)
Fear	48.4 (19.0)	55.8 (15.0)
Happiness	79.5 (7.5)	81.6 (6.5)
Sadness	64.3 (7.6)	64.1 (7.5)
Surprise	67.3 (7.9)	67.4 (10.4)
Neutral	81.2 (13.2)	85.2 (10.7)
False alarm rate [%]		
Anger	2.8 (2.6)	1.8 (1.4)
Disgust	3.1 (2.3)	2.4 (2.4)
Fear	1.1 (1.0)	1.5 (2.0)
Happiness	0.9 (2.6)	0.8 (1.4)
Sadness	2.1 (1.6)	1.9 (1.5)
Surprise	3.2 (2.7)	2.5 (2.7)
Non-identification rate [%]		
Anger	33.1 (9.3)	32.3 (7.7)
Disgust	23.6 (6.9)	22.0 (6.2)
Fear	23.6 (4.9)	22.0 (3.6)
Happiness	17.9 (5.7)	16.1 (5.9)
Sadness	31.8 (7.1)	31.9 (7.2)
Surprise	25.7 (6.4)	25.7 (4.9)
Reaction time [ms]		
Anger	1448.8 (260.1)	1416.5 (257.0)
Disgust	1526.0 (337.0)	1460.0 (353.4)
Fear	1946.0 (538.6)	1675.4 (382.1)
Happiness	1154.7 (182.1)	1095.4 (172.2)
Sadness	1264.4 (178.4)	1207.5 (178.7)
Surprise	1339.6 (265.4)	1286.6 (277.9)
Neutral	1285.1 (592.0)	1210.1 (307.8)
Emotional categorisation task		
Reaction time [ms]		
Positive	809.2 (148.9)	814.4 (159.5)
Negative	847.2 (147.6)	860.4 (209.7)
Faces dot probe task		
Vigilance bias score [ms]		
Masked positive	5.8 (32.8)	2.1 (38.2)
Masked negative	-0.2 (34.4)	6.3 (45.4)
Unmasked positive	3.8 (46.5)	-5.7 (37.8)
Unmasked negative	-3.9 (40.4)	2.0 (49.3)
Emotional recall task		
Hits [n correct]		
Positive	5.7 (3.1)	6.5 (3.3)
Negative	4.3 (2.6)	5.2 (2.9)
Intrusions [n wrong]		
Positive	2.8 (2.5)	2.6 (3.0)
Negative	1.3 (1.4)	1.0 (1.7)
Emotional recognition task		
Hit rate [%]		
Positive	82.9 (12.6)	85.7 (8.8)
Negative	70.5 (15.7)	69.9 (13.9)
False alarm rate [%]		
Positive	25.4 (15.6)	21.8 (16.5)
Negative	16.2 (11.1)	13.4 (9.6)
Reaction time [ms]		
Positive	944.4 (199.2)	916.8 (175.9)
Negative	1089.9 (241.9)	1063.9 (248.7)

Valence of recalled early memories

Although we explicitly refrained from prompting our participants towards the recall of specifically valenced early memories, there was a significant difference in terms of valence of these memories (one-way ANOVA: $F(1.5,72.7) = 102.5$, $p < 0.001$). The EM group recalled significantly more positive ($M = 4.7$, $SD = 1.5$) than negative ($M = 1.2$, $SD = 1.0$) memories ($t(49) = 10.9$, $p < 0.001$, $d = 1.5$), and also significantly more positive than neutral ($M = 1.0$, $SD = 1.0$) memories ($t(49) = 10.9$, $p < 0.001$, $d = 1.5$). There was no significant difference in the number of recalled negative versus neutral memories ($t(49) = 0.9$, $p = 0.40$). There was no significant correlation between number of positive, negative, or neutral memories recalled and change in cortisol AUC (positive memories: $\rho = 0.02$, $p = 0.93$, negative memories: $\rho = 0.01$, $p = 0.95$, neutral memories: $\rho = -0.04$, $p = 0.82$), FERT total hit rate (positive memories: $\rho = 0.03$, $p = 0.89$, negative memories: $\rho = -0.2$, $p = 0.38$, neutral memories: $\rho = 0.04$, $p = 0.84$), FERT reaction time (positive memories: $\rho = -0.2$, $p = 0.44$, negative memories: $\rho = -0.1$, $p = 0.54$, neutral memories: $\rho = 0.3$, $p = 0.12$), or EREC hits (positive memories: $\rho = -0.3$, $p = 0.17$, negative memories: $\rho = 0.3$, $p = 0.2$, neutral memories: $\rho = 0.07$, $p = 0.71$).

Discussion

This study explored potential effects of two mental exercises on emotional information processing and HPA axis activity in healthy volunteers. Contrary to our main hypothesis, we found no conclusive evidence that the three good things exercise induced a positive bias in emotional information processing. However, to our surprise the two mental exercises we studied showed valence-independent differential effects on emotional information processing. In addition, the early

memories exercise — but not the three good things exercise — also showed an effect on HPA axis activity.

Finding 1: Neither practice showed a consistent positive impact on subjective state

With regards to subjective state, neither treatment group showed a consistent improvement after the interventions. As in the last chapter with bright light treatment, this mirrors what is commonly observed in comparable experimental medicine studies probing effects of antidepressant interventions in healthy volunteers (Browning et al., 2007; Capitão et al., 2019; Harmer et al., 2003c, 2003a; Murphy et al., 2009; Walsh et al., 2018b). Analysis of the PANAS sub-scores suggested that the groups differed in changes in negative affect, with the TGT group but not the EM group increasing in negative affect after the intervention. However, none of the other subjective state measures showed a similar pattern. Therefore, this finding should be interpreted with caution. Furthermore, VAS anxious scores decreased slightly in both groups after the intervention but, again, this pattern was not observed in any other anxiety-related measure (e.g. VAS afraid or STAI state) and could be a simple effect of repeated testing.

Finding 2: The EM exercise, but not the TGT exercise, led to decreased salivary cortisol on awakening

Analysis of the cortisol awakening response showed a significant treatment group difference over time. Contrary to our expectations, it was the EM group and not the TGT group that exhibited decreased salivary cortisol levels after awakening following the intervention. Whilst this result was not predicted a priori and should be replicated by future research, it does raise two important points. First, it indicates that the EM exercise, at least in healthy volunteers and with regards to endocrine effects, might not be an inactive intervention, as is commonly assumed in the literature (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Seligman et

al., 2005). In fact, although explicitly not prompted, our participants recalled mostly positive memories, and it has previously been demonstrated that a modified version of the EM exercise where people were explicitly instructed to recall positive early life events had similar beneficial effects on wellbeing as the TGT exercise (Mongrain and Anselmo-Matthews, 2012). It might even be the case that the EM exercise exerts differential effects in depressed individuals (who might be more prone to access negative or overgeneralised early memories (Dillon and Pizzagalli, 2018)) compared to healthy volunteers (who might be more prone to access positive and specific early memories).

The results also raise the question as to why the two interventions had divergent effects on the cortisol awakening response. One possibility is that the memories recalled in the EM practice had a stronger personal relevance than those recalled in the TGT practice. Since participants recalled mostly positive early memories these might have been more soothing or relaxing. Alternatively, recalling an early life event and recalling events from the past 24 hours might recruit different neural systems (e.g. hippocampal areas) with different functional-anatomical access to and regulatory control over the HPA axis.

Finding 3: The two exercises showed differential valence-unspecific effects on emotional information processing

In the facial expression recognition task, the EM group outperformed the TGT group. The EM group exhibited not only more hits and less false alarms but also faster responses. This pattern was observable across several different emotions and thus suggests that the two mental practices showed a differential global effect on facial expression recognition. This contrasts with the emotion-specific effects that are commonly observed following antidepressant drug manipulations (Warren et al., 2015) — although see Cooper et al. (2015) for a comparable finding following

tianeptine treatment. Unfortunately, the interpretation of our results is complicated by the fact that the collected emotional processing data only allow for a between-groups comparison. Since our salivary cortisol measures suggest that the EM exercise is not an inactive placebo, we cannot treat it as a neutral reference point when comparing groups. In other words, while we can say with some confidence that the exercises showed divergent effects on facial expression recognition, we cannot currently say whether the TGT exercise decreased performance, the EM exercise increased it, or whether perhaps even both effects occurred. Furthermore, although participants were randomly allocated to treatments, there is of course also the possibility of pre-existing differences occurring as a chance-finding. Further research will be necessary to clarify this point.

In addition to the group differences in facial expression recognition, there was also a trend-wise group difference in the robust analyses of the emotional recall task. Again, the EM group, compared to the TGT group, recalled more words regardless of valence. This parallels the effects observed for facial expression recognition, lending further support to the idea that the practices might have had differential impact on emotional information processing independent of stimulus valence.

Study strengths and limitations

To our knowledge, this is the first study in the literature to assess effects of simple mental exercises on emotional information processing and salivary cortisol on awakening. The assay we employed has been used extensively and is well-validated (Huneke et al., 2017; Warren et al., 2015). Both of the neurobiological processes we studied are highly relevant for experimental neuropsychiatry, as they have not only been shown to function abnormally in depressed patients and those at risk for the disorder (Bhagwagar et al., 2005; Chan et al., 2007; Harmer and Pringle, 2017; Roiser et al., 2012; Vreeburg et al., 2009, 2010) but also to be sensitive

to antidepressant treatment (Harmer et al., 2003d, 2009a; Hill et al., 2003; Warren et al., 2015). Our results indicate that this sensitivity might also extend to simple psychological manipulations.

Whilst our study provides a first assessment of the effects of positive mental exercises on neurobiological measures sensitive to antidepressant treatment, its results must also be considered in the context of several limitations. First, the EM exercise, which we had originally chosen to use as a control intervention, showed a clear effect on the cortisol awakening response. This effect was entirely unpredicted and violated our assumption that the EM exercise could be treated as an inactive control treatment (a purpose for which it has been used repeatedly in the literature (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Seligman et al., 2005)). While this arguably constitutes an interesting finding by itself, it left us without a neutral comparison group for the analysis of the emotional processing data. Therefore, the interpretation of these data was limited to the description of relative differences between the treatment groups. It did not allow attribution of an effect to a specific practice.

Second, our study sample consisted of healthy volunteers without a personal or family history of psychiatric problems. Whilst this approach allows for an unconfounded assessment of neurobiological effects, it also limits the generalisability of results. This seems especially important given the fact that many positive psychology studies demonstrate their effects in people who are, overall, at least mildly depressed. In a similar vein, neurobiological effects might be smaller in healthy subjects and, although our sample size was comparatively large for an experimental medicine study, there is still a risk that we missed relevant effects due to a lack of power.

Third, we picked only two simple psychological interventions described in the field of positive psychology for assessment in this chapter. However, the positive psychology literature reports on a wide range of different mental practices (Bolier et al., 2013; Sin and Lyubomirsky, 2009; White et al., 2019) whose effects on emotional processing and HPA axis activity remain to be investigated in future studies.

Conclusion of Chapter 3

In conclusion, the study reported here suggests that brief psychological exercises might be able to affect the same neuroendocrine and neurocognitive processes that many treatments for depression affect. In contrast to a common assumption in the literature, at least in healthy volunteers, the EM exercise does not seem to be an inactive intervention but rather appears to have neuroendocrine effects. The EM exercise and the TGT exercise also seem to have divergent global (as opposed to emotion-specific) effects on emotional information processing. Unfortunately, due to the unexpected lack of an inactive control group in this study, it will be up to future research to clarify the contribution of each practice to this group difference. Future studies should replicate and confirm our findings using appropriate control interventions and also include clinical populations. In addition, the potential utility of brief mental exercises as a simple add-on intervention for conventional antidepressant pharmacotherapy deserves scientific evaluation.

Chapter 4: Assessing potential effects of subacute pramipexole treatment on emotional information processing

Preliminary note

The data described in this and the next two chapters were collected as part of a larger experimental medicine study that aimed to probe potential effects of subacute pramipexole treatment on a range of different hot cognitive processes, including effects on emotional information processing, reward and punishment processing, and the recognition and hedonic experience of different taste qualities. A detailed description of the overall study is provided here in Chapter 4, where we also explore effects of pramipexole on emotional information processing and subjective state. In Chapter 5, we then move on to discuss potential effects of pramipexole on reward and punishment processing. Finally, in Chapter 6, we probe a potential influence of pramipexole on taste recognition and the hedonic experience of appetitive and aversive gustatory stimuli.

Introduction

The dopamine D2/D3 receptor-preferring agonist pramipexole is currently being discussed widely as a potential novel pharmacological treatment option for depression (Cowen, 2017a; Tundo et al., 2019). Whilst preliminary pre-clinical (Lieberknecht et al., 2017; Ostadhadi et al., 2016; Schulte-Herbrüggen et al., 2012; Wang et al., 2018) and clinical data (Aiken, 2007; Cowen, 2017a; Fawcett et al., 2016; Kleeblatt et al., 2017; Romeo et al., 2018; Tundo et al., 2019) look promising, relatively little work has been done to date to identify potential mechanisms through which pramipexole could alleviate symptoms of depression. Neuropsychological tasks that assess how stimuli with emotional tone are being processed have been widely used to characterise cognitive effects of conventional

antidepressant drugs (Roiser et al., 2012; Warren et al., 2015). However, so far, no study has applied this approach to pramipexole.

Several converging lines of evidence suggest that pramipexole treatment could influence affective information processing. First and foremost, in addition to the serotonergic and noradrenergic system, the dopaminergic system also seems to play a role in hot cognition. For example, in patients with neuropsychiatric disorders (e.g. Parkinson's disease or schizophrenia) in which dopamine signalling abnormalities are well established, altered emotional information processing is a robust finding (Barkl et al., 2014; Chan et al., 2010; Gray and Tickle-Degnen, 2010; Healey et al., 2016; Kohler et al., 2010; Péron et al., 2012; Savla et al., 2013). Furthermore, pharmacological manipulations of the dopaminergic system also seem to impact on the processing of affective stimuli. For example, treatment with the dopamine D2 receptor antagonist sulpiride in healthy volunteers led to decreased recognition of anger in a facial expression recognition task (Lawrence et al., 2002). Similarly, treatment with the dopamine D2/D3 receptor antagonist amisulpride has been shown to impair recognition memory for emotional cues (Gibbs et al., 2007; Mehta et al., 2005). Moreover, treatment with levodopa has been reported to dampen amygdala activation during emotional perception (Delaveau et al., 2005, 2007) and experimentally lowering dopaminergic signalling activity by means of phenylalanine/tyrosine depletion can induce a negative bias in facial expression recognition (Cawley et al., 2017).

Second, the preferential molecular target of pramipexole, the dopamine D3 receptor, shows a relatively restricted distribution in the brain and is particularly highly expressed in mesolimbic regions implicated in emotional processing (Aiken, 2007; Piercey, 1998; Sokoloff and Le Foll, 2017; Sokoloff et al., 1990). Imaging data provide evidence that pramipexole does indeed bind to D3 receptors in these

regions in humans (Ishibashi et al., 2011). It has also been argued that the D3 receptor might play a role in the pathophysiology of depressive disorders (Leggio et al., 2013). For example, it could be demonstrated that dopamine D3 receptor-deficient mice show depression-like behaviour independent of motor changes (Moraga-Amaro et al., 2014) and that inflammation-induced depressive behaviour in mice is associated with decreased dopamine D3 receptor expression (Wang et al., 2018).

Third and final, pramipexole has also been shown to influence serotonergic neurotransmission (Chernoloz et al., 2009, 2012; Schulte-Herbrüggen et al., 2012). Hence, even if D2/D3 receptor agonism has no direct effect on hot cognitive processes, pramipexole could still influence emotional processing indirectly via altering serotonin function.

Taken together, the observations described above thus suggest that subacute pramipexole treatment could influence how the human brain processes information with emotional tone. In this chapter, we explicitly test this hypothesis in healthy volunteers. As in previous studies in this thesis, our working hypothesis was that pramipexole would influence emotional processing in line with the predictions of the CONEMATA; that is, induce a bias towards positive cues in different cognitive domains but without necessarily affecting subjective state.

Material and methods

Study sample

Forty healthy volunteers (20 female, 20 male), aged 18 to 43 years, without a personal or family history of any major mental disorder were recruited to take part in a larger experimental medicine study that aimed to explore depression-relevant neurocognitive effects of subacute pramipexole treatment. As in the foregoing chapters, the sample size was based on previously published experimental

medicine trials using a comparable design and outcome measures and was additionally increased to the maximum number of participants that could be feasibly recruited within the dedicated study period (Browning et al., 2007, 2011; Cooper et al., 2015, 2018; Harmer et al., 2003d, 2003a, 2004, 2009b, 2012; Murphy et al., 2008; Pringle et al., 2012; Schmidt et al., 2015, 2015; Walsh et al., 2018a; Warren et al., 2019). In an initial screening visit, participants were confirmed to be mentally and physically healthy, as assessed by a structured psychiatric interview (SCID-5) (First et al., 2015) and a general medical interview. In addition, basic demographic, physical, and psychological information was collected (see Table 12). The study was approved by the local ethics board. All study participants gave written informed consent prior to their inclusion in the trial. None of the study volunteers fulfilled any of the pre-specified exclusion criteria (see Table 11**Error! Reference source not found.**).

Study design and intervention

The study employed a parallel-group, placebo-controlled, double-blind design. All participants were randomly allocated to either pramipexole treatment or placebo (lactose). Both treatments were administered in indistinguishable capsules. Participants were instructed to take their treatment as a single dose in the evening. The daily dose of pramipexole started at 0.25 mg pramipexole salt and was subsequently increased by 0.25 mg in a stepwise manner every three days until a target dose of 1.0 mg pramipexole salt per day was reached. Participants took the target dose of 1.0 mg for at least three consecutive days before any on-drug behavioural assessments were conducted. After all testing was completed, pramipexole was tapered down over three days, decreasing the daily dose by 0.25 mg every day. During their participation, all study volunteers could reach a

medical doctor 24 hours a day via telephone in case of side effects or concerns related to the treatment.

Table 11: Exclusion criteria for the pramipexole study.

Exclusion criteria for the pramipexole study
1. Current or past psychiatric disorder (e.g. depression, bipolar disorder)
2. First-degree relative with a diagnosis of schizophrenia-spectrum or other psychotic disorder, or bipolar disorder
3. Body mass index not between 18 and 30
4. History of unexplained hallucinations or impulse control problems (e.g. pathological gambling)
5. Severe medical condition not stabilized at the time of the experiment (e.g. cardiovascular disease, epilepsy, asthma)
6. Severe heart or blood vessel disease
7. Postural hypotension
8. Any history of seizures
9. Lactose intolerance
10. Any current or past physical illness that has the potential to significantly affect mental functioning (e.g. epilepsy, hypothyroidism, Parkinson's disease, multiple sclerosis)
11. Pregnant, or lactating woman
12. Sexually active woman who does not use any medically accepted method of contraception
13. Current or previous intake (last three months) of any medication that has a significant potential to affect mental functioning (e.g. benzodiazepines, antidepressants, neuroleptics)
14. Any intake of recreational drugs in the last 3 months (e.g. marijuana, ecstasy)
15. Regular alcohol consumption of more than 14 units a week or excessive alcohol consumption up to three days before the experiment
16. Regular smoker (> 5 cigarettes per day)
17. Excessive caffeine user (> 6 caffeinated drinks per day)
18. History of recurrent rashes or history of allergic reactions to relevant substances (e.g. pramipexole)
19. Previous participation in a study using the same or similar tasks
20. Any contraindication to magnetic resonance imaging (e.g. metallic implant, severe claustrophobia)
21. Current participation in another study
22. In the researcher's opinion participation in the study could be harmful or severely distressing to the participant (e.g. intolerance of side effects) or the participant is not able to follow instructions or complete study tasks

Table 12: Basic demographic, physical, and psychological characteristics of 40 healthy volunteers randomly allocated to subacute treatment with either pramipexole or placebo (means with standard deviations in parentheses).

	Pramipexole (n = 21; 10 male)	**Placebo (n = 19; 10 male)**
Age	22.5 (3.7)	24.5 (6.9)
Body mass index	22.4 (2.6)	24.0 (2.9)
Years in full-time education	16.8 (2.9)	17.5 (3.1)
IQ estimate (Spot-the-word Test)	108.3 (8.1)	111.9 (7.6)
Neuroticism (Eysenck Personality Questionnaire)	4.2 (3.7)	4.3 (3.7)
Psychoticism (Eysenck Personality Questionnaire)	2.5 (2.1)	2.8 (2.1)
Extraversion (Eysenck Personality Questionnaire)	14.7 (4.5)	14.5 (3.7)
Lie (Eysenck Personality Questionnaire)	9.5 (4.6)	7.5 (3.4)
Trait Anxiety (State-Trait Anxiety Inventory)	31.2 (9.1)	32.1 (9.1)
Depression at inclusion (Beck Depression Inventory)	1.6 (1.7)	2.5 (4.0)

Assessment of subjective state

Subjective state was assessed once at baseline and once after the target dose of 1.0 mg pramipexole salt had been established using the following questionnaires: Befindlichkeits-Skala of mood and energy (BFS) (van Zerssen et al., 1974), Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), Beck Depression Inventory (BDI) (Beck et al., 1996), Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995), Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006), Oxford Happiness Questionnaire (OXH) (Hills and Argyle, 2002), and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP) (Weintraub et al., 2009).

Assessment of emotional information processing

Emotional information processing was assessed once at baseline and once after the target dose of 1.0 mg pramipexole salt had been established, using the Oxford Emotional Test Battery (ETB). The ETB has already been described in detail in Chapter 2. However, because a before-after design was employed in this study, a slightly modified version of the test battery was used: due to a limited number of validated emotional words being available in the ETB, the EMEM was excluded completely and the ECAT only contained 40 (rather than 60) words. In each visit, different task stimuli were used.

Assessment of side effects and blinding

Side effects were assessed after treatment was established using a standard side effect questionnaire. Blinding was checked by means of a forced-choice guess completed by the study participant and the assessor at the last study visit.

Statistical analysis

Analyses were conducted in SPSS (version 25.0) and R (version 3.6.1) using RStudio and the "tidyverse" package as well as "afex", and "WRS2". Subjective state measures were compared between groups using one-way ANCOVAs with post-treatment score as dependent variable, group as independent variable, and pre-treatment score as covariate. Emotional information processing was analysed using a three-way mixed ANOVA with group as the between-subjects factor and visit and emotion/valence as within-subjects factors, respectively. Effects of interest were group × visit interactions and group × emotion × visit interactions. Where the assumption of sphericity was broken, Greenhouse-Geisser correction was used. In order to corroborate results, change scores (post-treatment minus pre-treatment) were calculated for each emotion/valence and analysed using an alternative robust mixed-design analysis based on 20% trimmed means (Field and Wilcox, 2017; Field et al., 2012).[8] In the facial expression recognition task, scores for neutral faces were analysed using the same approach as for the subjective state measures. Side effects and randomization guesses were compared between groups using Fisher's exact test.

Results

Did pramipexole treatment affect subjective state?

Subjective state after treatment did not differ between groups when controlling for pre-treatment scores ($p > 0.05$ for all measures, see Table 13 for details).

[8] Current implementations of robust mixed-design analyses allow for one between-subjects and one within-subjects variable only, therefore change scores had to be used.

Table 13: Subjective state before and after pramipexole treatment. Values represent means with standard deviations in parentheses.

	Pramipexole		**Placebo**		
	Baseline	**On drug**	**Baseline**	**On drug**	**ANCOVA results**
BFS	11.7 (12.4)	15.4 (14.7)	13.8 (11.2)	14.8 (14.2)	$F(1,37) = 0.4$, $p = 0.51$
STAI state	28.9 (6.5)	27.8 (5.4)	28.6 (6.1)	29.1 (5.2)	$F(1,37) = 1.2$, $p = 0.28$
BDI	1.9 (2.5)	2.9 (3.4)	2.8 (3.3)	2.7 (3.3)	$F(1,36) = 0.9$, $p = 0.36$
PANAS pos. present	36.4 (7.7)	34.5 (8.3)	32.5 (8.6)	32.6 (7.9)	$F(1,37) = 0.5$, $p = 0.50$
PANAS neg. present	11.2 (1.5)	11.0 (1.5)	11.3 (1.3)	11.8 (2.7)	$F(1,37) = 2.1$, $p = 0.15$
PANAS pos. today	36.8 (8.0)	34.8 (9.1)	32.9 (8.2)	32.3 (8.1)	$F(1,37) = 0.1$, $p = 0.73$
PANAS neg. today	11.4 (2.0)	11.4 (1.7)	11.6 (1.7)	11.8 (2.4)	$F(1,37) = 0.4$, $p = 0.55$
PANAS pos. last week	37.7 (9.2)	37.0 (7.7)	34.2 (7.6)	34.6 (9.3)	$F(1,37) < 0.001$, $p > 0.99$
PANAS neg. last week	13.3 (2.8)	12.7 (3.2)	14.1 (4.1)	12.6 (2.7)	$F(1,37) = 0.1$, $p = 0.71$
SHAPS	0.5 (1.0)	0.7 (1.6)	0.2 (0.7)	0.3 (0.7)	$F(1,37) = 0.3$, $p = 0.61$
TEPS total	85.3 (10.0)	82.1 (9.5)	79.3 (8.2)	79.2 (10.0)	$F(1,37) = 0.7$, $p = 0.42$
TEPS anticipatory	47.1 (6.1)	44.6 (5.5)	42.1 (4.9)	42.3 (5.4)	$F(1,37) = 0.8$, $p = 0.38$
TEPS consummatory	38.1 (5.6)	37.5 (5.9)	37.3 (4.4)	36.8 (5.4)	$F(1,37) = 0.01$, $p = 0.91$
OXH	134.8 (19.2)	138 (18.4)	132.4 (19.6)	132 (19.7)	$F(1,37) = 3.1$, $p = 0.08$
QUIP	12.3 (8.3)	8.7 (8.5)	16.6 (11.2)	13.8 (10.4)	$F(1,37) = 1.0$, $p = 0.33$

Did pramipexole treatment affect emotional information processing?

Facial expression recognition task (FERT)

One participant was excluded from the analysis because they did not classify any of the fearful faces correctly at the post-treatment assessment, which suggests that they might have misunderstood the instructions or were not properly engaged in the task.

Analysis of FERT hit rates showed no significant treatment group × visit interaction ($F(1,37) = 0.3$, $p = 0.57$) and no significant treatment group × emotion × visit interaction ($F(3.5,129.3) = 0.3$, $p = 0.86$) (also see Figure 7). For FERT false alarm rates, there was also no significant treatment group × visit interaction ($F(1,37) = 0.2$, $p = 0.62$) and no significant treatment group × emotion × visit interaction ($F(3.6,132.8) = 0.3$, $p = 0.84$). A similar pattern was observed for FERT non-identification rates: no significant treatment group × visit interaction ($F(1,37) = 0.3$, $p = 0.62$) and no significant treatment group × emotion × visit interaction ($F(3.7,136.8) = 0.3$, $p = 0.90$). Finally, for FERT reaction times there was also no significant treatment group × visit interaction ($F(1,37) = 0.01$, $p = 0.91$) and no significant treatment group × emotion × visit interaction ($F(2.4,90.0) = 0.3$, $p = 0.78$). Hit rates ($F(1,35) = 2.5$, $p = 0.12$, one outlier excluded) and reaction times ($F(1,36) = 0.1$, $p = 0.80$) for neutral faces post-treatment also did not differ significantly between treatment groups when adjusted for pre-treatment scores. Complimentary robust-mixed design analyses on change scores led to the same overall conclusions as those reported above.[9] Also see Table 14.

[9] As an alternative approach, we also compared groups on signal detection theory measures (i.e. target sensitivity and response bias, calculated following Grier (1971)). This analysis confirmed the absence of a pramipexole-induced effect on facial expression recognition reported above.

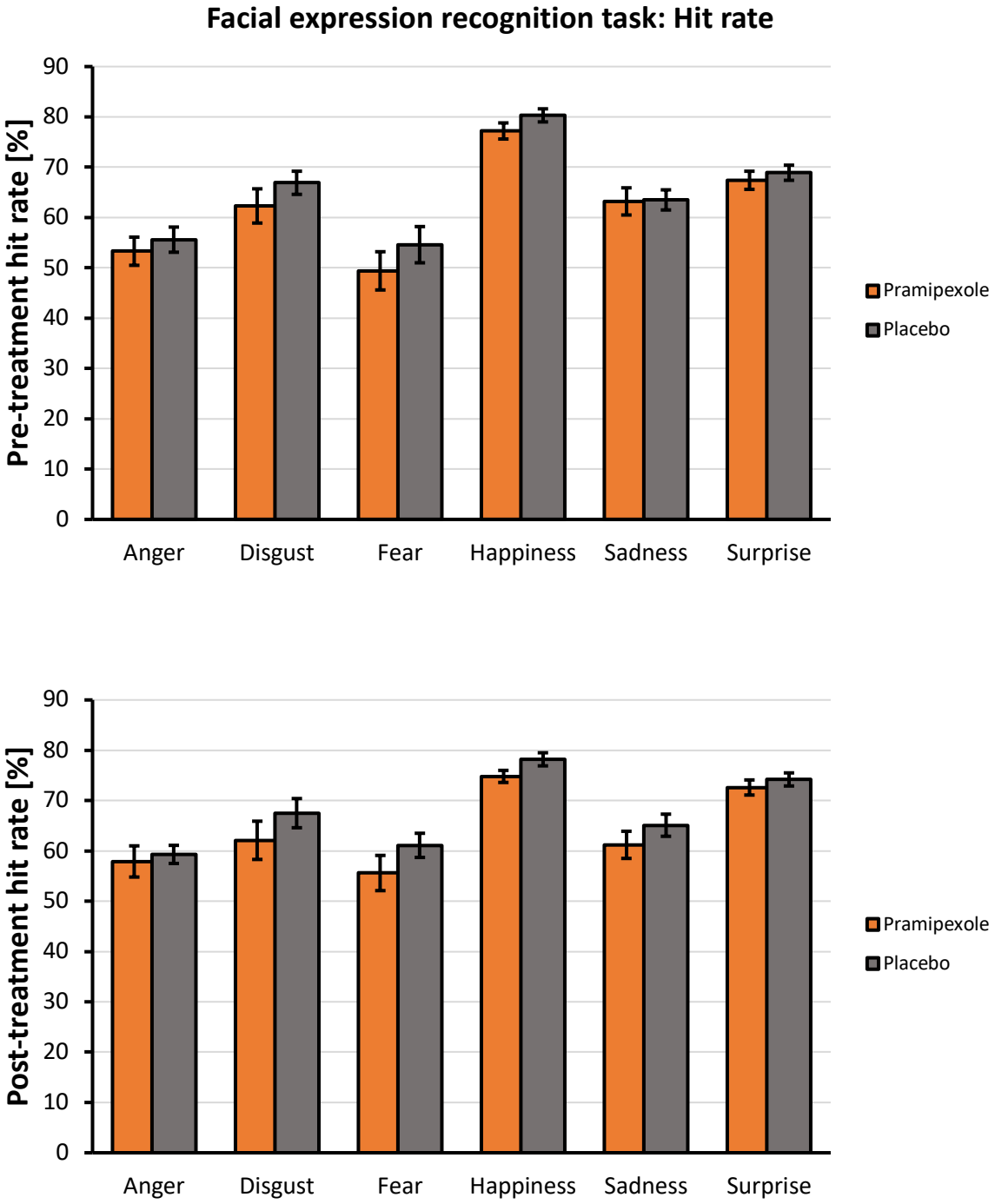


Figure 7: Hit rates (Mean ± 1 S.E.) for different emotions in the facial expression recognition task before and after treatment with either pramipexole or placebo. Pramipexole treatment did not change emotional information processing compared to placebo treatment.

Emotional categorisation task (ECAT)

Engagement in the task was appropriate, as indicated by median hit rates over 90% in both groups for either visit. Analysis of ECAT reaction times suggested that there was no significant treatment group × visit interaction ($F(1,38) = 1.2$, $p = 0.27$) and no treatment group × visit × valence interaction ($F(1,38) = 2.1$, $p = 0.16$). The complimentary robust-mixed design analysis on change scores led to the same overall conclusions as those reported above. Also see Table 14.

Faces dot probe task (FDOT)

Engagement in the task was appropriate, as indicated by median hit rates over 90% in both groups for either visit. Analysis of FDOT vigilance scores was performed separately for the masked and unmasked condition. In the masked condition, there was no significant treatment group × visit interaction ($F(1,38) = 0.3$, $p = 0.61$) and no treatment group × visit × valence interaction ($F(1,38) = 0.01$, $p = 0.92$). The same pattern was observed in the unmasked condition; there was no significant treatment group × visit interaction ($F(1,38) = 0.05$, $p = 0.83$) and also no treatment group × visit × valence interaction ($F(1,38) = 2.0$, $p = 0.16$). Complimentary robust-mixed design analyses on change scores led to the same overall conclusions as those reported above. Also see Table 14.

Emotional recall task (EREC)

With regards to the number of words correctly recalled, there was no significant treatment group × visit interaction ($F(1,38) = 0.01$, $p = 0.92$) and no treatment group × visit × valence interaction ($F(1,38) = 1.0$, $p = 0.31$). Complimentary analyses using robust-mixed design approaches on change scores led to the same overall conclusions. Regarding the number of incorrectly recalled words, there was also no treatment group × visit × valence interaction ($F(1,38) = 0.7$, $p = 0.41$). There

was, however, a trend-wise treatment group × visit interaction ($F(1,38) = 2.9$, $p = 0.10$), and this became significant ($p = 0.04$) in the robust analysis of change scores. The pramipexole group showed a greater increase in incorrectly recalled words independent of valence (in the absence of any clear baseline difference between groups). Also see Table 14.

Did the treatment groups differ in reported side effects and was blinding successful?

Comparison of self-reported side effects indicated that the treatment groups differed significantly for nausea but not for any of the other side effects that were assessed: The pramipexole group reported nausea significantly more often than the placebo group (61.9% versus 5.3%, Fisher's exact test: $p < 0.001$). Also see Table 15. Blinding was not fully achieved: Pramipexole-treated participants correctly guessed their treatment allocation in 61.9% of cases and placebo-treated participants in 84.2% of cases (Fisher's exact test: $p = 0.004$). The assessor correctly guessed treatment allocation in 71.4% of cases for pramipexole-treated participants and 84.2% of cases for placebo-treated participants (Fisher's exact test: $p = 0.001$).

Table 14: Performance in the Oxford Emotional Test Battery of 40 healthy volunteers randomly allocated to treatment with either pramipexole or placebo. Values represent means with standard deviations in parentheses.

	Pramipexole		**Placebo**	
	Baseline	**On drug**	**Baseline**	**On drug**
FERT				
Hit rate [%]				
Anger	53.3 (12.7)	57.9 (14.3)	55.6 (10.5)	59.3 (7.7)
Disgust	62.3 (15.8)	62.1 (17.5)	66.9 (9.6)	67.5 (12.6)
Fear	49.4 (17.2)	55.6 (16.2)	54.6 (15.2)	61.1 (10.2)
Happiness	77.2 (7.3)	74.8 (5.5)	80.3 (5.4)	78.2 (5.3)
Sadness	63.2 (12.5)	61.2 (12.3)	63.5 (8.5)	65.1 (9.3)
Surprise	67.4 (8.3)	72.6 (6.8)	68.9 (6.5)	74.2 (5.5)
Neutral	87.6 (12.6)	87.6 (17.6)	83.3 (12.4)	90.6 (10.0)
False alarm rate [%]				
Anger	1.7 (1.9)	2.1 (2.1)	1.7 (1.1)	1.8 (1.9)
Disgust	2.5 (2.0)	2.2 (1.7)	2.4 (1.7)	1.9 (1.4)
Fear	0.9 (1.2)	1.2 (1.2)	1.3 (0.9)	1.2 (0.9)
Happiness	0.5 (0.7)	0.7 (0.8)	0.5 (0.8)	0.6 (0.8)
Sadness	3.5 (3.3)	3.5 (2.7)	3.0 (2.4)	2.8 (2.4)
Surprise	3.4 (2.5)	2.0 (2.1)	2.5 (1.9)	1.6 (1.4)
Non-identification rate [%]				
Anger	35.6 (9.4)	34.3 (11.3)	33.8 (7.0)	32.8 (8.3)
Disgust	24.3 (7.2)	22.1 (8.5)	21.7 (5.2)	18.2 (7.4)
Fear	23.8 (6.1)	22.4 (5.1)	23.2 (2.5)	22.5 (4.5)
Happiness	19.3 (5.9)	21.0 (4.8)	16.8 (5.5)	18.6 (5.2)
Sadness	34.3 (11.9)	35.0 (10.8)	32.6 (7.7)	31.8 (8.9)
Surprise	27.0 (4.7)	23.5 (4.1)	25.8 (4.9)	21.0 (5.3)
Reaction time [ms]				
Anger	1396.9 (348.1)	1274.1 (202.4)	1429.6 (279.2)	1356.6 (231.3)
Disgust	1437.1 (307.3)	1245.3 (165.6)	1435.8 (247.4)	1246.1 (194.0)
Fear	1646.9 (446.1)	1443.8 (316.5)	1645.4 (325.7)	1456.9 (314.7)
Happiness	1039.8 (112.3)	999.3 (128.1)	1128.4 (140.7)	1028.4 (119.7)
Sadness	1165.5 (162.5)	1100.8 (157.7)	1159.9 (138.0)	1096.6 (129.6)
Surprise	1243.8 (231.5)	1078.8 (165.4)	1259.1 (208.5)	1121.9 (134.4)
Neutral	1074.4 (181.6)	1029.9 (169.1)	1128.2 (157.2)	1056.1 (159.8)
ECAT				
Reaction time [ms]				
Positive	748.0 (147.5)	771.1 (126.1)	724.9 (97.3)	802.4 (120.0)
Negative	799.0 (138.6)	823.0 (171.1)	835.3 (135.0)	869.3 (153.9)
FDOT				
Vigilance bias score [ms]				
Masked positive	8.1 (33.0)	9.5 (37.5)	-7.7 (38.4)	-11.0 (54.1)
Masked negative	-16.1 (40.5)	-8.0 (28.1)	-3.4 (43.8)	-2.9 (32.1)
Unmasked positive	4.0 (34.3)	-1.3 (40.3)	-4.9 (40.5)	4.9 (35.6)
Unmasked negative	-12.0 (40.0)	-2.4 (31.3)	-0.1 (46.0)	-10.7 (33.7)
EREC				
Hits [n correct]				
Positive	5.6 (2.5)	6.4 (3.2)	4.4 (1.2)	5.6 (2.7)
Negative	4.0 (2.3)	4.2 (2.2)	3.5 (1.0)	3.2 (2.1)
Intrusions [n wrong]				
Positive	2.4 (2.7)	8.9 (3.8)	3.2 (2.8)	7.9 (3.2)
Negative	1.4 (1.7)	5.1 (2.1)	1.5 (1.6)	4.4 (2.2)

Table 15: Self-reported side effects of 40 healthy volunteers randomly allocated to treatment with either pramipexole or placebo.

	Pramipexole	**Placebo**	**Fisher's exact test (two-sided)**
Sleeping problems	33.3%	26.3%	$p = 0.74$
Abnormal dreaming	19%	21.1%	$p = 1.00$
Headache	23.8%	21.1%	$p = 1.00$
Dizziness	33.3%	10.5%	$p = 0.13$
Somnolence	45%	21.1%	$p = 0.18$
Nausea	61.9%	5.3%	$p < 0.001$
Vomiting	19%	0.0%	$p = 0.11$
Constipation	4.8%	5.3%	$p = 1.00$
Fatigue	23.8%	21.1%	$p = 1.00$
Impulse control problems	9.5%	5.3%	$p = 1.00$
Hallucinations	0.0%	0.0%	-
Abnormal movements	4.8%	0.0%	$p = 1.00$

Discussion

In this chapter, we probed potential effects of subacute treatment with the dopamine D2/D3 receptor-preferring agonist pramipexole on subjective state and emotional information processing in healthy volunteers. Given that a growing number of studies (both in animals and humans) indicate potential antidepressant efficacy for pramipexole, we aimed to specifically test whether the drug could exert effects on emotional processing in healthy volunteers that mirror those of conventional antidepressant agents (Harmer et al., 2017; Warren et al., 2015). In brief, we found no conclusive evidence for such an effect.

Finding 1: Subacute pramipexole treatment showed no effect on subjective state

Although we assessed a broad range of different measures for subjective state (including mood, energy, anxiety, positive and negative affect, depression, impulsivity, happiness, and experience of pleasure), we found no conclusive evidence for an effect of pramipexole on any of these outcomes. Whilst this result is in line with the predictions of the CONEMATA and parallels what is commonly observed for conventional antidepressant drugs in healthy volunteers (Harmer et al., 2009a; Warren et al., 2015) it is at odds with data from other studies exploring effects of pramipexole treatment in healthy volunteers. For example, Campbell-Meiklejohn et al. (2011) and Freeman et al. (2013) both found reduced positive affect following pramipexole treatment. Similarly, Hamidovic et al. (2008) observed that pramipexole decreased subjective ratings of euphoria, intellectual efficiency, and energy. Further, Samuels et al. (2006a, 2006b) describe reduced contentedness and Drijgers et al. (2012) report increased feelings of anger, fatigue, and tension as well as decreased mood after pramipexole treatment. Moreover, Pizzagalli et al. (2008) report increased negative affect in pramipexole-treated participants (although the effect was linked to adverse physical side effects of the drug).

However, all foregoing studies investigated effects of acute pharmacological challenges and used comparatively low doses of pramipexole. As described earlier, such an approach likely has different effects compared to the subacute treatment we employed here, not only because step-wise titration allows for higher doses to be used, but also because longer treatment regimens might have different neuromolecular effects, such as desensitization of D2, 5-HT1A, and α2 auto-receptors and potentially also increased postsynaptic D2/D3 receptor expression (Chernoloz et al., 2009; Newton et al., 2015). One possible explanation for the divergent findings of our study and those of other authors might thus be afforded by the different treatment regimens and dosages used.

Finding 2: Subacute pramipexole treatment showed no conclusive antidepressant-like effect on emotional information processing

We found no clear-cut evidence for an antidepressant-like emotion- or valence-specific effect of pramipexole on the processing of stimuli with affective tone. Specifically, pramipexole did not induce more positively biased emotional information processing, an effect that is well-documented for conventional antidepressant drugs (Harmer et al., 2017; Warren et al., 2015). There are two important possible explanations for this finding.

First, the cognitive processes assessed by the ETB might be underpinned primarily by serotonergic and noradrenergic signalling activity. Thus, pharmacological modulation of dopaminergic activity via agonism at dopamine D2/D3 receptors might not be able to exert antidepressant-like effects on emotional processing. Although longer treatment with pramipexole has also been shown to indirectly influence serotonin neurotransmission (Chernoloz et al., 2009, 2012; Schulte-Herbrüggen et al., 2012), this effect might be too subtle to cause measurable effects, or alternatively might be counteracted by concurrent dopamine D2 and D3 receptor

stimulation. In the light of an accumulating amount of evidence suggesting an antidepressant effect of pramipexole, the observed null results regarding valence-specific effects on emotional processing are of interest insofar as they suggest that pramipexole's putative antidepressant effects might not be explainable within the theoretical framework of the CONEMATA. Rather, these effects might be brought about via a different (cognitive) mechanism than a shift towards positivity in the processing of information with emotional tone.

The results reported here are also interesting in the light of previous studies assessing effects of the norepinephrine-dopamine reuptake inhibitor bupropion, which affected emotional information processing in a way that parallels the effects of serotonergic and noradrenergic agents (Walsh et al., 2018b, 2018a). The observation that a "pure" D2/D3 dopaminergic manipulation with pramipexole did not show such effects, suggests that bupropion's influence on affective information processing might be brought about mainly via its effect on the noradrenergic system and/or the dopamine D1 receptor subfamily.

Second, our findings could also be an indicator for insufficient clinical efficacy of pramipexole for depressive disorders. Whilst a recent meta-analysis supported the idea that pramipexole can exert antidepressant effects, it also highlighted the need for additional randomised controlled clinical trials to more clearly establish pramipexole's clinical efficacy (Tundo et al., 2019). The Oxford ETB has been suggested to provide a sensitive assay for testing antidepressant efficacy in a human model, with ETB outcomes being predictive of results in randomised clinical trials (Warren et al., 2015). For example, similar to pramipexole, the NMDA antagonist memantine has previously been discussed as a potential novel antidepressant drug, showing promising effects in animal models and open-label trials (Warren et al., 2015). However when tested with the Oxford ETB, memantine

showed only very limited effects on emotional information processing (Pringle et al., 2012; Warren et al., 2015). In line with this finding, memantine eventually also failed to show robust clinical effects in randomised controlled trials (Warren et al., 2015). Although the evidence for pramipexole's antidepressant potential to date is clearer and more robust than it was for memantine, there is still a possibility that pramipexole eventually suffers a similar fate.

Of note, we did observe a possible influence of pramipexole on the number of wrongly recalled words in the emotional recall task. However, this effect was not valence-specific and was not predicted a priori. Whilst this finding could be interpreted in different ways (e.g. decreased risk-aversion, greater impulsivity, increased motivation), a comparable pattern was not observed in any other cognitive domain (e.g. facial expression recognition, emotional word categorisation). Given the relatively high number of comparisons we undertook here and the absence of a similar valence-unspecific effect in other tasks, this finding should thus be interpreted with caution.

Finding 3: Subacute pramipexole-treatment was feasible and well tolerated in healthy volunteers

In general, subacute pramipexole treatment was well tolerated by the participants of this study. Two volunteers dropped out of the study due to subjectively experienced side effects, but both had been allocated to placebo treatment.

The only side effect that was significantly different between treatment groups was nausea, which was reported about ten times more frequently in the pramipexole group compared to the placebo group. This is consistent with reports from other studies, where nausea is also commonly described as the most frequent side effect associated with pramipexole intake (Tundo et al., 2019). Whilst some authors have previously combined pramipexole treatment with the anti-emetic agent

domperidone (a dopamine D2 receptor antagonist that is thought to be active only peripherally) in order to attenuate the experience of nausea (Bellucci et al., 2019; Feld et al., 2014; Murray et al., 2019; Ye et al., 2017), it has been demonstrated that domperidone itself can exert central effects and might thus bias cognitive assessments (Samuels et al., 2007). In general, our participants tolerated the experienced nausea reasonably well and no-one in the pramipexole group decided to drop out of the study. The study thus also provides first evidence that subacute pramipexole treatment at higher doses is feasible in healthy volunteers — even in the absence of antiemetic medication such as domperidone — provided that participants are monitored closely, and the dose titration is conducted slowly and carefully.

From a different perspective, the presence of nausea in the pramipexole group can also be seen as a good indicator of participants' compliance with drug intake.

Study strengths and limitations

To our knowledge, this is the first study probing potential effects of subacute pramipexole treatment on subjective state and emotional information processing in healthy volunteers. The results add to a large corpus of literature probing valence-specific effects of conventional and potential novel antidepressant interventions on emotional information processing (Harmer and Cowen, 2013; Harmer et al., 2009a; Warren et al., 2015). The assay we employed has been widely used, is well-validated, and has been shown to be sensitive to and specific for pharmacological manipulations with conventional antidepressant drugs (Warren et al., 2015). In contrast to previous studies reported in the literature, we did not use single-dose pramipexole treatment but rather employed a subacute dosing scheme with comparatively high target doses. Compared to single-dose challenges, subacute pramipexole treatment has a higher clinical-ecological validity, especially when

considering that acute and subacute treatment regimens with dopaminergic drugs likely have divergent neuromolecular effects (Chernoloz et al., 2009, 2012; Martins et al., 2017; Tokunaga et al., 2012; Walsh et al., 2018b, 2018a).

Nevertheless, there are also some limitations that need to be mentioned. First, we only used subacute treatment for up to 15 days which is still relatively short compared to long-term treatment as is used clinically. Furthermore, although we administered a comparatively high dose for a healthy volunteer study (see Table 2 for other examples), our target dose (1.0 mg pramipexole salt) was still considerably lower than doses used for treatment-resistant depression (Fawcett et al., 2016; Tundo et al., 2019). Second, blinding was not fully achieved, and participants and researchers were able to guess treatment allocations to a certain extent, probably because of the frequent experience of nausea associated with pramipexole treatment. This should not pose a particular problem for our study, because the Oxford ETB is considered robust against placebo effects (Huneke et al., 2017). However, researchers designing future studies with pramipexole should take this issue into consideration and might want to explicitly control for treatment expectations. Third, we tested only healthy volunteers in a certain age range and without a personal or family history of mental health problems. Whilst this allows for a clearer assessment of cognitive effects, it limits the generalisability of results. Future studies therefore might want to also probe effects of pramipexole on emotional information processing in clinical populations. Finally, we did not measure pramipexole serum concentration or prolactin to ascertain compliance with drug intake, however, the high prevalence of nausea in the pramipexole group suggests that most participants adhered to their allocated study treatment.

Conclusion of Chapter 4

In conclusion, we found no clear evidence that subacute pramipexole treatment can influence subjective state or exert significant antidepressant-like effects on the processing of stimuli with affective tone. This suggests that dopamine D2/D3 receptor function probably does not play a significant role in emotional information processing and that the putative antidepressant effects of pramipexole might not be explainable via effects on social or emotion-related cognitive processes. Furthermore, we found nausea to be the only side effect that differed between treatment groups. Whilst nausea was highly prevalent in the pramipexole group, it did not lead to increased dropouts. Therefore, subacute pramipexole treatment without concurrent use of an anti-emetic (such as domperidone) seems to be feasible in healthy subjects and should be used in future trials to better understand potential antidepressant working mechanisms of the drug.

Chapter 5: The effects of subacute pramipexole treatment on learning from positive and negative outcomes in an information bias learning task

Introduction and background

Abnormalities in hot cognition that have been associated with depression include not only biased processing of information with emotional tone (Elliott et al., 2011; Roiser and Sahakian, 2017, 2013) but also disturbances in reward and punishment processing (Eshel and Roiser, 2010; Roiser and Sahakian, 2017, 2013). Such abnormalities in reacting to and learning from appetitive and aversive feedback have been suggested to play an especially important role in the development and maintenance of the difficult-to-treat symptom of depression that is anhedonia (Eshel and Roiser, 2010; Roiser and Sahakian, 2017). Therefore, in this chapter we expand our exploration of potential neurocognitive effects of pramipexole treatment to the domains of learning and decision-making based on appetitive and aversive feedback.

In doing so, we will focus on learning and decision-making under different conditions of "unexpected uncertainty" of outcomes (Pulcu and Browning, 2019). When learning about the regularities of an environment, the human brain faces the problem that many of the processes that determine and influence these regularities are hidden from direct observation (Pulcu and Browning, 2019).[10] In other words, the brain cannot directly "see" these underlying processes but rather has to make inferences about them based on their observable consequences in the environment. This can be illustrated by a simple everyday example: in a restaurant the customer at a table normally does not get to see the kitchen staff, however, they might still be able to infer who is in charge of preparing the food in the kitchen (e.g. the "chef"

[10] The following description of the basic ideas of expected and unexpected uncertainty are based on (and can be found in greater detail in) a recent review on the topic by Pulcu and Browning (2019).

versus the "apprentice") based on the quality of the food that is delivered to the table (e.g. "great" versus "mediocre").

However, in many contexts the relationship between a hidden process and its consequence is probabilistic. For example, the food we receive in our exemplary restaurant might be mediocre in 40% of the cases when the apprentice is cooking, however, since many things can go wrong in a kitchen, the food might also be mediocre in 10% of the cases when the chef is preparing the food. Thus, by ordering a single dish we would not be able to tell with complete certainty who is currently in charge at the hob. The type of uncertainty that is associated with such a situation is referred to as "expected uncertainty" — the learner knows that a predictive cue is associated with a specific outcome but there remains a certain degree of unreliability (Pulcu and Browning, 2019; Yu and Dayan, 2005). In the face of expected uncertainty, the more observations one has available the more confident one can become in one's estimate of the state of the hidden process in question (Pulcu and Browning, 2019). If we order more than one dish in our exemplary restaurant, we would become more certain in our inference about who is preparing the food at the moment.

Unfortunately, in real-world contexts things tend to be more complicated because the states of a hidden process can change over time. To stick with our restaurant example, while we are enjoying starters prepared by the chef, the apprentice might start their shift and take charge of the remaining courses. To accurately gauge the regularities of the environment, the human brain thus has to maintain estimates not only about the states of hidden processes but also about whether and how these states change over time (Pulcu and Browning, 2019). The uncertainty that arises because the state of a hidden process can change over time is referred to as "unexpected uncertainty" (Pulcu and Browning, 2019; Yu and Dayan, 2005). The

frequency with which the state of a hidden process changes in an environment is referred to as the "volatility" of that process (Pulcu and Browning, 2019). The higher the volatility of a process, the higher is the unexpected uncertainty associated with inferences about it.

When the brain tries to learn about a volatile process in the environment, it does not help to simply take into consideration as many past observations as possible (as in the case of expected uncertainty), because the state of the hidden process is not stable over time. To more accurately gauge the current state of affairs, it is better for the brain to base inferences on relatively recent observations only (*how* recent is a non-trivial question though) (Pulcu and Browning, 2019). For example, if the chef and the apprentice rotate in their kitchen duty roughly every few hours, information about whether the food was good or mediocre three days ago is of little help to estimate who is currently preparing meals. A better strategy would be to take into consideration only the quality of food of the last few dishes we ordered at the current visit to the restaurant.

If a hidden process is deemed to be more volatile, the brain needs to update its beliefs about this process "faster" to stay on track about the current state of affairs in the environment. Thus, when generating estimates about volatile processes, more recent observations should influence current beliefs to a stronger degree than more distant observations. In other words, a new outcome is more informative when the volatility of a process is high as compared to when volatility is low (Pulcu and Browning, 2017; Pulcu et al., 2019).

As described before, pramipexole treatment has shown promising effects in depressive disorders and is currently in discussion as a potential novel treatment for patients suffering from unipolar and bipolar depression (Cowen, 2017a; Fawcett et al., 2016; Tundo et al., 2019). Furthermore, in patients with Parkinson's disease

and restless legs syndrome, treatment with pramipexole has been associated with impulse control disorders such as gambling or hypersexual behaviour (Cornelius et al., 2010; Etminan et al., 2017; Seeman, 2015). These problems are characterised by excessive pursuit of and engagement in often pleasurable activities that are continued even in the face of negative consequences such as financial strain or interpersonal problems. One possible explanation for both these phenomena could be that pramipexole influences how informative the brain deems positive relative to negative outcomes. It could be the case, for example, that pramipexole treatment selectively increases the estimated information content for positive outcomes and/or decreases it for negative outcomes, similar to the positive biases in emotional processing that the CONEMATA describes for conventional antidepressant treatments.

The aim of this chapter was to directly test this hypothesis in a healthy volunteer model. To this end, we used an established information bias learning task where positive and negative outcomes are associated independently with different stimuli so that the volatility of the stimulus-outcome associations can be manipulated individually for appetitive and aversive outcomes. Using a simple computational reinforcement learning model, we derived learning rates and inverse temperatures for each participant to quantitatively estimate how informative they deemed positive and negative outcomes under different conditions of outcome volatility, and to what extent these beliefs guided their decision about the next action to take. In line with the theoretical background of the CONEMATA and the main objective of this thesis, we hypothesised that pramipexole would selectively increase the estimated information content of positive relative to negative outcomes and/or the extent to which beliefs about positive outcomes guided subsequent decisions. Thus,

we predicted that pramipexole treatment would selectively increase learning rates and/or inverse temperatures for appetitive relative to aversive outcomes.

Material and methods

Study sample, design and intervention

The data for this chapter were collected as part of a larger experimental medicine study that has already been described in detail in Chapter 4. Briefly, 40 healthy volunteers were randomly allocated to treatment with either pramipexole (dose titrated in 0.25 mg steps over about 10 days, peak dose 1.0 mg pramipexole salt per day) or placebo (lactose) in a parallel-group double-blind design. All participants underwent testing in an information bias learning task, both at baseline and when peak pramipexole doses were established.

Information bias learning task (IBLT)

In order to assess whether pramipexole might influence learning and decision-making based on appetitive and aversive outcomes, we employed a recently described information bias learning task (Pulcu and Browning, 2017; Pulcu et al., 2019). In each trial of this task, participants are presented with two abstract symbols (letters from the Agathodaimon font) on a computer screen and are asked to choose the symbol which they think will result in the best outcome. After a choice has been made, participants receive feedback. In each trial, one symbol is associated with a positive/appetitive outcome (i.e. winning a fixed amount of money) and one symbol is associated with a negative/aversive outcome (i.e. losing a fixed amount of money). Importantly, the positive and negative outcomes are independent of each other. This means that they can appear either behind two separate symbols or both behind the same symbol and knowing the position of one does not provide

information about the position of the other. To summarise, in each trial four different outcomes are possible:

(1) Win appears behind the chosen symbol and loss appears behind the unchosen symbol. The trial ends with the study participant winning money.

(2) Win appears behind the unchosen symbol and loss appears behind the chosen symbol. The trial ends with the study participant losing money.

(3) Win and loss both appear behind the chosen symbol. The trial ends with no change in monetary earnings.

(4) Win and loss both appear behind the unchosen symbol. Again, the trial ends with no change in monetary earnings.

Participants have to learn by trial and error which symbol is most likely to be associated with each outcome and then use this information to make choices that maximise their monetary earnings in the task. We assessed learning about positive and negative outcomes under three different conditions of outcome volatility: In the first condition, both wins and losses are volatile. In the second condition, wins are stable, and losses are volatile. In the third condition, wins are volatile, and losses are stable.

The task was presented on a standard computer monitor. The different outcome volatility conditions were presented in different blocks that were separated by short breaks. In the first block (160 trials), positive and negative outcomes were both volatile. In the second block (80 trials), the win outcome was volatile, and the loss outcome was stable. In the third block (80 trials), the win outcome was stable, and the loss outcome was volatile. The order of the second and third block was chosen randomly for each participant. Symbols stayed the same for each block but changed between blocks. In each trial, a fixation cross was presented in the middle of the screen with the abstract symbols appearing in equal distance from the cross on

either side. Below the fixation cross the total amount of money won so far was displayed, which was updated after each trial to include the most recent outcome. After a choice was made by button-press, win and loss outcomes were presented separately in random order accompanied by distinct simple sounds. Participants started the task with £1.50. Every win outcome increased the total amount by 15 pence, and every loss outcome decreased it by 15 pence. When an outcome was volatile in the task, its probability of being associated with a given symbol shifted between 0.15 and 0.85 in segments of 14 to 30 trials. In contrast, when an outcome was stable in the task, it was simply associated with a given symbol with a probability of 0.5 (that is, recent past outcomes gave no information about outcomes in the trials that followed).

Participants were instructed at the beginning of the task that they would be paid their total winnings in addition to a fixed study reimbursement.

The information bias learning task has previously been used to demonstrate adaptive learning in humans (Pulcu and Browning, 2017). It could be shown that study participants adjust their learning rate (i.e. the extent to which new input changes current beliefs about outcome associations) based on the volatility of outcomes (i.e. the frequency with which the associations between stimuli and outcomes change in the task) in an optimal manner (also see Behrens et al. (2007), Browning et al. (2015), Pulcu and Browning (2019)). Furthermore, it could be demonstrated that humans can hold separate estimates of the volatility of positive versus negative outcomes and adjust their learning rates independently based on the volatility of each outcome type, and that this process can be influenced pharmacologically (Pulcu and Browning, 2017; Pulcu et al., 2019).

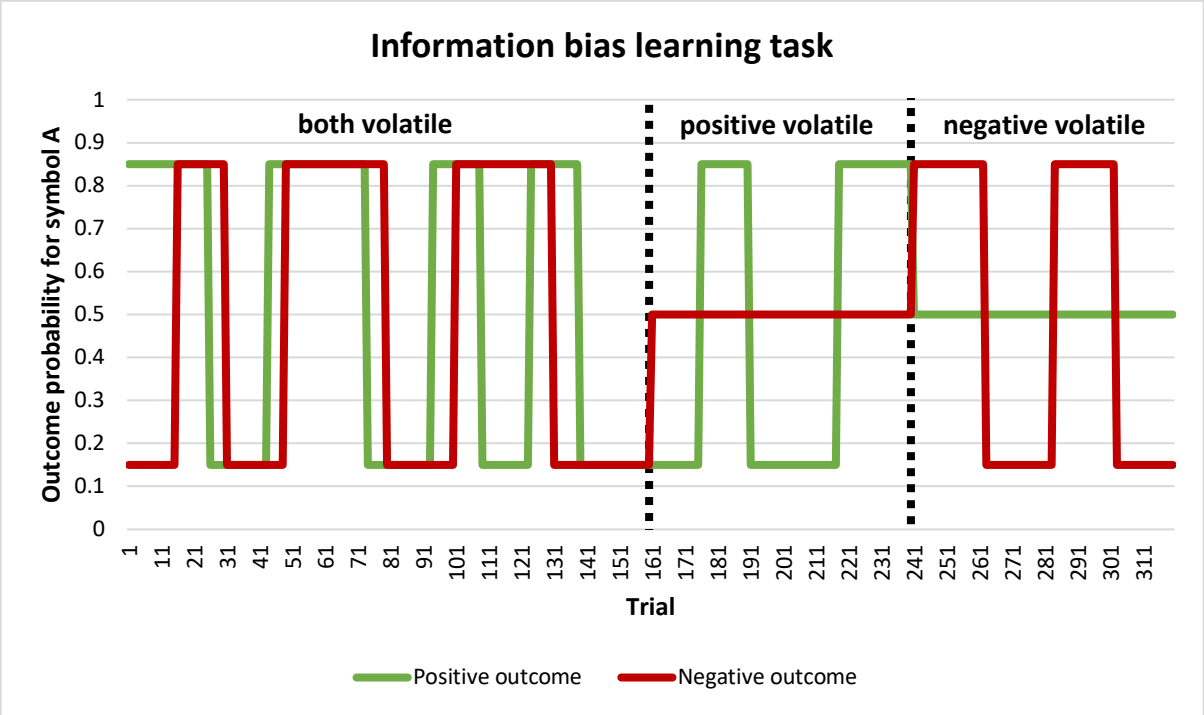


Figure 8: Exemplary depiction of outcome structure in the information bias learning task. There were three different outcome conditions: (1) both outcomes volatile, (2), positive outcome volatile and negative outcome stable, and (3) positive outcome stable and negative outcome volatile. When an outcome is volatile, its probability of being associated with a given symbol shifts between 0.15 and 0.85. When an outcome is stable, it is associated with a given symbol with a probability of 0.5.

Analysis

In order to assess how participants learned from positive and negative outcomes under different conditions of outcome volatility and how they used this information to guide their choices, behavioural models were fitted to participants' responses in the task. Data from three participants (all from the placebo group) were excluded from the analysis because they demonstrated no evidence of learning in the task (i.e. total money won was less than the initial £1.50) either at pre- or at post-treatment assessment. Thus, data from a total of 37 participants were analysed.

Our main outcome of interest in this chapter was the learning rate for positive and negative outcomes under different conditions of outcome volatility. To this end, a model was fitted to the data which has two learning rates (for both positive and negative outcomes, respectively), a single inverse temperature, and a choice bias term that allows for individual preferences towards a specific symbol (see the following section for a detailed description of the model). This model will be referred to as "Model 1" and has previously been shown to be the best fitting model for the task (Pike, 2018; Pulcu et al., 2019). It allowed us to test the hypothesis that pramipexole treatment would induce a positive bias, that is, increase learning rates for positive relative to negative outcomes.

In addition, we also compared the parameters of a model that has one learning rate, two separate inverse temperatures (for wins and losses respectively), and a choice bias term. This will be referred to as "Model 2". Model 2 fitted the data marginally better than Model 1 and allowed us to additionally assess whether pramipexole treatment changed the extent to which participants' choices were influenced by their beliefs about outcomes and whether this was specific to wins or losses.

Description of the main model used (Model 1)

The primary outcomes of interest in this chapter were the learning rates for positive and negative outcomes (i.e. wins and losses). These can be estimated separately using a mathematical model (Model 1) that has been developed in previous work using the information bias learning task (Pike, 2018; Pulcu et al., 2019). The model is based on the idea that, in a first step, the brain estimates separate probabilities for positive and negative outcomes to be associated with a given symbol. This estimate is updated after each trial (labelled by index i) following a Rescorla-Wagner learning rule (Rescorla and Wagner, 1972),

$$rwin_{(i+1)} = rwin_{(i)} + \alpha_{win}(winout_{(i)} - rwin_{(i)}),$$

$$rloss_{(i+1)} = rloss_{(i)} + \alpha_{loss}\big(lossout_{(i)} - rloss_{(i)}\big).$$

In these equations, $rwin_{(i)}$ (initialised at 0.5) represents the previously estimated probability for the win to be associated with symbol A on trial i (with the probability of the win being associated with the other symbol B being $1 - rwin_{(i)}$). The parameter $winout_{(i)}$ has a value of 1 if win was associated with symbol A on trial i and value 0 otherwise. The parameters $rloss_{(i)}$ and $lossout_{(i)}$ have equivalent meanings but for the negative (i.e. loss) outcome. Finally, the parameters α_{win} and α_{loss} represent the learning rates for wins and losses, respectively. Learning rates can range from 0 to 1 and determine the extent to which new win and loss outcomes change the estimated probabilities $rwin_{(i+1)}$ and $rloss_{(i+1)}$. A higher learning rate means that the probability estimate is influenced more strongly by recent outcomes. In a next step, the estimated outcome probabilities are used to calculate a single choice probability using the following sigmoid function:

$$P_{(i)} = \frac{1}{1 + e^{-(\beta(rwin_{(i)} - 0.5 + \frac{\varphi}{2}) - \beta(rloss_{(i)} - 0.5 - \frac{\varphi}{2}))}}.$$

In this equation, $P_{(i)}$ represents the probability that symbol A is chosen on trial i. The parameter β represents "inverse temperature" or "choice stochasticity". It ranges between 0 and ∞ and determines the extent to which a learner's current probability estimates of outcomes align with their actual decisions in the task. A larger β means that choices are more strongly governed by estimated outcome probabilities, that is, they become more deterministic (the learner tends to pick what they currently believe to be the best choice). In turn, a β close to 0 means that choices are barely influenced by current estimates of outcome probabilities and tend towards randomness (the learner does not make much use of their current beliefs about outcomes but rather picks more or less randomly). The parameter φ represents a bias term that allows to account for an individual preference to choose symbol A over symbol B.

Thus, we end up with a model comprising four free parameters (two learning rates α, one inverse temperature β, one choice bias φ). These parameters were estimated separately for each participant and task block. First, the joint posterior probability distribution of parameters over the parameter space given the participant's choices in the task was calculated. From this, a marginalised probability distribution for each parameter was obtained. Parameters were then estimated as their expected values given this distribution.

Alternative models

The behavioural models that we use in this chapter are based on models described in previous studies employing the information bias learning task. These models have been shown to outperform a range of other alternative models, however, it is important to also know how well our models individually fit the participants' choice data. Therefore, we compared the fit of our models using the Akaike

information criterion (AIC), which takes into consideration the likelihood of the estimated values of the free parameters whilst also penalising for model complexity (lower AIC scores indicate a better fit). Fits were calculated using the sum of AIC across blocks and visits. We also calculated model fits for simpler versions of our models (referred to as Models 2 to 7) for comparison. In the next paragraphs, a brief overview of all models considered is provided (for an overview of models, also see Table 16).

Model 1: This model has already been described in detail above. It contains two learning rates (α_{win} and α_{loss}), one inverse temperature (β), and a choice bias term (φ). This model was used to estimate separate learning rates for positive and negative outcomes. This model has been reported repeatedly as providing the best fit for the information bias learning task (Pike, 2018; Pulcu et al., 2019).

Model 2: This model is similar to Model 1 but comprises one learning rate (α), two individual inverse temperatures for positive and negative outcomes (β_{win} and β_{loss}), and a choice bias term (φ). This model allowed to estimate the extent to which current probability estimates drive participants' choices in the task.

Model 3: This model contains two learning rates (α_{win} and α_{loss}) and two inverse temperatures (β_{win} and β_{loss}). It has been described as having the best fit for the information bias learning task when compared to a range of qualitatively different models (e.g. Behren's Bayesian learner or a model including a risk parameter), but not Model 1 (Behrens et al., 2007; Pulcu and Browning, 2017).

Model 4: This is a simpler model which has just one learning rate (α), one inverse temperature (β) and one choice bias term (φ). This means that the model does not distinguish between wins and losses at all, but rather just takes the overall outcome ("value") associated with a symbol to guide subsequent choices.

Model 5 to 7: These models represent simpler variants of Models 1, 2, and 4 in that they do not contain a choice bias term.

We compared AIC values to select the best fitting model: Model 2 showed the best fit (mean total AIC = 490.5), followed closely by Model 1 (mean total AIC = 491.9).

Table 16: Overview of different models fitted to participants' choices in the information bias learning task.

	Number of learning rate parameters (α)	**Number of inverse temperatures (β)**	**Bias term (φ)**	**Comments**
Model 1	2	1	Yes	Repeatedly described as having the best fit for the information bias learning task (Pike, 2018; Pulcu et al., 2019); allows to assess learning from positive and negative outcomes. Mean AIC = 491.9
Model 2	1	2	Yes	Best fitting model in this study; allows to assess choice stochasticity for rewarding and punishing outcomes but not learning from positive and negative outcomes. Mean AIC = 490.5
Model 3	2	2	No	Originally described as having the best fit for the information bias learning task (Pulcu and Browning, 2017). Mean AIC = 502.0
Model 4	1	1	Yes	Model does not distinguish between win and loss outcomes. Mean AIC = 510.1
Model 5	2	1	No	Simpler variant of Model 1. Mean AIC = 505.5
Model 6	1	2	No	Simpler variant of Model 2. Mean AIC = 505.1
Model 7	1	1	No	Simpler variant of Model 4. Mean AIC = 519.5

Non-model-based analysis of learning

In order to complement our model-based analyses, we also conducted a non-model-based ("model-free") analysis. This approach allowed us to corroborate the observed results and to probe whether they depend on specific assumptions of the models used (Pulcu et al., 2019). In the information bias learning task, there are trials in which both outcomes encourage the same behaviour (e.g. win associated with symbol A and loss associated with symbol B encourages subsequent choice of symbol A). However, there are also trials in which the positive and the negative outcome encourage opposite behaviours (e.g. win and loss both associated with symbol A or neither win and loss associated with symbol A). These latter trial types provide a simple means by which to assess a bias in learning without using a computational model. If a study participant showed a relative bias towards positive outcomes, then one would expect that this person stuck with their chosen symbol if it was associated with both outcomes and changed their chosen symbol if it was associated with neither outcome (Pulcu et al., 2019). In contrast, if a person showed a learning bias towards negative outcomes, we would expect the opposite behaviour: They would stick with their choice if it was associated with neither outcome and change their choice if it was associated with both outcomes (Pulcu et al., 2019).

Statistical analysis of model parameters

All analyses were carried out in SPSS (version 25.0). To compare groups on model parameters, mixed-design ANOVAs were used. For each model, the first block (where both outcomes were volatile) was analysed separately from the last two blocks (where one outcome was volatile and the other one was stable), as they assess different effects. Group always served as the between-subjects factor and visit and valence (where applicable) served as within-subjects factors. Furthermore, for

analysis of the last two blocks, block type was added as a within-subjects factor. Model parameters were transformed to the infinite real line before analysis using a logit transformation for the learning rate and a log transformation for the inverse temperature. Untransformed values are reported in Figures for simplicity. Given that the aim of the study was to assess potential effects of pramipexole on the processing of reward and punishment related information, we were primarily interested in effects that included a treatment group × visit interaction. We were not interested in group differences independent of visit or simple effects of visit, hence they are not reported below (see Table 18 in Appendix for an overview of these effects). Analysis of model-free outcomes (e.g. monetary outcomes, switch rates, reaction times) were analysed in the same way. For switch rates, outcome type (i.e. both outcomes associated with symbol versus no outcome associated with symbol) was added as a within-subjects factor.

Results

Behavioural outcomes

Total money won

When comparing treatment groups in terms of total money won in the first block (both outcomes volatile), there was no significant group × visit interaction ($F(1,35) = 0.5$, $p = 0.50$). In terms of total money won in the last two blocks (one outcome stable and the other one volatile), there was also no group × visit interaction ($F(1,35) = 0.1$, $p = 0.74$) and no group × visit × block interaction ($F(1,35) = 1.9$, $p = 0.18$). Also see Figure 9.

Reaction time

Analysis of group differences in reaction times in the first block (both outcomes volatile) showed no significant group × visit interaction ($F(1,35) = 0.03$, $p = 0.86$).

Analysis of reaction times in the last two blocks (one outcome stable and the other one volatile) showed no group × visit interaction ($F(1,35) = 0.02$, $p = 0.89$), but a trend-wise group × visit × block interaction ($F(1,35) = 3.5$, $p = 0.07$). However, the latter depended on a single outlier. Once this data point was removed, the trend-wise interaction disappeared ($F(1,34) = 2.6$, $p = 0.11$). Also see Figure 10.

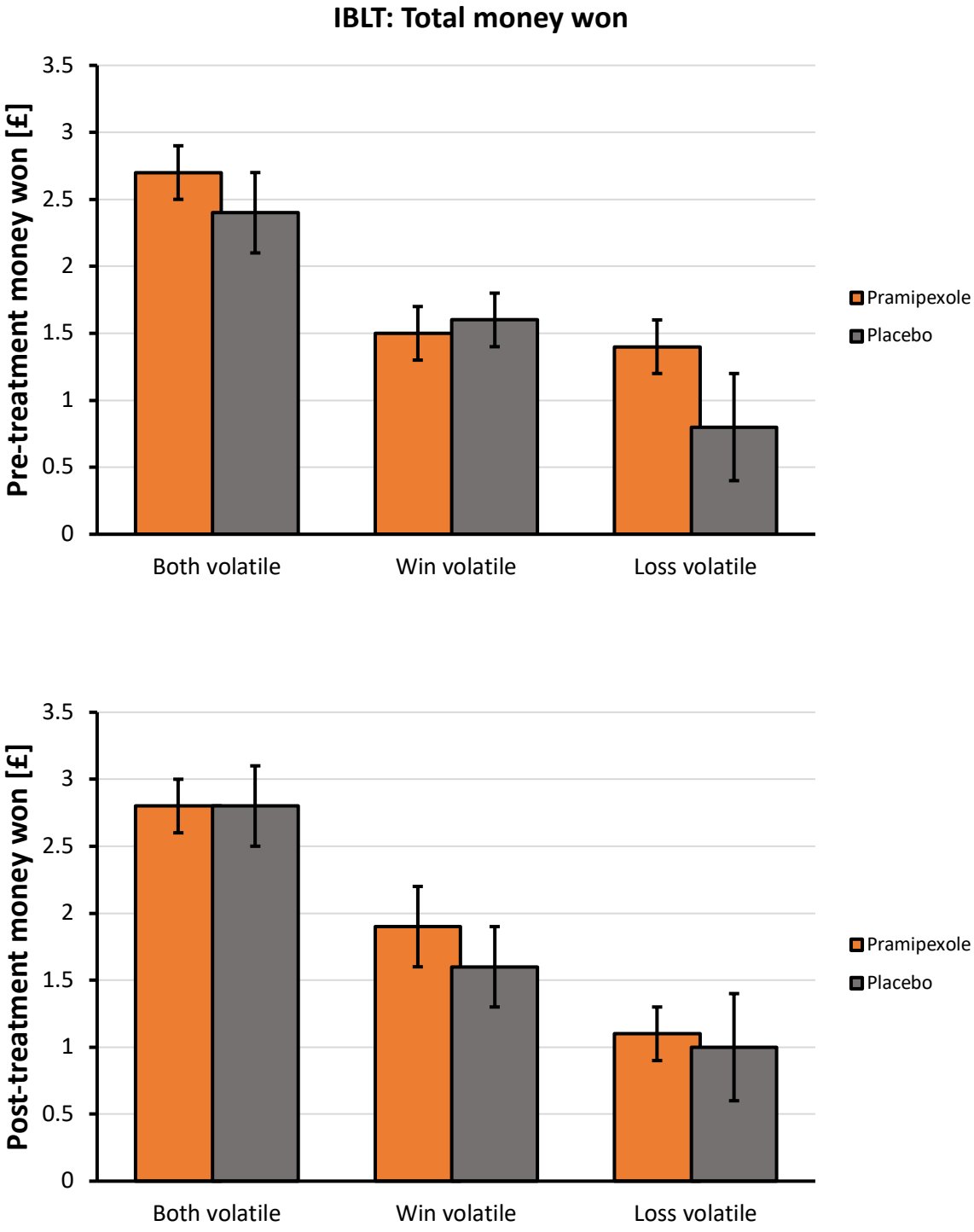


Figure 9: Total money won (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

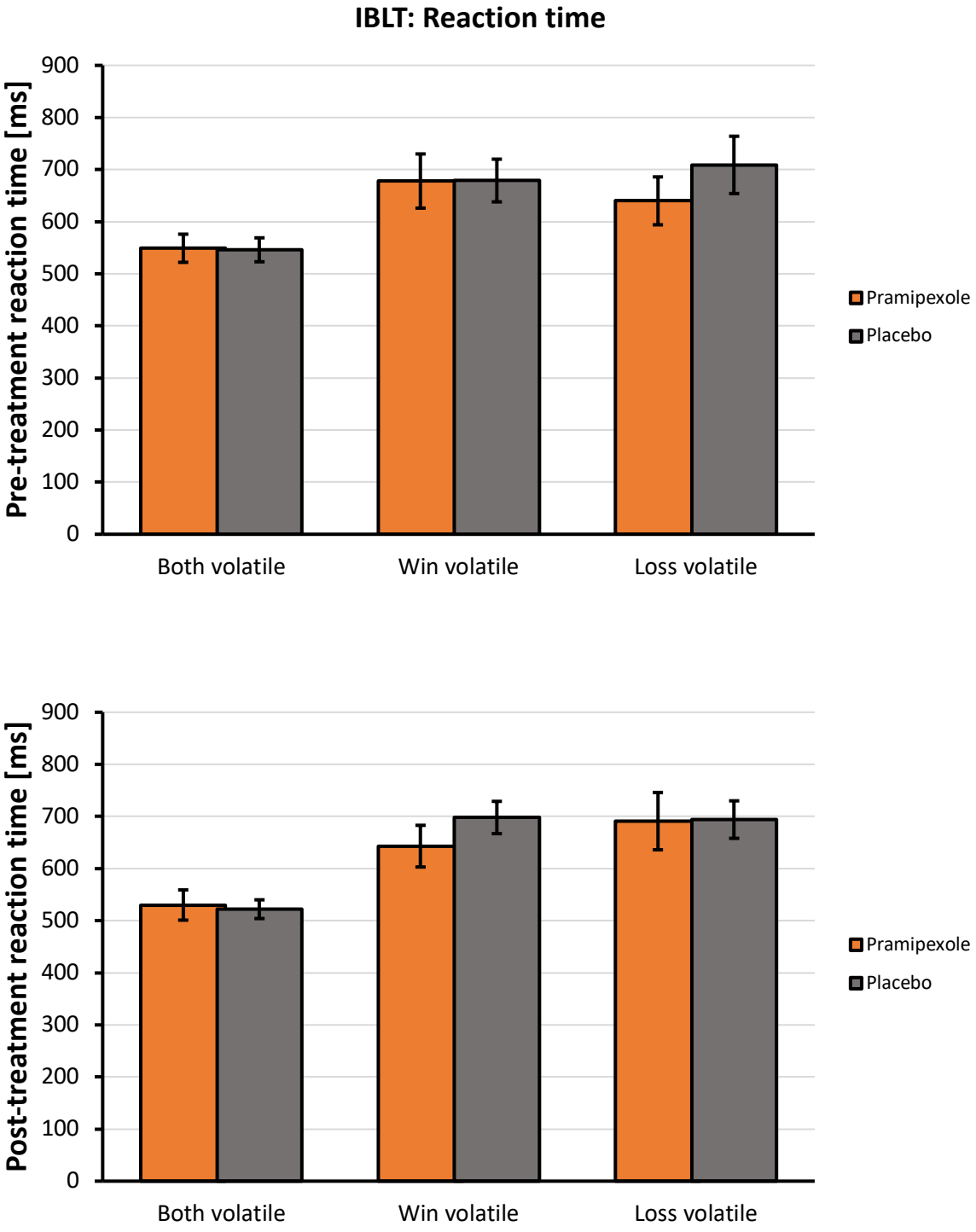


Figure 10: Reaction time (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

Model 1

Learning rates (α_{win} and α_{loss})

When comparing treatment groups in terms of learning rates (α_{win} and α_{loss}) in the first block (both outcomes volatile) there was no significant group × visit interaction ($F(1,35) = 0.7$, $p = 0.41$) and no group × visit × valence interaction ($F(1,35) = 0.1$, $p = 0.79$).

Comparison of learning rates in the second and third block showed no significant group × visit interaction ($F(1,35) = 0.04$, $p = 0.84$), no group × visit × valence interaction ($F(1,35) = 0.6$, $p = 0.46$), no group × visit × block interaction ($F(1,35) = 0.004$, $p = 0.95$), and no group × visit × valence × block interaction ($F(1,35) = 0.03$, $p = 0.86$) either. See Figure 11 and Figure 12.

Inverse temperature (β)

When comparing groups in terms of inverse temperatures (β) in the first block (both outcomes volatile) there was a significant group × visit interaction ($F(1,35) = 5.3$, $p = 0.03$). When comparing groups' inverse temperatures separately for each visit there was no significant baseline difference ($t(35) = 1.1$, $p = 0.26$) and no significant on-drug difference ($t(35) = 0.9$, $p = 0.35$). However, when inverse temperatures were compared separately for each group, there was a significant increase from pre-treatment to post-treatment in the placebo group ($t(15) = 3.0$, $p = 0.01$, $d = 0.7$), but no significant change in the pramipexole group ($t(20) = 0.8$, $p = 0.43$, $d = 0.2$).

Comparison of inverse temperatures in the second and third block showed no group × visit interaction ($F(1,35) = 1.2$, $p = 0.29$), and no group × visit × block interaction ($F(1,35) = 0.3$, $p = 0.59$). See Figure 13.

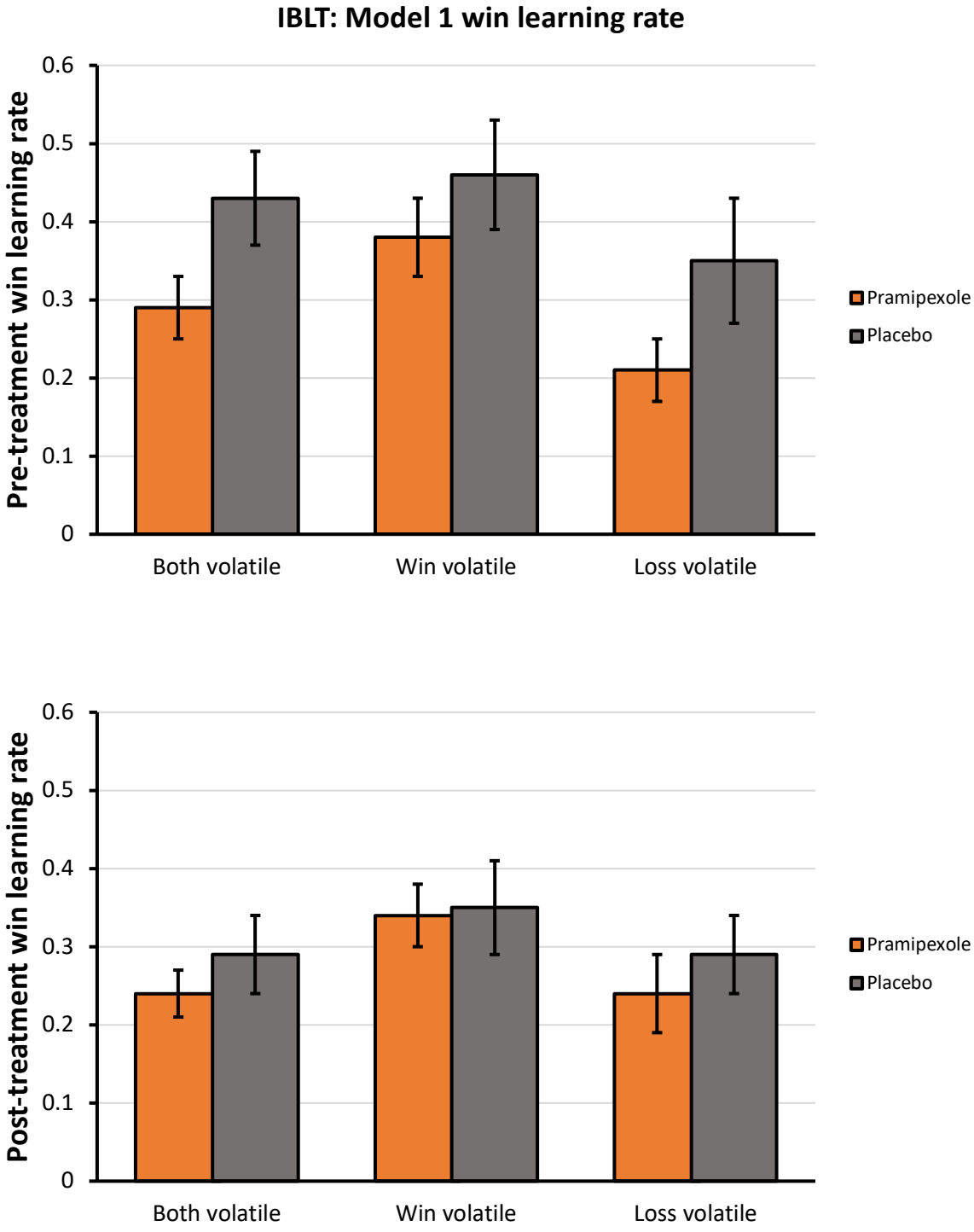


Figure 11: Model 1 win learning rate (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

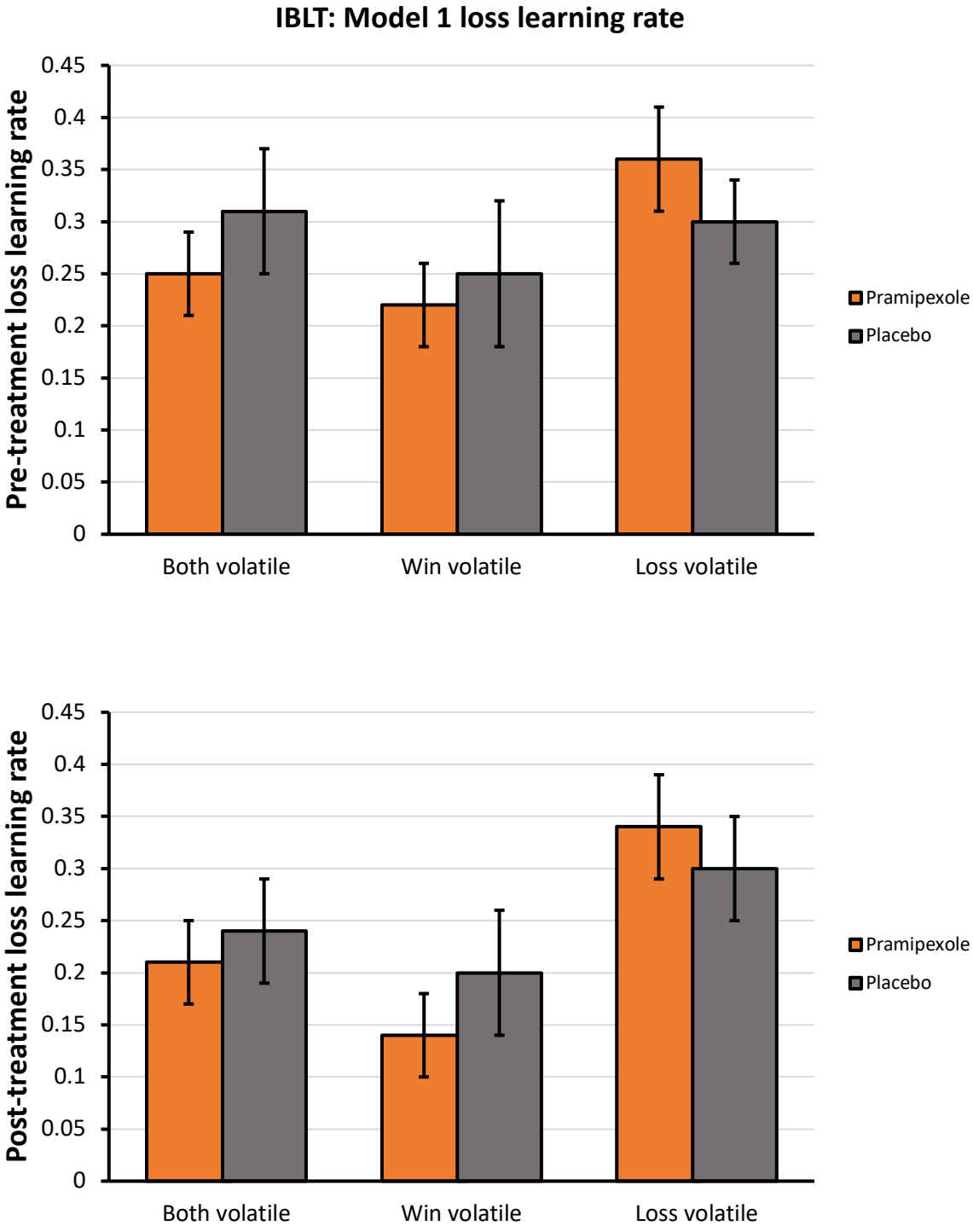


Figure 12: Model 1 loss learning rate (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

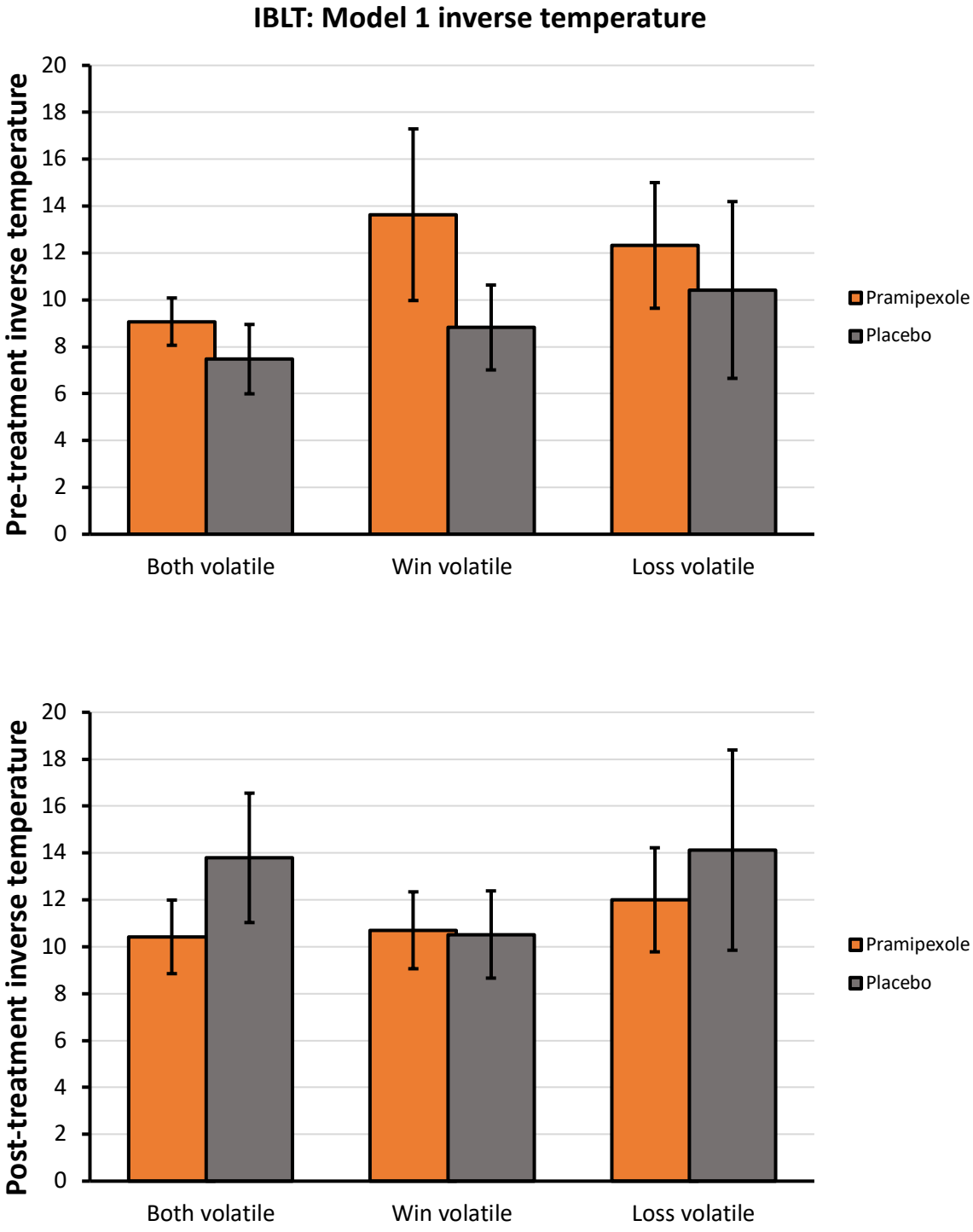


Figure 13: Model 1 inverse temperature (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

Model 2

Learning rate (α)

When comparing groups in terms of learning rates (α) in the first block (both outcomes volatile) there was no significant group × visit interaction ($F(1,35) = 0.3$, $p = 0.59$).

Comparison of learning rates for the second two blocks (one outcome volatile and the other stable, respectively) showed no group × visit interaction ($F(1,35) = 0.5$, $p = 0.50$) and no group × visit × block interaction ($F(1,35) = 0.006$, $p = 0.94$) either. See Figure 14.

Inverse temperature (β_{win} and β_{loss})

Analysis of inverse temperatures (β_{win} and β_{loss}) in the first block (both outcomes volatile) showed a significant group × visit interaction ($F(1,35) = 4.7$, $p = 0.04$), but no group × visit × valence interaction ($F(1,35) = 0.008$, $p = 0.93$). When comparing groups separately for each visit there was no significant baseline difference for positive and negative outcomes ($t(35) = -0.8$, $p = 0.40$ and $t(35) = -1.0$, $p = 0.33$, respectively). There was also no significant on-drug difference for positive and negative outcomes ($t(35) = 1.3$, $p = 0.21$ and $t(35) = 0.7$, $p = 0.49$, respectively). However, when inverse temperatures were compared separately for each group, there was a significant increase from pre-treatment to post-treatment in the placebo group for both positive ($t(15) = 2.6$, $p = 0.02$) and negative outcomes ($t(15) = 2.2$, $p = 0.045$). In contrast, there was no significant change in the pramipexole group; neither for positive ($t(20) = 0.8$, $p = 0.41$) nor for negative outcomes ($t(20) = 0.3$, $p = 0.75$).

Analysis of inverse temperatures in the second and third block showed no group × visit interaction ($F(1,35) = 2.6$, $p = 0.12$), no group × visit × valence

interaction ($F(1,35) = 0.2$, $p = 0.65$), no group × visit × block interaction ($F(1,35) = 0.4$, $p = 0.52$), and no group × visit × valence × block interaction ($F(1,35) = 0.1$, $p = 0.81$). See Figure 15 and Figure 16.

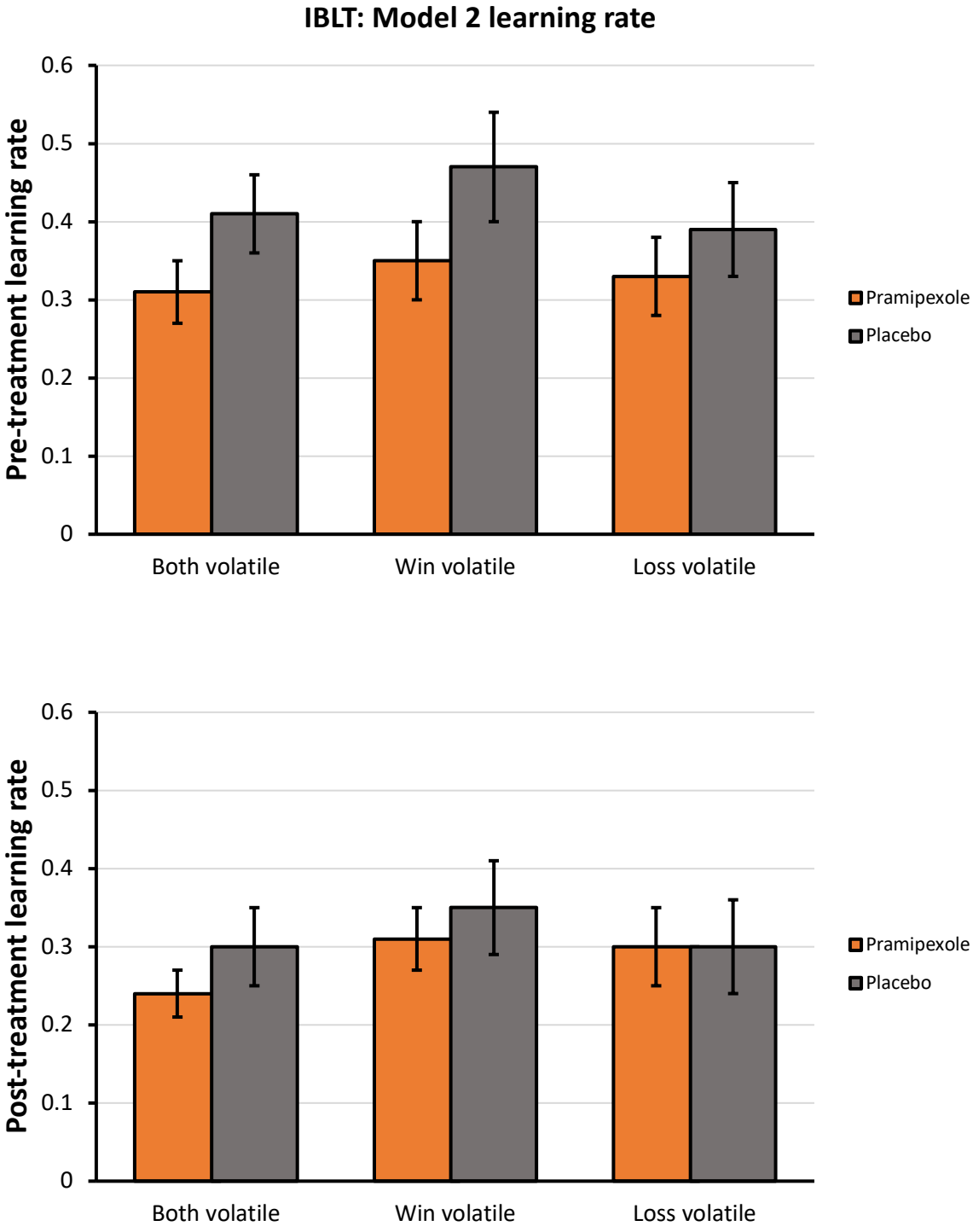


Figure 14: Model 2 learning rate (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

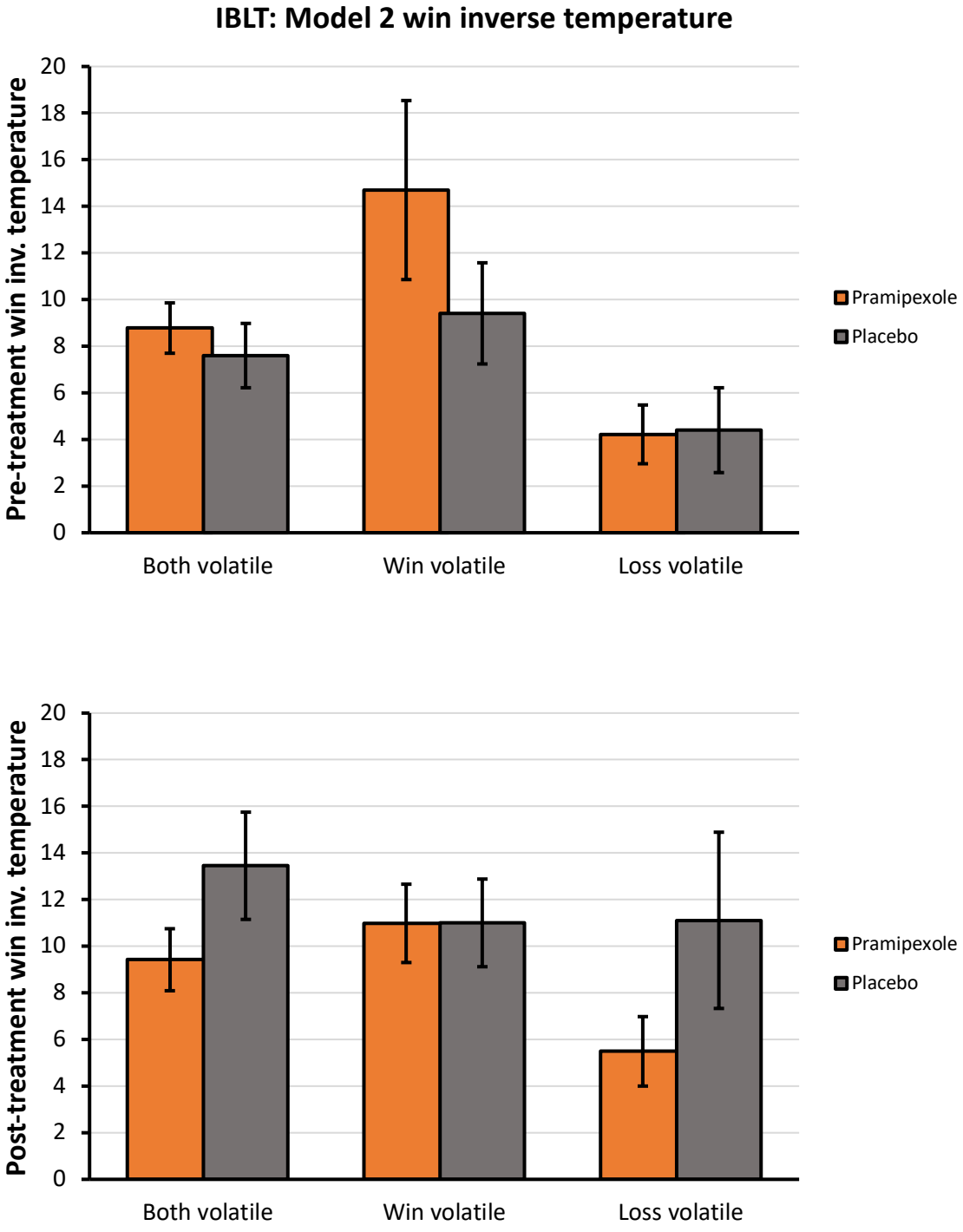


Figure 15: Model 2 win inverse temperature (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

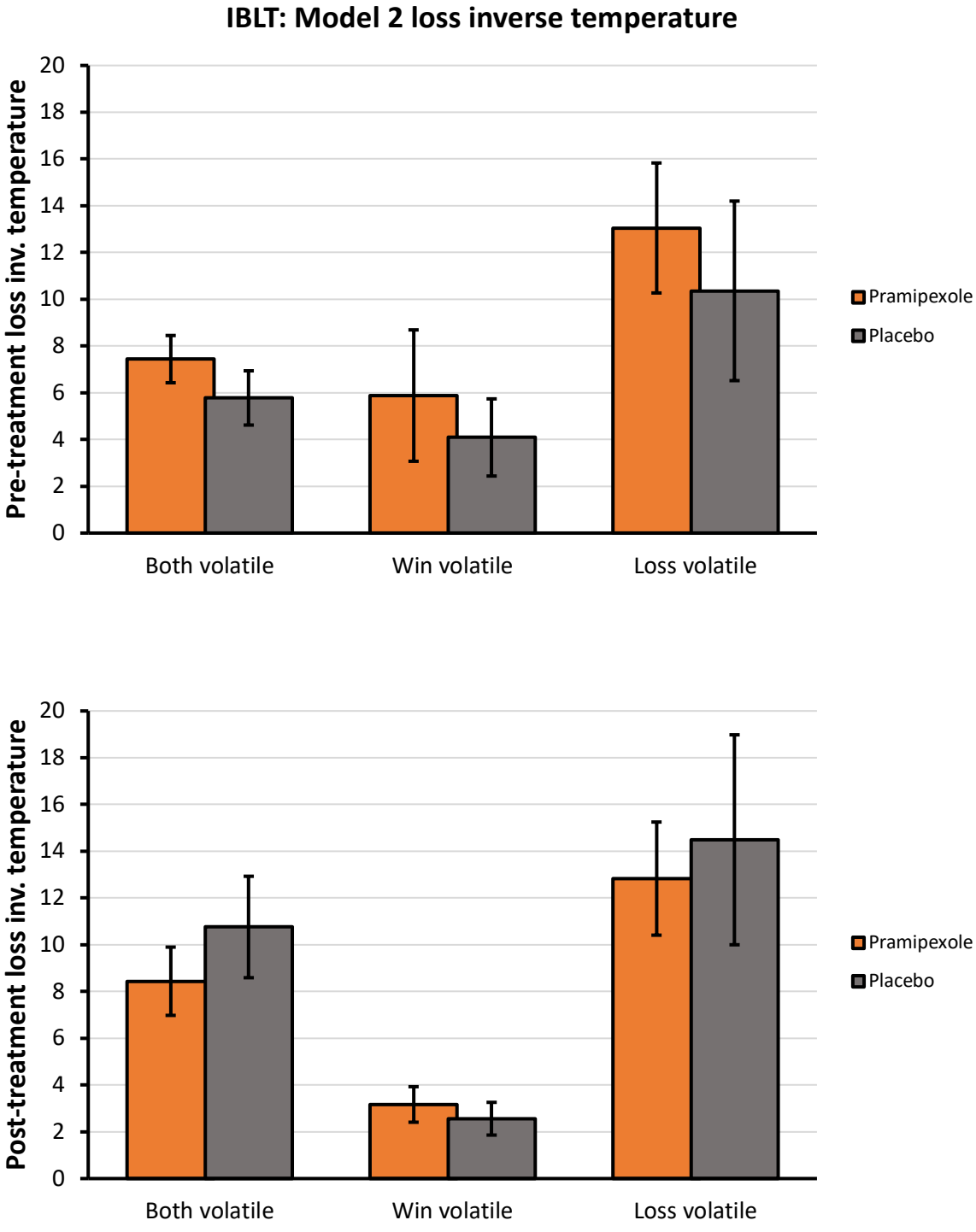


Figure 16: Model 2 loss inverse temperature (Mean ± 1 S.E.) for each block in the information bias learning task before and after treatment with either pramipexole or placebo.

Switch rates

When comparing treatment groups in terms of switch rates in the first block (both outcomes volatile), there was no significant group × visit interaction ($F(1,35) = 1.3$, $p = 0.26$) and no group × visit × outcome type interaction ($F(1,35) = 0.5$, $p = 0.47$). In terms of switch rates in the last two blocks (one outcome stable and the other one volatile), there was also no significant group × visit interaction ($F(1,35) = 0.7$, $p = 0.40$), no group × visit × block interaction ($F(1,35) = 0.006$, $p = 0.94$), and no group × visit × outcome type × block interaction ($F(1,35) = 0.7$, $p = 0.41$). There was a trend-wise group × visit × outcome type interaction ($F(1,35) = 3.5$, $p = 0.07$), but this interaction effect was driven primarily by a baseline difference between groups.

Discussion

This chapter explored potential effects of subacute pramipexole treatment on learning and decision-making based on positive and negative outcomes under different conditions of outcome volatility.

Finding 1: Pramipexole showed no clear-cut valence-specific effect on learning rates

Contrary to our main hypothesis in this chapter, we found no conclusive evidence that subacute pramipexole treatment induced a valence-specific effect on learning rates in either condition of outcome volatility. This complements our observations from Chapter 4 and provides further support to the conclusion that subacute pramipexole treatment does not exert clear-cut valence-specific effects on hot cognition. Interestingly, our findings contrast with a recent experimental medicine study on the cognitive effects of the angiotensin II receptor antagonist losartan (Pulcu et al., 2019). This study employed the same information bias learning task that was used here and found a clear valence-specific effect on learning rates. Losartan did not influence learning rates for negative outcomes but showed an

enhancing effect on learning rates for positive outcomes when both outcomes were volatile. This finding thus shows that losartan might be able to shift the estimated information content of appetitive outcomes relative to aversive outcomes. These results are interesting in the context of our study insofar as it has been suggested that the cognitive effects of losartan might be related to the drug's ability to influence the dopaminergic system (Gard, 2002; Pulcu et al., 2019). At least with regards to subacute stimulation of the dopamine D2 receptor subfamily, especially the dopamine D3 receptor, our data do not support an effect on the estimated information content of positive outcomes.

Finding 2: Placebo- but not pramipexole-treated participants increased in inverse temperatures at the second time of testing

Whilst we did not observe any effects on learning rates, we did find differential effects of treatments on inverse temperatures. The placebo group showed increased inverse temperature after treatment (i.e. at the second time of testing), however, this effect was absent in the pramipexole group. In other words, at baseline the groups' beliefs about outcomes guided their choices to a similar extent, yet, at the second time of testing, the placebo group increased in the extent to which choices were determined by participants' current beliefs whilst the pramipexole group did not. This pattern was observable in both models we analysed. Importantly, it was also independent of outcome valence and therefore not consistent with the hypothesis of a selective effect for positive relative to negative outcomes. Interestingly, there was no difference in monetary outcomes between groups, so the increased alignment of beliefs and choices in the placebo group seemed not to translate into improved performance.

Of course, the foregoing results were not predicted a priori and hence should be interpreted with caution. However, one possible explanation for our findings might

be afforded by thinking about the observed effects in terms of exploration and exploitation tendencies. In real-world environments with volatile outcomes, appropriate performance requires a delicate balance between exploiting what is currently being identified as the best option as well as exploring potential alternatives (Cinotti et al., 2019; Kaelbling et al., 1996; Sutton and Barto, 1998; Wilson et al., 2014). Theoretical and empirical neurobiological accounts of this exploration-exploitation problem have implicated tonic dopamine levels as crucial in the control of this balance (Cinotti et al., 2019). Specifically, lower levels of tonic dopamine have been suggested to lead to increased undirected/random exploration or "noise" in the choice process, which can be formally captured by a decrease in the inverse temperature parameter (Cinotti et al., 2019). Indeed, pramipexole treatment has been suggested to lead to decreased levels of tonic dopamine (Ye et al., 2017). Therefore, a relatively straightforward explanation for the pattern we observed could be that at the second time of testing in the information bias learning task, the increase in inverse temperature in the placebo group might represent a decreased tendency to explore, probably because participants were already familiar with the task environment. Pramipexole treatment, on the other hand, might have blocked this learning effect, keeping random exploration at the same level as when the task was conducted the first time. Our findings might thus add to the growing evidence that dopaminergic signalling activity is implicated in controlling the exploration-exploitation trade-off. Furthermore, it might show that subacute pramipexole treatment can influence this trade-off such that a tendency for exploration is maintained to a longer extent (or familiarity is acquired less quickly). Importantly, the lack of effects on learning rates suggest that subacute pramipexole treatment does not influence how informative outcomes are deemed, but rather seems to maintain random exploration in general

and block learning effects in repeated testing. Whether this effect could constitute a mechanism through which pramipexole exerts antidepressant efficacy (or induce impulse control problems as a side effect) deserves closer interrogation in future studies.

Study strengths and limitations

Whilst several studies to date have explored effects of single dose pramipexole challenge on learning and decision-making, to our knowledge this is the first attempt to investigate such effects following subacute treatment in healthy volunteers. As described before, this approach yields important additional information because acute pramipexole challenge and longer treatment regimens likely differ in their neurochemical and hence also in their behavioural effects. Since in clinical populations pramipexole is generally used on a long-term basis, subacute treatment as in our case is more relevant for understanding potential mechanisms of action of the drug. The information bias learning task we used allows us to concurrently assess learning and decision-making based on positive and negative outcomes under different conditions of outcome volatility. Furthermore, the task is well-validated in terms of strategies human learners use to navigate it (Pulcu and Browning, 2017; Pulcu et al., 2019). In addition, the use of this task in the context of a pharmacological challenge is novel; this is only the second study to date after Pulcu et al. (2019) to employ the information bias learning task to study cognitive effects of a drug. Finally, the computational modelling approach we employed allows for a fine-grained analysis of behaviour by quantitatively estimating parameters — such as learning rates and inverse temperatures — that are thought to govern psychological processes underlying performance in the task.

However, the results of this study also have to be seen in the light of several important limitations. First, the effects we observed were not predicted a priori.

Although interesting, they should be seen as preliminary until independently replicated.

Second, we studied healthy volunteers only. Whilst this approach allowed us to draw inferences about the effects of pramipexole treatment in the absence of confounding influences by concurrent psychopathology, the obtained results might not generalise to clinical populations. This is especially relevant for the work presented in this chapter, because data about patient behaviour in the information bias learning task is not available to date. Thus, the findings reported here should be replicated in patients with depressive disorders as well in order to ascertain that subacute pramipexole indeed shows no conclusive valence-specific effects.

Finally, the task we employed has not yet been validated in terms of its psychometric characteristics — particularly with regards to learning effects in the context of repeated testing. Whilst incomplete psychometric validation is a common (but widely neglected) problem in cognitive neuroscience research, it represents a particular limitation here, as our results are dependent on participants conducting the task repeatedly. Therefore, future studies should not only replicate our results directly and in clinical populations but should also aim to assess the information bias learning task in terms of its psychometric characteristics.

Conclusion of Chapter 5

To summarise, this is the first study to explore the effects of subacute pramipexole treatment on learning and decision-making based on reward and punishment under different conditions of outcome volatility. Whilst our results were not consistent with our primary hypothesis of a positive bias in learning rates after pramipexole treatment, we did observe a potential influence of pramipexole on inverse temperature, which could represent an effect of the drug on exploration-exploitation tendencies. Future studies should replicate the results reported here

and should also interrogate their role in pramipexole's potential antidepressant and neuropsychological side effects.

Chapter 6: The effects of subacute pramipexole treatment on taste experience

Introduction and background

In the recent past, several correlational studies have reported impaired taste recognition in patients with Parkinson's disease (Cecchini et al., 2014, 2015; Doty et al., 2015; Kim et al., 2011; Lang et al., 2006; Moberg et al., 2007). These observations raise the question of a relevant dopaminergic influence on gustatory functions. However, in the aforementioned studies most patients were on medication when taste function was assessed, which means that any observed impairment could simply be a side effect of treatment. Additionally, central nervous system structures that contribute to the processing of gustatory information (e.g. nucleus tractus solitarius, operculum, insula, orbitofrontal cortex) could also be directly affected by neurodegenerative processes (Cecchini et al., 2014; Doty et al., 2015; Shah et al., 2009). Therefore, a direct influence of dopaminergic signalling activity on gustatory functioning cannot be inferred from these correlational studies.

In this chapter, we probe a causal role of dopamine in gustatory processing by assessing taste function after experimental manipulation of dopaminergic activity with subacute pramipexole treatment. As part of the experimental medicine study described already in detail in Chapter 4 and Chapter 5, participants were also assessed with a standardised taste test following treatment with either pramipexole or placebo. This approach allowed us to probe potential causal effects of altered dopaminergic function on gustatory processing, unconfounded by concurrent neuropathological processes or clinical symptoms.

Although a number of studies have used pramipexole to probe the role of the dopaminergic system in neurocognitive functioning in healthy volunteers (for an

overview, see Table 2 in Chapter 1), whether pramipexole could affect taste recognition has not been assessed to date.

Our working hypothesis in this chapter was that in healthy volunteers pramipexole treatment would show opposite effects to those observed in Parkinson's disease, that is, a global improvement in taste recognition. Since pramipexole has previously also shown effects on neural activity during the passive receipt of pleasant and unpleasant taste samples (McCabe et al., 2013) — particularly in brain areas that are thought to contribute to the hedonic evaluation of taste — we additionally also decided to explore whether pramipexole could influence participants' subjective ratings of appetitive (sweet) and aversive (bitter) taste stimuli.

Material and methods

Study design, intervention, and study sample

The data discussed in this chapter have been collected as part of a larger experimental medicine study that has already been described in detail in Chapter 4. Please refer there for further information. To briefly remind the reader, 40 healthy volunteers were randomly allocated to subacute treatment with either pramipexole (stepwise titration, peak daily dose 1.0 mg of pramipexole salt) or placebo (lactose) in a parallel-group, double-blind study design. All participants completed the taste assessment after they had been on the peak dose for at least three consecutive days.

Materials and methods

Taste recognition was assessed using a validated and standardised commercial test kit ("Taste Strips", Burghart Messtechnik, Germany). In a nutshell, this assay uses filter paper strips that are impregnated with four basic taste qualities (sweet, sour, salty, and bitter) at four different intensity levels (that is, 16 taste samples in total).

In addition, three strips without any taste ("no-taste" samples) are part of the assessment as well.

The filter paper strips were presented to participants in a pseudo-random order with intensity levels of the taste samples increasing gradually and with no-taste samples interleaved. In each trial, participants were asked to place the filter paper strip on their tongue, close their mouth, move the strip on their tongue, and then identify the impregnated taste. Participants were asked to correctly classify each sample as either "sweet", "sour", "salty", "bitter", or "no taste".

A total accuracy score was calculated for each participant as the number of samples where a taste was correctly identified (e.g. sour presented and sample classified as sour). This score is the standard outcome measure of the test kit and can be used in a clinical setting for the assessment of taste impairments. In addition, we also calculated a mis-identification score, defined as the number of trials where a participant incorrectly classified any sample with a taste quality (e.g. sour presented and sample classified as sweet). Furthermore, no-taste identification scores (no-taste sample presented and classified as such) and non-identification scores (taste sample presented but classified as having no taste) were calculated as well.

Participants were also asked to rate each presented taste sample on two visual analogue scales (based on Arrondo et al. (2015)) that evaluated pleasantness (ranging from "Very unpleasant" to "Very pleasant") and disgustingness (ranging from "Not disgusting at all" to "Extremely disgusting").

Statistical analysis

Data analysis was carried out in SPSS (version 25.0). Taste recognition scores (accuracy, mis-identifications, no-taste accuracy, non-identifications) were compared between groups using independent t-tests. For significant group

differences, Cohen's d is reported as an effect size when groups had similar standard deviations and Glass's delta is reported when standard deviations were not similar. Pleasantness and disgust ratings were compared between groups using mixed-design ANOVAs with treatment group as between-subjects factor and taste as within-subjects factor. Where applicable, taste intensity was added as a within-subjects factor as well. For correlations of interest between outcome measures, Spearman's correlation was calculated.

Results

Taste recognition

One participant had to be excluded from the analysis because of an error in the administration of the test (not all 16 taste samples were presented).

When comparing taste accuracy scores (number of correct classifications of taste samples), there was a statistically significant group difference (mean difference ± standard error: 2.0 ± 0.9), with the pramipexole group showing higher scores compared to the placebo group ($t(37) = -2.4$, $p = 0.02$, $d = 0.8$) (also see Figure 17). Mis-identification scores (number of incorrect classifications of a sample as a taste) did not differ significantly between groups ($t(37) = 0.2$, $p = 0.81$) (also see Figure 18). Analysis of no-taste identification scores (number of correct classifications of a no-taste sample as such) showed no significant group difference either ($t(37) = -0.1$, $p = 0.94$) (also see Figure 19). In contrast, non-identification scores (number of incorrect classifications of a taste sample as having "no taste") differed significantly between groups again (mean difference ± standard error: 1.9 ± 0.8). Here the pramipexole group showed lower scores than the placebo group ($t(31.2) = 2.5$, $p = 0.02$, delta = 0.7) (also see Figure 20).

In order to additionally probe a potential influence of a specific taste quality on recognition performance, we also conducted group × taste mixed ANOVAs on taste

accuracy scores, mis-identification scores, and non-identification scores. For taste accuracy scores, this showed main effects of treatment group ($F(1,37) = 5.8$, $p = 0.02$) and taste ($F(2.6,94.4) = 14.4$, $p < 0.001$) but no group × taste interaction ($F(2.6,94.4) = 1.0$, $p = 0.37$). For mis-identification scores, there was a main effect of taste ($F(3,111) = 3.6$, $p = 0.02$) but not treatment group ($F(1,37) = 0.1$, $p = 0.81$) and no group × taste interaction ($F(3,111) = 0.1$, $p = 0.95$). For non-identification scores, there were main effects of treatment group ($F(1,37) = 6.2$, $p = 0.02$) and taste ($F(3,111) = 3.1$, $p = 0.03$), but no treatment group × taste interaction ($F(3,111) = 0.7$, $p = 0.53$). Also see Figure 23, Figure 24, and Figure 25 in the Appendix.

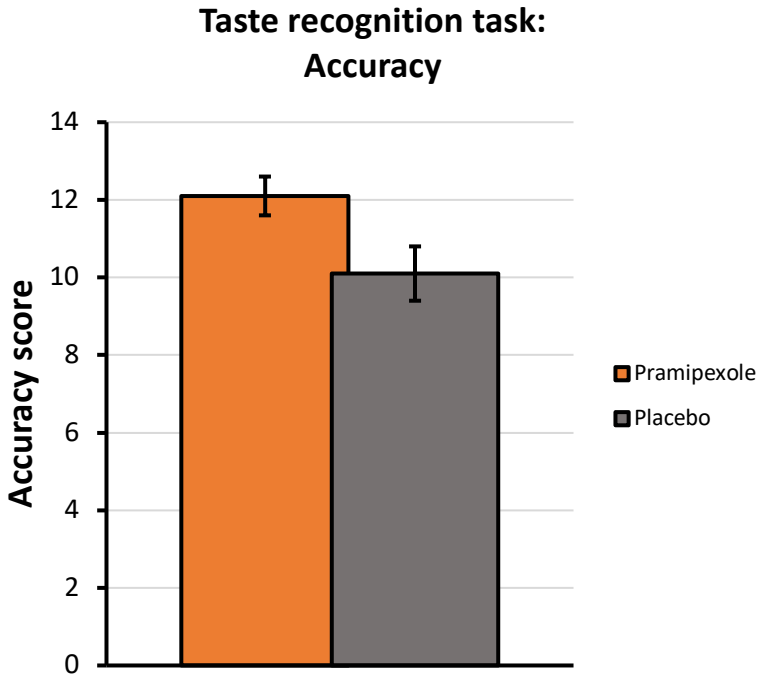


Figure 17: Accuracy scores (Mean ± 1 S.E) after treatment with either pramipexole or placebo. Pramipexole-treated participants showed significantly higher accuracy scores than placebo-treated participants, t(37) = -2.4, p = 0.02, d = 0.8.

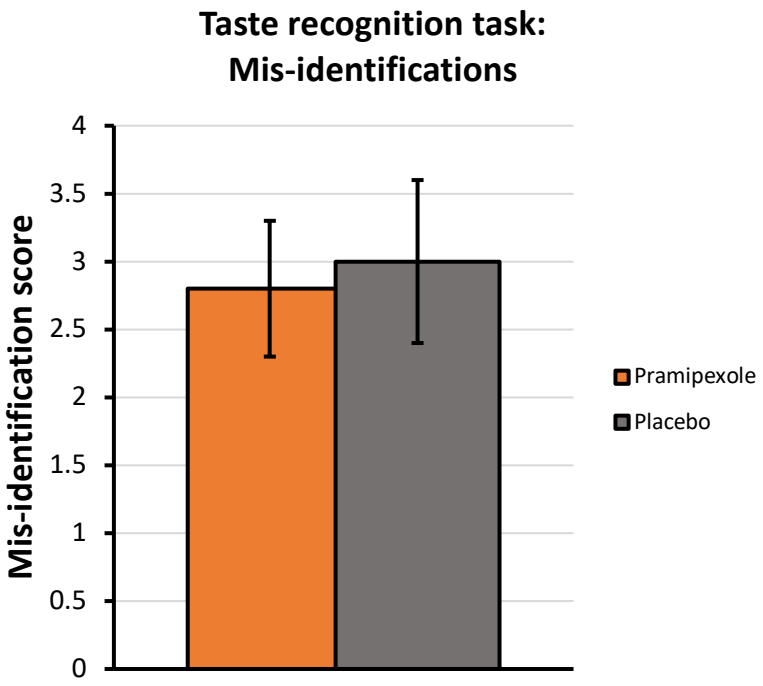


Figure 18: Mis-identification scores (Mean ± 1 S.E) after treatment with either pramipexole or placebo. There was no significant difference between treatment groups.

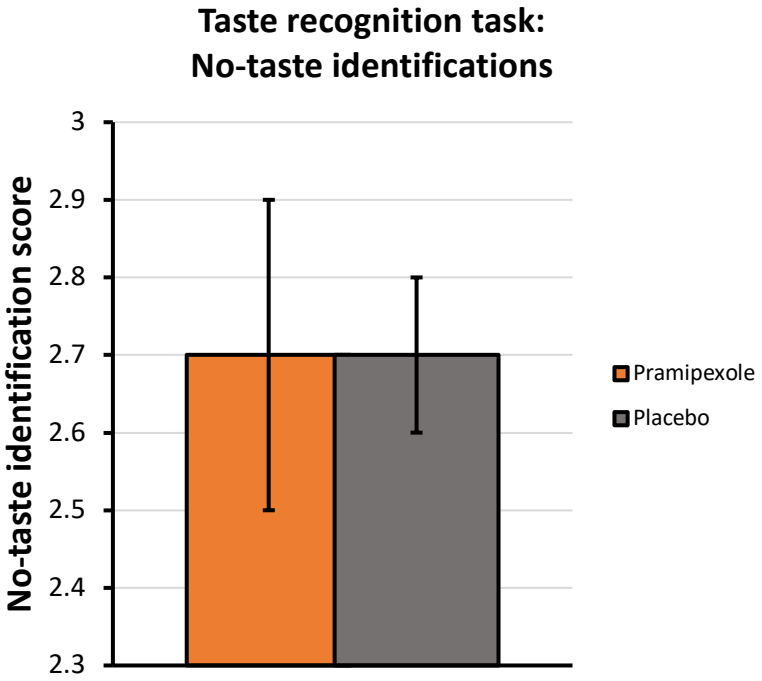


Figure 19: No-taste identification scores (Mean ± 1 S.E) after treatment with either pramipexole or placebo. There was no significant difference between treatment groups.

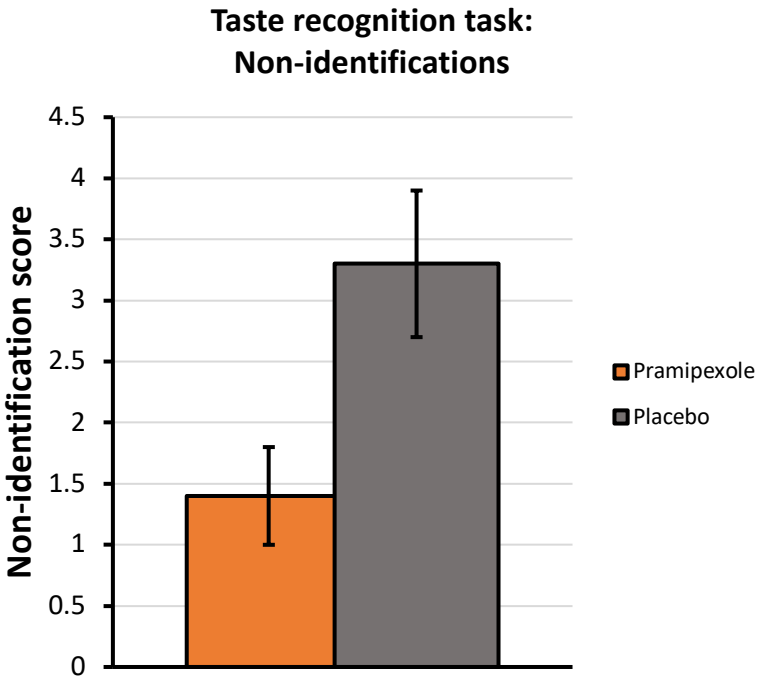


Figure 20: Non-identification scores (Mean ± 1 S.E) after treatment with either pramipexole or placebo. Pramipexole-treated participants incorrectly classified significantly less taste samples as having no taste, t(31.2) = 2.5, p = 0.02, delta = 0.7.

Pleasantness and disgustingness ratings of appetitive and aversive taste samples

In order to assess whether pramipexole could also affect the hedonic experience of taste stimuli, we compared pleasantness and disgustingness ratings for sweet (appetitive) and bitter (aversive) taste samples. Mixed-design ANOVAs (group × taste × intensity) showed no significant differences between treatment groups (no main effect of group and no interactions involving group for either measure, all p-values > 0.05).

However, as described in the previous section, the placebo group classified significantly more taste samples incorrectly as having "no taste", especially at the lower intensity levels, which could have confounded the hedonic evaluation. Therefore, next we compared only ratings for samples at the highest taste intensity level (i.e. where most participants identified taste samples correctly) and furthermore only included trials where a taste experience was reported. This analysis showed a significant group × taste interaction for both ratings, pleasantness ($F(1,34) = 6.5$, $p = 0.02$) and disgustingness ($F(1,34) = 4.9$, $p = 0.03$), but no main effect of group (pleasantness: $F(1,34) = 1.2$, $p = 0.29$, disgustingness: $F(1,34) = 0.3$, $p = 0.62$). Relative to the placebo group, the pramipexole group rated the sweet sample as less pleasant and more disgusting and the bitter sample as more pleasant and less disgusting. Also see Figure 21 and Figure 22.

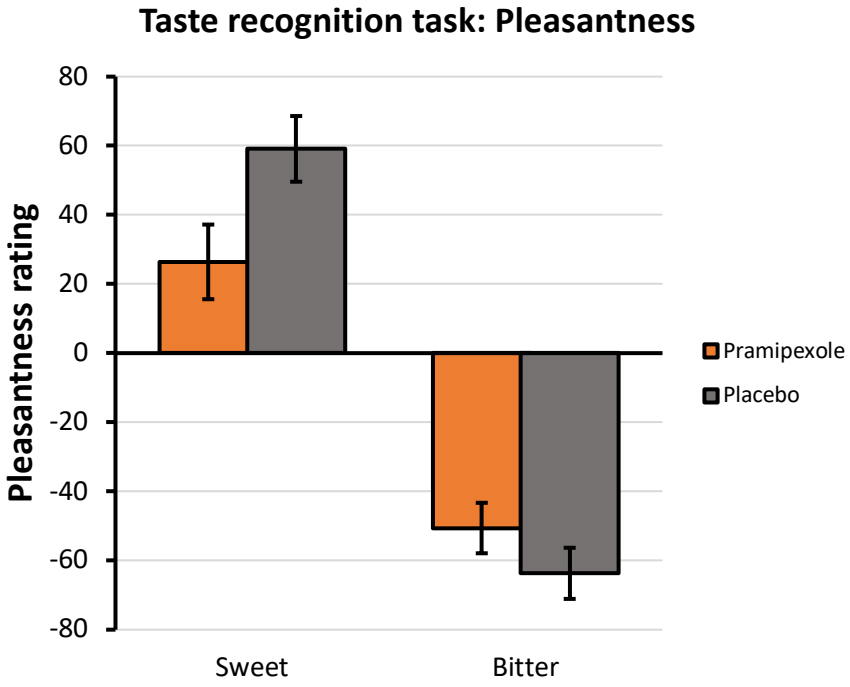


Figure 21: Pleasantness ratings (Mean ± 1 S.E) for sweet (appetitive) and bitter (aversive) taste samples at the highest intensity after treatment with either pramipexole or placebo. Pramipexole-treated participants rated sweet samples as less pleasant and bitter samples as more pleasant than placebo-treated participants.



Figure 22: Disgustingness ratings (Mean ± 1 S.E) for sweet (appetitive) and bitter (aversive) taste samples at the highest intensity after treatment with either pramipexole or placebo. Pramipexole-treated participants rated sweet samples as more disgusting and bitter samples as less disgusting than placebo-treated participants.

Correlation of outcome measures with side effects of pramipexole treatment

As described in more detail in Chapter 4, pramipexole treatment was associated with significantly more nausea than placebo treatment, which could potentially have influenced our results. Therefore, we correlated the severity of experienced nausea with taste accuracy scores, non-identification scores, and pleasantness and disgustingness ratings for samples at the highest intensity using Spearman's correlation. In the placebo group, there was no significant association between experienced nausea and any of the outcome measures (taste accuracy: $\rho = -0.4$, $p = 0.10$, non-identifications: $\rho = 0.4$, $p = 0.10$, pleasantness sweet: $\rho = 0.3$, $p = 0.30$, pleasantness bitter: $\rho = 0.1$, $p = 0.78$, disgustingness sweet: $\rho = -0.2$, $p = 0.37$, disgustingness bitter: $\rho = -0.1$, $p = 0.78$). In the pramipexole group, the only significant correlation was between nausea and disgust ratings for sweet samples ($\rho = 0.5$, $p = 0.03$), all other correlations were not significant (taste accuracy: $\rho = -0.2$, $p = 0.42$, non-identifications: $\rho = 0.2$, $p = 0.38$, pleasantness sweet: $\rho = -0.3$, $p = 0.13$, pleasantness bitter: $\rho = -0.2$, $p = 0.34$, disgustingness bitter: $\rho = 0.2$, $p = 0.33$).

Discussion

In this chapter, we assessed potential effects of subacute pramipexole treatment on taste recognition performance in a healthy volunteer model. In brief, we found that pramipexole treatment was associated with improved taste recognition. Furthermore, pramipexole potentially also blunted the hedonic experience of both appetitive and aversive taste samples.

Finding 1: Pramipexole-treated participants showed enhanced taste recognition

In line with our working hypothesis, pramipexole treatment showed effects on taste recognition that were opposite to those that have been reported for patients with Parkinson's disease. Pramipexole-treated participants, relative to those treated with

placebo, showed significantly higher taste accuracy scores and significantly lower non-identification scores. In other words, compared to the placebo group, the pramipexole group classified more taste samples correctly and made less mistakes classifying taste samples as having no taste. Importantly, this enhanced performance for recognising taste samples was not due to an increased tendency to classify any sample as a taste. If this was the case, we would expect a lower no-taste identification score and/or an increased mis-identification score in the pramipexole group — which we did not observe. In fact, both mis-identification scores and no-taste identification scores were roughly equal between groups. Importantly, there was no relationship between taste recognition performance and experienced nausea, so the observed effects of pramipexole cannot be explained by its side effects either.

Taken together, the foregoing results suggest that altering dopaminergic signalling activity can have a direct influence on gustatory functioning. This might point towards a potential mechanism that could explain impaired taste recognition in Parkinson's disease. However, it is worth noting that one previous study that assessed taste performance in patients with early-stage Parkinson's disease both on and off their medication (mostly carbidopa/levodopa) found no effect of dopaminergic drug treatment (Doty et al., 2015). Whilst this discrepancy could be explained by several different factors (e.g. patients versus healthy volunteers, different durations of treatment etc.) it may also indicate that the observed effects on taste recognition are specific to pramipexole, e.g. because of its preferential affinity for the dopamine D3 receptor. Alternatively, it could also be the case that taste recognition in Parkinson's disease patients is influenced by non-dopaminergic pathology.

Importantly, from a clinical perspective, our results also suggest that pramipexole (and potentially other dopaminergic drugs) could represent a viable pharmacological treatment option for impaired gustatory function. This potential application deserves further investigation, especially given that medicine currently lacks effective therapies for taste disorders such as (idiopathic) hypogeusia and ageusia (Kumbargere Nagraj et al., 2017).

Finding 2: Pramipexole-treated participants showed blunted hedonic evaluations of appetitive and aversive tastes

In addition to the effects reported above, we also found that participants treated with pramipexole showed blunted subjective ratings of sweet (appetitive) and bitter (aversive) taste samples. Relative to the placebo group, the pramipexole group showed lower pleasantness ratings for rewarding stimuli and higher pleasantness ratings for aversive stimuli. A comparable finding was obtained for disgustingness ratings. Interestingly, the observed patterns parallel effects previously reported on the neural level, whereby single-dose pramipexole treatment reduced activity in the dorsal anterior cingulate cortex in response to both rewarding and aversive taste stimuli (McCabe et al., 2013).

However, it is worth noting that the pattern we observed was not predicted a priori and only became statistically significant when we focused on the highest taste intensity levels. In addition, the positive correlation of nausea and disgust ratings for sweet samples in the pramipexole group suggests that there might have been at least a partial influence of this side effect on hedonic experience (albeit this was not significant for the other ratings). Therefore, the observed effects should be interpreted with caution until independently replicated.

Strengths and limitations

The investigation conducted in this chapter has several strengths and limitations that deserve highlighting. To begin with, to the author's knowledge, this is the first assessment of gustatory function following sub-acute dopaminergic manipulation using pramipexole. Because we assessed healthy volunteers, as opposed to patients, we were able to test potential effects of pramipexole treatment on taste function unconfounded by neuropathology or changes in clinical symptoms. Sub-acute pramipexole treatment has improved clinical-ecological validity compared to the more commonly used single-dose designs, which is especially important when considering that acute and repeated dopaminergic manipulations might exert differential neurochemical and neurocognitive effects (Martins et al., 2017; Walsh et al., 2018b, 2018a). In addition, the taste test we conducted is a standardised and validated assessment system for gustatory function that is commercially available. This should make future replication efforts of our findings relatively straightforward.

Nevertheless, there are also several limitations that need to be mentioned. First, we conducted a between-group comparison with a moderately sized sample of participants. Whilst such a study design is cost-effective and practical to conduct, it might lack sensitivity to detect smaller effects. Furthermore, although participants were randomly allocated, we did not conduct baseline measurements, so it is still possible that the observed group differences could simply be due to pre-existing chance-differences. Second, by relying on a single whole-mouth taste test, the study is limited in terms of its methodological generalisability. Future investigations should employ alternative gustatory assessments (e.g. regional taste assessment and electrogustometry, gustatory evoked potentials, neuroimaging during taste recognition), to better understand the effects of dopaminergic manipulation on

different levels of the gustatory processing hierarchy (e.g. tongue, cranial nerves, cortical areas). Finally, the investigation discussed here included healthy volunteers only. As a next step, our findings should be independently replicated in clinical populations (e.g. patients suffering from hypogeusia or ageusia) to assess the potential use of pramipexole as a pharmacological treatment for disorders of taste function.

Conclusion of Chapter 6

In conclusion, we found preliminary evidence that pramipexole can enhance taste recognition in healthy volunteers. In addition, pramipexole treatment might also blunt subjective evaluation of appetitive and aversive taste stimuli (but this pattern was not predicted a priori). Taken together, our findings suggest a potential role for dopaminergic signalling activity on gustatory functioning. Future studies should try to replicate our findings using within-subjects designs and larger samples, and also consider including complimentary taste assessments and clinical populations. Also, potential effects of pramipexole on hedonic experience should be evaluated in closer detail.

Chapter 7: General discussion

Synopsis

In this thesis, we assessed hot cognitive effects of three different potential novel antidepressant interventions, namely bright light treatment, a positive psychology practice, and pramipexole treatment. Our primary aim in this work was to test for each of these three treatments whether they could influence emotional information processing similar to conventional antidepressant drugs and in line with the CONEMATA (Harmer and Pringle, 2017; Harmer et al., 2009a, 2017; Roiser and Sahakian, 2013; Roiser et al., 2012; Walsh and Harmer, 2015; Warren et al., 2015). In other words, we investigated whether these treatments can induce a bias in hot cognition in favour of positive relative to negative information. In addition, and as a secondary interest, we also probed effects on other neurobiological processes relevant to individual interventions (e.g. HPA axis activity for the positive psychology practice, taste recognition for subacute pramipexole treatment). Bringing our findings together in a broader context, what conclusions can we draw from these investigations?

Table 17 gives an overview of the main findings for the individual studies that contributed to this thesis. First and foremost, we found no conclusive evidence for an antidepressant-like effect on emotional information processing in any of the treatments we studied. One possibility, of course, is that this is simply a chance negative finding or that it is the result of insufficient power in our study designs — increasing the sample size, improving measurement precision (e.g. by including more trials in the cognitive tasks), and using more powerful study designs (e.g. a cross-over design) would be able to remediate this limitation to a certain extent.

That said, another explanation for the results we observed could be that the previously reported clinical effects of the three interventions we studied might be

brought about through mechanisms different than the induction of a positive bias in hot cognition. Such mechanisms might be found in different physiological domains and could differ for treatments. For example, for bright light treatment, plausible alternative mechanisms might be an impact on circadian rhythms or an improvement of cold cognitive processes (also see Stephenson et al. (2012)). For the three good things exercise, antidepressant effects could be brought about by deliberate and repeated exposure to consciously recognised positive self-relevant information. Pramipexole treatment, on the other hand, could exert its effects by acting on motivational processes or, again, by improving cold cognitive processes. These potential alternative mechanisms remain to be explored in future studies.

One important assumption that underlies the approach we took in this work is that any effects observed in healthy volunteers can be considered representative of effects in clinical populations. In other words, we assumed that any effects on emotional information processing in healthy volunteers would be qualitatively similar to those in patients. This assumption is supported by research on conventional antidepressant drugs, which show qualitatively similar hot cognitive effects in patients and in healthy volunteers (Harmer et al., 2009a, 2017; Roiser and Sahakian, 2013; Warren et al., 2015). However, this assumption is not necessarily true for other treatments. There is a possibility that certain antidepressant treatments work in clinical populations because they correct an underlying abnormality that is not present in healthy people. In such a case, one would expect to see certain effects in a patient population, but not in healthy volunteers. Therefore, although we did not observe clear-cut effects on hot cognition in healthy individuals in the studies reported here, there is still a possibility that such effects could be measurable in patient populations. Future research exploring this issue should therefore also be encouraged.

Table 17: Overview of main findings from the three studies that contributed to this thesis.

Study	Chapter	Main findings	Conclusions/Comments
Bright light treatment study	Chapter 2	• Acute bright light treatment did not change subjective state • Acute bright light treatment did not influence emotional information processing • Sham negative ion treatment was associated with lower expectations of a general treatment effect compared to bright light treatment	The antidepressant effects of BLT are potentially not explicable within the theoretical framework of the CONEMATA The established sham-negative ion treatment protocol might not be suited for healthy volunteer studies as a placebo control Alternatively, the sham-negative ion protocol might no longer be a suitable placebo control (e.g. because more people know about bright light treatment nowadays)
Positive mental exercise study	Chapter 3	• There was no consistent positive effect of either mental practice on subjective state • The early memories practice, but not the three good things practice, led to decreased salivary cortisol on awakening • The early memories group, compared to the three good things group, showed enhanced facial emotion recognition performance independent of the emotion displayed • The early memories group, compared to the three good things group, showed a trend-wise enhancement of emotional recall performance independent of stimulus valence	The early memories practice does not seem to be an inert intervention in healthy volunteers and could be used as a potential intervention itself (e.g. as a positive early memories practice) The observed differential effect of the two exercises on facial expression recognition and emotional recall is difficult to interpret due to the unexpected lack of an inert control group
Pramipexole study	Chapter 4	• Subacute pramipexole treatment did not change subjective state • Subacute pramipexole treatment did not conclusively alter emotional information processing in an antidepressant-like way • Nausea was the most common side effect in the pramipexole group and the only side effect that significantly distinguished the two groups • Subacute pramipexole treatment at higher doses was well tolerated by healthy volunteers (no dropouts in the pramipexole group)	Pramipexole's putative antidepressant effects might not be explainable via effects on emotional information processing such as those described by the CONEMATA Healthy volunteer studies using higher doses of pramipexole are feasible even in the absence of antiemetic co-medication
	Chapter 5	• Subacute pramipexole treatment did not change monetary outcomes, reaction times, or switch rates for ambiguous trials • Subacute pramipexole treatment did not change learning rates • Subacute pramipexole treatment blocked a decrease in inverse temperatures from the first to the second time of testing	Pramipexole does not seem to induce valence-specific effects in reinforcement learning, however it might influence exploration-exploitation tendencies
	Chapter 6	• Subacute pramipexole treatment was associated with improved taste recognition performance independent of the presented taste quality • Subacute pramipexole treatment was associated with blunted hedonic evaluation of appetitive and aversive taste stimuli at the highest stimulus intensity	Pramipexole might improve taste recognition and could act as potential treatment for impaired gustatory function Effects on hedonic evaluation mimic previously observed neural effects

Although we did not observe any clear antidepressant-like effects on emotional information processing in any of the studies conducted for this thesis, we did obtain several other interesting findings in our investigations.

In the bright light study (Chapter 2), we found no conclusive effect of acute light treatment on mood — which runs counter to a common folk belief that being exposed to bright (sun)light makes one feel good. Furthermore, we observed a significant difference in participants' expectations of a general (unspecified) treatment effect between the bright light and the sham-placebo group. Whilst the sham-placebo protocol we employed is established in the literature and has been used repeatedly and successfully for patient populations (Desan et al., 2007; Eastman et al., 1998; Lam et al., 2016), our data indicate that it might be less suitable for healthy volunteers. Alternatively, bright light treatment might be better known as an antidepressant treatment today than it was when the protocol was originally developed and assessed, in which case it will be necessary to find better placebo control treatments for future bright light research.

In the mental exercise study (Chapter 3), we found that an early memories practice but not a three good things practice decreased salivary cortisol on awakening. This was surprising given that variants of the early memories practice are widely used as supposedly inert control exercises in positive psychology trials (Gander et al., 2013; Mongrain and Anselmo-Matthews, 2012; Seligman et al., 2005). Furthermore, the two mental exercises we studied were also associated with differential performance in facial expression recognition and emotional recall, with the early memories practice showing enhanced performance across emotions/valences compared to the three good things group. Importantly, in the daily early memories exercise, the healthy volunteers we studied remembered mostly positive early memories, which is less likely the case in people suffering from depression and

might explain why the early memory exercise showed effects in our study but not in studies including unhappy people or those with (mild) depressive symptoms.

The pramipexole study also led to several important observations. First, and especially relevant for future research, we demonstrated that subacute pramipexole treatment at higher doses is feasible in healthy volunteers. Compared to placebo, the only significant side effect we observed was nausea and even this was tolerated well by all participants, despite the fact that we did not use antiemetic co-medication, which, although commonly used, might be problematic due to under-appreciated confounding central effects (Samuels et al., 2007). Furthermore, although there were no valence-specific effects in learning and decision-making based on positive and negative feedback, we did observe a potential effect of pramipexole on exploration-exploitation tendencies. Specifically, placebo-treated participants showed a decrease in their tendency for random exploration at the second time of testing, but pramipexole treatment seemed to block this effect. This effect was not predicted a priori and therefore has to be interpreted with caution. However, it deserves further investigation in future studies, especially with regards to the question whether it could represent a potential mechanism of antidepressant action. In addition to the foregoing observations, pramipexole treatment was also found to be associated with increased taste recognition performance and blunted hedonic evaluation of appetitive and aversive taste samples. This effect is highly interesting for two reasons. First, it fits well into the current body of literature describing altered taste recognition in patients with Parkinson's disease (Cecchini et al., 2015) and a pramipexole-induced blunted neural response in the dorsal anterior cingulate cortex to both rewarding and punishing taste samples (McCabe

et al., 2013).[11] Second, and more importantly, it also points towards a potential utility of dopaminergic agents for the treatment of taste impairments, for which there are currently no pharmacological treatment options available.

Future directions

Based on the findings reported above, several potential lines of enquiry can be delineated along which future research might be conducted. First, given the exploratory nature of the study and the fact that all p-values were reported uncorrected for multiple comparisons, independent replications of the reported results in healthy volunteers are necessary in order to increase confidence in the observed patterns in the data and to weed out any potential false positive results. In a similar vein, future replications should also aim to increase their power to detect a meaningful between-group difference to ascertain that the observed null results were not simply false negative results. With regards to the mental exercise study, future replication efforts should also include a no-intervention control group, as we have seen in our study that the effects of even the simplest mental practices can be hard to predict.

Second, the potential absence of effects on hot cognitive processes we observed here should also be further interrogated using alternative tasks than the ETB and the information bias learning task employed as part of this work. There is a range of alternative/complimentary cognitive tasks that could be used in this context (see for example Walsh et al. (2018a) or Walsh et al. (2018b) for a different reward

[11] As a side note, these previously described neural effects of pramipexole were observed after a single-dose challenge but look qualitatively similar to the effects we observed after subchronic treatment. This could also mean that — at least with regards to gustatory processing — acute and repeated pramipexole challenge might have similar effects.

learning task used in an experimental medicine study of the antidepressant bupropion).

Third, potential effects on emotional information processing should also be assessed for all three interventions in patients with depression. Only if these turn out negative too, we can conclude with reasonable confidence that the clinical action of bright light treatment, positive mental practices, and pramipexole treatment cannot be explained within the theoretical framework of the CONEMATA.

Finally, the effects of pramipexole (and potentially other dopaminergic agents) on taste recognition performance should be assessed in patients suffering from taste impairments in order to clarify their potential clinical utility for the treatment of such disorders.

Conclusion

To conclude, in this thesis we studied three potential novel antidepressant interventions in healthy volunteers using an experimental medicine approach. Our data were not consistent with the induction of a positive bias in emotional information processing by any of the three interventions we assessed. This could be the result of insufficient power or could simply be a chance false negative finding. However , it could also suggest that the previously-reported clinical effects of these interventions could be brought about through a different mechanism than that described by the CONEMATA. We also observed several other interesting effects — for example a decrease in salivary cortisol following an early memories practice and a potential effect of pramipexole treatment on exploration-exploitation strategies as well as on taste recognition. These observations deserve closer scientific interrogation in the future and, if replicated, could potentially be translated into improved clinical treatments for patients.

Appendix

Appendix to Chapter 5

Table 18: Overview of all effects in analyses conducted in Chapter 5.

Total money won (both outcomes volatile)
Main effect of group: $F(1,35) = 0.3$, $p = 0.58$
Main effect of visit: $F(1,35) = 0.9$, $p = 0.35$
Total money won (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.9$, $p = 0.36$
Main effect of visit: $F(1,35) = 0.1$, $p = 0.71$
Main effect of block: $F(1,35) = 11.7$, $p = 0.002$
Group × block interaction: $F(1,35) = 0.4$, $p = 0.52$
Visit × block interaction: $F(1,35) = 0.6$, $p = 0.46$
Reaction time (both outcomes volatile)
Main effect of group: $F(1,35) = 0.03$, $p = 0.86$
Main effect of visit: $F(1,35) = 2.2$, $p = 0.15$
Reaction time (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.3$, $p = 0.59$
Main effect of visit: $F(1,35) = 0.1$, $p = 0.82$
Main effect of block: $F(1,35) = 0.2$, $p = 0.64$
Group × block interaction: $F(1,35) = 0.04$, $p = 0.83$
Visit × block interaction: $F(1,35) = 0.7$, $p = 0.41$
Model 1 learning rate (both outcomes volatile)
Main effect of group: $F(1,35) = 1.3$, $p = 0.27$
Main effect of visit: $F(1,35) = 4.3$, $p = 0.045$
Main effect of valence: $F(1,35) = 13.0$, $p < 0.001$
Group × valence interaction: $F(1,35) = 0.4$, $p = 0.52$
Visit × valence interaction: $F(1,35) = 0.3$, $p = 0.57$
Model 1 learning rate (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.7$, $p = 0.42$
Main effect of visit: $F(1,35) = 2.6$, $p = 0.11$
Main effect of valence: $F(1,35) = 5.3$, $p = 0.03$
Main effect of block: $F(1,35) = 0.03$, $p = 0.86$
Group × valence interaction: $F(1,35) = 2.1$, $p = 0.16$
Group × block interaction: $F(1,35) = 0.1$, $p = 0.82$
Visit × valence interaction: $F(1,35) = 0.1$, $p = 0.70$
Visit × block interaction: $F(1,35) = 2.1$, $p = 0.16$
Valence × block interaction: $F(1,35) = 80.1$, $p < 0.001$
Group × valence × block interaction: $F(1,35) = 7.2$, $p = 0.01$
Visit × valence × block interaction: $F(1,35) = 0.1$, $p = 0.82$
Model 1 inverse temperature (both outcomes volatile)
Main effect of group: $F(1,35) = 0.04$, $p = 0.85$
Main effect of visit: $F(1,35) = 9.9$, $p = 0.003$
Model 1 inverse temperature (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.1$, $p = 0.81$
Main effect of visit: $F(1,35) = 0.8$ $p = 0.39$
Main effect of block: $F(1,35) = 1.3$, $p = 0.26$
Group × block interaction: $F(1,35) = 0.2$, $p = 0.69$
Visit × block interaction: $F(1,35) = 0.007$, $p = 0.94$
Model 2 learning rate (both outcomes volatile)
Main effect of group: $F(1,35) = 1.8$, $p = 0.19$
Main effect of visit: $F(1,35) = 7.6$, $p = 0.01$
Model 2 learning rate (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.8$, $p = 0.37$
Main effect of visit: $F(1,35) = 3.6$, $p = 0.07$
Main effect of block: $F(1,35) = 5.4$, $p = 0.03$
Group × block interaction: $F(1,35) = 1.6$, $p = 0.21$
Visit × block interaction: $F(1,35) = 0.1$, $p = 0.79$
Model 2 inverse temperature (both outcomes volatile)
Main effect of group: $F(1,35) = 0.002$, $p = 0.96$
Main effect of visit: $F(1,35) = 7.9$, $p = 0.01$
Main effect of valence: $F(1,35) = 13.3$, $p < 0.001$
Group × valence interaction: $F(1,35) = 0.2$, $p = 0.69$
Visit × valence interaction: $F(1,35) = 0.02$, $p = 0.89$
Model 2 inverse temperature (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) < 0.001$, $p = 0.99$
Main effect of visit: $F(1,35) = 1.3$, $p = 0.26$
Main effect of valence: $F(1,35) = 6.9$, $p = 0.01$
Main effect of block: $F(1,35) = 0.8$, $p = 0.38$

Group × valence interaction: $F(1,35) = 2.5$, $p = 0.12$
Group × block interaction: $F(1,35) = 0.5$, $p = 0.50$
Visit × valence interaction: $F(1,35) = 3.6$, $p = 0.07$
Visit × block interaction: $F(1,35) = 1.9$, $p = 0.17$
Valence × block interaction: $F(1,35) = 186.4$, $p < 0.001$
Group × valence × block interaction: $F(1,35) = 4.8$, $p = 0.04$
Visit × valence × block interaction: $F(1,35) = 0.01$, $p = 0.91$
Switch rate (both outcomes volatile)
Main effect of group: $F(1,35) < 0.001$, $p = 0.98$
Main effect of visit: $F(1,35) = 2.0$, $p = 0.17$
Main effect of outcome type: $F(1,35) = 13.2$, $p < 0.001$
Group × outcome type interaction: $F(1,35) = 0.1$, $p = 0.82$
Visit × outcome type interaction: $F(1,35) = 0.6$, $p = 0.45$
Switch rate (one outcome stable, other outcome volatile)
Main effect of group: $F(1,35) = 0.2$, $p = 0.67$
Main effect of visit: $F(1,35) = 1.9$, $p = 0.18$
Main effect of outcome type: $F(1,35) = 5.7$, $p = 0.02$
Main effect of block: $F(1,35) = 0.1$, $p = 0.72$
Group × outcome type interaction: $F(1,35) = 0.7$, $p = 0.40$
Group × block interaction: $F(1,35) = 0.1$, $p = 0.72$
Visit × outcome type interaction: $F(1,35) = 0.002$, $p = 0.96$
Visit × block interaction: $F(1,35) = 0.1$, $p = 0.75$
Outcome type × block interaction: $F(1,35) = 39.7$, $p < 0.001$
Group × outcome type × block interaction: $F(1,35) = 5.2$, $p = 0.03$
Visit × outcome type × block interaction: $F(1,35) = 0.8$, $p = 0.39$

Appendix to Chapter 6

Performance in the taste recognition task across taste qualities

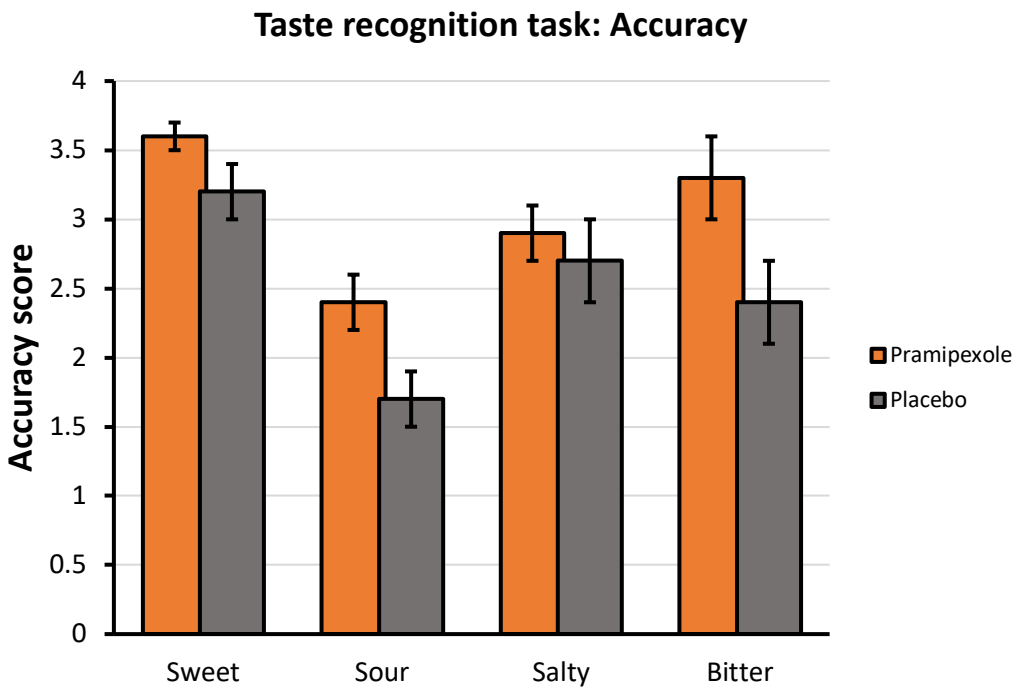


Figure 23: Accuracy scores (Mean ± 1 S.E.) for different taste qualities in the taste recognition task after treatment with either pramipexole or placebo. Pramipexole-treated participants showed significantly higher accuracy scores than placebo-treated participants independent of taste quality.

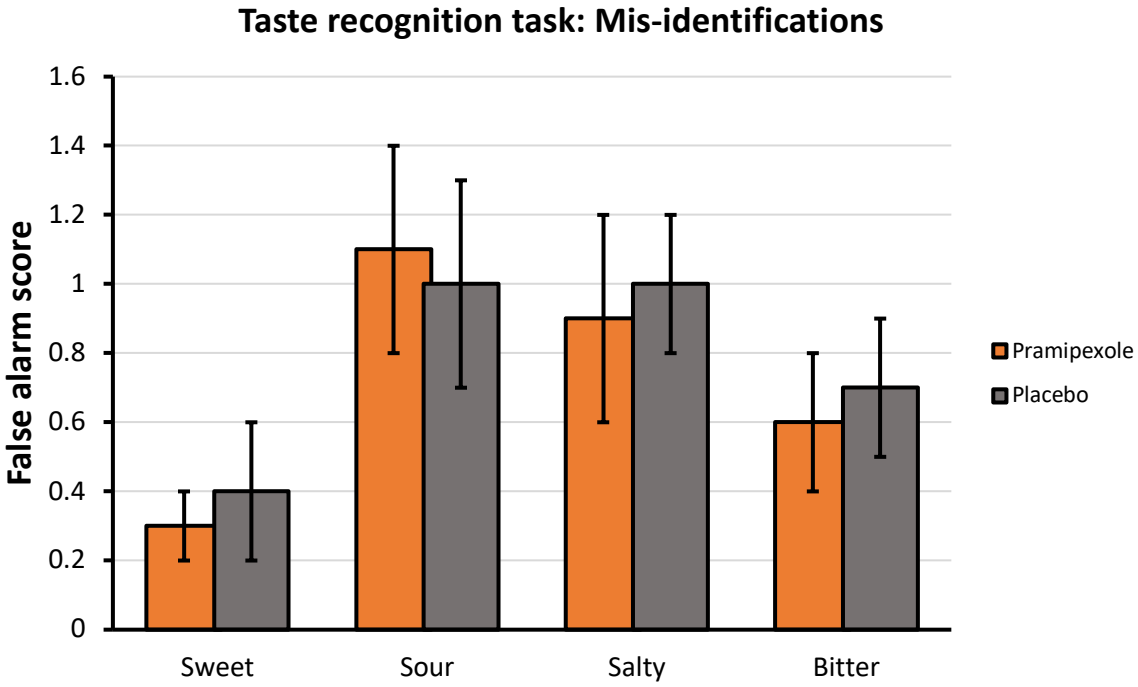


Figure 24: Mis-identification scores (Mean ± 1 S.E.) for different taste qualities in the taste recognition task after treatment with either pramipexole or placebo. Mis-identification scores did not differ significantly between treatments groups.

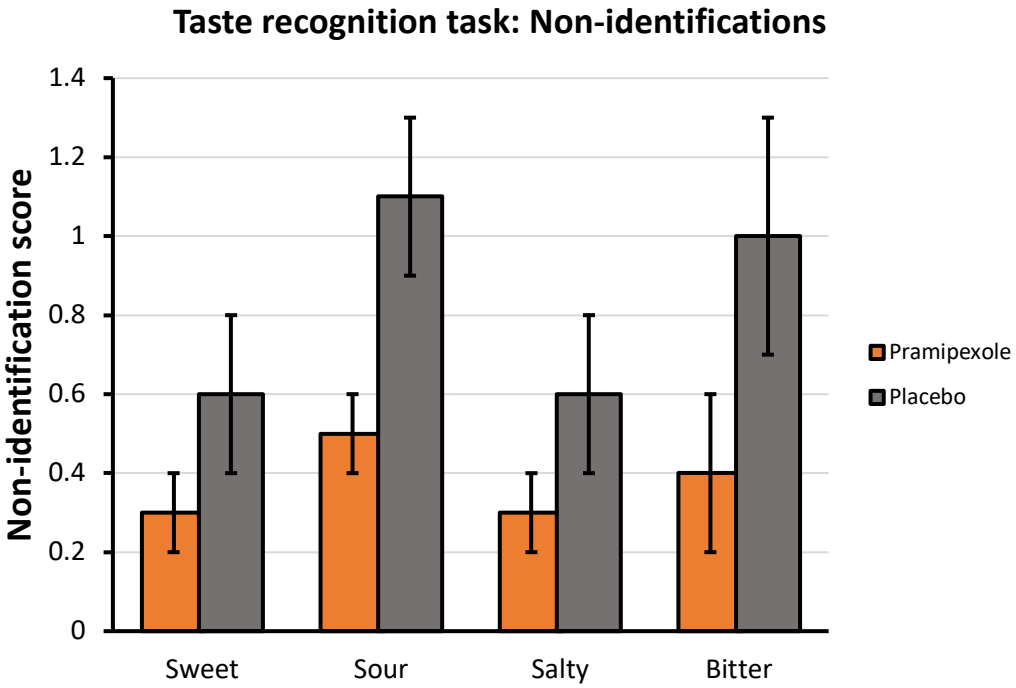


Figure 25: Non-identification scores (Mean ± 1 S.E.) for different taste qualities in the taste recognition task after treatment with either pramipexole or placebo. The pramipexole group showed significantly less non-identifications than the placebo group independent of taste quality.

References

Aiken, C.B. (2007). Pramipexole in psychiatry: a systematic review of the literature. J. Clin. Psychiatry *68*, 1230–1236.

Al-Karawi, D., and Jubair, L. (2016). Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. J. Affect. Disord. *198*, 64–71.

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (American Psychiatric Association).

Arnone, D., Horder, J., Cowen, P.J., and Harmer, C.J. (2008). Early effects of mirtazapine on emotional processing. Psychopharmacology (Berl.) *203*, 685–691.

Arrondo, G., Murray, G.K., Hill, E., Szalma, B., Yathiraj, K., Denman, C., and Dudas, R.B. (2015). Hedonic and disgust taste perception in borderline personality disorder and depression. Br. J. Psychiatry *207*, 79–80.

Baddeley, A.D., and Crawford, J.R. (2012). Spot the word 2. Administration, scoring and technical manual (Pearson).

Bai, T., Xie, W., Wei, Q., Chen, Y., Mu, J., Tian, Y., and Wang, K. (2017). Electroconvulsive therapy regulates emotional memory bias of depressed patients. Psychiatry Res. *257*, 296–302.

Barkl, S.J., Lah, S., Harris, A.W.F., and Williams, L.M. (2014). Facial emotion identification in early-onset and first-episode psychosis: A systematic review with meta-analysis. Schizophr. Res. *159*, 62–69.

Bayard, S., Langenier, M.C., and Dauvilliers, Y. (2013). Decision-making, reward-seeking behaviors and dopamine agonist therapy in restless legs syndrome. Sleep *36*, 1501–1507.

Beck, A., Steer, R., and Brown, G. (1996). Manual for the Beck Depression Inventory-II (San Antonio, TX: Psychological Corporation).

Behrens, T.E.J., Woolrich, M.W., Walton, M.E., and Rushworth, M.F.S. (2007). Learning the value of information in an uncertain world. Nat. Neurosci. *10*, 1214–1221.

Bellucci, G., Münte, T.F., and Park, S.Q. (2019). Resting-state dynamics as a neuromarker of dopamine administration in healthy female adults. J. Psychopharmacol. (Oxf.) *33*, 955–964.

Belujon, P., and Grace, A.A. (2017). Dopamine system dysregulation in major depressive disorders. Int. J. Neuropsychopharmacol. *20*, 1036–1046.

Bhagwagar, Z., Hafizi, S., and Cowen, P.J. (2003). Increase in concentration of waking salivary cortisol in recovered patients with depression. Am. J. Psychiatry *160*, 1890–1891.

Bhagwagar, Z., Hafizi, S., and Cowen, P.J. (2005). Increased salivary cortisol after waking in depression. Psychopharmacology (Berl.) *182*, 54–57.

Boggio, P.S., Bermpohl, F., Vergara, A.O., Muniz, A.L.C.R., Nahas, F.H., Leme, P.B., Rigonatti, S.P., and Fregni, F. (2007). Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. J. Affect. Disord. *101*, 91–98.

Bolier, L., Haverman, M., Westerhof, G.J., Riper, H., Smit, F., and Bohlmeijer, E. (2013). Positive psychology interventions: a meta-analysis of randomized controlled studies. BMC Public Health *13*, 119.

Bouthenet, M.-L., Souil, E., Martres, M.-P., Sokoloff, P., Giros, B., and Schwartz, J.-C. (1991). Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D2 receptor mRNA. Brain Res. *564*, 203–219.

Boyce, P., and Hopwood, M. (2013). Manipulating melatonin in managing mood. Acta Psychiatr. Scand. *128*, 16–23.

Bradley, B.P., Mogg, K., and Williams, R. (1995). Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. Behav. Res. Ther. *33*, 755–770.

Browning, M., Reid, C., Cowen, P.J., Goodwin, G.M., and Harmer, C.J. (2007). A single dose of citalopram increases fear recognition in healthy subjects. J. Psychopharmacol. (Oxf.) *21*, 684–690.

Browning, M., Grol, M., Ly, V., Goodwin, G.M., Holmes, E.A., and Harmer, C.J. (2011). Using an experimental medicine model to explore combination effects of pharmacological and cognitive interventions for depression and anxiety. Neuropsychopharmacology *36*, 2689–2697.

Browning, M., Holmes, E.A., Charles, M., Cowen, P.J., and Harmer, C.J. (2012). Using attentional bias modification as a cognitive vaccine against depression. Biol. Psychiatry *72*, 572–579.

Browning, M., Behrens, T.E., Jocham, G., O'Reilly, J.X., and Bishop, S.J. (2015). Anxious individuals have difficulty learning the causal statistics of aversive environments. Nat. Neurosci. *18*, 590–596.

Browning, M., Kingslake, J., Dourish, C.T., Goodwin, G.M., Harmer, C.J., and Dawson, G.R. (2019). Predicting treatment response to antidepressant medication using early changes in emotional processing. Eur. Neuropsychopharmacol. *29*, 66–75.

Brunoni, A.R., Zanao, T.A., Vanderhasselt, M.-A., Valiengo, L., de Oliveira, J.F., Boggio, P.S., Lotufo, P.A., Benseñor, I.M., and Fregni, F. (2014). Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression. Neuromodulation *17*, 138–142.

Bunney, W.E. (1965). Norepinephrine in depressive reactions: a review. Arch. Gen. Psychiatry *13*, 483.

Burdick, K.E., Braga, R.J., Gopin, C.B., and Malhotra, A.K. (2014). Dopaminergic influences on emotional decision making in euthymic bipolar patients. Neuropsychopharmacology *39*, 274–282.

Bzdok, D., and Meyer-Lindenberg, A. (2018). Machine learning for precision psychiatry: opportunities and challenges. Biol. Psychiatry Cogn. Neurosci. Neuroimaging *3*, 223–230.

Campbell-Meiklejohn, D., Wakeley, J., Herbert, V., Cook, J., Scollo, P., Ray, M.K., Selvaraj, S., Passingham, R.E., Cowen, P., and Rogers, R.D. (2011). Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacology *36*, 402–410.

Capitão, L.P., Chapman, R., Murphy, S.E., Harvey, C.-J., James, A., Cowen, P.J., and Harmer, C.J. (2019). A single dose of fluoxetine reduces neural limbic responses to anger in depressed adolescents. Transl. Psychiatry *9*, 30.

Carter, P.J., Hore, B., McGarrigle, L., Edwards, M., Doeg, G., Oakes, R., Campion, A., Carey, G., Vickers, K., and Parkinson, J.A. (2018). Happy thoughts: enhancing well-being in the classroom with a positive events diary. J. Posit. Psychol. *13*, 110–121.

Cawley, E., Tippler, M., Coupland, N.J., Benkelfat, C., Boivin, D.B., Aan Het Rot, M., and Leyton, M. (2017). Dopamine and light: effects on facial emotion recognition. J. Psychopharmacol. (Oxf.) *31*, 1225–1233.

Cecchini, M.P., Osculati, F., Ottaviani, S., Boschi, F., Fasano, A., and Tinazzi, M. (2014). Taste performance in Parkinson's disease. J. Neural Transm. *121*, 119–122.

Cecchini, M.P., Fasano, A., Boschi, F., Osculati, F., and Tinazzi, M. (2015). Taste in Parkinson's disease. J. Neurol. *262*, 806–813.

Chakhssi, F., Kraiss, J.T., Sommers-Spijkerman, M., and Bohlmeijer, E.T. (2018). The effect of positive psychology interventions on well-being and distress in clinical samples with psychiatric or somatic disorders: a systematic review and meta-analysis. BMC Psychiatry *18*, 211.

Chan, R.C.K., Li, H., Cheung, E.F.C., and Gong, Q. (2010). Impaired facial emotion perception in schizophrenia: A meta-analysis. Psychiatry Res. *178*, 381–390.

Chan, S.W.Y., Goodwin, G.M., and Harmer, C.J. (2007). Highly neurotic never-depressed students have negative biases in information processing. Psychol. Med. *37*, 1281–1291.

Chernoloz, O., Mansari, M.E., and Blier, P. (2009). Sustained administration of pramipexole modifies the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in the rat brain. Neuropsychopharmacology *34*, 651–661.

Chernoloz, O., El Mansari, M., and Blier, P. (2012). Long-term administration of the dopamine D3/2 receptor agonist pramipexole increases dopamine and serotonin neurotransmission in the male rat forebrain. J. Psychiatry Neurosci. *37*, 113–121.

Cinotti, F., Fresno, V., Aklil, N., Coutureau, E., Girard, B., Marchand, A.R., and Khamassi, M. (2019). Dopamine blockade impairs the exploration-exploitation trade-off in rats. Sci. Rep. *9*, 6770.

Clark, L., Chamberlain, S.R., and Sahakian, B.J. (2009). Neurocognitive mechanisms in depression: implications for treatment. Annu. Rev. Neurosci. *32*, 57–74.

Cooper, C.M., Whiting, D.A., Cowen, P.J., and Harmer, C.J. (2015). Tianeptine in an experimental medicine model of antidepressant action. J. Psychopharmacol. (Oxf.) *29*, 582–590.

Cooper, C.M., Godlewska, B., Sharpley, A.L., Barnes, E., Cowen, P.J., and Harmer, C.J. (2018). Interferon-α induces negative biases in emotional processing in patients with hepatitis C virus infection: a preliminary study. Psychol. Med. *48*, 998–1007.

Coppen, A. (1967). The biochemistry of affective disorders. Br. J. Psychiatry *113*, 1237–1264.

Cornelius, J.R., Tippmann-Peikert, M., Slocumb, N.L., Frerichs, C.F., and Silber, M.H. (2010). Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep *33*, 81–87.

Corrigan, M.H., Denahan, A.Q., Wright, E., Ragual, R.J., and Evans, D.L. (2000). Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress. Anxiety *11*, 58–65.

Costa, A., Peppe, A., Dell'Agnello, G., Caltagirone, C., and Carlesimo, G.A. (2009). Dopamine and cognitive functioning in de novo subjects with Parkinson's disease: Effects of pramipexole and pergolide on working memory. Neuropsychologia *47*, 1374–1381.

Cowen, P. (2017a). Backing into the future: pharmacological approaches to the management of resistant depression. Psychol. Med. *47*, 2569–2577.

Cowen, P. (2017b). Neuroendocrine and neurochemical processes in depression. In The Oxford Handbook of Mood Disorders, R.J. DeRubeis, and D.R. Strunk, eds. (Oxford University Press), pp. 190–200.

Crowley, S.K., and Youngstedt, S.D. (2012). Efficacy of light therapy for perinatal depression: a review. J. Physiol. Anthropol. *31*, 15.

Delaveau, P., Salgado-Pineda, P., Wicker, B., Micallef-Roll, J., and Blin, O. (2005). Effect of levodopa on healthy volunteers' facial emotion perception: an fmri study. Clin. Neuropharmacol. *28*, 255–261.

Delaveau, P., Salgado-Pineda, P., Micallef-Roll, J., and Blin, O. (2007). Amygdala activation modulated by levodopa during emotional recognition processing in healthy volunteers: a double-blind, placebo-controlled study. J. Clin. Psychopharmacol. *27*, 692–697.

Desan, P.H., Weinstein, A.J., Michalak, E.E., Tam, E.M., Meesters, Y., Ruiter, M.J., Horn, E., Telner, J., Iskandar, H., Boivin, D.B., et al. (2007). A controlled trial of the

Litebook light-emitting diode (LED) light therapy device for treatment of seasonal affective disorder (SAD). BMC Psychiatry *7*, 38.

Di Chiara, G., and Tanda, G. (1997). Blunting of reactivity of dopamine transmission to palatable food: a biochemical marker of anhedonia in the CMS model? Psychopharmacology (Berl.) *134*, 351–353.

Dillon, D.G., and Pizzagalli, D.A. (2018). Mechanisms of memory disruption in depression. Trends Neurosci. *41*, 137–149.

Docteur, A., Mirabel-Sarron, C., Guelfi, J.-D., Rouillon, F., and Gorwood, P. (2013). The role of CBT in explicit memory bias in bipolar I patients. J. Behav. Ther. Exp. Psychiatry *44*, 307–311.

Doty, R.L., Nsoesie, M.T., Chung, I., Osman, A., Pawasarat, I., Caulfield, J., Hurtig, H., Silas, J., Dubroff, J., Duda, J.E., et al. (2015). Taste function in early stage treated and untreated Parkinson's disease. J. Neurol. *262*, 547–557.

Drijgers, R.L., Verhey, F.R.J., Tissingh, G., van Domburg, P.H.M.F., Aalten, P., and Leentjens, A.F.G. (2012). The role of the dopaminergic system in mood, motivation and cognition in Parkinson's disease: a double blind randomized placebo-controlled experimental challenge with pramipexole and methylphenidate. J. Neurol. Sci. *320*, 121–126.

Dunlop, B.W., and Nemeroff, C.B. (2007). The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry *64*, 327–337.

Dziedzicka-Wasylewska, M., Willner, P., and Papp, M. (1997). Changes in dopamine receptor mRNA expression following chronic mild stress and chronic antidepressant treatment. Behav. Pharmacol. *8*, 607–618.

Eastman, C.I., Young, M.A., Fogg, L.F., Liu, L., and Meaden, P.M. (1998). Bright light treatment of winter depression: a placebo-controlled trial. Arch. Gen. Psychiatry *55*, 883–889.

Eaton, W.W., Muntaner, C., Smith, C., Tien, A., and Ybarra, M. (2004). Center for Epidemiologic Studies Depression Scale: review and revision (CESD and CESD-R). In The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, M.E. Maruish, ed. (Mahwah, NJ: Lawrence Erlbaum Associates Publishers), pp. 363–377.

Elliott, R., Zahn, R., Deakin, J.F.W., and Anderson, I.M. (2011). Affective cognition and its disruption in mood disorders. Neuropsychopharmacology *36*, 153–182.

Ersche, K.D., Roiser, J.P., Abbott, S., Craig, K.J., Müller, U., Suckling, J., Ooi, C., Shabbir, S.S., Clark, L., Sahakian, B.J., et al. (2011a). Response perseveration in stimulant dependence is associated with striatal dysfunction and can be ameliorated by a D2/3 receptor agonist. Biol. Psychiatry *70*, 754–762.

Ersche, K.D., Roiser, J.P., Lucas, M., Domenici, E., Robbins, T.W., and Bullmore, E.T. (2011b). Peripheral biomarkers of cognitive response to dopamine receptor agonist treatment. Psychopharmacology (Berl.) *214*, 779–789.

Eshel, N., and Roiser, J.P. (2010). Reward and punishment processing in depression. Biol. Psychiatry *68*, 118–124.

Etminan, M., Sodhi, M., Samii, A., Procyshyn, R.M., Guo, M., and Carleton, B.C. (2017). Risk of gambling disorder and impulse control disorder with aripiprazole, pramipexole, and ropinirole: a pharmacoepidemiologic study. J. Clin. Psychopharmacol. *37*, 102–104.

Eysenck, H.J., and Eysenck, S.B.G. (1975). Manual of the eysenck personality questionnaire (junior and adult) (Kent, UK: Hodder and Stoughton).

Fawcett, J., Rush, A.J., Vukelich, J., Diaz, S.H., Dunklee, L., Romo, P., Yarns, B.C., and Escalona, R. (2016). Clinical experience with high-dosage pramipexole in patients with treatment-resistant depressive episodes in unipolar and bipolar depression. Am. J. Psychiatry *173*, 107–111.

Feld, G.B., Besedovsky, L., Kaida, K., Münte, T.F., and Born, J. (2014). Dopamine d2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. J. Cogn. Neurosci. *26*, 2310–2320.

Fernandes, B.S., Williams, L.M., Steiner, J., Leboyer, M., Carvalho, A.F., and Berk, M. (2017). The new field of 'precision psychiatry.' BMC Med. *15*, 80.

Field, A.P., and Wilcox, R.R. (2017). Robust statistical methods: A primer for clinical psychology and experimental psychopathology researchers. Behav. Res. Ther. *98*, 19–38.

Field, A., Miles, J., and Field, Z. (2012). Discovering statistics using R (SAGE Publications Ltd).

First, M.B., Williams, J.B.W., Karg, R.S., and Spitzer, R.L. (2015). Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV) (Arlington, VA: American Psychiatric Association).

Fisher, P.M., Madsen, M.K., Mc Mahon, B., Holst, K.K., Andersen, S.B., Laursen, H.R., Hasholt, L.F., Siebner, H.R., and Knudsen, G.M. (2014). Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling. Biol. Psychiatry *76*, 332–339.

Forbes, E.E., Hariri, A.R., Martin, S.L., Silk, J.S., Moyles, D.L., Fisher, P.M., Brown, S.M., Ryan, N.D., Birmaher, B., Axelson, D.A., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am. J. Psychiatry *166*, 64–73.

Fredrickson, B.L. (2001). The role of positive emotions in positive psychology. Am. Psychol. *56*, 218–226.

Fredrickson, B.L. (2004). The broaden-and-build theory of positive emotions. Philos. Trans. R. Soc. B Biol. Sci. 1367–1377.

Fredrickson, B.L., and Joiner, T. (2002). Positive emotions trigger upward spirals toward emotional well-being. Psychol. Sci. *13*, 172–175.

Freeman, T.P., Morgan, C.J.A., Brandner, B., Almahdi, B., and Curran, H.V. (2013). Dopaminergic involvement in effort-based but not impulsive reward processing in smokers. Drug Alcohol Depend. *130*, 109–114.

Friedman, A., Friedman, Y., Dremencov, E., and Yadid, G. (2008). VTA dopamine neuron bursting is altered in an animal model of depression and corrected by desipramine. J. Mol. Neurosci. *34*, 201–209.

Friedrich, M.J. (2017). Depression is the leading cause of disability around the world. JAMA *317*, 1517–1517.

Fu, C.H.Y., Williams, S.C.R., Cleare, A.J., Scott, J., Mitterschiffthaler, M.T., Walsh, N.D., Donaldson, C., Suckling, J., Andrew, C., Steiner, H., et al. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol. Psychiatry *64*, 505–512.

Galbiati, A., Marelli, S., Giora, E., Zucconi, M., Oldani, A., and Ferini-Strambi, L. (2015). Neurocognitive function in patients with idiopathic restless legs syndrome before and after treatment with dopamine-agonist. Int. J. Psychophysiol. *95*, 304–309.

Gallant, H., Vo, A., Seergobin, K.N., and MacDonald, P.A. (2016). Pramipexole impairs stimulus-response learning in healthy young adults. Front. Neurosci. *10*, 374.

Gander, F., Proyer, R.T., Ruch, W., and Wyss, T. (2013). Strength-based positive interventions: further evidence for their potential in enhancing well-being and alleviating depression. J. Happiness Stud. *14*, 1241–1259.

Gard, P.R. (2002). The role of angiotensin II in cognition and behaviour. Eur. J. Pharmacol. *438*, 1–14.

Gard, D.E., Gard, M.G., Kring, A.M., and John, O.P. (2006). Anticipatory and consummatory components of the experience of pleasure: A scale development study. J. Res. Personal. *40*, 1086–1102.

Geoffroy, P.A., Schroder, C.M., and Bourgin, P. (2018). Light treatment in depression: an antique treatment with new insights. Sleep Med. Rev. *40*, 218–219.

Gibbs, A.A., Naudts, K.H., Spencer, E.P., and David, A.S. (2007). The role of dopamine in attentional and memory biases for emotional information. Am. J. Psychiatry *164*, 1603–1609.

Gilboa-Schechtman, E., Erhard-Weiss, D., and Jeczemien, P. (2002). Interpersonal deficits meet cognitive biases: memory for facial expressions in depressed and anxious men and women. Psychiatry Res. *113*, 279–293.

Golden, R.N., Gaynes, B.N., Ekstrom, R.D., Hamer, R.M., Jacobsen, F.M., Suppes, T., Wisner, K.L., and Nemeroff, C.B. (2005). The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am. J. Psychiatry *162*, 656–662.

Gray, H.M., and Tickle-Degnen, L. (2010). A meta-analysis of performance on emotion recognition tasks in Parkinson's disease. Neuropsychology *24*, 176–191.

Grier, J.B. (1971). Nonparametric indexes for sensitivity and bias: Computing formulas. Psychol. Bull. *75*, 424–429.

Güler, A.D., Ecker, J.L., Lall, G.S., Haq, S., Altimus, C.M., Liao, H.-W., Barnard, A.R., Cahill, H., Badea, T.C., Zhao, H., et al. (2008). Melanopsin cells are the principal conduits for rod–cone input to non-image-forming vision. Nature *453*, 102–105.

Hamidovic, A., Kang, U.J., and de Wit, H. (2008). Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers: J. Clin. Psychopharmacol. *28*, 45–51.

Hamilton, J.P., and Gotlib, I.H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. Biol. Psychiatry *63*, 1155–1162.

Harmer, C., and Pringle, A. (2017). Neuropsychological mechanisms of depression and treatment. In The Oxford Handbook of Mood Disorders, R.J. DeRubeis, and D.R. Strunk, eds. (Oxford: Oxford University Press), pp. 201–213.

Harmer, C.J., and Cowen, C.J. (2013). 'It's the way that you look at it'—a cognitive neuropsychological account of SSRI action in depression. Philos. Trans. R. Soc. B Biol. Sci. *368*, 20120407.

Harmer, C.J., Hill, S.A., Taylor, M.J., Cowen, P.J., and Goodwin, G.M. (2003a). Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. Am. J. Psychiatry *160*, 990–992.

Harmer, C.J., Rogers, R.D., Tunbridge, E., Cowen, P.J., and Goodwin, G.M. (2003b). Tryptophan depletion decreases the recognition of fear in female volunteers. Psychopharmacology (Berl.) *167*, 411–417.

Harmer, C.J., Bhagwagar, Z., Perrett, D.I., Völlm, B.A., Cowen, P.J., and Goodwin, G.M. (2003c). Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology *28*, 148–152.

Harmer, C.J., Bhagwagar, Z., Shelley, N., and Cowen, P.J. (2003d). Contrasting effects of citalopram and reboxetine on waking salivary cortisol. Psychopharmacology (Berl.) *167*, 112–114.

Harmer, C.J., Shelley, N.C., Cowen, P.J., and Goodwin, G.M. (2004). Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am. J. Psychiatry *161*, 1256–1263.

Harmer, C.J., Heinzen, J., O'Sullivan, U., Ayres, R.A., and Cowen, P.J. (2008). Dissociable effects of acute antidepressant drug administration on subjective and emotional processing measures in healthy volunteers. Psychopharmacology (Berl.) *199*, 495–502.

Harmer, C.J., Goodwin, G.M., and Cowen, P.J. (2009a). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br. J. Psychiatry *195*, 102–108.

Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G.M., and Cowen, P.J. (2009b). Effect of acute antidepressant administration on negative affective bias in depressed patients. Am. J. Psychiatry *166*, 1178–1184.

Harmer, C.J., de Bodinat, C., Dawson, G.R., Dourish, C.T., Waldenmaier, L., Adams, S., Cowen, P.J., and Goodwin, G.M. (2011). Agomelatine facilitates positive versus negative affective processing in healthy volunteer models. J. Psychopharmacol. (Oxf.) *25*, 1159–1167.

Harmer, C.J., Charles, M., McTavish, S., Favaron, E., and Cowen, P.J. (2012). Negative ion treatment increases positive emotional processing in seasonal affective disorder. Psychol. Med. *42*, 1605–1612.

Harmer, C.J., Duman, R.S., and Cowen, P.J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry *4*, 409–418.

Harrison, P., Cowen, P., Burns, T., and Fazel, M. (2018). Depression. In Shorter Oxford Textbook of Psychiatry, (Oxford: Oxford University Press), pp. 193–232.

Hasler, G., Fromm, S., Carlson, P.J., Luckenbaugh, D.A., Waldeck, T., Geraci, M., Roiser, J.P., Neumeister, A., Meyers, N., Charney, D.S., et al. (2008). Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and healthy subjects. Arch. Gen. Psychiatry *65*, 521–531.

Hasler, G., Luckenbaugh, D.A., Snow, J., Meyers, N., Waldeck, T., Geraci, M., Roiser, J., Knutson, B., Charney, D.S., and Drevets, W.C. (2009). Reward processing after catecholamine depletion in unmedicated, remitted subjects with major depressive disorder. Biol. Psychiatry *66*, 201–205.

Healey, K.M., Bartholomeusz, C.F., and Penn, D.L. (2016). Deficits in social cognition in first episode psychosis: A review of the literature. Clin. Psychol. Rev. *50*, 108–137.

Hill, S.A., Taylor, M.J., Harmer, C.J., and Cowen, P.J. (2003). Acute reboxetine administration increases plasma and salivary cortisol. J. Psychopharmacol. (Oxf.) *17*, 273–275.

Hills, P., and Argyle, M. (2002). The Oxford happiness questionnaire: a compact scale for the measurement of psychological well-being. Personal. Individ. Differ. *33*, 1073–1082.

van der Hoek, T.C., Bus, B.A.A., Matui, P., van der Marck, M.A., Esselink, R.A., and Tendolkar, I. (2011). Prevalence of depression in Parkinson's disease: effects of disease stage, motor subtype and gender. J. Neurol. Sci. *310*, 220–224.

Homan, P., Neumeister, A., Nugent, A.C., Charney, D.S., Drevets, W.C., and Hasler, G. (2015). Serotonin versus catecholamine deficiency: behavioral and neural effects of experimental depletion in remitted depression. Transl. Psychiatry *5*, e532.

Hori, H., and Kunugi, H. (2013). Dopamine agonist-responsive depression: dopamine and depression. Psychogeriatrics *13*, 189–195.

Huneke, N.T., Walsh, A.E., Brown, R., Browning, M., and Harmer, C.J. (2017). No evidence for an acute placebo effect on emotional processing in healthy volunteers. J. Psychopharmacol. (Oxf.) *31*, 1578–1587.

Ishibashi, K., Ishii, K., Oda, K., Mizusawa, H., and Ishiwata, K. (2011). Binding of pramipexole to extrastriatal dopamine D2/D3 receptors in the human brain: a positron emission tomography study using 11C-FLB 457. PLOS ONE *6*, e17723.

Jeste, D.V., Palmer, B.W., Rettew, D.C., and Boardman, S. (2015). Positive psychiatry: its time has come. J. Clin. Psychiatry *76*, 675–683.

Kaelbling, L.P., Littman, M.L., and Moore, A.W. (1996). Reinforcement learning: a survey. J. Artif. Intell. Res. *4*, 237–285.

Kaltenboeck, A., and Harmer, C. (2019). Can non-pharmacological antidepressant treatments influence the processing of affective information? In Cognitive Dimensions of Major Depressive Disorder, (Oxford: Oxford University Press), pp. 257–268.

Kanen, J.W., Ersche, K.D., Fineberg, N.A., Robbins, T.W., and Cardinal, R.N. (2019). Computational modelling reveals contrasting effects on reinforcement learning and cognitive flexibility in stimulant use disorder and obsessive-compulsive disorder: remediating effects of dopaminergic D2/3 receptor agents. Psychopharmacology (Berl.) *236*, 2337–2358.

Kim, H.-J., Jeon, B.S., Lee, J.-Y., Cho, Y.-J., Hong, K.-S., and Cho, J.-Y. (2011). Taste function in patients with Parkinson disease. J. Neurol. *258*, 1076–1079.

Kleeblatt, J., Betzler, F., Kilarski, L.L., Bschor, T., and Köhler, S. (2017). Efficacy of off-label augmentation in unipolar depression: a systematic review of the evidence. Eur. Neuropsychopharmacol. *27*, 423–441.

Kohler, C.G., Walker, J.B., Martin, E.A., Healey, K.M., and Moberg, P.J. (2010). Facial emotion perception in schizophrenia: a meta-analytic review. Schizophr. Bull. *36*, 1009–1019.

Kram, M.L., Kramer, G.L., Ronan, P.J., Steciuk, M., and Petty, F. (2002). Dopamine receptors and learned helplessness in the rat: an autoradiographic study. Prog. Neuropsychopharmacol. Biol. Psychiatry *26*, 639–645.

Kumbargere Nagraj, S., George, R.P., Shetty, N., Levenson, D., Ferraiolo, D.M., and Shrestha, A. (2017). Interventions for managing taste disturbances. Cochrane Database Syst. Rev. CD010470.

Lam, R.W., and Levitan, R.D. (2000). Pathophysiology of seasonal affective disorder: a review. J. Psychiatry Neurosci. *25*, 469–480.

Lam, R.W., Levitt, A.J., Levitan, R.D., Michalak, E.E., Cheung, A.H., Morehouse, R., Ramasubbu, R., Yatham, L.N., and Tam, E.M. (2016). Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry *73*, 56–63.

Lang, C.J.G., Leuschner, T., Ulrich, K., Stößel, C., Heckmann, J.G., and Hummel, T. (2006). Taste in dementing diseases and parkinsonism. J. Neurol. Sci. *248*, 177–184.

Lawrence, A.D., Calder, A.J., McGowan, S.W., and Grasby, P.M. (2002). Selective disruption of the recognition of facial expressions of anger: Neuroreport *13*, 881–884.

Layous, K., Chancellor, J., and Lyubomirsky, S. (2014). Positive activities as protective factors against mental health conditions. J. Abnorm. Psychol. *123*, 3–12.

LeGates, T.A., Fernandez, D.C., and Hattar, S. (2014). Light as a central modulator of circadian rhythms, sleep and affect. Nat. Rev. Neurosci. *15*, 443–454.

Leggio, G.M., Salomone, S., Bucolo, C., Platania, C., Micale, V., Caraci, F., and Drago, F. (2013). Dopamine D3 receptor as a new pharmacological target for the treatment of depression. Eur. J. Pharmacol. *719*, 25–33.

Lieberknecht, V., Cunha, M.P., Junqueira, S.C., Coelho, I. dos S., de Souza, L.F., dos Santos, A.R.S., Rodrigues, A.L.S., Dutra, R.C., and Dafre, A.L. (2017). Antidepressant-like effect of pramipexole in an inflammatory model of depression. Behav. Brain Res. *320*, 365–373.

Lieverse, R., Van Someren, E.J.W., Nielen, M.M.A., Uitdehaag, B.M.J., Smit, J.H., and Hoogendijk, W.J.G. (2011). Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch. Gen. Psychiatry *68*, 61–70.

Lyubomirsky, S., and Layous, K. (2013). How do simple positive activities increase well-being? Curr. Dir. Psychol. Sci. *22*, 57–62.

Malcolm, C.P., Cowen, P.J., and Harmer, C.J. (2009). Research letter: High-density negative ion treatment increases positive affective memory. Psychol. Med. *39*, 1930–1932.

Mannie, Z.N., Harmer, C.J., and Cowen, P.J. (2007). Increased waking salivary cortisol levels in young people at familial risk of depression. Am. J. Psychiatry *164*, 617–621.

Martins, D., Mehta, M.A., and Prata, D. (2017). The "highs and lows" of the human brain on dopaminergics: evidence from neuropharmacology. Neurosci. Biobehav. Rev. *80*, 351–371.

Maruani, J., and Geoffroy, P.A. (2019). Bright light as a personalized precision treatment of mood disorders. Front. Psychiatry *10*, 85.

Masurier, M.L., Cowen, P.J., and Harmer, C.J. (2007). Emotional bias and waking salivary cortisol in relatives of patients with major depression. Psychol. Med. *37*, 403–410.

Mathews, A., and MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. Cogn. Emot. *16*, 331–354.

McCabe, C., Cowen, P.J., and Harmer, C.J. (2009). Neural representation of reward in recovered depressed patients. Psychopharmacology (Berl.) *205*, 667–677.

McCabe, C., Harwood, J., Brouwer, S., Harmer, C.J., and Cowen, P.J. (2013). Effects of pramipexole on the processing of rewarding and aversive taste stimuli. Psychopharmacology (Berl.) *228*, 283–290.

Mehta, M.A., Hinton, E.C., Montgomery, A.J., Bantick, R.A., and Grasby, P.M. (2005). Sulpiride and mnemonic function: effects of a dopamine D2 receptor antagonist on working memory, emotional memory and long-term memory in healthy volunteers. J. Psychopharmacol. (Oxf.) *19*, 29–38.

Meyer, J.H., Krüger, S., Wilson, A.A., Christensen, B.K., Goulding, V.S., Schaffer, A., Minifie, C., Houle, S., Hussey, D., and Kennedy, S.H. (2001). Lower dopamine transporter binding potential in striatum during depression: Neuroreport *12*, 4121–4125.

Miskowiak, K., and Carvalho, A. (2014). 'Hot' cognition in major depressive disorder: a systematic review. CNS Neurol. Disord. - Drug Targets *13*, 1787–1803.

Miskowiak, K.W., Macoveanu, J., Jørgensen, M.B., Støttrup, M.M., Ott, C.V., Jensen, H.M., Jørgensen, A., Harmer, J., Paulson, O.B., Kessing, L.V., et al. (2018). Neural response after a single ECT session during retrieval of emotional self-referent words in depression: a randomized, sham-controlled fMRI study. Int. J. Neuropsychopharmacol. *21*, 226–235.

Mitchell, J., Vella-Brodrick, D., and Klein, B. (2010). Positive psychology and the internet: a mental health opportunity. E-J. Appl. Psychol. *6*, 30–41.

Moberg, P.J., Balderston, C.C., Rick, J.H., Roalf, D.R., Weintraub, D., Kleiner-Fisman, G., Stern, M.B., and Duda, J.E. (2007). Phenylthiocarbamide (PTC) perception in Parkinson disease: Cogn. Behav. Neurol. *20*, 145–148.

Mongrain, M., and Anselmo-Matthews, T. (2012). Do positive psychology exercises work? A replication of Seligman et al. (2005). J. Clin. Psychol. *68*, 382–389.

Moraga-Amaro, R., Gonzalez, H., Pacheco, R., and Stehberg, J. (2014). Dopamine receptor D3 deficiency results in chronic depression and anxiety. Behav. Brain Res. *274*, 186–193.

Morein-Zamir, S., Craig, K.J., Ersche, K.D., Abbott, S., Muller, U., Fineberg, N.A., Bullmore, E.T., Sahakian, B.J., and Robbins, T.W. (2010). Impaired visuospatial associative memory and attention in obsessive compulsive disorder but no evidence for differential dopaminergic modulation. Psychopharmacology (Berl.) *212*, 357–367.

Morriss, R., Garland, A., Nixon, N., Guo, B., James, M., Kaylor-Hughes, C., Moore, R., Ramana, R., Sampson, C., Sweeney, T., et al. (2016). Efficacy and cost-effectiveness of a specialist depression service versus usual specialist mental health

care to manage persistent depression: a randomised controlled trial. Lancet Psychiatry *3*, 821–831.

Mulinari, S. (2012). Monoamine theories of depression: historical impact on biomedical research. J. Hist. Neurosci. *21*, 366–392.

Murphy, S.E., Downham, C., Cowen, P.J., and Harmer, C.J. (2008). Direct effects of diazepam on emotional processing in healthy volunteers. Psychopharmacology (Berl.) *199*, 503–513.

Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., and Harmer, C.J. (2009). Effect of a single dose of citalopram on amygdala response to emotional faces. Br. J. Psychiatry *194*, 535–540.

Murphy, S.E., Wright, L.C., Browning, M., Cowen, P.J., and Harmer, C.J. (2019). A role for 5-HT4 receptors in human learning and memory. Psychol. Med. 1–9.

Murray, G.K., Knolle, F., Ersche, K.D., Craig, K.J., Abbott, S., Shabbir, S.S., Fineberg, N.A., Suckling, J., Sahakian, B.J., Bullmore, E.T., et al. (2019). Dopaminergic drug treatment remediates exaggerated cingulate prediction error responses in obsessive-compulsive disorder. Psychopharmacology (Berl.) *236*, 2325–2336.

Nagy, H., Levy-Gigi, E., Somlai, Z., Takáts, A., Bereczki, D., and Kéri, S. (2012). The effect of dopamine agonists on adaptive and aberrant salience in Parkinson's disease. Neuropsychopharmacology *37*, 950–958.

Newton, T.F., Haile, C.N., Mahoney, J.J., Shah, R., Verrico, C.D., De La Garza, R., and Kosten, T.R. (2015). Dopamine D3 receptor-preferring agonist enhances the subjective effects of cocaine in humans. Psychiatry Res. *230*, 44–49.

NICE (2009). Depression in adults: recognition and management.

Oldham, M.A., and Ciraulo, D.A. (2014). Bright light therapy for depression: a review of its effects on chronobiology and the autonomic nervous system. Chronobiol. Int. *31*, 305–319.

Ostadhadi, S., Imran Khan, M., Norouzi-Javidan, A., and Dehpour, A.-R. (2016). Antidepressant effect of pramipexole in mice forced swimming test: A cross talk between dopamine receptor and NMDA/nitric oxide/cGMP pathway. Biomed. Pharmacother. *81*, 295–304.

Pail, G., Huf, W., Pjrek, E., Winkler, D., Willeit, M., Praschak-Rieder, N., and Kasper, S. (2011). Bright-light therapy in the treatment of mood disorders. Neuropsychobiology *64*, 152–162.

Pariante, C.M., and Lightman, S.L. (2008). The HPA axis in major depression: classical theories and new developments. Trends Neurosci. *31*, 464–468.

Péron, J., Dondaine, T., Le Jeune, F., Grandjean, D., and Vérin, M. (2012). Emotional processing in Parkinson's disease: a systematic review. Mov. Disord. *27*, 186–199.

Piercey, M. (1998). Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson's disease. Clin. Neuropharmacol. *21*, 141–151.

Pike, A.C. (2018). Eating disorders and compulsivity: neural, computational, and psychopharmacological approaches. DPhil thesis. University of Oxford.

Pizzagalli, D.A., Evins, A.E., Schetter, E.C., Frank, M.J., Pajtas, P.E., Santesso, D.L., and Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology (Berl.) *196*, 221–232.

Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., and Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am. J. Psychiatry *166*, 702–710.

Pizzagalli, D.A., Berretta, S., Wooten, D., Goer, F., Pilobello, K.T., Kumar, P., Murray, L., Beltzer, M., Boyer-Boiteau, A., Alpert, N., et al. (2019). Assessment of striatal dopamine transporter binding in individuals with major depressive disorder: in vivo positron emission tomography and postmortem evidence. JAMA Psychiatry *76*, 854.

Pjrek, E., Friedrich, M.-E., Cambioli, L., Dold, M., Jäger, F., Komorowski, A., Lanzenberger, R., Kasper, S., and Winkler, D. (2020). The efficacy of light therapy in the treatment of seasonal affective disorder: a meta-analysis of randomized controlled trials. Psychother. Psychosom. *89*, 17–24.

Portella, M.J., Harmer, C.J., Flint, J., Cowen, P., and Goodwin, G.M. (2005). Enhanced early morning salivary cortisol in neuroticism. Am. J. Psychiatry *162*, 807–809.

Pringle, A., Browning, M., Cowen, P.J., and Harmer, C.J. (2011). A cognitive neuropsychological model of antidepressant drug action. Prog. Neuropsychopharmacol. Biol. Psychiatry *35*, 1586–1592.

Pringle, A., Parsons, E., Cowen, L., McTavish, S., Cowen, P., and Harmer, C. (2012). Using an experimental medicine model to understand the antidepressant potential of the *N* -Methyl-D-aspartic acid (NMDA) receptor antagonist memantine. J. Psychopharmacol. (Oxf.) *26*, 1417–1423.

Proyer, R.T., Gander, F., Wellenzohn, S., and Ruch, W. (2014). Positive psychology interventions in people aged 50–79 years: long-term effects of placebo-controlled online interventions on well-being and depression. Aging Ment. Health *18*, 997–1005.

Proyer, R.T., Wellenzohn, S., Gander, F., and Ruch, W. (2015). Toward a better understanding of what makes positive psychology interventions work: predicting happiness and depression from the person × intervention fit in a follow-up after 3.5 years. Appl. Psychol. Health Well-Being *7*, 108–128.

Pruessner, J.C., Wolf, O.T., Hellhammer, D.H., Buske-Kirschbaum, A., von Auer, K., Jobs, S., Kaspers, F., and Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci. *61*, 2539–2549.

Pulcu, E., and Browning, M. (2017). Affective bias as a rational response to the statistics of rewards and punishments. ELife e27879.

Pulcu, E., and Browning, M. (2019). The misestimation of uncertainty in affective disorders. Trends Cogn. Sci. *23*, 865–875.

Pulcu, E., Shkreli, L., Holst, C.G., Woud, M.L., Craske, M.G., Browning, M., and Reinecke, A. (2019). The Effects of the Angiotensin II Receptor Antagonist Losartan on Appetitive Versus Aversive Learning: A Randomized Controlled Trial. Biol. Psychiatry *86*, 397–404.

Quoidbach, J., Mikolajczak, M., and Gross, J.J. (2015). Positive interventions: an emotion regulation perspective. Psychol. Bull. *141*, 655–693.

Rashid, T. (2015). Positive psychotherapy: a strength-based approach. J. Posit. Psychol. *10*, 25–40.

Redlich, R., Bürger, C., Dohm, K., Grotegerd, D., Opel, N., Zaremba, D., Meinert, S., Förster, K., Repple, J., Schnelle, R., et al. (2017). Effects of electroconvulsive therapy on amygdala function in major depression – a longitudinal functional magnetic resonance imaging study. Psychol. Med. *47*, 2166–2176.

Reinecke, A., Waldenmaier, L., Cooper, M.J., and Harmer, C.J. (2013). Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. Biol. Psychiatry *73*, 1064–1070.

Rescorla, R.A., and Wagner, A.R. (1972). A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In Classical Conditioning II: Current Research and Theory, A.H. Black, and W.F. Prokasy, eds. (New York: Appleton-Century-Crofts), pp. 64–99.

Riba, J., Krämer, U.M., Heldmann, M., Richter, S., and Münte, T.F. (2008). Dopamine agonist increases risk taking but blunts reward-related brain activity. PLOS ONE *3*, e2479.

Ridout, N., Astell, A., Reid, I., Glen, T., and O'Carroll, R. (2003). Memory bias for emotional facial expressions in major depression. Cogn. Emot. *17*, 101–122.

Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., and Cabeza, R. (2011). Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. J. Psychiatr. Res. *45*, 577–587.

Rock, P.L., Goodwin, G.M., Wulff, K., McTavish, S.F., and Harmer, C.J. (2016). Effects of short-term quetiapine treatment on emotional processing, sleep and circadian rhythms. J. Psychopharmacol. (Oxf.) *30*, 273–282.

Roiser, J., and Sahakian, B.J. (2017). Information processing in mood disorders. In The Oxford Handbook of Mood Disorders, R.J. DeRubeis, and D.R. Strunk, eds. (Oxford: Oxford University Press), pp. 179–189.

Roiser, J.P., and Sahakian, B.J. (2013). Hot and cold cognition in depression. CNS Spectr. *18*, 139–149.

Roiser, J.P., Elliott, R., and Sahakian, B.J. (2012). Cognitive mechanisms of treatment in depression. Neuropsychopharmacology *37*, 117–136.

Romeo, B., Blecha, L., Locatelli, K., Benyamina, A., and Martelli, C. (2018). Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: efficacy and safety. J. Psychopharmacol. (Oxf.) *32*, 385–396.

Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y., Mueller, P.S., Newsome, D.A., and Wehr, T.A. (1984). Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch. Gen. Psychiatry *41*, 72–80.

aan het Rot, M., Coupland, N., Boivin, D.B., Benkelfat, C., and Young, S.N. (2010). Recognizing emotions in faces: effects of acute tryptophan depletion and bright light. J. Psychopharmacol. (Oxf.) *24*, 1447–1454.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry *163*, 1905–1917.

Samuels, E.R., Hou, R.H., Langley, R.W., Szabadi, E., and Bradshaw, C.M. (2006a). Comparison of pramipexole and amisulpride on alertness, autonomic and endocrine functions in healthy volunteers. Psychopharmacology (Berl.) *187*, 498–510.

Samuels, E.R., Hou, R.H., Langley, R.W., Szabadi, E., and Bradshaw, C.M. (2006b). Comparison of pramipexole and modafinil on arousal, autonomic, and endocrine functions in healthy volunteers. J. Psychopharmacol. (Oxf.) *20*, 756–770.

Samuels, E.R., Hou, R.H., Langley, R.W., Szabadi, E., and Bradshaw, C.M. (2007). Comparison of pramipexole with and without domperidone co-administration on alertness, autonomic, and endocrine functions in healthy volunteers. Br. J. Clin. Pharmacol. *64*, 591–602.

Santesso, D.L., Evins, A.E., Frank, M.J., Schetter, E.C., Bogdan, R., and Pizzagalli, D.A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. Hum. Brain Mapp. *30*, 1963–1976.

Sarchiapone, M., Carli, V., Camardese, G., Cuomo, C., Di Giuda, D., Calcagni, M.-L., Focacci, C., and De Risio, S. (2006). Dopamine transporter binding in depressed patients with anhedonia. Psychiatry Res. Neuroimaging *147*, 243–248.

Savla, G.N., Vella, L., Armstrong, C.C., Penn, D.L., and Twamley, E.W. (2013). Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr. Bull. *39*, 979–992.

Schildkraut, J.J., Gordon, E.K., and Durell, J. (1965). Catecholamine metabolism in affective disorders: I. J. Psychiatr. Res. *3*, 213–228.

Schmidt, K., Cowen, P.J., Harmer, C.J., Tzortzis, G., Errington, S., and Burnet, P.W.J. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology (Berl.) *232*, 1793–1801.

Schueller, S.M. (2012). Personality fit and positive interventions: extraverted and introverted individuals benefit from different happiness increasing strategies. Psychology *3*, 1166–1173.

Schulte-Herbrüggen, O., Vogt, M.A., Hörtnagl, H., Gass, P., and Hellweg, R. (2012). Pramipexole is active in depression tests and modulates monoaminergic transmission, but not brain levels of BDNF in mice. Eur. J. Pharmacol. *677*, 77–86.

Schwartz, R.S., and Olds, J. (2015). The psychiatry of light. Harv. Rev. Psychiatry *23*, 188–194.

Seeman, P. (2015). Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. Synapse *69*, 183–189.

Seligman, M.E.P. (2005). Positive psychology, positive prevention, and positive therapy. In Handbook of Positive Psychology, C.R. Snyder, and S.J. Lopez, eds. (Oxford University Press), pp. 3–9.

Seligman, M.E.P. (2011). Flourish: a new understanding of happiness and well-being, and how to achieve them (London: Brealey).

Seligman, M.E.P., and Csikszentmihalyi, M. (2000). Positive psychology: an introduction. Am. Psychol. *55*, 5–14.

Seligman, M.E.P., Steen, T.A., Park, N., and Peterson, C. (2005). Positive psychology progress: empirical validation of interventions. Am. Psychol. *60*, 410–421.

Seligman, M.E.P., Rashid, T., and Parks, A. (2006). Positive psychotherapy. Am. Psychol. *61*, 774–788.

Sexton, J.B., and Adair, K.C. (2019). Forty-five good things: a prospective pilot study of the Three Good Things well-being intervention in the USA for healthcare worker emotional exhaustion, depression, work–life balance and happiness. BMJ Open *9*, e022695.

Shah, M., Deeb, J., Fernando, M., Noyce, A., Visentin, E., Findley, L.J., and Hawkes, C.H. (2009). Abnormality of taste and smell in Parkinson's disease. Parkinsonism Relat. Disord. *15*, 232–237.

Sharp, T., and Cowen, P.J. (2011). 5-HT and depression: is the glass half-full? Curr. Opin. Pharmacol. *11*, 45–51.

Sheldon, K.M., and King, L. (2001). Why positive psychology is necessary. Am. Psychol. *56*, 216–217.

Shepherd, J., Oliver, M., and Schofield, G. (2015). Convergent validity and test–retest reliability of the Authentic Happiness Inventory in working adults. Soc. Indic. Res. *124*, 1049–1058.

Shepherd, T.A., Edelstyn, N.M.J., Mayes, A.R., and Ellis, S.J. (2013). Second-generation dopamine agonists and recollection impairments in Parkinson's disease. J. Neuropsychol. *7*, 284–305.

Shiroma, P.R., Thuras, P., Johns, B., and Lim, K.O. (2014). Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression: emotion recognition in late-life depression. Int. J. Geriatr. Psychiatry *29*, 1132–1139.

Simon, G.E., Khandker, R.K., Ichikawa, L., and Operskalski, B.H. (2006). Recovery from depression predicts lower health services costs. J. Clin. Psychiatry *67*, 1226–1231.

Sin, N.L., and Lyubomirsky, S. (2009). Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. J. Clin. Psychol. *65*, 467–487.

Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., and Trigwell, P. (1995). A scale for the assessment of hedonic tone: The Snaith-Hamilton pleasure scale. Br. J. Psychiatry *167*, 99–103.

Sokoloff, P., and Le Foll, B. (2017). The dopamine D3 receptor, a quarter century later. Eur. J. Neurosci. *45*, 2–19.

Sokoloff, P., Giros, B., Martres, M.-P., and Bouthenett, M.-L. (1990). Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature *347*, 146–151.

Spielberger, C., Gorssuch, R., Lushene, P., Vagg, P., and Jacobs, G. (1983). Manual for the State-Trait Anxiety Inventory (Palo Alto, CA: Consulting Psychologists Press, Inc.).

Stephenson, K.M., Schroder, C.M., Bertschy, G., and Bourgin, P. (2012). Complex interaction of circadian and non-circadian effects of light on mood: Shedding new light on an old story. Sleep Med. Rev. *16*, 445–454.

Sutton, R.S., and Barto, A.G. (1998). Reinforcement learning: An introduction. (Cambridge, MA: MIT Press).

Taghvaienia, A., and Alamdari, N. (2020). Effect of positive psychotherapy on psychological well-being, happiness, life expectancy and depression among retired teachers with depression: a randomized controlled trial. Community Ment. Health J. *56*, 229–237.

Tandberg, E., Larsen, J.P., and Aarsland, D. (1996). The occurrence of depression in Parkinson's disease: a community-based study. Arch. Neurol. *53*, 175–179.

Tavares, J.V.T., Drevets, W.C., and Sahakian, B.J. (2003). Cognition in mania and depression. Psychol. Med. *33*, 959–967.

Terman, M., and Terman, J.S. (1999). Bright light therapy: side effects and benefits across the symptom spectrum. J. Clin. Psychiatry *60*, 799–808.

Terman, M., and Terman, J.S. (2005). Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectr. *10*, 647–663.

Tokunaga, N., Choudhury, M.E., Nishikawa, N., Nagai, M., Tujii, T., Iwaki, H., Kaneta, M., and Nomoto, M. (2012). Pramipexole upregulates dopamine receptor D2 and D3 expression in rat striatum. J. Pharmacol. Sci. *120*, 133–137.

Tundo, A., Filippis, R., and De Crescenzo, F. (2019). Pramipexole in the treatment of unipolar and bipolar depression. a systematic review and meta-analysis. Acta Psychiatr. Scand. *140*, 116–125.

Tuunainen, A., Kripke, D.F., and Endo, T. (2004). Light therapy for non-seasonal depression. Cochrane Database Syst. Rev. *2*, CD004050.

Vandewalle, G., Maquet, P., and Dijk, D.-J. (2009). Light as a modulator of cognitive brain function. Trends Cogn. Sci. *13*, 429–438.

Vandewalle, G., Schwartz, S., Grandjean, D., Wuillaume, C., Balteau, E., Degueldre, C., Schabus, M., Phillips, C., Luxen, A., Dijk, D.J., et al. (2010). Spectral quality of light modulates emotional brain responses in humans. Proc. Natl. Acad. Sci. *107*, 19549–19554.

Vandewalle, G., Hébert, M., Beaulieu, C., Richard, L., Daneault, V., Garon, M.-L., Leblanc, J., Grandjean, D., Maquet, P., Schwartz, S., et al. (2011). Abnormal hypothalamic response to light in seasonal affective disorder. Biol. Psychiatry *70*, 954–961.

Vetulani, J., and Sulser, F. (1975). Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. Nature *257*, 495–496.

Vreeburg, S.A., Hoogendijk, W.J.G., Pelt, J. van, DeRijk, R.H., Verhagen, J.C.M., Dyck, R. van, Smit, J.H., Zitman, F.G., and Penninx, B.W.J.H. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch. Gen. Psychiatry *66*, 617–626.

Vreeburg, S.A., Hartman, C.A., Hoogendijk, W.J.G., Dyck, R. van, Zitman, F.G., Ormel, J., and Penninx, B.W.J.H. (2010). Parental history of depression or anxiety and the cortisol awakening response. Br. J. Psychiatry *197*, 180–185.

Walsh, A.E., and Harmer, C.J. (2015). The cognitive neuropsychological model of antidepressant response. Curr. Opin. Psychol. *4*, 124–130.

Walsh, A.E.L., Browning, M., Drevets, W.C., Furey, M., and Harmer, C.J. (2018a). Dissociable temporal effects of bupropion on behavioural measures of emotional and reward processing in depression. Philos. Trans. R. Soc. B Biol. Sci. *373*, 20170030.

Walsh, A.E.L., Huneke, N.T.M., Brown, R., Browning, M., Cowen, P., and Harmer, C.J. (2018b). A dissociation of the acute effects of bupropion on positive emotional processing and reward processing in healthy volunteers. Front. Psychiatry *9*, 482.

Wang, J., Jia, Y., Li, G., Wang, B., Zhou, T., Zhu, L., Chen, T., and Chen, Y. (2018). The dopamine receptor D3 regulates lipopolysaccharide-induced depressive-like behavior in mice. Int. J. Neuropsychopharmacol. *21*, 448–460.

Warren, M.B., Pringle, A., and Harmer, C.J. (2015). A neurocognitive model for understanding treatment action in depression. Philos. Trans. R. Soc. B Biol. Sci. *370*, 20140213.

Warren, M.B., Cowen, P.J., and Harmer, C.J. (2019). Subchronic treatment with St John's wort produces a positive shift in emotional processing in healthy volunteers. J. Psychopharmacol. (Oxf.) *33*, 194–201.

Watkins, P.C., Mathews, A., Williamson, D.A., and Fuller, R. (1992). Mood-congruent memory in depression: emotional priming or elaboration? J. Abnorm. Psychol. *101*, 581–586.

Watson, D., Clark, L.A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. *54*, 1063–1070.

Weintraub, D., Hoops, S., Shea, J.A., Lyons, K.E., Pahwa, R., Driver-Dunckley, E.D., Adler, C.H., Potenza, M.N., Miyasaki, J., Siderowf, A.D., et al. (2009). Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov. Disord. *24*, 1461–1467.

Wellenzohn, S., Proyer, R.T., and Ruch, W. (2016). How do positive psychology interventions work? A short-term placebo-controlled humor-based study on the role of the time focus. Personal. Individ. Differ. *96*, 1–6.

White, C.A., Uttl, B., and Holder, M.D. (2019). Meta-analyses of positive psychology interventions: The effects are much smaller than previously reported. PLOS ONE *14*, e0216588.

Wilson, R.C., Geana, A., White, J.M., Ludvig, E.A., and Cohen, J.D. (2014). Humans use directed and random exploration to solve the explore–exploit dilemma. J. Exp. Psychol. Gen. *143*, 2074–2081.

Winter, C., von Rumohr, A., Mundt, A., Petrus, D., Klein, J., Lee, T., Morgenstern, R., Kupsch, A., and Juckel, G. (2007). Lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area enhance depressive-like behavior in rats. Behav. Brain Res. *184*, 133–141.

Wirz-Justice, A., Benedetti, F., and Terman, M. (2013). Chronotherapeutics for affective disorders. A clinician's manual for light and wake therapy. (Basel: Karger).

Wood, A.M., and Tarrier, N. (2010). Positive clinical psychology: a new vision and strategy for integrated research and practice. Clin. Psychol. Rev. *30*, 819–829.

Woodworth, R.J., O'Brien-Malone, A., Diamond, M.R., and Schüz, B. (2016). Happy days: positive psychology interventions effects on affect in an n-of-1 trial. Int. J. Clin. Health Psychol. *16*, 21–29.

Woodworth, R.J., O'Brien-Malone, A., Diamond, M.R., and Schüz, B. (2017). Web-based positive psychology interventions: a reexamination of effectiveness. J. Clin. Psychol. *73*, 218–232.

Wüst, S., Wolf, J., Hellhammer, D.H., Federenko, I., Schommer, N., and Kirschbaum, C. (2000). The cortisol awakening response - normal values and confounds. Noise Health *7*, 77–85.

Xu, Y.-Y., Feng, Z.-Q., Xie, Y.-J., Zhang, J., Peng, S.-H., Yu, Y.-J., and Li, M. (2018). Frontal alpha EEG asymmetry before and after positive psychological interventions for medical students. Front. Psychiatry *9*, 432.

Yang, X.Q., Glizer, D., Vo, A., Seergobin, K.N., and MacDonald, P.A. (2016). Pramipexole increases go timeouts but not no-go errors in healthy volunteers. Front. Hum. Neurosci. *10*, 523.

Ye, Z., Hammer, A., Camara, E., and Münte, T.F. (2011). Pramipexole modulates the neural network of reward anticipation. Hum. Brain Mapp. *32*, 800–811.

Ye, Z., Hammer, A., and Münte, T.F. (2017). Pramipexole modulates interregional connectivity within the sensorimotor network. Brain Connect. *7*, 258–263.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S., and Yamawaki, S. (2014). Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Soc. Cogn. Affect. Neurosci. *9*, 487–493.

Young, A.W., Rowland, D., Calder, A.J., Etcoff, N.L., Seth, A., and Perrett, D.I. (1997). Facial expression megamix: tests of dimensional and category accounts of emotion recognition. Cognition *63*, 271–313.

Yu, A.J., and Dayan, P. (2005). Uncertainty, neuromodulation, and attention. Neuron *46*, 681–692.

van Zerssen, D., Strian, F., and Schwarz, D. (1974). Evaluation of depressive states, especially in longitudinal studies. Mod. Probl. Pharmacopsychiatry *7*, 189–202.

Zhao, X., Ma, J., Wu, S., Chi, I., and Bai, Z. (2018). Light therapy for older patients with non-seasonal depression: a systematic review and meta-analysis. J. Affect. Disord. *232*, 291–299.