Environmental modulation of antidepressant drug action: insights from the Combined Antidepressant and Behavioural Intervention (CABIN) study

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ABSTRACT

Major Depressive Disorder (MDD) affects approximately three in every hundred people in the UK each week, incurring substantial societal and economic costs. While effective treatments exist, only about 30% of patients respond to their first prescribed antidepressant, and 30-65% may not benefit from cognitive behavioural therapy. Evidence suggests that environmental factors – such as employment status, educational attainment, financial security, and social support – can influence antidepressant treatment success. This underscores the need to better understand how these treatments work, for whom they are effective, and how they might be optimally combined to enhance therapeutic outcomes.

The cognitive neuropsychological model of antidepressant drug action posits that Selective Serotonin Reuptake Inhibitors (SSRIs) do not directly alter mood but rather act to reverse the negative emotional processing biases characteristic of depression. Over time, such positive shifts in automatic perception, memory, attention and learning are thought to lead to mood improvement through interactions with the environment. Importantly, the model predicts that environmental factors play a role in mediating treatment response; specifically, that a positive environmental context may provide optimal conditions for antidepressant-induced biases to be expressed and reinforced.

This thesis provides the first experimental test in humans of the hypothesis that environmental enrichment can augment the early effects of SSRIs on emotional and reward processing, which research has identified as candidate biomarkers of clinical effectiveness. Employing an experimental medicine approach, we assessed changes in emotional processing and reward learning as early indicators of antidepressant efficacy under different environmental conditions.

Data are presented from the Combined Antidepressant and Behavioural Intervention (CABIN) study – a large, parallel-group, randomised, placebo-controlled experimental medicine study. A total of 134 participants with low mood and low activity levels were

randomised to receive a two-week course of either placebo, citalopram alone, or citalopram augmented with behavioural activation (BA) as a proxy for environmental enrichment. Participants completed online questionnaires and computerised tasks assessing emotional processing and reward learning before and after the intervention. Continuous actigraphy measurements, ecological momentary assessments of mood, and salivary cortisol samples were also collected.

Given the focus on biomarkers of antidepressant response, exploratory clinical outcomes related to depression, anxiety, and reward-specific assessments are presented in **Chapter 3**. **Chapter 4** tests the hypothesis that environmental enrichment via BA enhances antidepressant-induced changes in emotional processing, as measured by the Emotional Test Battery (ETB). **Chapter 5** explores whether environmental enrichment modulates SSRI effects on reward and punishment learning. In **Chapter 6**, we examine ecological momentary assessments of positive and negative affect as markers of early mood improvement and affective variability, a core risk factor for depression. **Chapter 7** investigates the restoration of typical circadian rhythms as a potential mechanism by which BA may enhance SSRI effects, looking at rest-activity patterns measured through actigraphy and waking salivary cortisol levels.

Contrary to expectations, all three treatment groups – including placebo – showed significant improvements in depression and anxiety scores over the two-week period. The combined intervention of citalopram and BA did not significantly enhance participants' perceptions of environmental reward availability or behavioural activation beyond citalopram alone. This raises questions about the effectiveness of our environmental enrichment manipulation via BA and whether it was sufficient to elicit the expected changes in the biomarkers explored. Possibly owing to our online data collection protocol, we were unable to replicate previous findings of antidepressant-induced positive shifts in affective processing biases across several cognitive-emotional tasks, although some evidence of processing speed facilitation for positive stimuli with added BA was observed. Our hypotheses that BA might reduce

affective variability, increase physical activity levels, or promote more regular rest-activity patterns were also not supported by the data presented here.

Notably, we observed effects on punishment learning: citalopram appeared to promote less stable decision-making following negative feedback – a pattern that was reversed with the addition of BA. Further research is needed to determine whether these effects are adaptive or maladaptive and to elucidate their relationship with treatment outcomes.

As the first study to formally test the role of environmental enrichment in response to antidepressant treatment in human participants, several limitations are acknowledged, including the absence of a placebo and BA control group, remote data collection methods, limited intervention duration, and the use of a volunteer sample. Despite these limitations, this doctoral research contributes valuable insights and encourages continued investigation into the effects of the environmental context in antidepressant treatment using different methods of environmental enrichment. Future studies could be designed to draw clearer parallels between changes in emotional processing and social or rewarding experiences, potentially leading to more effective combined treatment strategies for MDD.

This thesis contains approximately 50,000 words.

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1 CHAPTER 1: INTRODUCTION

1.1 THE BURDEN OF MAJOR DEPRESSIVE DISORDER

Major Depressive Disorder (MDD) is a common psychiatric condition characterised by pervasive low mood as well as changes in sleep, appetite, and cognition. In the UK, it is estimated that three out of every hundred people meet criteria for MDD in any given week (McManus, 2016). The economic impact is substantial; in 2008, the annual cost to the economy was estimated at £20.2–23.8 billion, encompassing healthcare services, lost earnings, and reduced productivity (McCrone et al., 2008).

The COVID-19 pandemic exacerbated the mental health crisis, with data from the Office for National Statistics (ONS) revealing a significant rise in moderate or severe depressive symptoms among adults in Great Britain. Before the pandemic, 10% of individuals surveyed between July 2019 and March 2020 reported such symptoms, a figure that increased to 21% by early 2021 (Leach et al., 2021). Although this proportion decreased to 16% by October 2022 (Baker & Kirk-Wade, 2024), the persistent elevation underscores the enduring impact of the pandemic on mental health and the need for accessible, safe, and effective treatments.

1.2 CURRENT TREATMENTS FOR MAJOR DEPRESSIVE DISORDER

Depression has long been recognised as involving both psychological and biological components, with clinical depression understood to result from the complex interplay between psychological, behavioural, and biological factors (Akiskal & McKinney, 1973). Correspondingly, a variety of treatment options are available, targeting these different dimensions of major depression.

In the 2022/23 period, approximately 1.2 million individuals in the UK started treatment with psychological interventions, such as talking therapies (Baker & Kirk-Wade, 2024). In parallel, around 8.6 million people were prescribed antidepressant medication during that same year

(NHS Business Services Authority, 2024). These figures highlight the widespread use of both psychological and pharmacological approaches in addressing MDD.

1.2.1 Pharmacological and psychological monotherapies

Selective serotonin reuptake inhibitors (SSRIs) are the first-choice medication for depression in the UK, as recommended by National Institute of Health and Care Excellence (NICE) guidelines (National Institute for Health and Care Excellence, 2022). SSRIs work by blocking the reuptake or serotonin into the presynaptic neuron after signalling, resulting in increased availability of serotonin at the synapse. However, this increase in synaptic serotonin is unlikely to fully account for their therapeutic effects (Cowen & Browning, 2015). Instead, SSRIs are thought to exert their benefits through downstream effects on synaptic plasticity and emotional processing (Cowen & Browning, 2015; Harmer & Cowen, 2013). Despite their demonstrated efficacy compared to placebo (Cipriani et al., 2018), only about 30% of patients respond to their first prescribed antidepressant, and around 30% never recover and are considered treatment-resistant (Warden et al., 2007).

By far the most examined type of psychological treatment for depression is cognitive behavioural therapy (CBT). CBT works on the premise that inaccurate negative beliefs about the self, the world and the future are crucial for the development and maintenance of depressive disorders. These maladaptive thinking patterns, first described by Aaron Beck in the 1960s, are referred to as the “cognitive triad” of vulnerability to depression (Beck, 1967) and are primary targets for restructuring and reframing as part of CBT. Several large meta-analytic studies have demonstrated that CBT is effective as a treatment for major depression, with comparable outcomes to pharmacotherapy but not superior to other psychotherapies (Cuijpers, Berking, et al., 2013; Cuijpers, Miguel, et al., 2023). Moreover, compared to antidepressant medication, the therapeutic effects of CBT may be more sustained after treatment end, with pooled estimates from 38 studies showing a significant difference at 6-12 month follow-up (Cuijpers, Miguel, et al., 2023). CBT also benefits from a variety of delivery options including telephone and online formats, which have been shown to

be as efficacious as in-person CBT (Cuijpers, Noma, et al., 2019). Nevertheless, non-response may occur in approximately 30-65% of all patients in CBT treatment (Hofmann et al., 2012), with predictors of non-response including more severe symptoms, complex trauma, comorbid anxiety, male gender, younger age and dissatisfaction with the therapeutic relationship (Button, Turner, et al., 2015; Rozental et al., 2019; Shafierizi et al., 2024; Skar et al., 2022; Solomonov et al., 2021).

More recently, there has been a surge in the use of behavioural approaches to treating depression, with Behavioural Activation (BA) amassing a strong evidence base. BA was originally developed in the 1970s by Lewinsohn, who proposed that depression results from a lack of positive reinforcement in one's environment (Lewinsohn, 1974; Lewinsohn & Graf, 1973; Lewinsohn & Libet, 1972; MacPhillamy & Lewinsohn, 1974). Consequently, the aim of early BA therapy was to increase the frequency of pleasurable activities in the lives of patients. Although the effects of BA were examined in several randomised trials in the 1970s (Barrera, 1979; Zeiss et al., 1979), it subsequently fell out of favour in the 1980s and 1990s with the rise of cognitive therapy. The resurgence of BA in the early 2000s was sparked by research showing that the behavioural components of CBT, such as activity scheduling, were often as effective as the full CBT package (Jacobson et al., 2000, 2001; Jacobson & Gortner, 2000). Since then, BA has been developed into a standalone intervention, with demonstrable efficacy in addressing depression symptoms (Cuijpers et al., 2007, 2020; Cuijpers, Karyotaki, et al., 2023; Dimidjian et al., 2006, 2017; Ekers et al., 2008, 2014; Richards et al., 2016).

One of the key strengths of BA is its relative simplicity compared to full CBT. The core principle of BA is that therapists help patients identify activities that improve their mood and encourage them to engage more in these positive activities, using tools such as activity monitoring and scheduling. This approach doesn’t require patients to work through complex thought patterns, which can be a challenging and time-intensive process for many. As a result, BA can be delivered by practitioners who aren't necessarily fully trained

psychotherapists or clinical psychologists. A landmark randomised trial in the UK found that BA delivered by nurses in primary care was just as effective as full CBT provided by highly trained therapists (Richards et al., 2016).

Despite its effectiveness, BA, like other monotherapies, may not fully address the complexities of depression for all individuals, with response rates estimated to be around 65% (Cuijpers, Karyotaki, et al., 2023; Ekers et al., 2011). This has led to growing interest in exploring whether combining psychological interventions like BA or CBT with pharmacological treatments may offer more robust and comprehensive solutions for managing depression.

1.2.2 Combination therapies

NICE guidelines recommend individual CBT together with an antidepressant for treating a new episode of moderate to severe depression (National Institute for Health and Care Excellence, 2022). This is based on evidence suggesting that combination treatments are more efficacious for reducing depression symptoms than either pharmacotherapy or psychotherapy alone (Hollon et al., 2005; Khan et al., 2012), with the evidence for combined treatment being slightly stronger in comparison to sole pharmacotherapy (Cuijpers et al., 2009; Cuijpers, Miguel, et al., 2023; Hollon et al., 2014; Khazanov et al., 2021). Combined treatment has been suggested to decrease suicidal ideation, a major concern in MDD patients (Khazanov et al., 2021), and to be most beneficial for individuals with severe, nonchronic depression (Hollon et al., 2014).

While combination therapies often outperform monotherapies, this is not universally the case, as evidenced by studies that have found no added benefit in certain contexts. For example, adding mindfulness-based cognitive therapy to maintenance antidepressant medication did not further reduce the risk for relapse in a sample of recurrently depressed patients who were in remission at the time of the trial (Huijbers et al., 2015). In another study of healthy individuals investigating cognitive changes in response to treatment, participants who received both a cognitive bias modification intervention and an SSRI for seven days

showed smaller alterations in emotional memory than either therapy alone (Browning et al., 2011). Specifically, each intervention on its own produced a significant reduction in the number of negative words correctly recognised by participants, whereas the combination of interventions produced no change from baseline. Moreover, effect sizes in favour of combined therapy over pharmacotherapy alone have been small to moderate (Cohen's d or Hedge's g values of 0.30-0.50); these effect sizes, while statistically significant, suggest that the additional benefit of combination therapy over monotherapy may be modest for many patients, leaving potential for optimising combined treatment approaches.

Research to date suggests there may be specific circumstances when treatments should or shouldn't be combined, e.g., for current depression rather than remission periods. However, there have not been many empirical studies looking at optimal ways to combine treatments. In clinical practice, psychological therapy is often the first line of treatment for individuals with mild to moderate depression. However, if there is insufficient improvement within the first few weeks (4–6 weeks), antidepressant medication can be added (National Institute for Health and Care Excellence, 2022). In cases where depression symptoms are so severe that engagement in therapy is initially difficult, antidepressants may be started first to reduce symptoms such as lethargy, hopelessness, and lack of motivation. Once symptoms improve, typically after 4–6 weeks of medication, psychological therapy can be introduced. This allows patients to engage more fully in therapeutic work, as seen in studies like the STAR*D trial (Warden et al., 2007), which recommended adding psychotherapy for patients who didn't fully respond to pharmacotherapy after several weeks. Nevertheless, no studies have directly compared early vs late augmentation of antidepressant treatment with psychotherapy, leaving a sizeable gap in our understanding of how best to optimise treatment timing and sequencing for improved patient outcomes.

1.2.3 Towards a mechanistic approach to depression treatment

The limitations of current monotherapies and the uncertainties surrounding the optimal combination of treatments underscore a significant gap in our understanding of how best to

clinically manage depression. To address this, research in the past two decades has slowly adopted a mechanistic approach to depression treatment. This approach involves developing further understanding of the underlying biological, psychological, and behavioural processes through which different interventions for MDD exert their effects. Rather than focusing solely on symptom alleviation, a mechanistic perspective seeks to identify and target the specific pathways and mechanisms that contribute to the onset and persistence of depressive symptoms.

This mechanistic approach offers several benefits. Firstly, it can lead to the development of more precise and effective interventions by pinpointing key processes that, when modified, result in substantial therapeutic gains. For instance, understanding how neural circuitry related to emotion regulation or cognitive biases contributes to depression can inform treatments that specifically address these areas. Secondly, this approach facilitates a move towards personalised medicine. By identifying individual differences in the mechanisms underlying each person's depression – such as neurochemical imbalances, inflammation, altered circadian rhythms, disrupted neural circuitry related to emotion processing or dysfunctional thought patterns – clinicians can tailor interventions to better meet unique patient needs. A mechanistic approach also increases opportunities for combining therapies in a more informed way. By elucidating how medications and psychotherapies affect overlapping or complementary mechanisms, treatments can be combined more strategically to maximise their synergistic potential.

Adopting this framework also bridges the gap between clinical practice and basic research. It encourages the use of biomarkers, neuroimaging, and other objective measures to assess treatment impact, providing more precise indicators of therapeutic success than symptom reports alone. This evolving understanding, particularly in the context of how antidepressant drugs may alter emotional biases, provides a foundation for more sophisticated treatment strategies that harness both biological and psychological mechanisms.

1.3 THE COGNITIVE NEUROPSYCHOLOGICAL MODEL OF ANTIDEPRESSANT DRUG ACTION

The cognitive neuropsychological model of antidepressant drug action (Godlewska & Harmer, 2021; Harmer, Goodwin, et al., 2009; Harmer & Cowen, 2013) was developed to explain the delay in the therapeutic effects typically seen after starting antidepressant treatment. While some studies have reported early mood improvements with antidepressants in as little as 1-2 weeks (Posternak & Zimmerman, 2005; Taylor et al., 2006), it is typically the case that sustained improvement is not evident until 4-6 weeks into treatment (Frazer & Benmansour, 2002; Mitchell, 2006). This contrasts sharply with the molecular, cellular, and chemical effects of antidepressants, which are thought to occur within hours to days of administration (Etievant et al., 2020; Nichols et al., 2023; Ramos-da-Silva et al., 2021). The cognitive neuropsychological model resolves this discrepancy by suggesting that the early biological effects of antidepressants are translated into clinical response through their impact on the processing of emotionally salient information, particularly the reduction of negative bias. According to this model, the remediation of negative bias is a crucial early step in treatment and occurs before the more noticeable clinical improvements.

Importantly, the model assigns a significant role to environmental interaction in antidepressant efficacy. It posits that, for a clinical effect to emerge, the positive affective biases induced by the antidepressant need to be expressed and reinforced through interactions with one's (social) environment. This hypothesis helps explain the delay in clinical effects, as time is required for individuals to respond to environmental cues and learn from their new emotional perspective (i.e., changes in emotional bias would be expected to improve environmental interactions across time, leading to the formation of new positive associations and gradual improvements in mood). It could also explain why antidepressants may not have a therapeutic effect for all patients – for example those entrenched in toxic or unchanging environments that hinder the expression of positive biases. This implies that

enhancing environmental enrichment could facilitate the therapeutic effects of antidepressants, pointing toward the advantage of a combined therapeutic strategy involving both medication and environmental engagement. A schematic representation of the cognitive neuropsychological model is illustrated in Figure 1.1.

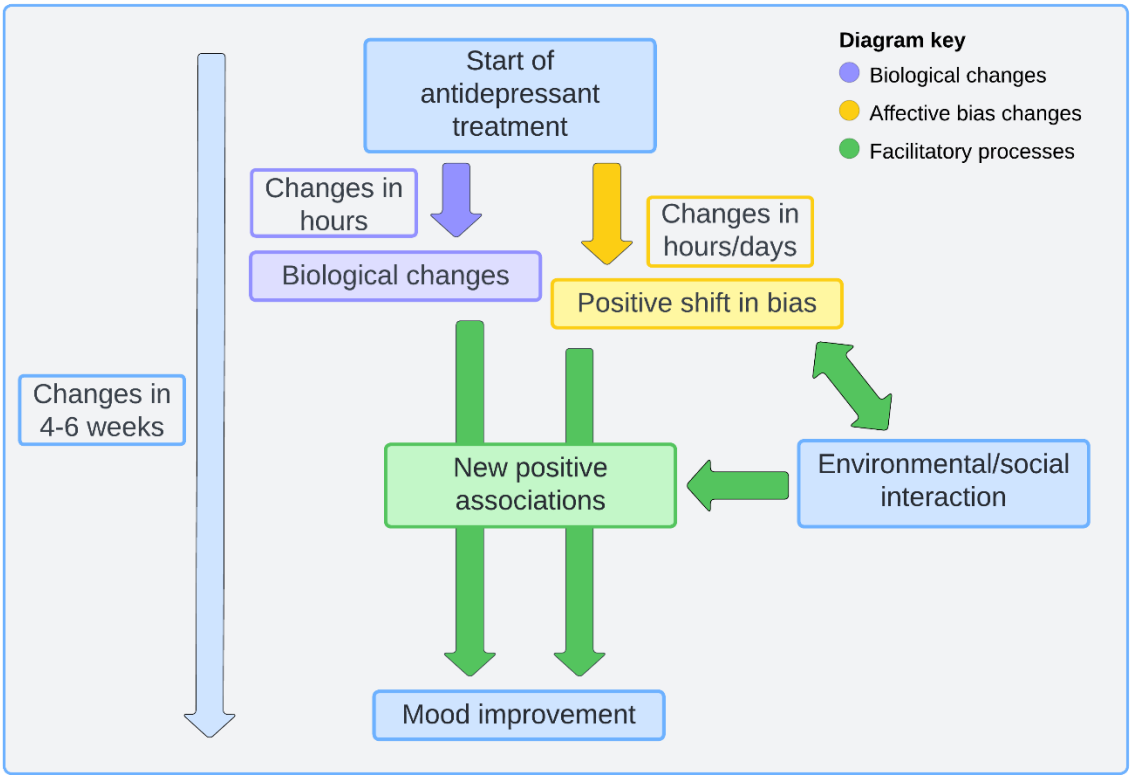


Figure 1.1. A schematic representation of the neuropsychological model of antidepressant drug action, adapted from Godlewska & Harmer (2021). In this model, environmental interaction provides a platform for enacting positive shifts in affective bias driven by antidepressant drug administration, which may in turn reinforce these biases before translating into mood improvement through the formation of new positive associations.

1.3.1 Negative affective bias in major depression

A primary hypothesis of the cognitive neuropsychological model of antidepressant drug action is that dysfunctional affective cognitive processes should be reliably detectable in currently depressed patients across various cognitive domains. This proposition is not new; as mentioned earlier when discussing the origins of cognitive behavioural therapy, the existence of a negative bias in information processing in depression became prominent in the 1960s with the emergence of Beck's "cognitive triad" (Beck, 1967, 1979). The theory proposed that negative beliefs about the self, the world and the future in depression result in a vicious cycle of negative feelings, thoughts and behaviours, which can act both as a trigger

and maintaining factor for depressive symptoms. Since then, a wealth of behavioural and neuroimaging evidence has substantiated the claims of disturbances in affective cognition in depression (Clark et al., 2009; Elliott et al., 2011).

Indeed, negative biases in emotional processing have been reliably demonstrated across several domains of emotional cognitive processing, including perception, attention, memory, and reward processing (Robinson & Roiser, 2016; Roiser et al., 2012; Roiser & Sahakian, 2013). For example, deficits in the identification of facial expressions of emotion have been consistently reported in depression. While some studies suggest a general decrease in sensitivity to both positive and negative expressions (Persad & Polivy, 1993; Rubinow & Post, 1992), others have found that depressed patients display a greater propensity towards labelling neutral faces as sad compared to non-depressed controls (Gilboa-Schechtman et al., 2002; Gur et al., 1992; Surguladze et al., 2004). Additionally, some research indicates that depressed patients show reduced sensitivity to happy faces, requiring more intense expressions to correctly label happiness (Joormann & Gotlib, 2006; Yoon et al., 2009). These discrepancies may stem from differences in study designs or participant characteristics but collectively highlight alterations in emotional perception.

Similar negative biases have been found in emotional memory, where depressed participants preferentially remember negative material when presented with lists of emotionally laden words (Bradley et al., 1995; Direnfeld & Roberts, 2006; Dunbar & Lishman, 1984), though this finding has not been replicated as consistently (Baños et al., 2001; Danion et al., 1995) . Attention is also biased towards negative information in depression; on an emotional Stroop task, where participants were asked to name the colour in which words were displayed, depressed patients took longer to name the colour of negative emotional words compared to controls, suggesting greater difficulty disengaging from negative information (Broomfield et al., 2007; Williams et al., 1996). Further findings using an affective Go/No-Go task testing response inhibition showed that depressed patients were slowed compared with controls when responding to happy but not to sad targets,

representing a bias away from positive information (Murphy et al., 1999). On tasks involving reward and punishment learning, depression has been associated with exaggerated responses to punishment or negative feedback (Eshel & Roiser, 2010; Murphy et al., 2003), as well as a reduced sensitivity to reward (Halahakoon et al., 2020; Huys et al., 2013; Kunisato et al., 2012; Pizzagalli et al., 2008; Steele et al., 2007).

More recently, functional Magnetic Resonance Imaging (fMRI) studies have supported behavioural findings and suggested that negative affective biases in depression may result from dysfunctional limbic-cortical circuits (Dichter et al., 2009; Fales et al., 2008). In a healthy state, the reactivity of structures responsible for fast automatic processing of emotionally salient information – such as the amygdala, ventral striatum, and insula – is adequately regulated by higher-order structures like the dorsolateral prefrontal cortex (dlPFC). In depression, the extended limbic system often shows hyperactivity (Drevets, 2001; Klug et al., 2024; Mayberg, 2003; Peluso et al., 2009; Wong et al., 2022), while regulatory structures involved in top-down control are hypoactive, potentially leading to inadequate modulation of emotional responses. For instance, in a study by Fales et al., patients with depression showed enhanced amygdala activity in response to fear-related compared to neutral distractor faces, whereas non-depressed controls exhibited increased dlPFC activity for the same stimuli, suggesting compensatory regulation (Fales et al., 2008).

Importantly, negative biases in emotional perception, memory and attention have also been found in individuals at risk for depression, such as participants high in neuroticism without a history of depression (Chan et al., 2007), children and adolescents at high genetic risk (Joormann et al., 2007, 2010) and individuals with a history of depression who subsequently recovered (Milders et al., 2010). This points towards a causal role or at least a trait vulnerability conferred by negative affective biases in the development of depressive symptoms. Over time, such consistently biased input may shift the default automatic processing of affective information more negatively, creating stable, dysfunctional, self-reinforcing negative schemata that works to maintain the depressive state. Therefore,

negative affective biases not only play a critical role in the development and maintenance of depression but also represent a valuable target for therapeutic interventions aimed at modifying these maladaptive cognitive processes.

1.3.2 Negative affective bias reduced by acute and short-term antidepressant use

Another core assumption of the cognitive neuropsychological model of antidepressant drug action is that SSRIs do not directly affect mood. Instead, SSRIs are proposed to alter the brain's processing of emotional stimuli, allowing symptoms of depression to remit gradually as the bottom-up biases contributing to them are attenuated or abolished.

Supporting this hypothesis, experimental medicine studies conducted over the last two decades have shown that SSRIs have early effects on emotional cognition in both healthy and depressed populations, and that these precede clinically significant changes in depressive symptomatology (Browning et al., 2007; Harmer, Bhagwagar, Perrett, et al., 2003; Harmer et al., 2004, 2006, 2008; Harmer, O'Sullivan, et al., 2009; Murphy, Yiend, et al., 2009). These effects often manifest as a reduction in the negative processing biases discussed earlier in the introduction (Clark et al., 2009; Elliott et al., 2011; Roiser et al., 2012; Roiser & Sahakian, 2013), as well as an increase in processing accuracy and speed for positive valence stimuli. For example, one week of treatment with citalopram was found to decrease recognition of negative facial expressions and increase the relative recall of positive versus negative words in healthy volunteers (Harmer et al., 2004).

Findings related to reward processing are mixed. Some studies suggest SSRIs increase reward sensitivity, potentially reversing abnormal response patterns seen in depression (Scholl et al., 2017; Treadway & Zald, 2011). However, other studies indicate that SSRIs may reduce learning from rewards and increase sensitivity to punishment (Michely et al., 2022). Additionally, some research reports decreased sensitivity to both reward and punishment with chronic SSRI treatment (Langley et al., 2023). These conflicting results may stem from SSRIs' indirect modulation of dopaminergic pathways involved in reward processing (Dremencov et al., 2009; Sekine et al., 2007; Shuto et al., 2020; Yoshino et al.,

2002), or reflect emotional blunting caused by SSRI treatment in some cases, which manifests as a reduction in the strength of both positive and negative emotions (Price et al., 2009).

Pharmaco-MRI studies have further demonstrated that SSRIs exert early effects on the neural networks implicated in depression and thought to sustain the affective processing biases observed behaviourally. Antidepressants modulate activity in key brain regions, such as the medial prefrontal cortex, anterior cingulate, and amygdala, increasing responses to positive emotional information while dampening responses to negative stimuli (Anderson et al., 2011; Harmer et al., 2006; Komulainen et al., 2016; Maron et al., 2016; Miskowiak et al., 2007; R. Norbury et al., 2009; Rawlings et al., 2010). A meta-analysis of 60 fMRI studies confirmed increased limbic activity in response to positive stimuli in depressed but not healthy subjects treated with SSRIs (Ma, 2015).

Importantly in the context of the neuropsychological model, positive changes in affective bias were found to be predictive of later clinical improvement in several studies (Browning et al., 2019; Godlewska et al., 2016; Shiroma et al., 2014; Tranter et al., 2009), suggesting that negative bias remediation is important for future response to treatment. In the context of MDD, response is typically defined as a reduction of 50% or more in symptom severity scores from baseline after treatment, as measured using standardised clinical scales such as the Hamilton Depression Rating Scale (HAMD) or Beck Depression Inventory (BDI). An fMRI study by Godlewska et al. showed that neural response to fearful versus happy facial expressions after one week of escitalopram treatment could differentiate between SSRI responders and non-responders at six weeks, with responders exhibiting a greater reduction in neural activity to fearful versus happy facial expressions after seven days across a network of regions including the anterior cingulate, insula, amygdala and thalamus (Godlewska et al., 2016). Crucially, HAMD scores after seven days did not significantly differ between responders and non-responders, confirming positive shifts in emotional processing can occur in the absence of significant changes in mood.

Similar findings were observed using behavioural measures of affective bias change. Browning et al. found that, in a group of primary care patients with depression treated with SSRIs, the combination of changes in a facial emotion recognition task and subjective symptoms after seven days of treatment was the best predictor of response after 4-6 weeks, achieving 77% accuracy in predicting response versus non-response to treatment in the training sample used as a basis for the model and 60% accuracy in an independent sample (Browning et al., 2019). Despite these promising results, it remains unclear whether a change in bias is necessary for clinical response. Further work is needed to increase the accuracy with which these shifts can predict treatment outcomes.

Overall, these findings support the hypothesis that early positive shifts in emotional processing are important for future antidepressant response and suggest that these shifts precede mood improvement.

1.4 The importance of the environment in Major Depressive Disorder treatment

Lastly, a fundamental proposition of the cognitive neuropsychological model of antidepressant drug action is that, while a positive shift in emotional processing is important for clinical improvement, it is not sufficient on its own. Engagement with one's (social) environment is also essential, allowing patients to relearn emotion-relevant associations within the more positive context created by the remediation of negative emotional bias. A natural extension of this idea is that environmental enrichment – characterised by an increased presence of environmental reinforcers such as positive social interactions, spending time in nature, physical activities, pet companionship, or tangible rewards like enjoying a nice meal or buying a new book – might facilitate antidepressant drug action. Specifically, antidepressants positively bias perception, and environmental enrichment provides more positive outcomes that the patient can notice. Although further research is needed to test this aspect of the model, recent studies have begun to provide support.

1.4.1 Environment-dependent effects of antidepressants in human studies

Although no studies have directly tested environmental modulation of antidepressant effects in humans, this hypothesis is indirectly supported by reports showing a positive correlation between antidepressant outcomes and socioeconomic factors, which can serve as proxies for environmental enrichment. Individuals with a low income who suffer from depression are less likely to respond to antidepressants than those in middle- and high-income groups (Cohen et al., 2009), an inequality which has been acknowledged by the World Health Organisation (World Health Organisation, 2010). Other factors that affect response to antidepressants are employment, length of education, security such as that offered by private insurance and social support (Chiarotti et al., 2017; Shiroma et al., 2014). This line of evidence supports a role for the environment in antidepressant drug response, as financial stability may offer more opportunity for patients to participate in hobbies and activities from which they can derive positive and meaningful reinforcement.

For example, in a small sample of individuals with late-life depression, an early bias shift predicted treatment response only in patients who received adequate self-reported social support (Shiroma et al., 2014). Improved recognition of mildly intense happy expressions after seven days of citalopram treatment predicted response after eight weeks, but only when combined with participants' baseline social support, measured by the Interpersonal Support Evaluation List (ISEL; S. Cohen & Hoberman, 1983). Further exploration of this important aspect of the cognitive neuropsychological model is warranted, especially in the light of its practical therapeutic implications.

1.4.2 Environment-dependent effects of antidepressants in animal studies

Stronger support for a role of the environment in modulating antidepressant treatment outcomes comes from animal models of SSRI function. Apart from early cognitive effects on non-conscious emotional bias, antidepressants are also understood to affect the neuroplasticity of the brain. This has been well-documented in several rodent models, showing that long-term administration of SSRIs can reinstate ocular dominance plasticity in

the visual cortex (Maya Vetencourt et al., 2008), increase field excitatory post-synaptic potentials in the amygdala to facilitate fear extinction (Karpova et al., 2011) and increase brain-derived neurotrophic factor levels (Björkholm & Monteggia, 2016).

Recent animal studies (Alboni et al., 2017; Branchi et al., 2013) showed that such effects may also be dependent on the environment. In a hallmark study, Branchi et al. treated mice with fluoxetine in one of four different conditions: A – a positive environmental switch, where fluoxetine treatment coincided with moving the animal from a stressful to an enriched environment; B – a negative environmental switch, where fluoxetine treatment coincided with moving the animal from an enriched to a stressful environment; C – a constant stressful environment, which was maintained at the start of treatment with fluoxetine; D – a constant enriched environment, which was maintained at the start of treatment with fluoxetine. Analyses comparing anhedonia-like behaviour (saccharin preference), corticosterone levels and brain-derived neurotrophic factor (BDNF) levels before treatment and at the end of the treatment period showed that treatment with fluoxetine led to an amelioration of the depression-like phenotype in condition A (positive switch), but a more pronounced worsening in both physiological and behavioural endpoints in condition B (negative switch). When fluoxetine was administered in a constant environment, it did not lead to a difference in the animals' pre and post treatment measurements except for corticosterone levels (Branchi et al., 2013). Thus, it seems that antidepressants may increase sensitivity to the effects of the environment, both positive and negative.

The behavioural results (saccharine preference) have been subsequently replicated in a follow-up study (Alboni et al., 2017), although findings at the molecular and cellular level are not as consistent. It also remains unclear if, in this animal model, increasing serotonin levels leads to increased susceptibility to the environment itself or increased susceptibility to *change* within the environment, given that limited effects were seen when fluoxetine was administered in constant environmental conditions.

Importantly, animal models also support a role for serotonergic antidepressants in the learning of new positive action-outcome associations, which the cognitive neuropsychological model proposes develop through interaction with the environment (Stuart et al., 2013, 2015). This has been demonstrated using a rodent affective bias test, in which rats encounter two independent positive experiences (digging in different types of bedding and finding a food reward) during repeated learning sessions (Stuart et al., 2013). These are performed on separate days under either neutral conditions or during a pharmacological manipulation (e.g., antidepressant drug administration). Subsequently, the rats are administered a choice preference test, where both previously rewarded types of bedding are presented together and the rat's choices recorded. Treatment with venlafaxine before, but not after the learning sessions reliably induced a bias for the venlafaxine-associated bedding type in the preference test. This suggests that antidepressants can enhance new learning by increasing the relative value attributed to an experience, rather than altering already learned associations (Stuart et al., 2013, 2015). Rats also made significantly more choices for the bedding-reward associations learnt during exposure to an enriched environment, which afforded play with other animals in a highly enriched arena. This indicates that the social enrichment may induce a positive affective bias similar to the effects seen following antidepressant drug treatment.

Taken together, these findings support a role for the environment in modulating antidepressant treatment outcomes at both clinical and pre-clinical levels.

1.4.3 Environmental enrichment as an add-on to antidepressant treatment

To date, evidence from multiple threads highlights the importance of the environment in antidepressant treatment. Findings from both human and animal studies suggest that increased environmental enrichment may lead to more positive outcomes by facilitating the translation of antidepressant-mediated emotional processing change and increases in brain plasticity into clinical improvement. These predictions may not necessarily represent competing views but rather different levels of analysis; emotional bias is understood to be

affected before changes in plasticity would be expected (indeed, even after a single acute dose of an SSRI), and environmental reinforcement could well act as an enhancer at both levels. Nevertheless, the hypothesis that a patient's living environment can affect the course of antidepressant therapy, either in terms of clinical outcomes or underlying mechanisms, has not been explicitly tested in humans.

One way to experimentally facilitate changes to a person's environment could be via adjunct psychological therapy. However, evidence for the effectiveness of combined pharmacological-psychological treatments is mixed, as reviewed previously in this chapter, particularly when cognitive therapy approaches are added to antidepressants. While a meta-analysis by Cuijpers et al. suggests combined treatment may be more efficacious than treatment with antidepressant medication alone (Cuijpers, Miguel, et al., 2023), other studies have found little benefit of combining SSRIs with cognitive training, particularly from a mechanistic perspective, where the combination treatment led to smaller alterations in emotional memory than either therapy alone (Browning et al., 2011). The reasons for this discrepancy could be two-fold; firstly, cognitive therapy does not suit all depressed patients and may not always equate to a positive environmental change. Secondly, SSRIs and cognitive therapy may target similar mechanisms at a neuropsychological level, i.e., automatic processing biases (Reinecke et al., 2013, 2014), meaning that their combined effects could be additive but not synergistic.

Simpler interventions that encourage individuals to interact with the environment in a positive way may, in this sense, be better suited for combination with antidepressant treatment. Behavioural activation (BA), introduced earlier, already benefits from a strong evidence base (Ekers et al., 2014; Richards et al., 2016) and has been associated with increased frequency of rewarding experiences (Nagy et al., 2020).

BA can be viewed as a source of positive environmental change as its main focus is on increasing patients' engagement with meaningful and rewarding activities in their daily lives. It does so through techniques such as activity monitoring, planning and scheduling, and

troubleshooting obstacles that prevent scheduled activities from taking place. By systematically scheduling activities that are enjoyable or provide a sense of accomplishment, BA enhances exposure to positive environmental stimuli; this enrichment occurs as patients interact more actively with their surroundings, breaking the cycle of avoidance and withdrawal that often accompanies depression.

A key strength of BA is its flexibility and ability to be personalised to suit individual patient needs. Therapists work collaboratively with patients to identify activities that align with their personal interests, values, and life circumstances. This individualised approach ensures that the environmental changes are relevant and motivating for each person, whether that involves social interaction, physical exercise, or creative pursuits. By tailoring the intervention, BA not only enriches the patients' environment but also empowers them to take an active role in their recovery, increasing the likelihood of sustained engagement (Kanter et al., 2010). Unlike other psychological therapies, BA provides a straightforward experimental manipulation of positive environmental change, allowing the environmental dependency hypothesis of the cognitive neuropsychological model to be empirically tested.

1.4.4 Use of affective bias change as a biomarker of treatment efficacy

The cognitive neuropsychological model of antidepressant drug action proposes an early shift in affective processing bias as a candidate biomarker of future clinical response. A biomarker is a measurable indicator of a biological process or condition, often used to predict or monitor disease progression or treatment response. The use of reliable biomarkers is particularly important when the outcomes of treatment can be assessed only after a lengthy period, as is the case for antidepressant treatment where sustainable improvements in self-reported mood are typically only seen 4–6 weeks into treatment (Frazer & Benmansour, 2002; Mitchell, 2006). In such situations, early measurement of biomarkers enables the rapid screening of promising treatments, including combinations of pharmacological and psychological interventions, without the need for prolonged and costly clinical trials.

As described in this chapter, cognitive emotional tasks of perception, memory, and attention are reliably sensitive to early cognitive modifications triggered by antidepressants – changes that occur well before significant clinical effects are expected and are associated with later response. These behavioural tests are also straightforward to administer and do not require sophisticated equipment.

An effective way to utilise these tasks is within an experimental medicine framework, which focuses on assessing treatment potential by observing immediate biological or cognitive changes. By adopting this approach, we can investigate whether environmental enrichment through behavioural activation (BA) amplifies the early cognitive effects of antidepressants, indicating a promising treatment strategy.

1.5 THESIS AIMS AND HYPOTHESES

As highlighted thus far, the neuropsychological model of antidepressant drug action has led to substantial advances in our understanding of how selective serotonin reuptake inhibitors (SSRIs) exert their clinical effects. Moreover, the model makes clear, testable predictions about the role of the environment in antidepressant treatment and offers a framework within which the combination of pharmacological and psychological treatments may be better understood in mechanistic terms.

Nevertheless, despite indirect evidence from human and animal studies, the hypothesis that a patient's living environment modulates antidepressant treatment outcomes has never been experimentally tested in humans. To address this gap and ultimately improve clinical outcomes for patients with major depressive disorder, the overall purpose of this thesis is to devise an experimental test for this hypothesis and provide a stepping stone toward understanding when and how environmental change may facilitate pharmacotherapy. This was achieved through a large interventional study examining the effects of an online behavioural activation (BA)-augmented citalopram treatment compared to citalopram alone and placebo – the Combined Antidepressant and Behavioural Intervention (CABIN) study.

Briefly, a community sample of 134 participants experiencing self-reported low mood and low activity levels were recruited through university and social media advertisement. Participants were randomised into one of three groups, each undergoing two weeks of either: 1) placebo alone, 2) citalopram alone or 3) citalopram and behavioural activation training. Each participant was asked to complete a series of questionnaires and computerised tasks measuring emotional cognition and reward processing before and after the two-week intervention. The full methodology for the CABIN study is described in Chapter 2.

In the CABIN study, we aimed to experimentally manipulate environmental enrichment through adjunct psychological therapy while administering the SSRI citalopram. We selected BA as a proxy for environmental enrichment due to its strong evidence base and its association with increased rewarding experiences (Nagy et al., 2020). We hypothesised that BA-enhanced antidepressant treatment would facilitate early changes in emotional processing, as measured by the Emotional Test Battery (ETB), which has been extensively used in previous research to assess cognitive modifications induced by antidepressants (Browning et al., 2007; Harmer, Bhagwagar, Perrett, et al., 2003; Harmer et al., 2004; Murphy, Yiend, et al., 2009; Walsh, Huneke, et al., 2018). Using an experimental medicine approach, we employed changes in emotional and reward processing as early indicators of an antidepressant's potential for clinical effectiveness in different environmental conditions, following the cognitive neuropsychological model described earlier.

In the process of building this understanding of environmental effects in antidepressant treatment, and in keeping with the mechanistic nature of the study, we assessed several domains of functioning that may be relevant to the effectiveness of citalopram, BA, or both. A more detailed introduction to these concepts is provided within each chapter. This thesis will address these domains in the following order:

1.5.1 Effects of a BA-enriched SSRI intervention on mood, anxiety, and reward-specific self-assessments

(Chapter 3)

In Chapter 3, we present the demographic and lifestyle characteristics of our sample and examine how the combined BA and citalopram intervention affects self-reported mood and anxiety symptoms, as well as measures related to behavioural activation and the availability of environmental rewards. Given that this research was conducted within an experimental medicine framework, with a short intervention length of two weeks, we treated clinical outcomes as exploratory. Nevertheless, previous research has shown that online BA can significantly improve self-reported mood after four weeks of treatment and increase behavioural activation – defined as the degree to which individuals are content with their daily activities – after two weeks (Ruzickova et al., 2023).

While SSRIs typically achieve their full clinical effect after four to six weeks (Frazer & Benmansour, 2002; Mitchell, 2006), early mood improvements with antidepressants have been documented (Posternak & Zimmerman, 2005; Taylor et al., 2006). The specific timeframe of clinical effects for combined pharmacological and psychological treatments has not been extensively studied, raising the possibility that these effects may be accelerated when the two are used together, particularly if BA and SSRIs have synergistic effects.

Since the purpose of our BA intervention was to experimentally manipulate levels of environmental enrichment, we sought to assess whether this was achieved through questionnaire measures of behavioural activation and the perceived availability of environmental rewards. Based on previous findings from online BA interventions (Ruzickova et al., 2023) and the design of our study, we hypothesised that these measures would show elevated scores in the Citalopram + BA group compared to the Citalopram-only group after two weeks of treatment.

1.5.2 Effects of a BA-enriched SSRI intervention on emotional processing

(Chapter 4)

Chapter 4 addresses the main model-driven hypothesis of the study: that environmental factors modulate antidepressant drug efficacy, conceptualised here through an experimental medicine lens as early positive changes in affective processing biases. Using the Emotional Test Battery (ETB), we assessed whether adjunct BA enhances the cognitive-emotional effects of citalopram, providing valuable insight into this understudied aspect of the neuropsychological model of antidepressant drug action.

Building on the literature reviewed in this chapter, we assessed three key aspects of cognitive-emotional processing: perception (Facial Expression Recognition Task; FERT), categorisation (Emotional Categorisation Task; ECAT), and memory (Emotional Recall – EREC – and Emotional Recognition Memory – EMEM – tasks). Additionally, we examined reward and punishment learning – another crucial aspect of emotional cognition (Roiser et al., 2012) – which is discussed in detail in Chapter 5.

We hypothesised that BA-enriched antidepressant treatment would facilitate early changes in emotional processing, as measured by the ETB, compared to citalopram alone after two weeks of treatment. Central to this hypothesis was the expectation that the combined treatment would promote a bias toward positive material across different cognitive-emotional tasks. For example, on perceptual and categorisation tasks such as the FERT and ECAT, we anticipated that participants receiving the combined treatment would demonstrate improved accuracy and faster reaction times when identifying positive facial expressions and words compared to negative ones.

Similarly, in memory tasks such as the EREC and EMEM, we expected the BA-enriched group to show enhanced recall and recognition of positive valence words over negative ones. This may also be reflected in an increased number of positive intrusions – instances where participants falsely recall positive words that were not originally presented – indicating a heightened positive bias in memory processes.

1.5.3 Effects of a BA-enriched SSRI intervention on reward and punishment learning *(Chapter 5)*

In Chapter 5, we explore how the combined intervention influences reward and punishment learning, as assessed through the Probabilistic Instrumental Learning Task (Pizzagalli et al., 2005). By examining changes in reinforcement learning processes, we aim to understand whether environmental enrichment through BA contributes to improved reward sensitivity when used alongside citalopram.

Individuals with MDD often exhibit deficits in reward learning, showing reduced sensitivity to rewards and difficulty adjusting behaviour based on reinforcement (Halahakoon et al., 2020; Pizzagalli et al., 2008). Additionally, MDD is linked to maladaptive responses to negative feedback: some studies indicate hypersensitivity to punishment, manifested as a reversal of behaviour following negative outcomes (Murphy et al., 2003), while others suggest a general failure to effectively utilise negative feedback (Holmes & Pizzagalli, 2007).

In contrast to other areas of affective processing, such as perception, attention and memory, the effects of antidepressants on reinforcement learning remain inconclusive. While some studies suggest SSRIs increase reward sensitivity (Scholl et al., 2017), others report impaired reward-based learning and heightened sensitivity to punishment (Michely et al., 2022).

Reward processing has been proposed as a candidate mechanism through which BA monotherapy achieves clinical effectiveness, given its focus on increasing engagement with rewarding activities (Janssen et al., 2020; Nagy et al., 2020). Neuroimaging studies suggest BA may enhance striatal response to rewards (Dichter et al., 2009), and BA-induced changes in reward network functioning are associated with clinical improvement (Carl et al., 2016; Walsh et al., 2017). By increasing exposure to rewarding experiences, BA may help correct the reward sensitivity deficits observed in depression.

Thus, we hypothesised that the combined intervention would improve reward sensitivity in individuals with mild to moderate depression. Specifically, we expected that the BA-enriched

citalopram intervention will enhance participants' ability to learn from rewards and mitigate any SSRI-induced blunting of reward responsiveness.

1.5.4 Effects of a BA-enriched SSRI intervention on daily self-reported mood and affective variability

(Chapter 6)

Chapter 6 investigates the effects of the BA-enriched citalopram treatment on daily mood fluctuations and affective variability. Using experience sampling techniques (Tsanas et al., 2016), we assessed real-time changes in emotional states to determine the combined intervention's impact on day-to-day mood regulation.

Although SSRIs are typically thought to take 4–6 weeks for full effect, evidence suggests that they may produce therapeutic benefits earlier (Posternak & Zimmerman, 2005; Taylor et al., 2006), and early mood improvements are associated with better longer-term outcomes (Gorwood et al., 2015; Szegedi et al., 2009). Cognitive-behavioural treatments, including BA, have also shown rapid mood improvements within the first two-to-four sessions (Cuijpers, Hollon, et al., 2013; Lambert, 2013), and both SSRIs and BA may impact affective variability – a key factor linked to depressive illness severity, poor prognosis and depression risk (Angst et al., 2003; Patel et al., 2015; Sultson et al., 2024).

Affective variability, also referred to as mood instability, refers to frequent and intense emotional fluctuations in response to both positive and negative events (Thompson et al., 2011). It is closely associated with many symptoms of depression, including negative affect and neuroticism (Miller et al., 2009; Miller & Pilkonis, 2006). Mood instability may perpetuate negative affective biases by distorting how individuals interpret events and make decisions, leading to negative outcomes that reinforce depressive symptoms (Kircanski et al., 2012). Reducing affective variability could therefore be crucial in breaking the cycle of negative cognitive-emotional processing.

Both SSRIs and BA may impact mood instability in different ways. SSRIs can initially exacerbate mood instability due to side effects like "activation syndrome" (Harada et al., 2008) or flatten affect due to emotional blunting (Goodwin et al., 2017; Price et al., 2009),

making their net effect complex and patient-dependent. In contrast, BA promotes consistent activity and coping strategies, potentially stabilising mood swings by fostering a sense of control over daily activities (Scherer, 2022). We hypothesised that BA-enriched SSRI treatment would not only improve mood trajectories over the course of the two-week treatment period but also reduce affective variability compared to citalopram alone.

1.5.5 Effects of a BA-enriched SSRI treatment on biological markers of circadian rhythm

(Chapter 7)

Finally, Chapter 7 examines the effects of the combined treatment on biological markers of circadian rhythm, specifically rest-activity patterns and waking cortisol levels. We used actigraphy watches and salivary cortisol measurements to explore potential physiological mechanisms by which environmental enrichment through BA may enhance the effectiveness of antidepressant medication.

In addition to the mood and cognitive symptoms that characterise depressive disorders, physiological changes are also commonly reported. Circadian rhythm disruptions, including altered rest-activity cycles and hormone rhythms, are prevalent in MDD (Vadnie & McClung, 2017). Patients with MDD often display irregular rest-activity patterns, such as reduced physical activity and flattened circadian rest-activity fluctuations (Difrancesco et al., 2022; Lyall et al., 2018). While SSRIs improve depressive symptoms, their effects on activity levels remain unclear, with some evidence suggesting that SSRI users exhibit less overall physical movement compared to non-users, even after controlling for depression severity (Heinz et al., 2022). In contrast, BA encourages increased physical and social activity, which may improve rest-activity cycles and promote more consistent routines (Pentecost et al., 2015). We also examined cortisol rhythms, specifically the Cortisol Awakening Response (CAR), a key marker of circadian health. In healthy individuals, a higher CAR is associated with reduced distress responses to daily hassles and may signal better coping with mundane stressors (Powell & Schlotz, 2012). Depression has been linked to both heightened and blunted CAR (Eikeseth et al., 2019; Vreeburg et al., 2009), and SSRIs like citalopram have

been shown to increase salivary cortisol levels when administered acutely and over the short term, potentially normalising HPA axis function (Harmer, Bhagwagar, Shelley, et al., 2003; Pariante et al., 2004). BA may further enhance CAR through increased physical activity and structured routines (Drogos et al., 2019).

We hypothesised that the combination treatment would improve circadian rhythm disruptions associated with MDD and better equip participants to handle daily stressors. Specifically, we expected increased physical activity, more consistent rest-activity patterns, and a more robust CAR compared to citalopram alone.

2 CHAPTER 2: AN EXPERIMENTAL MEDICINE STUDY OF THE EFFECTS OF ENVIRONMENTAL ENRICHMENT ON ANTIDEPRESSANT DRUG ACTION (CABIN STUDY)

2.1 INTRODUCTION AND STUDY AIMS

As introduced in Chapter 1, the neuropsychological model of antidepressant drug action is supported by evidence from both behavioural and functional neuroimaging studies, following both acute and repeated SSRI administration in healthy volunteers, individuals at high risk of MDD and MDD patients (Harmer, Goodwin, et al., 2009; Harmer & Cowen, 2013; Pringle et al., 2011; Roiser et al., 2012). The model also implies a role for the environment in the success of antidepressant treatment, as a crucial interface between the information-processing biases induced by an antidepressant drug and subsequent clinical change (Godlewska & Harmer, 2021). Despite strong indirect evidence from antidepressant efficacy trials and animal studies, this hypothesis had never been previously tested in humans.

The Combined Antidepressant and Behavioural Intervention (CABIN) study was a parallel group, randomised, placebo-controlled experimental medicine study, designed to explore whether the early cognitive effects of the SSRI citalopram are modulated by different levels of environmental enrichment. A community sample of 134 participants experiencing self-reported low mood and low activity levels was recruited through university/social media advertisement. Participants were randomised into one of three groups, each undergoing two weeks of either: 1) placebo alone, 2) citalopram alone or 3) citalopram and behavioural activation training. The presence/absence of environmental enrichment was modulated through provision of two weeks of behavioural activation (BA) training to a third of the sample.

Each participant was asked to complete a series of questionnaires and computerised tasks measuring emotional cognition and reward processing before and at the end of the two-week intervention. By comparing the combined effects of citalopram and BA to those of citalopram

alone and placebo alone on performance of emotional cognition tasks (Emotional Test Battery (ETB)), the study tested whether the early cognitive changes induced by antidepressants are augmented in the context of a more rewarding environment. The primary hypothesis was that the participant group receiving citalopram and BA will show greater changes in emotional cognition in the expected direction (decrease in negative bias/increase in positive bias) compared to the citalopram alone and placebo alone groups after the two-week intervention. The effects of environmental enrichment of SSRI drug action via BA on measures of cognitive-emotional processing are explored in Chapter 4.

Furthermore, the study aimed to explore several potential mechanisms by which BA provision could enhance the effects of SSRIs, both mechanistically and clinically; these included shifts in reward processing (as measured by the Probabilistic Instrumental Learning Task (PILT) and explored in Chapter 5), reducing affective variability (as measured through daily "Mood Zoom" ratings and explored in Chapter 6), and restoring typical rest-activity and hormone circadian rhythms (as measured through actigraphy and waking cortisol levels and explored in Chapter 7).

2.2 STUDY DESIGN

The CABIN study was approved by the University of Oxford Medical Sciences research ethics committee (MS-IDREC) under reference R74013/RE009. It was registered on ClinicalTrials.gov under reference NCT05627154. It was carried out in accordance with the approved protocol, as well as Good Clinical Practice (GCP) standards and the Declaration of Helsinki. All participants provided written informed consent.

Participants completed six study visits over a period of four to seven weeks. Following a two-step screening process, participants were randomised to receive two weeks of either placebo alone, citalopram alone, or citalopram together with behavioural activation training. An online test battery comprising several questionnaires and emotional processing tasks was administered both before and at the end of the two-week intervention. Whilst enrolled in

the study, participants wore an actigraphy watch and responded to a daily mood rating questionnaire in “Mood Zoom” format (Tsanas et al., 2016) for three weeks; this allowed for approximately one week of pre-treatment actigraphy and mood data collection, followed by continued monitoring throughout the two-week treatment. Saliva samples were collected before and at the end of the two-week intervention to measure waking salivary cortisol. Figure 2.1 displays a summary of the study design and timeline.

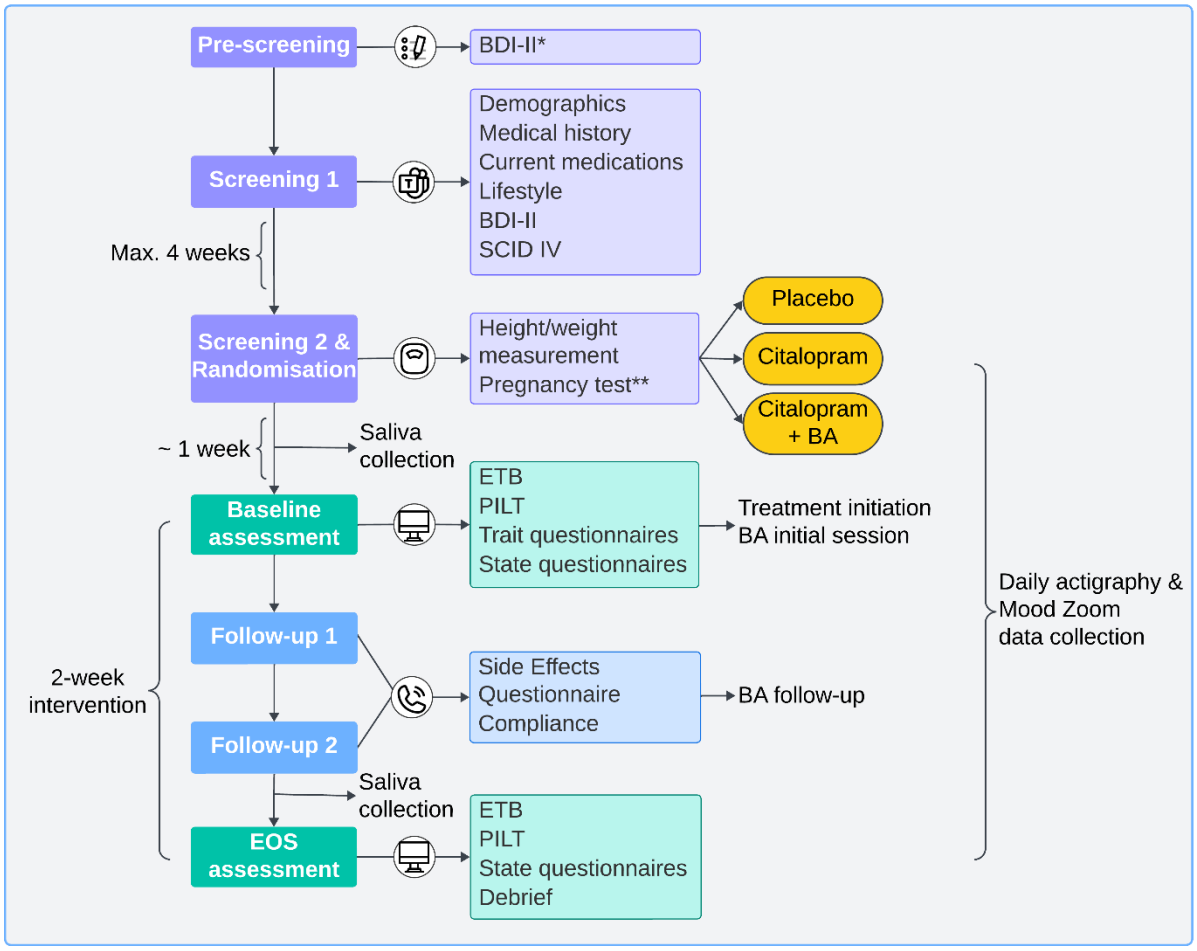


*Figure 2.1. A schematic representation of the CABIN study protocol. *BDI-II at Screening 1 was administered omitting question 9 (suicidality item). **Pregnancy test administered if the participant’s sex at birth was female*

2.3 PARTICIPANT RECRUITMENT

A community sample of 134 participants experiencing self-reported low mood and activity levels was recruited over a period of 31 months (May 2021 – November 2023). Participants were recruited through word-of-mouth, emails to University and college mailing lists

(including Oxford Brookes University), posters located in community settings and University departments, social media posts and ads (Facebook and Instagram), as well as through websites (Daily Info: https://www.dailyinfo.co.uk/, Call for Participants: https://www.callforparticipants.com/ and MQ: Participate: https://participate.mqmentalhealth.org/researchers/). Starting in October 2021, the research team outsourced social media advertisement to Lindus Health, a contract research organisation (CRO) with considerable expertise in participant recruitment for clinical trials and associated clinical studies (https://www.lindushealth.com/). Figure 2.2 displays the number of participants recruited, screened, and tested.

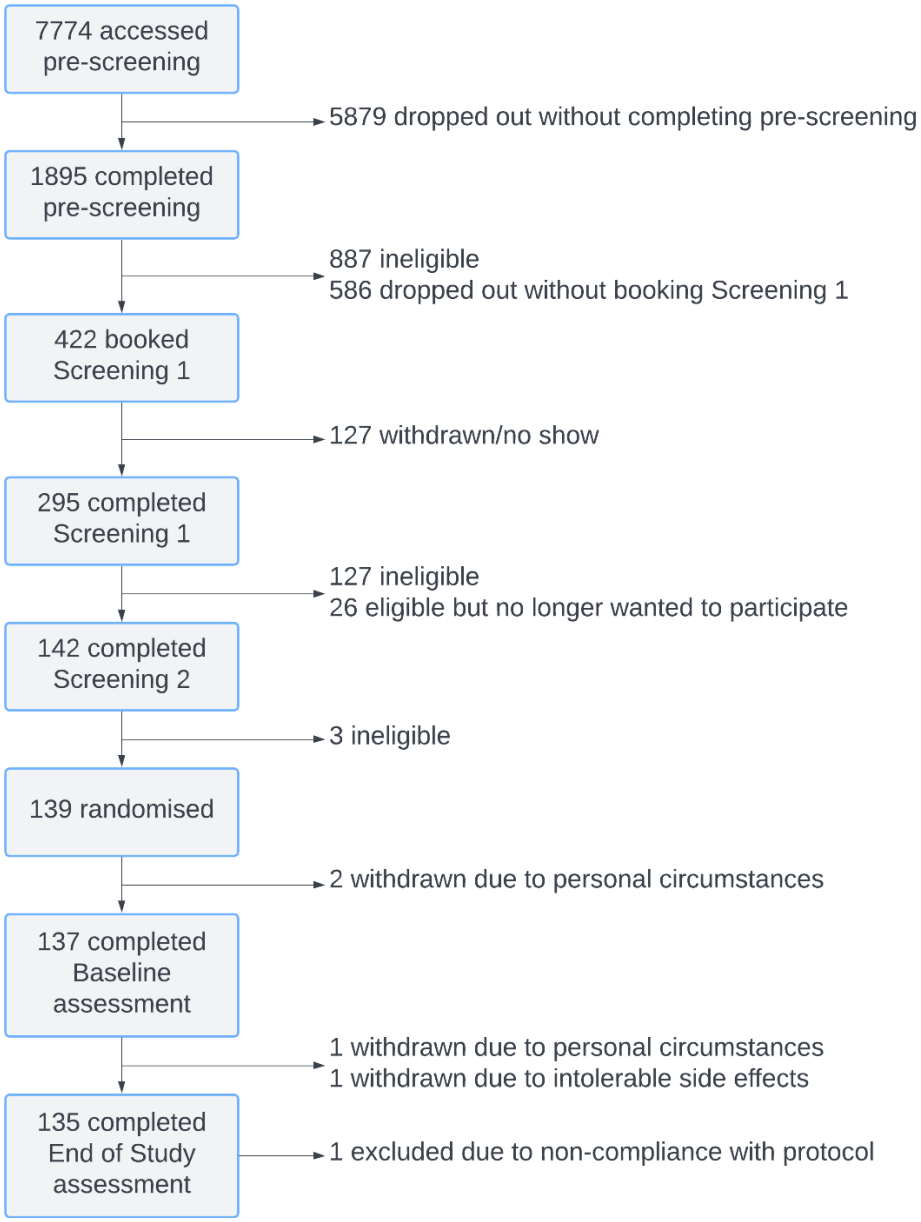


Figure 2.2. Participants recruited, screened and tested for the CABIN study

Both participants who withdrew after randomisation had been randomised to the Citalopram group. Of the two participants withdrawn after Baseline assessment, one was in the Citalopram group, and one was in the Citalopram + BA group. The participant excluded due to non-compliance was in the Citalopram + BA group.

2.4 PARTICIPANT SCREENING

2.4.1 Pre-screening

Prospective participants were able to access the study pre-screening questionnaire either directly through a link/QR code on the study adverts or through contact with the research team. The pre-screener consisted of 20 questions from the Beck Depression Inventory-II (BDI-II) questionnaire and assessed whether participants might fit the study definition of low mood, which was operationalised as a score of 10-30 inclusive on the BDI-II. BDI-II question 9, “Suicidal Thoughts or Wishes”, was omitted from the pre-screening questionnaire due to inability to contact and provide support to participants at this stage in the study, as no personal or contact data were collected from ineligible participants.

2.4.2 Screening

Participants were invited to take part in the study based on their BDI-II score at pre-screening falling between the values of 10 and 30 (inclusive). Upon completing the pre-screening questionnaire and their score falling within this range, they were invited to book a full online screening with the research team on a date and time of their choice (hereafter referred to as “Screening 1”). During Screening 1, the researcher collected information pertaining to the participant’s demographics, medical history, currently used medications and lifestyle and performed the Structured Clinical Interview for DSM-V, Researcher Version (SCID-5 RV). The participant was also invited to re-complete the BDI-II questionnaire, this time inclusive of question 9, to obtain a final study entry score.

Participants were invited to a further in-person screening appointment, hereafter referred to as “Screening 2”, if their BDI-II score remained between 10 and 30 (inclusive) and they were in good general health. They were excluded if they had a history of or current axis I or II psychiatric disorder (excluding MDD and anxiety disorders), a history of or current neurological or developmental disorder, or a contraindication to taking citalopram. They were also excluded if they had used antidepressants or other medications to treat low mood in the

six months prior to screening or if they were currently receiving psychological therapy for low mood. A full list of our inclusion and exclusion criteria are provided in Tables 2.1 and 2.2.

At Screening 2, participants had their height and weight measured to confirm their body mass index (BMI), and participants whose sex at birth was female underwent a pregnancy test. Participants were excluded if pregnant, severely underweight/overweight, or experienced changes in circumstances since Screening 1 that rendered them unsuitable for the study in the opinion of the study medic. They were otherwise informed of their eligibility and offered to be formally included in the study, i.e., randomised.

Table 2.1. Inclusion criteria for the CABIN study

Inclusion criteria
Aged 18-65 years (inclusive)
UK resident for the duration of the study
Fluent in English
Normal/corrected to normal vision
BDI-II score ≥ 10
Low self-reported activity levels
Willing and able to give informed consent
Access to laptop/computer & keyboard setup and a reliable internet connection

Table 2.2. Exclusion criteria for the CABIN study

Exclusion criteria
Antidepressant treatment or medication prescribed to treat depression/low mood, currently or in the last six months
Current psychological therapy of any kind
Current or past probable diagnosis of psychosis, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorder or any eating disorder, as indicated by the SCID-5 RV
Current or past diagnosis of any personality disorder (e.g. borderline personality disorder) according to self-report
Judged to be at clinical high risk of suicide
Past suicide attempt
Current or past hospitalisation for mental health reasons

Exclusion criteria
1st degree relative with diagnosis of bipolar disorder
Diagnosis of a developmental disorder (e.g. autism spectrum disorder, attention deficit hyperactivity disorder) according to self-report*
Diagnosis of a neurological disorder (e.g. epilepsy, multiple sclerosis) according to self-report
BDI-II score > 30
Current use of medication that might interact with the effects of citalopram
Known contraindication to citalopram**
Any other current or past medical condition which in the opinion of the study medic may interfere with the safety of the participant or the scientific integrity of the study
Heavy use of cigarettes (> 20 cigarettes per day)
Heavy use of caffeine (drink > 4 250ml cups/cans of coffee/energy drinks per day)
Severely underweight or overweight in a manner that renders them unsuitable for the study in the opinion of the study medic
Severe lactose intolerance (due to the study involving administration of a lactose placebo)
Pregnancy (as determined by urine pregnancy test taken during the Screening 2 visit), breast feeding or plans to become pregnant
Participation in a study using similar cognitive-emotional tasks in the past six months
Participation in another drug study in the past three months

* The definition for developmental disorders excludes cases of mild dyslexia or dyscalculia where, in the opinion of the study team, such difficulties would not interfere with the performance of the tasks required in this study.
**contraindications to taking citalopram include a past allergic reaction to citalopram, diagnosis of a cardiovascular condition, glaucoma, type 1 or type 2 diabetes, diagnosis of epilepsy, undergoing electroconvulsive treatment (ECT), or current use of any other medication that is associated with prolonged QT-interval.

2.4.3 Randomisation and study intervention

During the Screening 2 visit, eligible participants were randomised into one of three groups, each undergoing two weeks of either: 1) taking a daily dose of a lactose placebo (placebo group), 2) taking a daily dose of the SSRI citalopram (citalopram group) or 3) taking a daily dose of the SSRI citalopram and receiving concomitant behavioural activation training (citalopram + BA group). Random allocation into one of three treatment groups was stratified by birth sex.

Participants were provided with their 14-day supply of study medication (citalopram or placebo), a kit for saliva sample collection and a GENEActiv wrist-worn actigraphy watch.

They were not to start taking the study medication until approximately a week later, to allow for pre-treatment collection of actigraphy data, daily mood ratings in “Mood Zoom” format, as well as questionnaire and task outcomes of interest. Participants randomised into the citalopram + BA group were informed at this point that they would receive the psychological therapy and provided with materials to start activity tracking.

Due to the nature of the BA intervention, the study was single blinded only to citalopram or placebo administration. As the primary researcher was the one administering the BA, both the participants and the primary researcher were aware of who did or did not receive the psychological intervention. However, participants were not aware that receiving BA meant they were also taking citalopram. The primary researcher, on the other hand, was aware of this and was only blinded to drug allocation in the BA-free groups.

2.4.3.1 Study medication and compliance

Participants were instructed to take their study medication in the evening, after having dinner and before going to sleep; this was to minimise interference from known citalopram side effects such as sleepiness and dizziness. They received a nightly reminder text message at a time previously agreed with the study team and were asked to reply to this text with the time they had taken their daily capsule to promote compliance. Where participants did not have a UK phone number that could receive these texts, they were asked to set a recurring alarm on their phone while on call with the study researcher at the end of their Baseline assessment (5/134 participants). Of the remaining 129 participants, 65.1% confirmed all 14 capsules were taken and 94.6% sent 10 or more confirmation texts. There were three participants who reported missing one dose of their study medication; two were in the Citalopram group and one was in the Citalopram + BA group.

Physical symptoms associated with the use of SSRI medication (i.e., side-effects) were recorded before, throughout, and at the end of the two-week intervention, with the severity of

six commonly experienced symptoms self-reported by participants at Baseline assessment, Follow-up 1, Follow-up 2, and End of Study assessment.

2.4.3.2 Behavioural activation therapy and compliance

Participants randomised to the citalopram + BA group underwent three 1:1 behavioural activation training sessions during the two-week intervention, in most cases administered by the study primary researcher although qualified back-up was available to cover sickness and holidays. These involved working through the "Get active, feel good!" booklet developed at the University of Exeter (Farrand et al., 2014) and accessible at: https://cedar.exeter.ac.uk/media/universityofexeter/schoolofpsychology/cedar/documents/liiapt/BAcPAc_Intervention_Final_2.pdf). This booklet-based online paradigm has been successfully used in another online study of behavioural activation and emotional processing (Ruzickova et al., 2023).

The programme of work was supervised by a Psychological Wellbeing Practitioner (PWP) from a local National Health Service (NHS) Talking Therapies (formerly Improving Access to Psychological Therapies, IAPT) service. Researchers involved in BA administration received 15 hours of training prior to the start of the study, with special emphasis on adapting the booklet contents for remote use. At the end of the training period, each researcher submitted recordings of three practice BA sessions for evaluation and sign-off. Once recruitment started, ongoing support from the PWP was available where needed.

For most participants, the first session was scheduled to coincide with taking the first dose of study medication that same day. All participants had their first BA session within the first two days of starting the study medication. The first session centred on psychoeducation about depression and behavioural activation as a viable treatment option, and goal setting for the two-week intervention. Prior to the first BA session, participants had been provided with materials for activity monitoring if randomised to this condition during Screening 2. The purpose of this was to obtain information about the participants' daily schedule and activities

that would make it possible to personalise the intervention from the very first session, as well as to better fit the booklet content to the study timeline.

BA session 2 coincided with participants' Follow-up 1 appointment. Participants were asked about progress on their behavioural activation goals and offered help with goal setting for the next few days.

BA session 3 coincided with participants' Follow-up 2 appointment. The researcher guided participants through a "staying well" exercise aimed at identifying concrete ways in which they could continue applying behavioural activation techniques post study end.

All 45 participants randomised to this condition attended all three behavioural activation training sessions.

2.5 MEASURES

2.5.1 Questionnaire measures

All questionnaire measures were administered online, via Qualtrics during the screening process (Qualtrics, Provo, UT, USA. https://www.qualtrics.com) and via Gorilla Experiment Builder (https://gorilla.sc/; Anwyl-Irvine et al., 2020) during the Baseline and End of Study assessments.

2.5.1.1 Baseline questionnaires

The following questionnaires were used to characterise our participant sample and were administered at Baseline assessment only.

2.5.1.1.1 State-Trait Anxiety Inventory (STAI) trait version

The Trait version of the State-Trait Anxiety Inventory (STAI) assesses a person's general tendency to respond with anxiety across various situations. It consists of 20 items scored on a Likert scale from 1 (almost never) to 4 (almost always), with higher scores indicating greater trait anxiety out of a maximum score of 80. The STAI has demonstrated high internal consistency (α = .90) and construct validity in clinical settings (Spielberger, 1983).

2.5.1.1.2 Behavioural Inhibition System/Behavioural Approach System (BIS/BAS) scales

The Behavioural Inhibition System/Behavioural Approach System (BIS/BAS) scales are a self-report instrument comprising 24 items divided into four sub-scales: BIS, BAS Drive, BAS Reward Responsiveness, and BAS Fun-Seeking. The BAS sections measure motivation toward desired goals or rewards, while the BIS section assesses the desire to avoid unpleasant situations (Carver & White, 1994; Rizvi et al., 2016). Each item is rated on a 4-point Likert scale, from 1 (very true for me) to 4 (very false for me) with higher scores indicating stronger approach/avoidance tendencies. Total scores for each subscale range as follows: BIS (7-28), BAS Drive (4-16), BAS Reward Responsiveness (5-20), and BAS Fun-Seeking (4-16). While traditionally used with young, healthy individuals and psychopathic populations, the BIS/BAS scales have been found to have favourable reliability ($p = 0.88$) in patients with anxiety and mood disorders (Campbell-Sills et al., 2004).

2.5.1.1.3 Multidimensional Scale of Perceived Social Support (MSPSS)

The Multidimensional Scale of Perceived Social Support (MSPSS) is a self-report instrument designed to measure perceived social support from three sources: family, friends, and significant others. It consists of 12 items, with each item rated on a 7-point Likert scale ranging from 1 (very strongly disagree) to 7 (very strongly agree). The total score for each subscale ranges from 4 to 28, with higher scores indicating greater perceived social support. The MSPSS has been widely used across diverse populations and has demonstrated high reliability ($\alpha > .90$) and strong validity in various studies (Dahlem et al., 1991; Zimet et al., 1988), including those focusing on individuals with mood and anxiety disorders (Canty-Mitchell & Zimet, 2000).

2.5.1.2 Clinical outcome questionnaires

The following questionnaires were used to compare exploratory self-reported treatment outcomes between the different groups and were administered at both Baseline and End of Study assessments.

2.5.1.2.1 Beck Depression Inventory – II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a widely used self-report instrument designed to assess the severity of depression in adults. It consists of 21 items, each rated on a 4-point scale from 0 to 3, where 0 indicates the absence of a symptom and 3 represents the most severe manifestation. Total scores range from 0 to 63, with higher scores indicating more severe depressive symptoms. Typically, BDI-II scores are interpreted as follows: 0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression, and 29-63: severe depression (Beck et al., 1996). The BDI-II has demonstrated excellent psychometric properties, with high internal consistency (α = .91) and strong validity across various populations, including clinical and non-clinical groups (Beck et al., 1996; Wang & Gorenstein, 2013).The BDI-II is particularly useful in both clinical settings and research studies to monitor treatment outcomes and the severity of depression.

2.5.1.2.2 State-Trait Anxiety Inventory (STAI) state version

The State version of the State-Trait Anxiety Inventory (STAI) is a widely used self-report instrument designed to assess the intensity of anxiety symptoms experienced at a particular moment in time. It consists of 20 items scored on a Likert scale from 1 (not at all) to 4 (very much), with higher scores indicating greater anxiety. Total scores range from 20 to 80, with higher scores indicating more severe anxiety. Typically, STAI-S scores are interpreted as follows: 20-39: no/mild anxiety, 40-59: moderate anxiety, and 60-80: severe anxiety (Spielberger, 1983). The STAI has demonstrated high internal consistency (α = .90) and construct validity in clinical settings (Spielberger, 1983).

2.5.1.2.3 Behavioural Activation for Depression Scale (BADS)

The Behavioural Activation for Depression Scale (BADS) is a self-report instrument designed to assess the degree to which individuals are contented with the scope and breadth of activities they undertake in their daily lives, an essential component of behavioural activation therapy for depression. It comprises 25 items, each rated on a 7-point Likert scale from 0 (not at all true for me) to 6 (completely true for me). The BADS comprises four subscales,

each measuring Activation, Avoidance/Rumination, Work/School Impairment, and Social Impairment. The total score for the BADS is calculated as the total for the Activation subscale plus the reverse score of the other three subscales, with higher scores indicating greater engagement in rewarding activities and lower scores indicating reduced activation. The BADS has demonstrated good psychometric properties, including adequate internal consistency (α = .79) and strong construct validity, making it a valuable tool for assessing behavioural activation interventions in clinical and research settings (Kanter et al., 2007, 2009).

2.5.1.2.4 Environmental Reward Observation Scale (EROS)

The Environmental Reward Observation Scale (EROS; Armento & Hopko, 2007) is a ten-item instrument designed to assess access to positive environmental reinforcement. Each item is rated on a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree), with higher scores indicating greater access to environmental rewards. The original study demonstrated good psychometric properties with a one-dimensional model fit (RMSEA = .06; GFI = .92; NFI = .90) and high reliability (α = .88) (Armento & Hopko, 2007). The EROS has proven versatile across different populations and settings, and has previously been used to predict depression severity in caregivers (Vázquez González et al., 2019).

2.5.1.3 Physical Symptoms Questionnaire (CABIN PSQ)

The Physical Symptoms Questionnaire (PSQ) was specifically devised for the CABIN study and comprised six commonly experienced physical symptoms (i.e., side effects) associated with SSRI treatment, namely: nausea, dizziness, dry mouth, headache, agitation, and anxiety. Each symptom was scored on a scale from 0 (absent) to 3 (severe). The total score for the PSQ was calculated as the sum of the ratings for all six symptoms, and thus ranged from 0 to 18, with higher scores indicating more severe physical symptoms.

The PSQ was administered twice online via Gorilla Experiment Builder at Baseline and End of Study assessments, and twice over the telephone/videoconferencing software by a trained study researcher at Follow-up 1 and 2.

2.5.2 Computerised Tasks

Five computerised tasks were administered online via Gorilla Experiment Builder (https://gorilla.sc/; Anwyl-Irvine et al., 2020) at Baseline and End of Study (EOS) assessments. All participants completed the tasks on a computer or laptop responsive to keyboard commands and used the same input device (mouse or touchpad) during both assessments. The tasks were presented in a fixed order for all participants, with different stimuli used at Baseline and EOS to minimise practice effects.

2.5.2.1 Emotional Task Battery (ETB)

The Emotional Task Battery (ETB) is comprised of four validated, computerised cognitive-emotional tasks designed to assess emotional facial recognition, emotional word categorisation and emotional memory. Previous research has shown good test-retest reliability for a laboratory-based version of the ETB (Thomas et al., 2016).

The ETB has been found to be sensitive to the early effects of antidepressant administration on emotional processing, prior to clinical changes in mood (Harmer et al., 2004). ETB tasks were completed in the order detailed below, with the addition of the Probabilistic Instrumental Learning Task (PILT) described later in this chapter between the Emotional Categorisation (ECAT) and Emotional Recall (EREC) tasks.

2.5.2.1.1 Facial Expression Recognition Task (FERT)

The primary emotional processing task in the ETB is the Facial Expression Recognition Task (FERT), in which participants are asked to identify the expression of faces presented briefly on screen. Faces can show an expression of happiness, sadness, fear, anger, disgust, or surprise, or are neutral. The degree of emotion shown by each face can vary from 10% to

100% intensity, in steps of 10%. Participants are asked to indicate the expression on the face by clicking one of seven correspondingly labelled buttons.

Each face is presented for 500ms, and participants have 15 seconds to make a response. The CABIN FERT had a total of 250 trials divided into four blocks, with breaks at 25%, 50% and 75% completion. Faces were presented in the same fixed, pseudo-randomised order to all participants, with emotions, intensities and actors balanced across blocks.

A graphical representation of the FERT is presented in Figure 2.3.

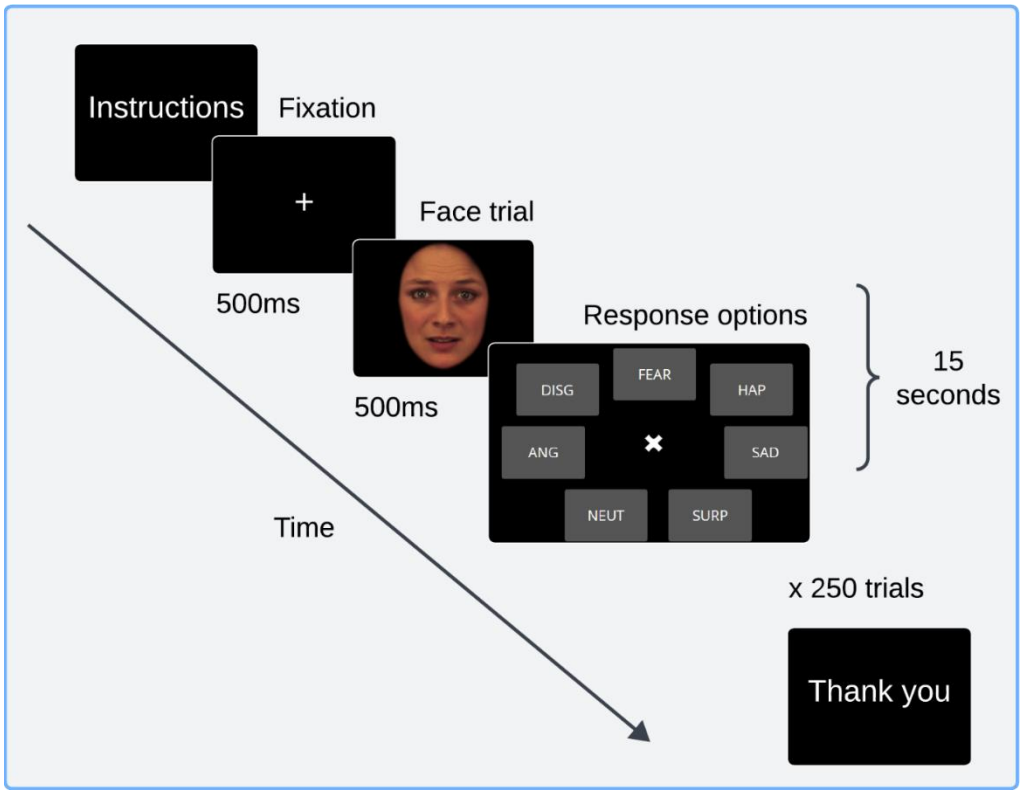


Figure 2.3. Graphical representation of the Facial Expression Recognition Task (FERT)

2.5.2.1.2 Emotional Categorisation Task (ECAT)

In the Emotional Categorisation Task (ECAT), participants are asked to decide whether they would “like” or “dislike” to be described as positive and negative personality characteristic words presented briefly on screen, in the context of imagining they have overheard a third party describing them as such.

The ECAT consists of 40 words (20 positive and 20 negative) in a single block, each presented for three seconds. During these three seconds, participants must make a response, by pressing the “L” key on their keyboard to indicate liking being associated with the descriptor or the “D” key to indicate disliking being associated with the descriptor. The CABIN ECAT had the 40 words presented in a randomised order which was refreshed for each participant. The task used words from the recently published UK norms of Raslescu et al. (Raslescu et al., 2023), with the positive and negative words used matched for word length, imageability and frequency of use.

A graphical representation of the ECAT is presented in Figure 2.4.

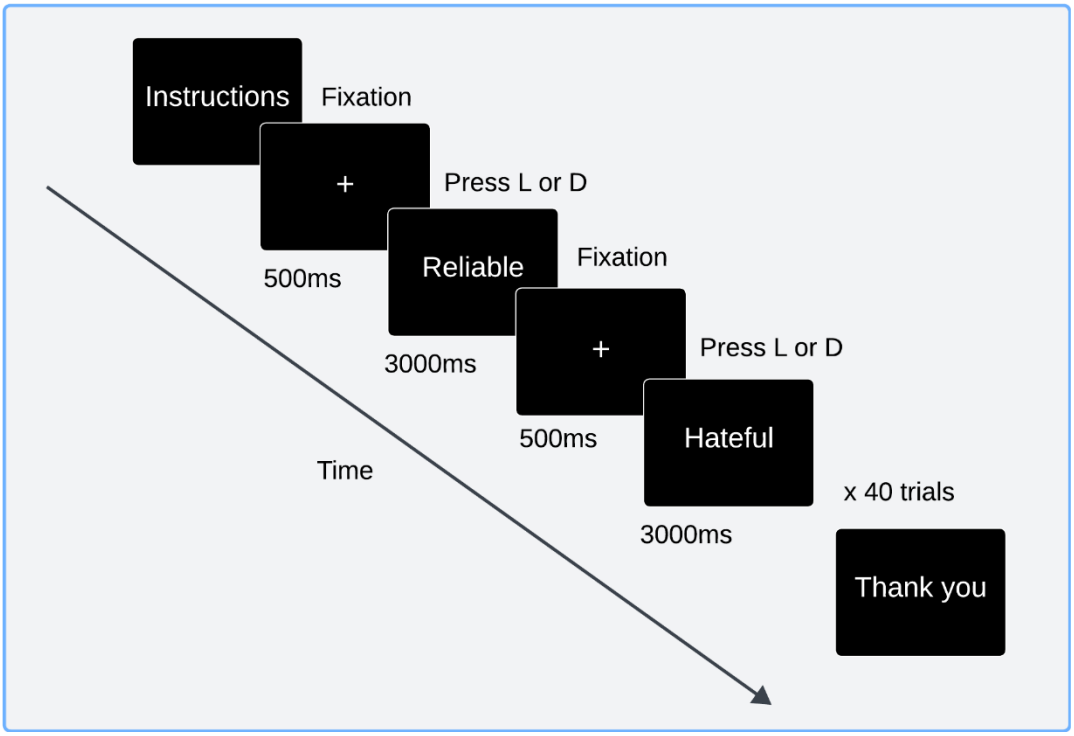


Figure 2.4. Graphical representation of the Emotional Categorisation Task (ECAT)

2.5.2.1.3 Emotional Recall Task (EREC)

In the Emotional Recall Task (EREC), participants are given three minutes to recall as many words previously presented during the ECAT as possible and type them into a box presented on-screen. CABIN participants were aware they would be asked to recall words from the ECAT. The words recalled by each participant were rated as correct/incorrect and

as positive/negative by two independent researchers, with a third researcher resolving any discrepancies. All researchers were blind to group allocation at the time of rating.

A graphical representation of the EREC is presented in Figure 2.5.

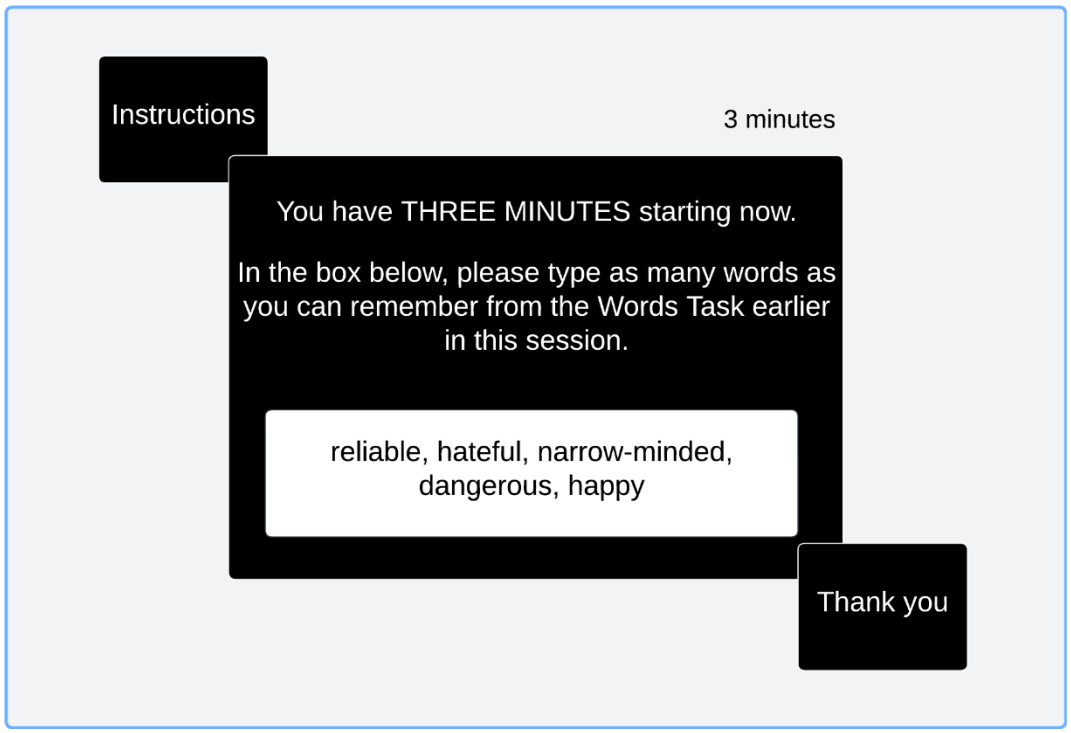


Figure 2.5. Graphical representation of the Emotional Recall Task (EREC)

2.5.2.1.4 Emotional Memory Task (EMEM)

In the Emotional Memory Task (EMEM), participants are asked to indicate whether words briefly presented on screen were previously presented in the ECAT and are thus "familiar" or were not previously presented during the ECAT and are thus "novel" distractor words.

The EMEM consists of 80 words (40 familiar and 40 novel) in a single block, each presented for three and a half seconds. During these three and a half seconds participants must make a response, by pressing the "F" key on their keyboard to indicate a "familiar" word or the "N" key to indicate a "novel" word. The CABIN EMEM had the 80 words presented in a randomised order which was refreshed for each participant. The task used distractor words from the recently published UK norms of Raslescu et al. (2023), with the "familiar" and

"novel" words used matched for valence (positive/negative), word length, imageability and frequency of use.

A graphical representation of the EMEM is presented in Figure 2.6.

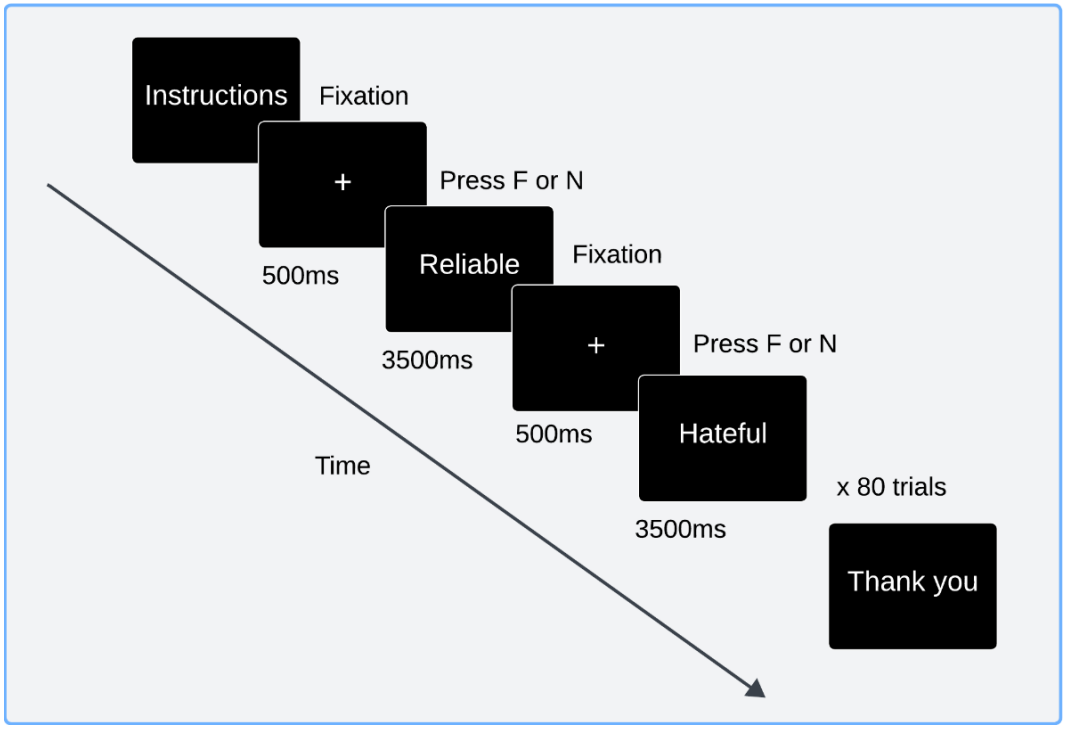


Figure 2.6. Graphical representation of the Emotional Memory Task (EMEM)

2.5.2.2 Probabilistic Instrumental Learning Task (PILT)

The Probabilistic Instrumental Learning Task (PILT) measures learning from rewards and punishments (Halahakoon et al., 2024; Pizzagalli et al., 2005). On each trial, participants are asked to make a choice between two abstract symbols presented on-screen, which have reciprocal probabilities (0.7 vs 0.3) of leading to a beneficial or non-beneficial outcome. On "win" trials, the beneficial outcome is winning money (20 pence), and the non-beneficial outcome is not winning money (no change). On "loss" trials, the beneficial outcome is not losing money (no change), and the non-beneficial outcome is losing money (-20 pence). Win and loss symbol pairs are always different, such that both learning about rewards and learning about punishments can be interrogated separately. Participants are asked to make their choice by clicking on the symbol they believe will lead to the most advantageous

outcome. Following their choice, they are presented with visual feedback of the trial outcome (a win, loss, or no change in their task winnings).

Each choice is presented for 5 seconds, within which participants must make a response. The CABIN PILT had a total of 180 trials divided into three blocks, with breaks at 33% and 66% completion. Different pairs of stimuli were used for the win and loss conditions within each block. Symbol choices were presented in the same fixed, pseudo-randomised order to all participants, and symbol presentation side (left or right of the fixation cross) was balanced. Participants were informed of the probabilistic nature of the task and were told that the aim was to win as much money as possible.

A graphical representation of the PILT is presented in Figure 2.7.

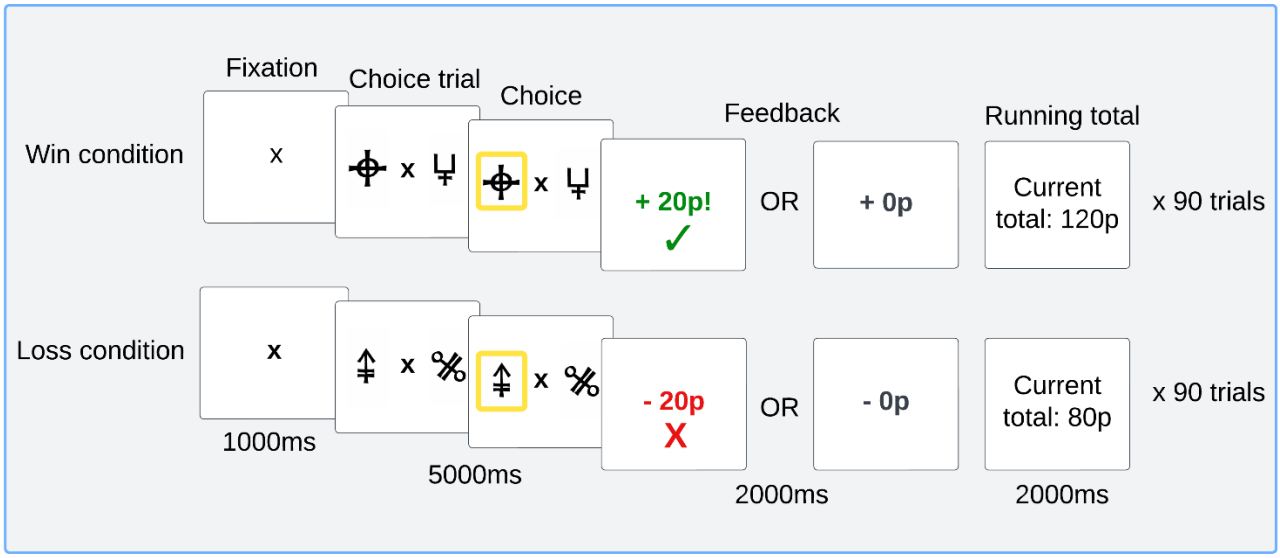


Figure 2.7. Graphical representation of the Probabilistic Instrumental Learning Task (PILT)

2.5.3 Actigraphy

Most CABIN participants (131/134; 97.8%) were equipped with wrist worn GENEActiv Original actigraphy watches (ActivInsights Ltd, UK), which they wore consecutively for approximately 21 days from Screening 2 to their EOS assessment. The remaining 2.2% did not wear the watches due to work-related restrictions on wrist-worn devices (2 participants) or non-consent to actigraphy data collection (1 participant).

Participants were set up with their actigraphy device at Screening 2. Devices were configured by the study team using the GENEActiv software (ActivInsights Ltd, UK), which required each participant's height, weight, and BMI to be entered. Actigraphy watches were given to participants to wear immediately after being configured and recording started immediately. Participants were asked to wear the devices on their non-dominant wrist for 24 hours a day for the duration of their participation in the study, which amounted to approximately 21 days from their Screening 2 visit. They were made aware the devices were waterproof and had light and activity sensors. The wrist side where the watch was ultimately fitted was recorded. To optimise battery life for the three-week period, the device sampling frequency was set to 25Hz. Participants returned their actigraphy watches to the research team via post after their EOS assessment. Data were extracted from the devices upon receipt, again using the GENEActiv software, and trimmed such that analyses only encompassed 21 days' worth of recording from each participant (the two weeks of active treatment plus the 7 days directly before treatment start).

The primary actigraphy measures of interest were the activity level, onset, and onset variability of participants' most active 10h period of a 24h day (M10 activity, M10 onset and M10 onset variability), as well as the activity level, onset, and onset variability of participants' least active 5h period in a 24h day (L5 activity, L5 onset and L5 onset variability). Methods specific to actigraphy data pre-processing and analysis are further detailed in Chapter 6.

2.5.4 Mood Zoom

For approximately 21 days between randomisation at Screening 2 and their EOS assessment, participants were asked to complete a daily mood assessment in "Mood Zoom" format (Tsanas et al., 2016). This consisted of rating six different affective states (anxious, happy, sad, angry, irritable, energetic) on a 1-7 Likert scale according to how well these described the participant's mood on each day. Thus, 1 meant the state was "not at all" descriptive of the participant's mood, while 7 meant the state was "very much" descriptive of the participant's mood. The link to the daily Mood Zoom was texted to the participant's

phone, at the same time each day. Compliance with the Mood Zoom was high, with 94% of participants continuing to provide responses into the final treatment week. At the end of data collection, responses were trimmed such that analyses only encompassed 21 days' worth of data from each participant (the two weeks of active treatment plus the 7 days directly before treatment start).

2.5.5 Waking salivary cortisol

To measure waking salivary cortisol pre- and post-treatment, participants were provided with mailable saliva collection "kits" which contained an instruction sheet, six Starstedt Salivette® tubes and two pre-paid postage boxes specifically designed for biological samples. Pre-intervention samples were collected during the approximately weeklong period between Screening 2 and Baseline assessment, on a day agreed with the study researcher. Participants collected saliva the samples to fill the first three tubes, at 15-minute intervals starting immediately upon waking and finishing 30 minutes later. Post-intervention samples were collected in an identical fashion, to fill the remaining three tubes, on either day 13 (second to last) or 14 (last day) of treatment. On both occasions, participants were instructed to mail the samples back to the research team on the day of collection.

Saliva samples were processed within the Oxford Health Biomedical Research Centre (OH BRC) laboratory and rendered acellular by centrifugation within seven days of receipt to comply with the Human Tissue Act (HTA) and with the Departmental Policy on waste disposal. The OH BRC laboratory operates a COVID-secure sample handling policy, with sample handling only allowed within the Class II biohazard hood with specific risk assessments in place. Each acellular sample was split into two aliquots to allow for repeated cortisol assays, resulting in six aliquots per participant, per timepoint. The aliquots were then frozen at -20 degrees and the Salivette® destroyed. Prior to assay, saliva samples were stored in the OH BRC lab in a pseudonymised form and were not linked to any personal identifiers. The assays were carried out in duplicate within the OH BRC laboratory using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit (Salimetrics Salivary Cortisol

ELISA Kit, assay #1-3002). Any excess saliva remaining at the end of the study was disposed of within six months according to HTA guidelines and the Departmental Standard Operating Procedures (SOPs) for sample disposal.

2.6 STATISTICAL ANALYSIS

2.6.1 Sample size calculation

To conduct an appropriate sample size calculation, one must first identify the effect of interest, and the statistical model employed to test for this effect. Our primary task of interest was the FERT, with the corresponding outcome measure of interest being the percentage accuracy in identifying positive (happiness, surprise) and negative (sadness, fear, anger, disgust) expressions. Previous studies investigating the effect of citalopram on emotional processing in healthy volunteers have found post-treatment differences in percentage accuracy for positive facial expression recognition between a citalopram-treated group and a placebo-treated group of M_{drug} = 64.62%, SE_{drug} = 3.66 vs. $M_{placebo}$ = 60.00%, $SE_{placebo}$ = 7.22, corresponding to an effect size of Cohen's d ~ 0.8 (Murphy, Norbury, et al., 2009).

We used G*Power 3.1.9.7 (Faul et al., 2007) to compute the sample size needed to detect a statistically significant difference between any two groups with $p < 0.017$ (Bonferroni corrected for number of planned group comparisons), power = 0.9 and Cohen's d = 0.8. The required sample was calculated as being N= 44 per group, as illustrated in Figure 2.8. Therefore, our achieved sample size of 134 participants ($N_{Placebo}$ = 45; $N_{Citalopram}$ = 44; $N_{Citalopram + BA}$ = 45) should be sufficient to detect statistically significant differences in FERT accuracy scores for positive expressions between the different intervention groups.

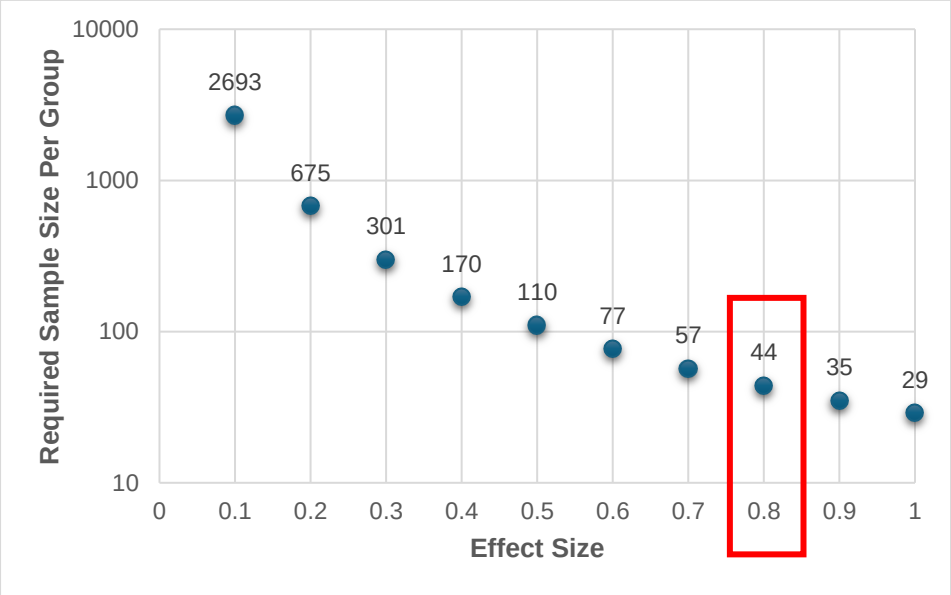


Figure 2.8. Required sample size per group for the CABIN study, plotted against effect size, with p = 0.017 and power = 0.9

2.6.2 Data description

As noted above, the primary outcome measure for the CABIN study is the percentage accuracy in identifying positive and negative facial expressions in the FERT post-treatment (i.e., at EOS assessment). A list of all outcome measures considered in this thesis is provided in Table 2.3, together with the timepoints included in the statistical analyses.

Table 2.3. Outcome measures for the CABIN Study

Measure	Outcomes	Timepoint(s)
PSQ	**Total score**, calculated as the sum of six physical symptoms rated 0-3.	Baseline assessment, Follow-up 1, Follow-up 2, EOS assessment
BDI-II	**Total score,** calculated as the sum of 21 individual items rated 0-3.	Screening, Baseline and EOS assessments
STAI-S	**Total score**, calculated as the sum of 20 individual items rated 1-4.	Baseline and EOS assessments
BADS	**Total score,** calculated as the sum of 25 individual items rated 0-6. **Subscale scores** for the Activation, Avoidance/Rumination, Work/School Impairment and Social Impairment subscales.	Baseline and EOS assessments

Measure	Outcomes	Timepoint(s)
EROS	**Total score**, calculated as the sum of 10 individual items rated 1-4.	Baseline and EOS assessments
ECAT	**Reaction time** (in milliseconds) for trials with correct responses.	Baseline and EOS assessments
FERT	**Recognition accuracy (%)** for each emotion, and for positive (happiness, surprise) and negative (sadness, fear, anger, disgust) emotions considered separately. **Unbiased hit rate** for each emotion, as described by Wagner (Wagner, 1993); this is a measure of emotion identification accuracy which accounts for response bias, i.e. any general tendency to identify a particular emotion when it is not present. It is calculated as: $$UBHR = \frac{H^2}{(H+M)\ x\ (H+FA)}$$ Where: • $Hits\ (H)$ are correct identifications of the target emotion • $Misses\ (M)$ are misses where the target emotion was present but not identified as such • $False\ Alarms\ (FA)$ are incorrect identifications of the target emotion. **Misclassifications**, or the number of times an emotion was identified without being present (i.e., the number of times participants responded "angry" when the actual expression was any of the other six). **Reaction time** (in milliseconds) for trials with correct responses.	Baseline and EOS assessments
EREC	**Number of words correctly recalled** (positive and negative). **Number of intrusions** (positive and negative), i.e. words falsely recalled which were not part of the original word categorisation task.	Baseline and EOS assessments
EMEM	**Percentage identification accuracy** for positive/negative and familiar/novel words. **Reaction time** (in milliseconds) for trials with correct responses.	Baseline and EOS assessments
PILT	**Percentage of trials in which the participant chose the advantageous symbol** out of the pair (e.g. the symbol with 0.7 probability of gaining money on "win" trials, and the symbol with 0.3 probability of losing money in the "loss" trials). Performance was assessed	Baseline and EOS assessments

Measure	Outcomes	Timepoint(s)
	over the final 20 trials in each block as this is where learning typically plateaus (Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018). **Percentage of "win-stay" trials,** defined as trials on which the previous trial (*n* – 1) was rewarded (received either win or no loss feedback) and the choice on the current trial *n* is the same as the choice on trial *n* – 1 (i.e., the participant "stayed" with the same choice made on the previous trial following an advantageous outcome) (Iyer et al., 2020). Performance was assessed over the final 20 trials in each block as this is where learning typically plateaus (Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018). **Percentage of "lose-shift" trials,** defined as trials on which the previous trial (*n* – 1) was not rewarded (received no win or loss feedback) and the choice on the current trial *n* differs from the choice on trial *n* – 1 (i.e., the participant "shifted" their choice following a disadvantageous outcome) (Iyer et al., 2020). Performance was assessed over the final 20 trials in each block as this is where learning typically plateaus (Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018). **Reaction time to choice** (in milliseconds) for trials with correct responses.	
Mood Zoom	**Daily rating** for positive affect items (happy, energetic), negative affect items (sad, anxious) and irritability items (irritable, angry) over 21 study days, analysed individually and by study week (baseline, treatment week 1, treatment week 2). **Root Mean Square of Successive Differences (RMSSD)** for positive affect, negative affect and irritability, calculated for each study week (baseline, treatment week 1, treatment week 2). The RMSSD is a measure of variability that quantifies the short-term fluctuations in a time series. It is calculated by taking the squared root of the average of the squared differences between successive observations: $$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}$$ Where:	Seven days pre-treatment and 14 days during treatment, split into Baseline week, treatment week 1, treatment week 2

Measure	Outcomes	Timepoint(s)
	• *N* is the total number of observations • x_i is the value of the *i*-th observation • x_{i+1} is the value of the (*i* + 1)-th observation.	
Actigraphy	**M10 activity,** or activity levels over the most active 10 hours in a 24-hour period. **M10 onset,** defined as onset of M10. **M10 onset variability,** defined as the Root Mean Square of Successive Differences (RMSSD) of M10 onsets, separately for each study week (baseline, treatment week 1, treatment week 2). **L5 activity,** or activity levels over the least active five hours in a 24-hour period. **L5 onset,** defined as onset of L5. **L5 onset variability,** defined as the Root Mean Square of Successive Differences (RMSSD) of L5 onsets, separately for each study week (baseline, treatment week 1, treatment week 2).	Seven days pre-treatment and 14 days during treatment, split into Baseline week, treatment week 1, treatment week 2
Salivary cortisol	**Delta Cortisol Awakening Response (ΔCAR)**, calculated as cortisol T3 – cortisol T1. **Area under the curve with respect to increase (AUCi)**, calculated as: $AUCi = \left(\frac{cortisol_{T2} - cortisol_{T1}}{2} \times 15\right) + \left(\frac{cortisol_{T2} - cortisol_{T1} + cortisol_{T3} - cortisol_{T1}}{2} \times 15\right)$ **Area under the curve with respect to the ground (AUCg)**, calculated as: $AUCg = \left(\frac{cortisol_{T1} + cortisol_{T2}}{2} \times 15\right) + \left(\frac{cortisol_{T2} + cortisol_{T3}}{2} \times 15\right)$ Where: • $cortisol_{T1}$ is the cortisol level measured immediately upon waking • $cortisol_{T2}$ is the cortisol level measured 15 minutes after waking • $cortisol_{T3}$ is the cortisol level measured 30 minutes after waking and is thought to correspond to the peak cortisol response (Wüst et al., 2000) and	Pre- and post-treatment

Measure	Outcomes	Timepoint(s)
	• 15 represents the time interval (in minutes) between each measurement.	

2.6.3 Data cleaning and outlier removal

We took a conservative approach to data cleaning and outlier removal, detailed below for each type of data collected. The aim was to retain as many data points as possible to reduce bias, increase generalisability and preserve statistical power. The full sample of 134 participants was included in the analysis of exploratory clinical outcomes measured via questionnaires.

2.6.3.1 Computerised tasks

For all computerised tasks, reaction times were plotted for all participants and all trials, separately for the Baseline and EOS assessments. Trials where participants responded in under 200ms were counted as incorrect responses when computing task accuracy outcomes and were otherwise excluded from endpoint calculation/analysis, as it was deemed implausible that a person would be able to register the on-screen stimulus and respond thoughtfully within that timeframe. Similarly, trials where the maximum response time elapsed (i.e., timeout trials) were counted as incorrect responses when computing measures of accuracy and were otherwise excluded from endpoint calculation/analysis. Trials where the participant responded incorrectly were excluded from analysis of reaction times (RTs).

Participants were only excluded from the analysis of an ETB task if they:

a. self-reported confusion/lack of understanding of a task, or otherwise responding differently than instructed e.g., pressing “F” in the EMEM task if a word was familiar to the participant at all, not just in the context of the previous ECAT.

b. had periods of non-response (i.e., timeouts) amounting to 25% of a task or more, **and** these timeouts followed a particular pattern e.g., heavily concentrated in the second half of the task, responding only to “like” trials on the ECAT etc.

c. on the EMEM task, achieved <50% accuracy overall (i.e., performed below chance).

d. on the EREC task, recalled >50% of the words in the ECAT, in the same order as originally presented, which could be indicative of the participant writing them down instead of recalling them from memory.

Below or above-average performance outside of the contexts mentioned above was not considered reason enough for exclusion. For each ETB task, sensitivity analyses were planned to exclude all participants who self-reported technical difficulties with the task, but which the researcher was not able to match to their response patterns, and all participants with timeouts affecting 25% of the task or more, but where these did not follow a particular pattern and were not accompanied by any other reason for exclusion listed above.

In the case of transient internet outages which only affected a small number of trials (<10% of the task) and which the researcher was able to identify through a combination of participant self-report and examination of the task log file, all effort was made to preserve the existing data and endpoints were recalculated after excluding the affected trials. Only two participants had their FERT endpoints recalculated due to such transient internet issues, one for their Baseline assessment and one for their EOS assessment.

Participants who were excluded from the ECAT analyses were also excluded from the analyses of the two associated memory tasks (EREC and EMEM) at that specific timepoint, unless other evidence suggested that they had indeed paid attention to the words in the categorisation task.

Participants were only excluded from the analysis of the PILT if they:

a. self-reported confusion/lack of understanding of the task, or otherwise responding differently than instructed e.g., choosing their favourite-looking stimulus instead of the monetarily advantageous one.

b. had periods of non-response (i.e., timeouts) amounting to 25% of all **loss trials** or more; this is because, due to an error in task development, not responding or "timing out" on loss trials always led to not losing money, which participants could have used as an alternative strategy.

c. responded inflexibly, i.e., chose only the right-hand or left-hand stimulus in two blocks or more.

d. on either win or loss trials, achieved 0% accuracy when averaging across the last 20 trials of each block (i.e., did not pick the advantageous stimulus a single time in those trials).

Below or above-average performance outside of the contexts mentioned above was not considered reason enough for exclusion. Sensitivity analyses were planned to exclude all participants who achieved <50% accuracy across both win and loss trials, and participants with periods of non-response affecting 25% of the task or more, across both win and loss trials. Table 2.4 summarises the number of trials and participants excluded from computerised task analyses.

Table 2.4. Summary of trials and participants excluded from the analysis of CABIN computerised tasks

Measure	Baseline trials excluded[1]	EOS trials excluded[1]	Baseline participants excluded[1]	EOS participants excluded[1]
ECAT	105 (1.96%)	104 (1.94%)	2 (1.49%)	1 (0.75%)
FERT	68 (0.20%)	59 (0.18%)	0 (0%)	0 (0%)
EREC	n/a	n/a	2 (1.49%)	3 (2.24%)
EMEM	185 (1.73%)	164 (1.53%)	5 (3.73%)	9 (6.72%)
PILT	105 (1.96%)	104 (1.94%)	8 (5.97%)	12 (8.96%)

[1] N (%)

2.6.3.2 Actigraphy

Actigraphy data from 126 participants were included in our analyses. Eight participants were excluded for reasons as follows:

- Device loss (two participants)

- Technical problems with recording (one participant)
- Early removal due to skin sensitivity (one participant)
- Error in setting device sampling frequency (one participant)
- Data collection impractical as participant was not allowed to wear any watches/jewellery due to the nature of their job (two participants)
- Unwilling to wear actigraphy device (one participant).

Sensitivity analyses accounted for the number of days of actigraphy data collected from each participant and the seasonality of observations. Additionally, three participants wore the actigraphy device on their dominant rather than non-dominant wrist. Participants were instructed to wear the device on their non-dominant hand as this typically exhibits less movement during daily activities compared to the dominant hand, and such placement could thus result in reduced motion artifacts. A further sensitivity analysis assessed the impact of wearing the device on the dominant wrist, by excluding these participants.

2.6.3.3 Mood Zoom

No participants were excluded from analyses of “Mood Zoom” data. The number of days’ worth of data was calculated for each participant and used as an additional covariate in our sensitivity analyses.

2.6.3.4 Waking cortisol

Participants were excluded from analysis if they did not provide all three saliva samples at both timepoints, either due to participant error or postage failure (seven participants) or did not take the saliva samples as per protocol (e.g., participant not adhering to 15-minute time intervals between samples; seven participants). This left a total sample of 120 participants for analysis of waking cortisol levels.

2.6.4 Statistical analysis approach

Analyses were performed using R Statistical Software (version 4.0.3 “Bunny-Wunnies Freak Out”; R Core Team, 2020). Analysis code will be made open access wherever possible and can be accessed at https://osf.io/7av2m/.

Basic demographics and baseline questionnaire measures were analysed descriptively, using means and standard deviations for continuous variables and percentages for categorical variables.

For the exploratory clinical outcomes presented in Chapter 3, a repeated measures analysis of variance (rANOVA) approach was used, with treatment group as the between-subjects factor and timepoint as the within-subjects factor. As we were interested in both group differences and symptom course, we explicitly included timepoint as a factor in the model. Where the assumption of normality was strongly violated (as assessed by a significant Shapiro-Wilk test and Q-Q plots), non-parametric alternatives were used to test for the effects of treatment group (Kruskal-Wallis test) and timepoint (Friedman test).

For other outcome measures presented in Table 3, analyses of covariance (ANCOVA) were used. The dependent variables in these models included only data collected during or after the treatment period, with baseline measurements included as covariates. Treatment group was included as the between-subjects factor, while within-subject factors (such as valence or emotion conditions in the computerised tasks) were specified according to the individual outcome measure. Models were adjusted for additional covariates of interest, as described in the individual data chapters. This approach not only increases statistical power by reducing error variance but also provides a clearer estimate of the effect of the intervention on post-treatment outcomes, helping to account for initial group differences and allowing for a more accurate comparison of treatment effects.

Significant interactions were followed up using contrasts of Estimated Marginal Means (EMMs) derived from the fitted models. EMMs represent the predicted means of the

outcome variable, averaged over the levels of other factors in the model and adjusted for covariates. Thus, contrasts between EMMs are analogous to t-tests, but they account for the model structure, including residuals and covariates, to estimate differences between the levels of the variable of interest. Where multiple comparisons raised the probability of a type-I error, the Bonferroni correction was used to adjust the significance threshold for p-values.

Unless otherwise specified, we first compared the Placebo and Citalopram-only groups to test for the effects of taking the SSRI medication (as opposed to the inert placebo) on the given outcome measure. A second model then compared the Citalopram and Citalopram + BA groups, testing whether the addition of BA modulated the effect of the drug. This two-step approach allowed us to disentangle the distinct and combined effects of medication and psychotherapy.

2.6.4.1 Statistical robustness and advanced statistical methods

In addition to analyses of (co)variance, linear mixed models (LMMs) were employed where appropriate to account for individual participant variability in outcome measures. Participant ID was included as a random intercept to control for random effects attributable to individual differences in symptom severity, task performance, activity level or affect.

For exploratory clinical outcomes, repeated measures ANOVAs (rANOVAs) were followed up with LMMs to obtain more precise estimates of symptom severity change between Baseline and EOS assessments.

For computerised tasks, actigraphy, and “Mood Zoom” data, LMMs were fitted *prior* to applying the ANCOVA, using the ***lmer*** function in R. Fixed effects of interest (e.g., treatment group, stimulus valence, baseline performance as a covariate) were included in the model to assess their impact on the outcome variable. After fitting the model, the ***anova*** function was applied to the ***lmer*** output to test the significance of the fixed effects, isolating their contribution to the overall model fit.

Importantly, LMMs are robust to non-normality of the raw data, provided the model residuals follow a normal distribution. To ensure this assumption was met, all model residuals were graphically inspected using histograms and QQ plots. Where necessary, we also performed separate analyses using non-parametric statistical methods to verify our findings.

To assess statistical robustness, sensitivity analyses were conducted as described in section 2.6.3, i.e., excluding participants who experienced technical difficulties and participants with high numbers of non-patterned timeouts in the computerised tasks. Discrepancies between sensitivity and primary analyses are noted in Chapters 4–7.

2.7 DISCUSSION

This experimental medicine study was designed to assess whether the early cognitive changes induced by antidepressant drugs are increased in the context of a more rewarding environment and to elucidate the mechanisms by which Behavioural Activation (BA), as a proxy for environmental enrichment, may potentiate antidepressant effects. It employed three treatment arms (Placebo, Citalopram and Citalopram + BA) assessed on a variety of questionnaire, computer task and biological outcome measures.

Strengths of the CABIN study include the relatively large sample size for an experimental medicine protocol, the broad phenotyping of study participants, as well as the placebo-controlled design.

By far the most notable limitation of the study design is the absence of a Placebo + Behavioural Activation treatment group. The omission of this fourth treatment group, while improving the feasibility of the study, makes it challenging to determine whether any observed effects are due to the combined treatment or if BA alone could have produced similar outcomes. It also makes it difficult to distinguish between additive effects of receiving the combined treatment (i.e., two treatments being better than one) and potential synergistic effects that environmental enhancement might have on antidepressant drug action. For example, if improvements are observed in the speed or accuracy of positive emotional

processing as hypothesised, it would be difficult to establish whether these effects are equal to the sum of the individual effects of Citalopram and BA on emotional processing or whether BA, as a proxy for environmental enrichment, enhances the effects of SSRI medication on emotional processing further and above what might be expected from additive effects (Godlewska & Harmer, 2021).

Although it does not completely address this design limitation, we can use previous published research to gain an understanding of the effects of behavioural activation alone on emotional processing. Ruzickova et al. used a very similar online BA protocol over four weeks and assessed participants on the same battery of cognitive emotional tasks (Ruzickova et al., 2023). While they did find that the group receiving online BA had a larger decrease in accuracy for recognising negative faces at week 4 compared to a passive control group, after excluding participants on antidepressants, this effect was no longer significant. This suggests that the observed effects of BA on emotional processing may be driven by concurrent antidepressant use; alternatively, it may reflect a reduction in statistical power after excluding participants on medication, leaving the study underpowered to detect the original effect. This caveat notwithstanding, BA has further been hypothesised to alleviate depression through different mechanisms, such as enhancing reward anticipation at both behavioural and neural level (Karimpour-Vazifehkhorani et al., 2020; Nagy et al., 2020).

What *can* be determined through the present study is where the combination of treatments produces unique outcomes that are not attributable to Citalopram alone. Differences between the Citalopram only and Citalopram + BA groups can indicate where the drug effects are modulated through the provision of BA, even if the independent effects of BA cannot be fully isolated. As such, observing heightened positive emotional processing biases in the combined treatment group compared to the Citalopram only group would still support the neuropsychological model of antidepressant drug action as it would indicate environmental enrichment does indeed potentiate the known effects of SSRIs on emotional processing (Harmer et al., 2004, 2004; Harmer, Goodwin, et al., 2009; Harmer & Cowen,

2013; Murphy, Norbury, et al., 2009). Furthermore, the study adds to the body of literature on combining pharmacotherapy and psychotherapy for MDD, where no definitive evidence exists on when in the course of treatment they may be best co-prescribed (Dunlop, 2016; Guidi & Fava, 2021; Karyotaki et al., 2016; Prescott & White, 2017).

Another limitation of the study design is the lack of complete blinding, particularly the fact that participants allocated to the Citalopram + BA group were aware they would start the psychological intervention prior to completing the Baseline assessment. To address this limitation and increase transparency, we compared BDI-II scores at Screening with those at Baseline assessment, to check for any expectation effects and/or spontaneous recovery. The results of this analysis are presented in Chapter 3. The lack of complete blinding was also attenuated by the online data collection protocol used, which meant the primary researcher was not directly involved in collecting either pre- or post-treatment outcome data.

A final consideration relates to the standardisation and reproducibility of our BA protocol, which could have been a source of confounding variables. Whilst every effort was made to tailor the BA intervention to individual participants' goals, the broad structure and content covered in the three sessions described in section 4.3.2 above was the same for every participant. Moreover, all participants allocated to the Citalopram + BA condition attended all three BA sessions, meaning there will be no differences driven by participants attending a different number of sessions. However, the study did not employ a formal measure of tolerability or impact of the BA sessions, beyond the BADS and EROS questionnaires administered at End of Study assessment; in the absence of such a measure, limited conclusions can be drawn about the success of achieving the intended experimental manipulation of environmental enrichment through increasing the frequency participants engaged in rewarding activities. This complicates the interpretation of any null results and should be considered when discussing the impact of treatment on study outcomes in subsequent chapters.

3 CHAPTER 3: THE EFFECTS OF A BEHAVIOURAL ACTIVATION-ENRICHED SSRI INTERVENTION ON MOOD, ANXIETY AND REWARD-SPECIFIC SELF-ASSESSMENTS

3.1 INTRODUCTION

Demographic variables such as age, gender, and educational background, along with lifestyle characteristics like physical activity levels and social support, significantly shape individuals' experiences of depression and their responses to treatment. Research has shown that older adults may experience slower or less robust responses to antidepressants (Tedeschini et al., 2011), and gender differences in depression prevalence and treatment outcomes are also well-documented (LeGates et al., 2019; Salk et al., 2017). Additionally, socioeconomic factors – including employment status and income – can influence access to health resources and environmental enrichment, both of which may moderate treatment efficacy (Chiarotti et al., 2017; Finegan et al., 2018; Jakubovski & Bloch, 2014). In studies with independent group designs, like the CABIN study, ensuring that groups are well-matched in terms of these characteristics is critical.

It is also well-recognised that clinical research often suffers from non-representative samples, with underrepresentation of certain groups, such as racial and ethnic minorities, socioeconomically disadvantaged individuals, carers, full time workers, and those who do not reside near study sites (Witham et al., 2020). This limits the external validity of study results and reduces the applicability of findings to broader populations. The COVID-19 pandemic, however, spurred the development of online research infrastructure, opening opportunities for hybrid study designs that combine in-person and remote components. In the CABIN study, only one in-person visit was required, with the remainder of the intervention and data collection conducted remotely. By offering this flexibility, we aimed to include individuals typically excluded from research due to geographical, time, or caregiving constraints, which we hoped would increase the diversity of our sample and improve the generalisability of our findings.

As this was an experimental medicine study with primary outcomes focused on biomarkers of antidepressant response, clinical outcomes were treated as exploratory but crucial in understanding the full scope of treatment effects alongside the mechanistic (biomarker) findings. Establishing that baseline levels of depression and anxiety severity did not differ between groups was crucial to ensure valid comparisons throughout the study. Given that the timeframe of clinical effects for combined pharmacological and psychological interventions has not been extensively studied, we also explored whether these effects could be accelerated when Selective Serotonin Reuptake Inhibitors (SSRIs) and behavioural activation (BA) are used together.

Previous research has shown that online BA can significantly improve self-reported mood after four weeks of treatment and increase behavioural activation – defined as the degree to which individuals feel content with their daily activities – after just two weeks (Ruzickova et al., 2023). Our study seeks to extend these findings by investigating how the addition of BA to citalopram treatment not only influences participants' engagement in reinforcing activities (behavioural activation) but also their perceptions of environmental reward, following a shorter, two-week intervention period.

To assess these outcomes, we employed two validated measures: the Behavioral Activation for Depression Scale (BADS) and the Environmental Reward Observation Scale (EROS). The BADS is designed to measure the degree to which individuals engage in activities that are positively reinforcing and align with their personal values, providing insight into how effectively BA promotes behavioural change (Kanter et al., 2007). On the other hand, the EROS measures the perceived availability of environmental rewards – how much satisfaction and positive reinforcement individuals feel they derive from their surroundings and daily activities (Armento & Hopko, 2007). By using these scales, we were able to capture both the behavioural activation component and the broader sense of reward availability in participants' environments. Based on previous research linking BA to increased engagement in rewarding activities, we hypothesised that participants in the Citalopram +

BA group would show higher scores on both the BADS and EROS compared to the Citalopram-only group after two weeks of treatment.

Thus, this chapter first provides a comprehensive overview of the demographic, lifestyle and baseline psychological traits of the CABIN study sample. We then investigate the symptom trajectory and group differences across several clinical measures, including depression symptomatology, state anxiety, behavioural activation, and perceived environmental reward availability, as described above. Finally, we assess the prevalence of physical symptoms commonly associated with SSRI treatment.

3.2 METHODS

3.2.1 Sample

Data from all participants (N Placebo = 45, N Citalopram = 44, N Citalopram + BA = 45) were included in these analyses.

3.2.2 Measures

3.2.2.1 Demographics and baseline questionnaire measures

Demographic and lifestyle data were collected from all study participants at Screening 1. To further characterise our sample, baseline measures of trait anxiety (State-Trait Anxiety Inventory – Trait subscale), behavioural approach/inhibition (Behavioural Inhibition System/Behavioural Approach System Scales) and social support (Multidimensional Scale of Perceived Social Support) were administered at Baseline assessment.

3.2.2.2 Exploratory clinical measures

Depression symptoms were assessed four times over the course of the study, at Pre-screening, Screening, Baseline assessment and End of Study (EOS) assessment, using the Beck Depression Inventory-II. Because question 9 (suicidality item) was omitted from the questionnaire at Pre-screening (see Chapter 2) and the total scores are hence non-comparable, we only analysed the latter three timepoints.

Several other clinical measures were assessed two times over the course of the study, at Baseline and EOS assessments: state anxiety (State-Trait Anxiety Inventory – State subscale), behavioural activation (Behavioural Activation for Depression Scale), and perceived access to environmental reinforcement (Environmental Reward Observation Scale).

Physical symptoms commonly associated with SSRI treatment were assessed four times over the course of the study, twice via online questionnaires at Baseline and EOS assessments and twice during researcher-led phone/video calls at Follow-ups 1 and 2.

3.2.3 Analysis of demographic and clinical data

Demographic, lifestyle, and baseline questionnaire measures were analysed descriptively, using means and standard deviations for continuous variables and percentages for categorical variables. Clinical outcomes (e.g., depression, anxiety, behavioural activation, environmental reward) were analysed using repeated measures ANOVA (rANOVA), with treatment group (either Placebo vs Citalopram or Citalopram vs Citalopram + BA) as the between-subjects factor and timepoint as the within-subjects factor. rANOVAs were followed up with linear mixed models (LMMs) to estimate changes from Baseline to EOS while accounting for between-participant differences. As Physical Symptom Questionnaire (PSQ) scores were not normally distributed, the non-parametric Kruskal-Wallis test was used to assess treatment group effects at each timepoint.

3.3 RESULTS - PARTICIPANT DEMOGRAPHICS AND LIFESTYLE CHARACTERISTICS

Demographic characteristics, for each treatment group, are presented in Table 3.1. This was a majority female, white, highly educated sample. The mean age of participants was 31.53 years (SD = 11.89), and most were native English speakers. The three treatment groups were well-matched across these characteristics.

Table 3.1. Demographic characteristics of the CABIN study sample by treatment group

Characteristic	***Placebo***, *N=45*	***Citalopram***, *N=44*	***Citalopram + BA***, *N=45*
Birth sex, n (%)			
Female	29 (64%)	27 (61%)	29 (64%)
Male	16 (36%)	17 (39%)	16 (36%)
Gender, n (%)			
Female	29 (64%)	27 (61%)	28 (62%)
Male	16 (36%)	17 (39%)	15 (33%)
Non-binary	0 (0%)	0 (0%)	1 (2.2%)
Other	0 (0%)	0 (0%)	1 (2.2%)
Age, mean (SD)	32.56 (11.76)	31.16 (11.16)	30.89 (12.88)
Ethnicity, n (%)			
White/Caucasian	36 (80%)	24 (55%)	31 (69%)
Asian/British Asian	2 (4.4%)	4 (9.1%)	5 (11%)
Black/Black British	2 (4.4%)	4 (9.1%)	2 (4.4%)
Chinese/British Chinese	3 (6.7%)	5 (11%)	1 (2.2%)
Mixed race	2 (4.4%)	4 (9.1%)	3 (6.7%)
Other	0 (0%)	3 (6.8%)	3 (6.7%)
Highest education, n (%)			
GCSE/CSE/O-levels	1 (2.2%)	1 (2.3%)	0 (0%)
A-levels or equivalent	5 (11%)	9 (20%)	14 (31%)
Undergraduate degree	17 (38%)	16 (36%)	13 (29%)
Postgraduate degree	22 (49%)	18 (41%)	18 (40%)
Years in education, mean (SD)	18.13 (2.93)	17.66 (2.92)	17.06 (2.89)
Employment status, n (%)			
Employed full-time	25 (56%)	19 (43%)	14 (31%)
Employed part-time	3 (6.7%)	5 (11%)	4 (8.9%)
Student	13 (29%)	19 (43%)	22 (49%)
Unemployed	3 (6.7%)	1 (2.3%)	4 (8.9%)
Retired	1 (2.2%)	0 (0%)	1 (2.2%)
Marital status, n (%)			
Unmarried	36 (80%)	32 (73%)	37 (82%)
Married/civil partnership	6 (13%)	12 (27%)	7 (16%)
Divorced	2 (4.4%)	0 (0%)	1 (2.2%)
Widowed	1 (2.2%)	0 (0%)	0 (0%)
Household income, n (%)			
<£16,000/year	6 (13%)	3 (6.8%)	6 (13%)
£16-29,999/year	4 (8.9%)	4 (9.1%)	9 (20%)

Characteristic	***Placebo***, *N=45*	***Citalopram***, *N=44*	***Citalopram + BA***, *N=45*
£30-59,999/year	20 (44%)	16 (36%)	15 (33%)
£60-89,999/year	11 (24%)	9 (20%)	8 (18%)
£90-119,999/year	2 (4.4%)	6 (14%)	4 (8.9%)
>£120,000/year	2 (4.4%)	6 (14%)	3 (6.7%)
Native English speaker, n (%)	31 (69%)	33 (75%)	32 (71%)
Handedness, n (%)			
Right-handed	35 (78%)	41 (93%)	35 (78%)
Left-handed	10 (22%)	3 (6.8%)	9 (20%)
Ambidextrous	0 (0%)	0 (0%)	1 (2.2%)

Lifestyle characteristics, for each treatment group, are presented in Table 3.2. In terms of daily activity patterns, it is worth noting that the proportion of participants who did not perform any daily exercise was higher in the Placebo group compared to the active treatment groups; however, the sample generally met the requirement of self-identifying as "low in activity", with over 40% of participants performing little (< 30 minutes) or no daily exercise. The three treatment groups were well-matched on all other lifestyle characteristics.

Table 3.2. Lifestyle characteristics for the CABIN study sample, by treatment group

Characteristic	***Placebo***, *N=45*	***Citalopram***, *N=44*	***Citalopram + BA***, *N=45*
Height (cm), mean (SD)	171.50 (10.72)	170.13 (8.59)	169.24 (9.08)
Weight (kg), mean (SD)	74.00 (14.65)	73.17 (11.93)	69.74 (13.64)
BMI, mean (SD)	25.09 (4.07)	25.27 (3.80)	24.34 (4.45)
Smoker, n (%)	3 (6.7%)	4 (9.1%)	3 (6.7%)
Weekly alcohol units, mean (SD)	6.24 (7.00)	4.43 (4.35)	4.64 (4.88)
Daily caffeine cups, mean (SD)	2.09 (1.38)	1.91 (1.38)	2.07 (1.67)
COVID-19 status, n (%)			
Diagnosed and recovered	21 (47%)	17 (39%)	25 (56%)
Diagnosed and still ill	0 (0%)	0 (0%)	1 (2.2%)
Suspected and recovered	2 (4.4%)	5 (11%)	2 (4.4%)
No COVID-19	22 (49%)	22 (50%)	17 (38%)
Living arrangements, n (%)			
Living alone	10 (22%)	4 (9.1%)	6 (13%)
Living with partner/family	19 (42%)	19 (43%)	16 (36%)
Shared flat or house	16 (36%)	21 (48%)	23 (51%)

Characteristic	***Placebo***, *N=45*	***Citalopram***, *N=44*	***Citalopram + BA***, *N=45*
Daily time outside, n (%)			
No time spent outside	0 (0%)	0 (0%)	1 (2.2%)
<30 minutes	11 (24%)	6 (14%)	4 (8.9%)
30 minutes – 2 hours	21 (47%)	21 (48%)	30 (67%)
3 – 5 hours	9 (20%)	15 (34%)	8 (18%)
6+ hours	4 (8.9%)	2 (4.5%)	2 (4.4%)
Daily exercise, n (%)			
No exercise	10 (22%)	1 (2.3%)	2 (4.4%)
<30 minutes	12 (27%)	17 (39%)	15 (33%)
30 minutes – 2 hours	22 (49%)	20 (45%)	22 (49%)
3 – 5 hours	0 (0%)	6 (14%)	4 (8.9%)
6+ hours	1 (2.2%)	0 (0%)	2 (4.4%)

3.4 RESULTS - BASELINE QUESTIONNAIRES

The means and standard deviations of baseline questionnaire scores, for each treatment group, are presented in Table 3.3. The CABIN sample had relatively high trait anxiety scores, comparable to clinical samples with depression and anxiety disorders, and higher than those of non-clinical volunteers (Bieling et al., 1998; Kennedy et al., 2001; Potvin et al., 2011).

In terms of Behavioural Approach/Behavioural Inhibition, participants' scores were again similar to those previously reported in clinically depressed individuals (Kasch et al., 2002), though on the three Behavioural Approach scales (Reward Responsiveness, Drive and Fun-Seeking) there was substantial overlap with scores reported in healthy population studies as well (Cooper et al., 2007; Demianczyk et al., 2014). Nevertheless, on the Behavioural Inhibition (BIS) subscale in particular, CABIN participants scored higher than reported norms for non-clinical participants as well as large community samples (Jorm et al., 1998). BIS hyperactivity could be indicative of increased sensitivity to unpleasant stimuli and punishment, and is consistent with the presence of high anxiety, worry, and restlessness.

Scores on the Multidimensional Scale of Perceived Social Support in the CABIN sample are higher than those reported in a sample of psychiatric outpatients with a Major Depression diagnosis, but below those reported in a student comparison sample with a low percentage of psychopathology (Clara et al., 2003). While there are no established cutoffs for the MSPSS scale, it has been suggested that total scores over 30 represent medium perceived support, while scores over 61 represent high perceived support (Greenspace (US), 2020); this would suggest that, on average, CABIN participants had medium-to-high self-reported levels of social support, in all three treatment groups.

Table 3.3. Baseline questionnaire descriptives by treatment group

Questionnaire measure **Mean (SD)**	***Placebo***, *N=45*	***Citalopram***, *N=44*	***Citalopram + BA***, *N=45*
STAI-T total	52.09 (9.88)	52.61 (9.72)	54.69 (9.73)
BAS Reward Responsiveness subscale	16.00 (2.04)	16.09 (2.75)	16.49 (1.75)
BAS Drive subscale	9.58 (2.33)	10.66 (2.36)	10.36 (1.96)
BAS Fun-Seeking subscale	10.91 (2.75)	11.57 (2.71)	11.76 (2.62)
BIS scale	22.56 (3.49)	23.32 (3.41)	23.36 (3.38)
MSPSS total	57.69 (12.86)	60.91 (13.19)	55.49 (13.01)
MSPSS Significant Other subscale	20.36 (6.40)	21.09 (5.64)	18.64 (6.66)
MSPSS Family subscale	17.44 (5.82)	18.61 (6.09)	17.09 (6.10)
MSPSS Friends subscale	19.89 (5.87)	21.20 (4.23)	19.76 (4.68)

STAI-T = State-Trait Anxiety Inventory – Trait subscale
BAS = Behavioural Approach System
BIS = Behavioural Inhibition System
MSPSS = Multidimensional Scale of Perceived Social Support

3.5 RESULTS – EXPLORATORY CLINICAL OUTCOMES

3.5.1 Depression symptoms (BDI-II)

Figure 3.1 illustrates the distribution of participants based on their Beck Depression Inventory – II (BDI-II) score severity classification at Screening and Baseline assessment. As anticipated based on the study's inclusion criteria, the CABIN sample primarily comprised individuals with mild (BDI-II score > 13) to moderate (BDI-II score > 19) levels of depression.

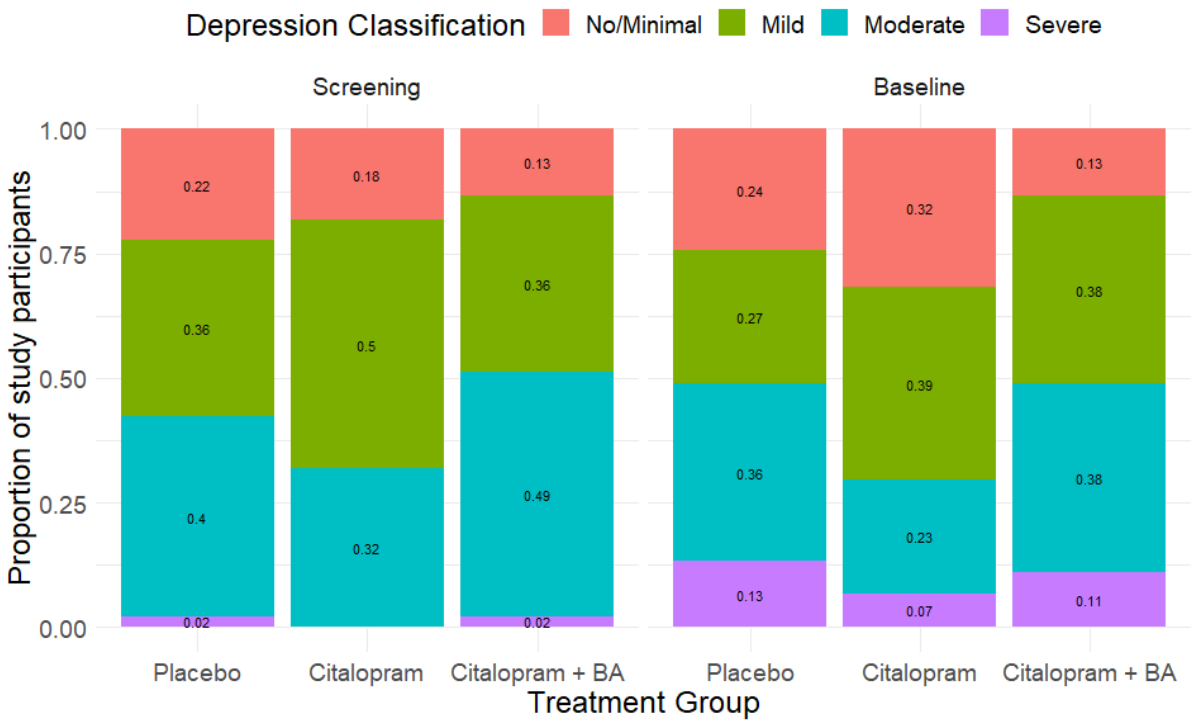


Figure 3.1. Distribution of depression severity classifications by treatment group at Screening and Baseline assessment

We first confirmed that no significant changes in BDI-II scores occurred in the ~5 weeks between initial screening and Baseline assessment for any of the treatment groups; this was important as participants assigned to the Citalopram + BA group were aware they would be receiving the psychological therapy following randomisation, which could have potentially impacted their mood. Moreover, given the relatively long period between initial screening and treatment start, spontaneous recovery was a concern. BDI-II scores did not change between initial screening and Baseline assessment for any of the three treatment groups (all $p > 0.50$), which suggests that any subsequent changes from Baseline to End of Study are attributable to the start of study treatment.

Mean BDI-II scores over the course of the study are illustrated in Figure 3.2, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

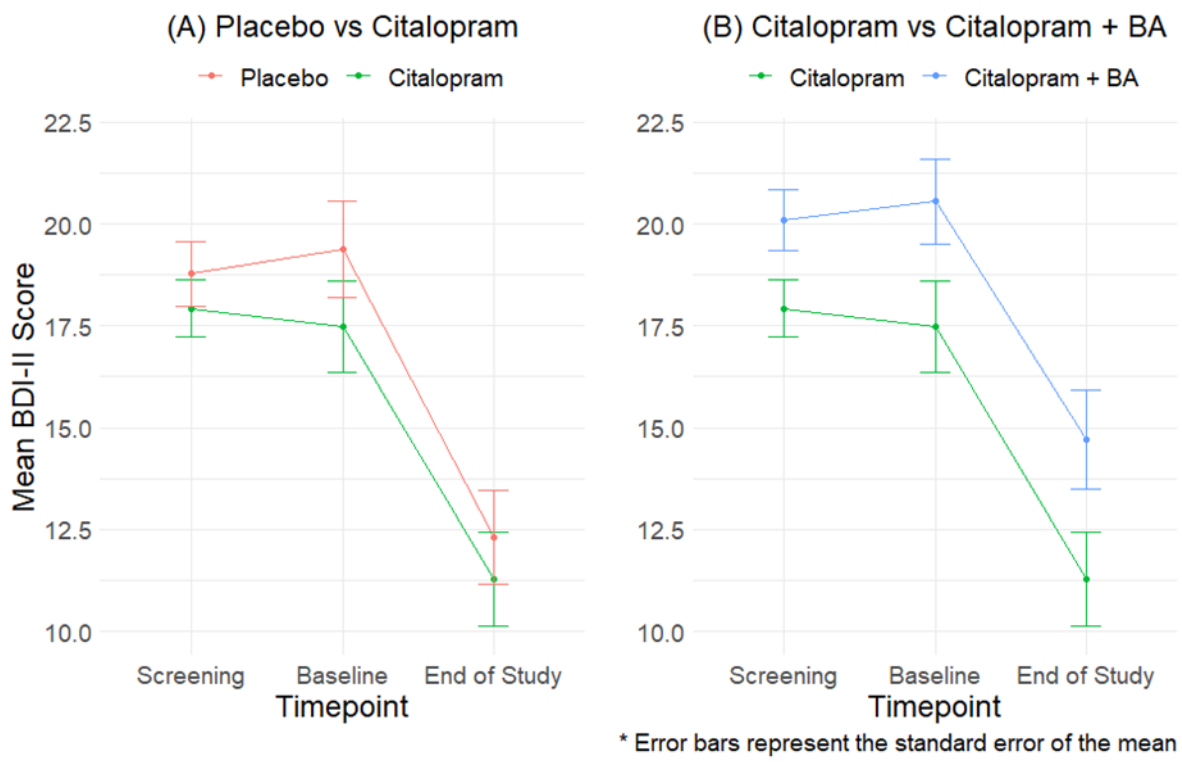


Figure 3.2. Mean Beck Depression Inventory – II (BDI-II) scores by timepoint for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

3.5.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on depression scores as measured by the BDI-II ($F(1, 87) = 1.05$, $p = 0.309$), nor a significant treatment group and timepoint interaction ($F(1, 87) = 0.33$, $p = 0.570$). The main effect of timepoint was statistically significant ($F(1, 87) = 77.13$, $p < 0.001$), indicating that BDI-II scores at EOS assessment (model-adjusted mean = 11.8, SE = 0.81, 95% CI: 10.2 to 13.4) were significantly lower than at Baseline assessment (model-adjusted mean = 18.4, SE = 0.81, 95% CI: 16.8 to 20.0) across both treatment groups.

3.5.1.2 Citalopram vs Citalopram + BA comparison

We observed a significant main effect of treatment group ($F(1, 87) = 5.13$, $p = 0.026$), indicating that depression scores as measured by the BDI-II were higher for the Citalopram + BA group (model-adjusted mean = 17.6, SE = 1.01, 95% CI: 15.6 to 19.6) compared to the Citalopram only group (model-adjusted mean = 14.4, SE = 1.02, 95% CI: 12.3 to 16.4)

across timepoints. We also observed a significant main effect of timepoint ($F(1, 87) = 73.69$, $p < 0.001$); BDI-II scores at EOS assessment (model-adjusted mean = 13.0, SE = 0.80, 95% CI: 11.4 to 14.6) were significantly lower than at Baseline assessment (model-adjusted mean = 19.0, SE = 0.80, 95% CI: 17.4 to 20.6) across both treatment groups. The interaction between treatment group and timepoint was not significant ($F(1, 87) = 0.07$, $p = 0.798$).

3.5.1.3 Estimated changes in depression symptoms

To estimate changes in BDI-II scores between the Baseline and EOS assessments, we fitted a linear mixed effects model that included all three treatment groups, using participant ID as a random intercept to account for individual variability in depression severity. The coefficient estimate for the EOS timepoint was -7.07 (SE = 1.02, t = -6.93, $p < 0.001$) suggesting that, on average, BDI-II scores decreased by approximately 7 points between the two assessments, irrespective of treatment group. Given an average BDI-II score at Baseline of 19.15, this corresponds to an approximate 37% reduction in depression symptoms. These changes did not vary by treatment group.

3.5.2 Anxiety symptoms (STAI-S)

Much of the CABIN participant sample had Baseline State-Trait Anxiety Inventory – State subscale (STAI-S) scores typically classified as “high” anxiety (Spielberger, 2012); this is illustrated in Figure 3.3.

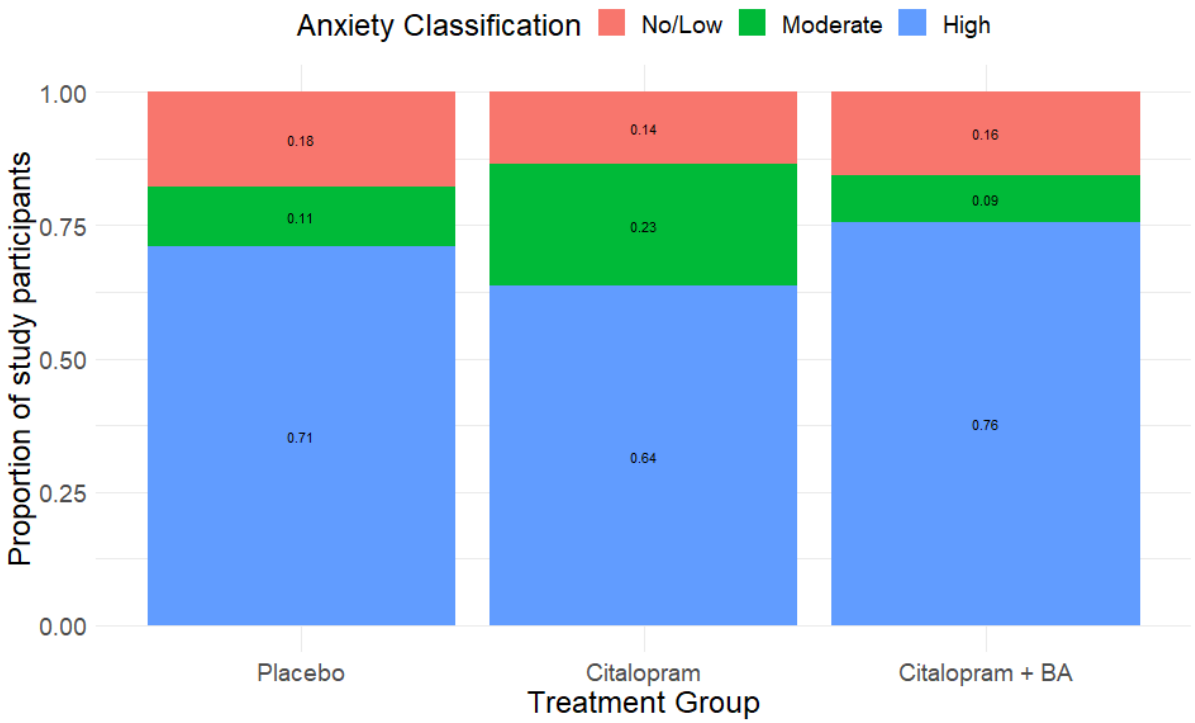


Figure 3.3. Distribution of anxiety severity classifications by treatment group at Baseline assessment

Mean STAI-S scores over the course of the study are illustrated in Figure 3.4, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

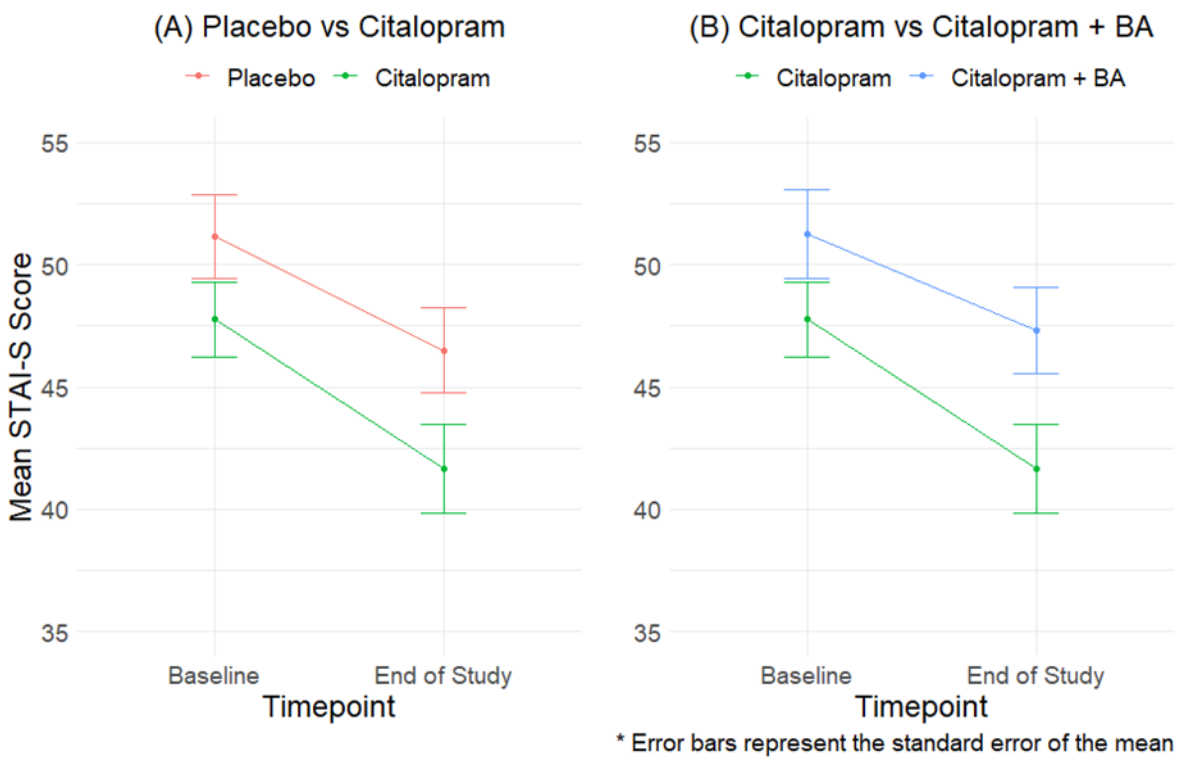


Figure 3.4. Mean State-Trait Anxiety Inventory – State (STAI-S) scores by timepoint for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

3.5.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on anxiety scores as measured by the STAI-S ($F(1, 87) = 3.62$, $p = 0.060$), nor a significant treatment group and timepoint interaction ($F(1, 87) = 0.45$, $p = 0.502$). The main effect of timepoint was statistically significant ($F(1, 87) = 25.19$, $p < 0.001$), indicating that STAI-S scores at EOS assessment (model-adjusted mean = 44.1, SE = 1.20, 95% CI: 41.7 to 46.5) were significantly lower than at Baseline assessment (model-adjusted mean = 49.5, SE = 1.20, 95% CI: 47.1 to 51.8) across both treatment groups.

3.5.2.2 Citalopram vs Citalopram + BA comparison

We observed a significant main effect of treatment group ($F(1, 87) = 4.40$, $p = 0.039$), indicating that anxiety scores as measured by the STAI-S were higher for the Citalopram + BA group (model-adjusted mean = 49.3, SE = 1.54, 95% CI: 46.2 to 52.4) compared to the Citalopram only group (model-adjusted mean = 44.7, SE = 1.55, 95% CI: 41.6 to 47.8)

across timepoints. We also observed a significant main effect of timepoint ($F(1, 87) = 19.31$, $p < 0.001$); STAI-S scores at EOS assessment (model-adjusted mean = 44.5, SE = 1.23, 95% CI: 42.1 to 46.9) were significantly lower than at Baseline assessment (model-adjusted mean = 49.5, SE = 1.23, 95% CI: 47.1 to 52.0) across both treatment groups. The interaction between treatment group and timepoint was not significant ($F(1, 87) = 0.91$, $p = 0.343$).

3.5.2.3 Estimated changes in anxiety symptoms

To estimate changes in STAI-S scores between the Baseline and EOS assessments, we fitted a linear mixed effects model that included all three treatment groups, using participant ID as a random intercept to account for individual variability in anxiety severity. The coefficient estimate for the EOS timepoint was -4.67 (SE = 1.52, t = -3.06, p = 0.003) suggesting that, on average, STAI-S scores decreased by approximately 4.7 points between the two assessments, irrespective of treatment group. Given an average STAI-S score at Baseline of 50.08, this corresponds to an approximate 9% reduction in anxiety symptoms. These changes did not vary by treatment group.

3.5.3 Behavioural activation (BADS)

Mean Behavioural Activation for Depression Scale (BADS) scores over the course of the study are illustrated in Figures 3.5 and 3.6, separately for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison.

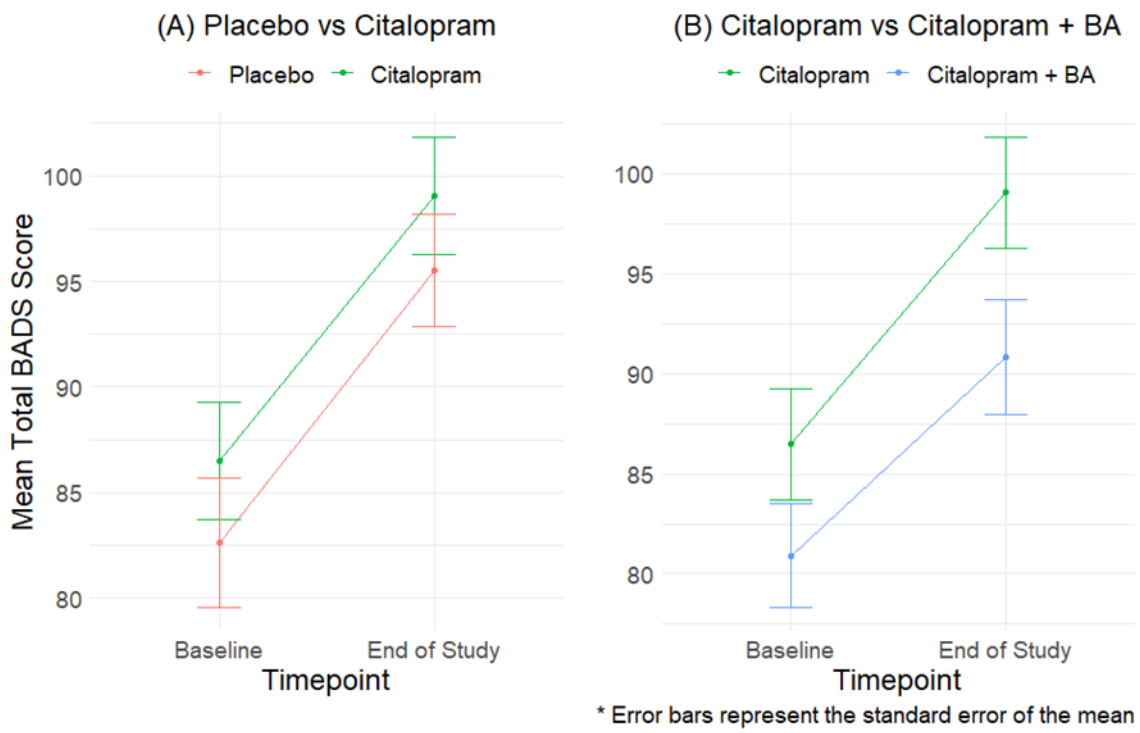


Figure 3.5. Mean total Behavioural Activation for Depression Scale (BADS) scores by timepoint for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

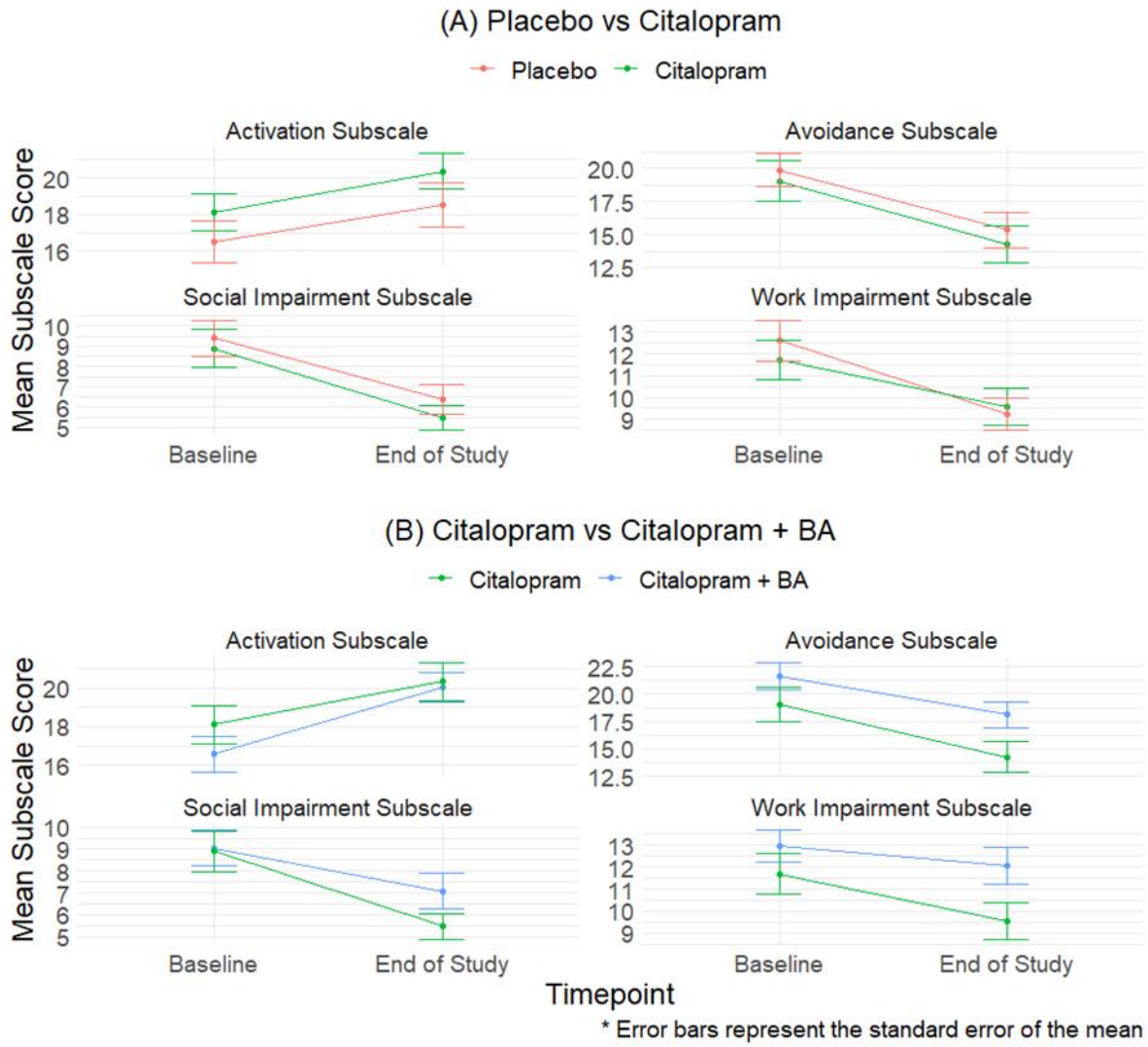


Figure 3.6. Mean Behavioural Activation for Depression Scale (BADS) subscale scores by timepoint for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

3.5.3.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on behavioural activation as measured by the BADS ($F(1, 87) = 1.07$, $p = 0.305$), nor a significant treatment group and timepoint interaction ($F(1, 87) = 0.008$, $p = 0.929$). The main effect of timepoint ($F(1, 87) = 50.81$, $p < 0.001$) was statistically significant, indicating that BADS scores at EOS assessment (model-adjusted mean = 97.3, SE = 2.00, 95% CI: 93.3 to 101.3) were significantly higher than at Baseline assessment (model-adjusted mean = 84.5, SE = 2.00, 95% CI: 80.6 to 88.5) across both treatment groups.

When examining each BADS subscale separately, all ANOVA analyses showed a significant main effect of timepoint, indicating a significant change between the Baseline and EOS assessments across all subscales (all $p \leq 0.001$). There were no significant main effects of treatment group or significant treatment group and timepoint interactions (all $p > 0.245$).

3.5.3.2 Citalopram vs Citalopram + BA comparison

We observed a significant main effect of treatment group ($F(1, 87) = 4.02$, $p = 0.048$), indicating that participants' engagement in goal-directed activities and reduction of avoidance behaviours, as measured by the BADS, was lower in the Citalopram + BA group (model-adjusted mean = 85.9, SE = 2.42, 95% CI: 81.1 to 90.7) compared to the Citalopram only group (model-adjusted mean = 92.8, SE = 2.45, 95% CI: 87.9 to 97.6) across timepoints. We also observed a significant main effect of timepoint ($F(1, 87) = 38.37$, $p < 0.001$); BADS scores at EOS assessment (model-adjusted mean = 94.9, SE = 1.95, 95% CI: 91.1 to 98.8) were significantly higher than at Baseline assessment (model-adjusted mean = 83.7, SE = 1.95, 95% CI: 79.8 to 87.5) across both treatment groups. The interaction between treatment group and timepoint was not significant ($F(1, 87) = 0.54$, $p = 0.463$).

When examining each BADS subscale separately, all ANOVA analyses showed a significant main effect of timepoint, indicating a significant change between the Baseline and EOS assessments across all subscales (all $p \leq 0.002$). There were no significant main effects of treatment group or significant treatment group and timepoint interactions (all $p > 0.053$), although the main effect of treatment group approached significance for the Avoidance subscale ($F(1, 87) = 3.86$, $p = 0.053$). Here, there was a trend-level tendency for Avoidance scores to be higher in the Citalopram + BA group (model-adjusted mean = 19.9, SE = 1.15, 95% CI: 17.6 to 22.1) compared to the Citalopram only group (model-adjusted mean = 16.6, SE = 1.16, 95% CI: 14.3 to 19.0) across timepoints.

3.5.3.3 Estimated changes in behavioural activation

To estimate changes in BADS scores between the Baseline and EOS assessments, we fitted a linear mixed effects model that included all three treatment groups, using participant ID as a random intercept to account for individual variability in behavioural activation. The coefficient estimate for the EOS timepoint was 12.91 (SE = 2.56, t = 5.04, p < 0.001) suggesting that, on average, BADS scores increased by approximately 12.9 points between the two assessments, irrespective of treatment group. Given an average BADS score at Baseline of 83.31, this corresponds to an approximate 16% increase in participants' engagement in reinforcing activities. These changes did not vary by treatment group.

3.5.4 Environmental reward (EROS)

Mean Environmental Reward Observation Scale (EROS) scores over the course of the study are illustrated in Figure 3.7, separately for (A) the Placebo vs Citalopram comparison and (B) the Citalopram vs Citalopram + BA comparison.

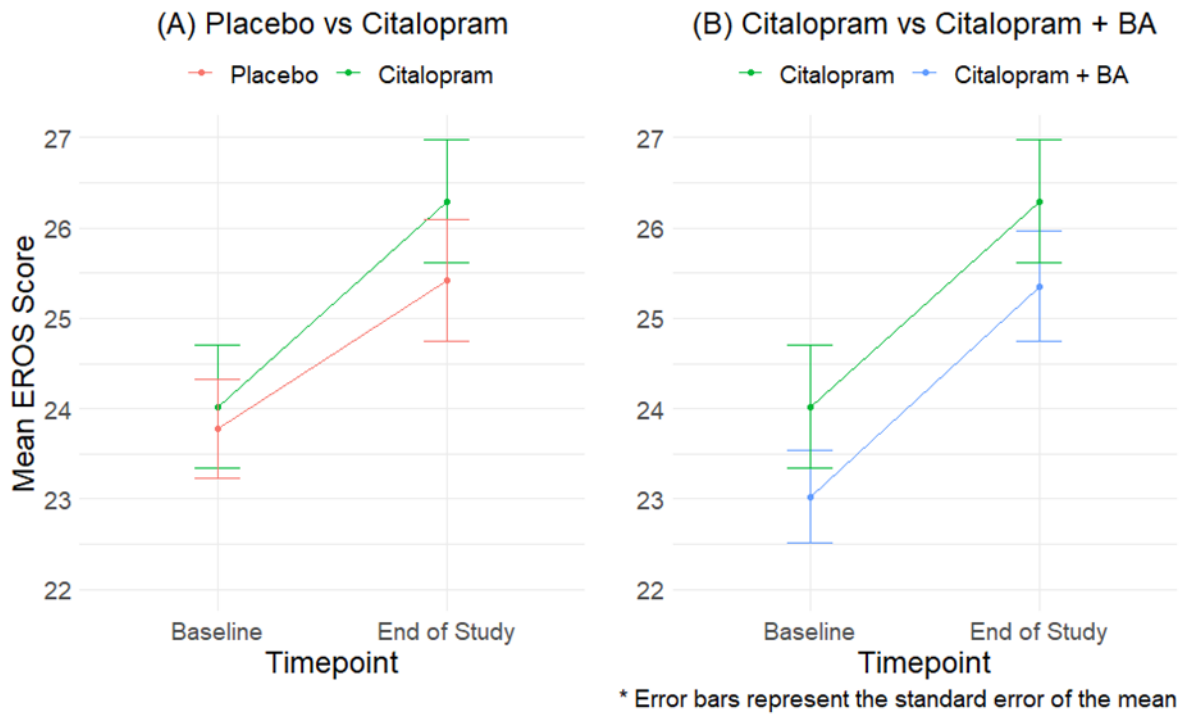


Figure 3.7. Mean Environmental Reward Observation Scale (EROS) scores by timepoint for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

3.5.4.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on participants' perception of environmental reward availability as measured by the EROS ($F(1, 87) = 0.44$, $p = 0.510$), nor a significant treatment group and timepoint interaction ($F(1, 87) = 0.80$, $p = 0.373$). The main effect of timepoint was statistically significant ($F(1, 87) = 31.16$, $p < 0.001$), indicating that EROS scores at EOS assessment (model-adjusted mean = 25.9, SE = 0.46, 95% CI: 25.0 to 26.8) were significantly higher than at Baseline assessment (model-adjusted mean = 23.9, SE = 0.46, 95% CI: 23.0 to 24.8) across treatment groups.

3.5.4.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on participants' EROS scores ($F(1, 87) = 1.43$, $p = 0.235$), nor a significant treatment group and timepoint interaction ($F(1, 87) = 0.007$, $p = 0.932$). The main effect of timepoint was statistically significant ($F(1, 87) = 42.39$, $p < 0.001$), indicating that EROS scores at EOS assessment (model-adjusted mean = 25.8, SE = 0.44, 95% CI: 24.9 to 26.7) were significantly higher than at Baseline assessment (model-adjusted mean = 23.5, SE = 0.44, 95% CI: 22.6 to 24.4) across treatment groups.

3.5.4.3 Estimated changes in perceived environmental reward

To estimate changes in EROS scores between the Baseline and EOS assessments, we fitted a linear mixed effects model that included all three treatment groups, using participant ID as a random intercept to account for individual variability in perception of environmental reward. The coefficient estimate for the EOS timepoint was 1.64 (SE = 0.50, t = 3.28, p = 0.001) suggesting that, on average, EROS scores increased by approximately 1.6 points between the two assessments irrespective of treatment group. Given an average EROS score at Baseline of 23.60, this corresponds to an approximate 7% increase in participants' perception of environmental reward availability. These changes did not vary by treatment group.

3.5.5 Physical symptoms questionnaire (CABIN PSQ)

The quartile distribution of total Physical Symptoms Questionnaire (PSQ) scores by timepoint and treatment group is presented in Figure 3.8. The PSQ total score is calculated by summing the ratings for six physical symptoms, each of which is scored from 0 (absent) to 3 (severe), yielding a total possible score range of 0 to 18. Higher scores indicate more severe physical symptoms. In the CABIN dataset, the PSQ scores are relatively low overall, suggesting a mild burden of physical symptoms across participants.

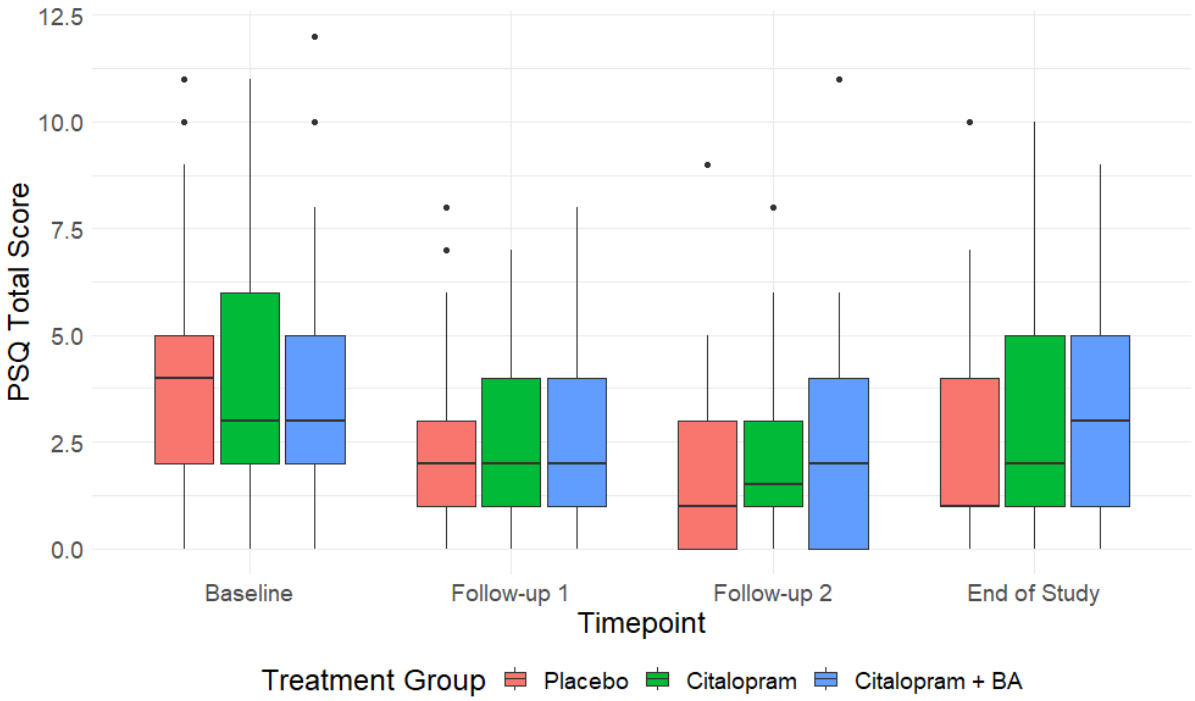


Figure 3.8. Quartile distribution of Physical Symptom Questionnaire (PSQ) scores by timepoint and treatment group

The time course of physical symptoms across the four study assessments separated by treatment group and the specific symptom assessed is presented in Figure 3.9. There were high initial reports of anxiety and, to a lesser extent, agitation at the Baseline assessment, followed by a subsequent decline. Additionally, the two active treatment groups reported higher levels of nausea, dizziness, and dry mouth compared to the Placebo group from Follow-up 1 through to the End of Study assessment. However, these differences appear relatively small, and average ratings for these symptoms remained minimal.

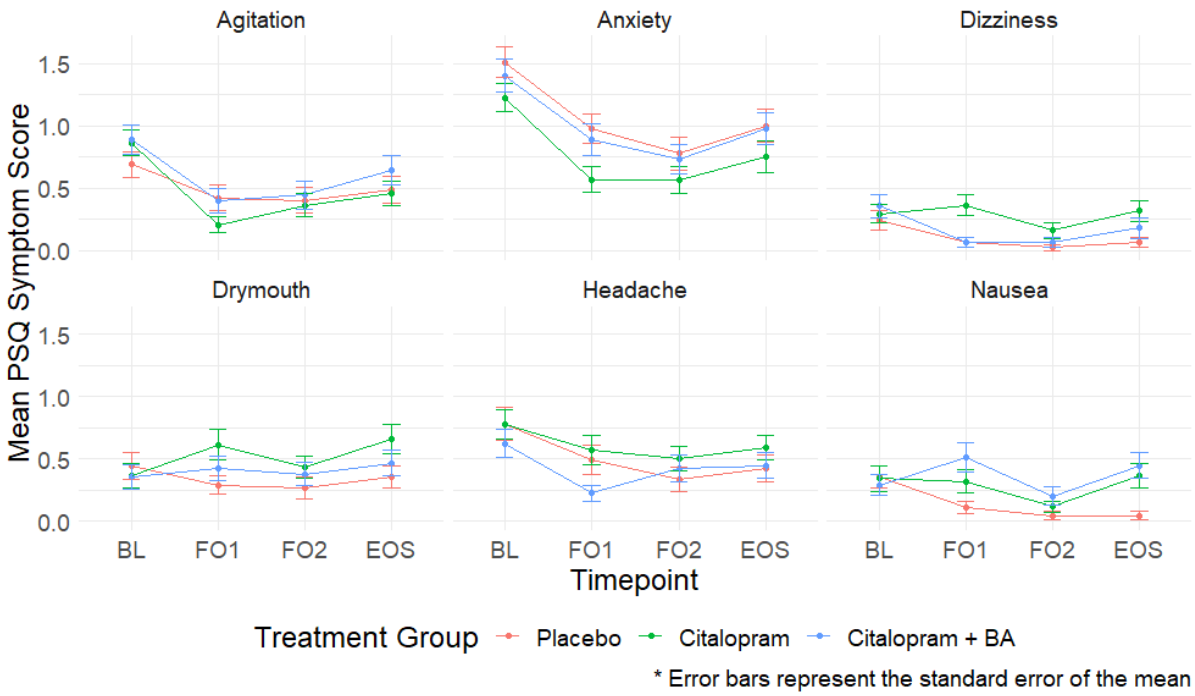


Figure 3.9. Physical Symptom Questionnaire (PSQ) scores by timepoint and treatment group. BL = Baseline assessment, FO1 = Follow-up 1, FO2 = Follow-up 2, EOS = End of Study assessment

3.5.5.1 All-group comparison

There were no significant differences between the three treatment groups at any of the four timepoints (all $p > 0.221$), indicating that the distribution of physical symptom scores was similar across the groups.

3.6 Discussion

The present study succeeded in recruiting a large community sample of individuals with self-reported low mood and activity levels. The three treatment groups were well-matched in terms of demographic and lifestyle factors, which lends scientific integrity to the between-group comparisons reported. However, it is also important to consider the extent to which the sample recruited is representative of the broader population.

Firstly, 63.4% of participants reported being born female, and 62.6% identified with the female gender. The 60:40 female-to-male split is reflective of the general use of psychological therapy services in the UK (Office for National Statistics, 2022), and may also

reflect gender differences in the prevalence of depressive disorders (Albert, 2015; Bromet et al., 2011; Salk et al., 2017). While predominantly female samples are not unusual in psychiatric research, understanding the mechanisms of treatment action across sexes and genders remains of great importance, as sex differences in antidepressant response have been noted (Khan et al., 2005; LeGates et al., 2019). Although our study did not specifically investigate sex differences in treatment response, a strength is the equal distribution of sexes and genders across all three treatment groups, achieved through stratifying our randomisation code.

Secondly, 68% of participants were white, with 32% belonging to diverse ethnic backgrounds. The CABIN sample accurately reflects the ethnicity make-up in the Southeast of England, where most participants were recruited from: 7% Asian, 2.4% Black, 2.8% Mixed Race, 78.8% White British, 7.5% White Other, 1.5% Other Ethnic Group. It is also representative of the ethnic group distribution in England and Wales as a whole: 9.3% Asian, 4% Black, 2.9% Mixed Race, 74.4% White British, 7.4% White Other, 2.2% Other Ethnic Group (Office for National Statistics, 2021).

Education and income levels, however, were higher in our sample than at national level; 76% of participants reported a household income near to or above the 2022 national median of £32,300 (Office for National Statistics, 2023a). Moreover, 77.6% of participants had achieved a bachelor's degree or above, compared to 33.8% of the UK population at the time of the last Census (Office for National Statistics, 2023b). Participants were specifically selected to exclude those with comorbidities outside depression and anxiety disorders, were generally in good health and, outside self-identifying as physically inactive, did not endorse harmful habits. The majority of participants did not smoke and averaged below the National Health Service (NHS) recommended maximum of 14 units of alcohol per week in all treatment groups (National Health Service, 2022). Participants' average body mass index (BMI) was slightly below the 2021 UK national average of 27.4 (NHS England Digital, 2022). A higher socioeconomic standing has been linked to more favourable outcomes in

depression treatment with both SSRIs and psychological therapy (Finegan et al., 2018; Jakubovski & Bloch, 2014), which makes our findings difficult to generalise to more disadvantaged populations. More effort needs to be made to address current inequalities in mental health care for people with depression and anxiety (Gilburt & Mallorie, 2024; Hodgson et al., 2020).

In terms of clinical presentation, participants in the CABIN study experienced self-reported mild-to-moderate depression at Baseline; 34.6% of participants had BDI-II scores that fell into the "mild" depression category (<19) and 32.3% had BDI-II scores that fell into the "moderate" depression category (<30). It is further suggested by our trait and state anxiety data that the majority of participants also had high levels of anxiety; 70.3% participants had Baseline STAI-S scores which would be classified as "high" anxiety (>45), and trait anxiety scores for the sample matched those previously reported in clinical populations (Kennedy et al., 2001). This is something to keep in mind as the results of the present study are discussed; while SSRIs and behavioural activation are frontline treatments for major depression, they have also demonstrated efficacy in anxiety disorders (Baldwin et al., 2014; Carl et al., 2020; Hopko et al., 2016) and mechanistic explanations of SSRI function may be similar across both disorders (Di Simplicio et al., 2014).

Although previous research with online behavioural activation (Ruzickova et al., 2023) suggested that the two-week intervention might not be long enough to impact clinical symptoms, we assessed mood and anxiety outcomes to see if the interaction of pharmacological and psychological treatments could accelerate clinical effects. No significant differences in clinical symptoms (depression/anxiety) were observed between the three treatment groups at End of Study assessment, suggesting that the combined intervention did not result in accelerated improvements within this short timeframe. This may be due to the relatively short duration of both the citalopram and the behavioural activation interventions, which were likely insufficient to meaningfully impact self-reported clinical outcomes. Nevertheless, all three treatment groups showed significant improvements in

depression and anxiety scores from the start to the end of the two-week intervention, though no changes were seen between Screening and Baseline assessment. This improvement could be partly attributed to placebo/expectation effects, which are commonly observed in antidepressant studies, particularly in samples with mild-to-moderate depression (Kirsch et al., 2008; Rief et al., 2009).

Interestingly, meta-analyses indirectly comparing the effects of psychological therapy with those of pill placebos have similarly found smaller differences in favour of the active treatment, as opposed to comparisons to no-treatment or waitlist controls (Cuijpers et al., 2014; Prioleau et al., 1983). Furthermore, in the CABIN study, the frequency of participant-experimenter contact was standardised between treatments, the only difference being increased contact *duration* for the Citalopram + BA group. As frequency and intensity of interaction between patient and therapist are well-known factors determining the efficacy of psychotherapy (Erekson et al., 2015), the observed improvements may reflect psychological and contextual factors, including participant expectations and therapeutic contact, which contribute to perceived mental health benefits.

Our hypothesis that the behavioural activation intervention might affect reward-specific self-assessments such as the Behavioural Activation for Depression Scale or Environmental Reward Observation Scale is not supported by the data. There are several possible explanations for these results; while the length of the BA protocol in this study was informed by previous research showing positive discrimination between a BA and control group after two weeks of online sessions (Ruzickova et al., 2023), it is still much shorter than the 8-16 regular sessions recommended by the National Institute of Care Excellence (NICE) guidelines for clinical practice (National Institute for Health and Care Excellence, 2022). As BA relies on an iterative process of goal setting and troubleshooting, it could be that our short protocol succeeded in helping participants develop an awareness of current behaviours affecting their mood but did not allow sufficient time for consistently implementing practical changes to these. The fact that the CABIN study took place at the tail-end of the

COVID-19 pandemic is also noteworthy, as it followed a period of significant disruption to daily routines (Appleby et al., 2022; Li et al., 2023) which could have posed further obstacles to goals set during BA therapy.

A last consideration is that participants in the Citalopram + BA group may have been more unwell than participants in the Citalopram only group, as evidenced by their higher BDI-II and STAI-S scores and lower BADS scores across timepoints. Although a recent meta-analysis found no evidence that baseline severity moderates the effects of either pharmacotherapy or psychotherapy (Tröger et al., 2024), other studies have linked more severe symptoms to both better and poorer treatment outcomes (Chekroud et al., 2016; Driessen et al., 2010; Fournier et al., 2010). In light of this, we decided to control for Baseline depression severity in all our subsequent analyses, and this remains an important consideration as biomarkers of treatment response are discussed in the following chapters.

In terms of side effects, citalopram was well-tolerated, with post-Baseline average SEQ symptom scores in the two active groups ranging from 0.19 for dizziness to 0.75 for anxiety out of a maximum of 3. It is likely the higher levels of side effects reported at Baseline assessment were largely driven by participants' reports of anxiety (and, to a lesser extent, agitation) as this was a relatively high-anxious sample. Nevertheless, the lack of a difference between treatment groups at any timepoint suggest the relative uniformity of these experiences across the whole sample.

In summary, we recruited a large community sample with low mood and activity levels, well-matched in demographic and lifestyle factors. Our sample was predominantly female (63.4%) and white (68%), with higher education and income levels compared to the general UK population. The majority of participants reported mild-to-moderate depression and high anxiety at baseline. No differences in depression and anxiety symptoms were observed between the treatment groups at the end of the two-week intervention, though all groups showed significant improvement, possibly due to placebo/expectation effects. Contrary to

hypotheses, the Citalopram + BA group did not show a distinct advantage in reward-specific assessments. The brief duration of the BA protocol may have been insufficient for significant behavioural changes, particularly in the context of post-pandemic disruptions to daily routines. This is an experimental medicine study with exploratory clinical outcomes; however, these results are important context for the interpretation of the cognitive and physiological outcome measures presented in subsequent chapters.

4 CHAPTER 4: THE EFFECTS OF A BEHAVIOURAL ACTIVATION-ENRICHED SSRI INTERVENTION ON EMOTIONAL PROCESSING

4.1 INTRODUCTION

The cognitive neuropsychological model of antidepressant drug action suggests that selective serotonin reuptake inhibitors (SSRIs) facilitate the gradual remission of depressive symptoms by reducing non-conscious negative biases in information processing (Godlewska & Harmer, 2021; Harmer, Goodwin, et al., 2009; Harmer & Cowen, 2013). This is supported by a wealth of evidence from experimental medicine studies over the past 15-20 years, which have demonstrated that SSRIs produce early effects on emotional cognition in both healthy and depressed individuals. These effects, which precede significant clinical changes in depressive symptoms, often manifest as a reduction in negative biases in emotional processing (attention, memory, categorisation) and an increase in the accuracy and speed of processing positive stimuli (Di Simplicio et al., 2014; Harmer et al., 2004; Murphy, Norbury, et al., 2009; Tranter et al., 2009; Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018). This is important because negative processing biases are thought to play a crucial role in maintaining depressive symptoms, and positive changes in these biases have been predictive of later clinical improvement (Browning et al., 2019; Shiroma et al., 2014). The transition from implicit cognitive changes to explicit mood improvements is believed to occur through interaction with one's environment and the re-learning of positive action-outcome associations (Godlewska & Harmer, 2021). Thus, the cognitive neuropsychological model suggests that the therapeutic effects of SSRIs may be enhanced by environmental enrichment or targeted psychological treatments. The purported vehicle for change is a feedback loop through which emotional biases initially induced by the antidepressant facilitate positive environmental interaction, which might in turn accentuate these biases before ultimately translating into a change in mood.

While formal studies in humans are lacking, indirect evidence from both human and animal studies supports a role for the environment in affecting antidepressant treatment outcomes at both clinical and pre-clinical levels. In humans, higher socioeconomic status correlates with better antidepressant treatment response (Cohen et al., 2009), with factors such as employment, education, insurance security, and social support also influencing antidepressant efficacy (Chiarotti et al., 2017; Shiroma et al., 2014). In rodent models, there is experimental evidence to suggest that the positive effects of fluoxetine on brain plasticity (e.g., increased BDNF levels), stress reduction, and anhedonia occur only in enriched environments (Branchi et al., 2013). Nevertheless, the hypothesis that a patient's living environment affects antidepressant therapy outcomes has not been explicitly tested in humans.

In the CABIN study, we aimed to experimentally enrich participants' environments through adjunct psychological therapy while administering the SSRI citalopram. We selected behavioural activation (BA) as a proxy for environmental enrichment due to its strong evidence base and its association with having increased rewarding experiences (Dimidjian et al., 2017). We hypothesised that BA-enhanced antidepressant administration will facilitate early changes in emotional processing as measured by the Emotional Task Battery (ETB) compared to the antidepressant alone after two weeks of treatment.

Based on previous research utilising the ETB, we hypothesised that two weeks of BA-enhanced citalopram treatment, compared with citalopram alone, would be associated with:

- Higher recognition accuracy for positive vs negative facial expressions on the Facial Expression Recognition Task (FERT) – this served as our key measure of emotional processing in the context of this chapter.
- Lower reaction times when correctly identifying positive vs negative facial expressions on the Facial Expression Recognition Task (FERT).

- Lower reaction times when correctly categorising positive vs negative personality descriptor words on the Emotional Categorisation Task (ECAT).
- A higher number of positive vs negative personality descriptor words correctly recalled on the Emotional Recall task (EREC).
- A higher number of positive vs negative intrusions (personality descriptor words falsely recalled which were not part of the original word categorisation task) made on the Emotional Recall task (EREC).
- Higher recognition accuracy for positive vs negative familiar personality descriptor words on the Emotional Recognition Memory task (EMEM).
- Lower reaction times when correctly recognising positive vs negative familiar personality descriptor words on the Emotional Recognition Memory task (EMEM).

4.2 METHODS

4.2.1 Tasks and variables

Participants randomised to either two weeks of placebo, citalopram, or citalopram + behavioural activation completed the ETB (Harmer et al., 2004; Harmer, O'Sullivan, et al., 2009; Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018) online via Gorilla Experiment Builder at both Baseline and End of Study assessments. The ETB is comprised of four computerised tasks measuring facial expression recognition (FERT), emotional categorisation (ECAT) and emotional memory (EREC, EMEM). The four tasks are described in detail in Chapter 2. The task order was: FERT, ECAT, EREC, EMEM and did not vary across participants.

For most ETB tasks, the endpoints analysed corresponded to (percentage) accuracy and reaction times for positive/negative items. On the FERT and EREC, we were interested not only in participants' accuracy but also the patterns of mistakes they made on the tasks, and so we also analysed incorrect responses (misclassifications and intrusions).

For the FERT task, we additionally computed the unbiased hit rate (UBHR) for each facial expression and each participant. The UBHR is a measure of identification accuracy which adjusts for response bias, i.e. any tendency participants might have to overuse or underuse particular available categories (Wagner, 1993). In simpler terms, the UBHR penalises participants who might have a bias towards labelling a certain category (e.g., happy facial expressions) more than it is present in the stimuli, giving a more truthful representation of their ability to accurately recognise facial expressions. The UBHR is calculated by dividing the squared number of correct identifications of a category (also called "hits") by the total number of presentations of said category multiplied by the number of times the category was (correctly or incorrectly) chosen by the participant:

$$UBHR = \frac{H^2}{(H + M)\ x\ (H + FA)}$$

Where:

- $Hits\ (H)$ are correct identifications of the target category (e.g., correctly recognising a "happy" facial expression when it is truly "happy")
- $Misses\ (M)$ are misses where the target category was present but not identified as such (e.g., failing to recognise "happy" when the facial expression is "happy")
- $False\ Alarms\ (FA)$ are incorrect identifications of the target category (e.g., identifying "happy" when the face presented is another facial expression).

4.2.2 Sample

All 134 participants completed both online assessments, however some had to be excluded from individual task analyses due to very poor performance or misunderstanding task requirements. Our criteria for participant exclusion are described in more detail in Chapter 2; still, analysis sample sizes remained sufficiently large, with a complete dataset for the FERT, 133 data points for the ECAT, 131 for the EREC and 125 for the EMEM tasks. The sample breakdown by treatment group for each ETB task is presented in table 4.1.

Table 4.1. Sample breakdown by treatment group for each of the four Emotional Task Battery (ETB) tasks

Task	N Placebo	N Citalopram	N Citalopram + BA
FERT	45	44	45
ECAT	45	44	44
EREC	45	43	43
EMEM	45	39	41

4.2.3 Analysis of ETB data

For each task, the End of Study (EOS) assessment endpoints described in Table 3 (Chapter 2) were each entered as dependent variables (DVs) into separate analyses of covariance (ANCOVA). Treatment group (Placebo vs Citalopram or Citalopram vs Citalopram + BA) was used as the between-subjects factor and emotion/valence as the within-subjects factor, with word familiarity included as an additional within-subjects factor for the EMEM task. The corresponding task endpoints and BDI-II scores at Baseline assessment were included as covariates in all analysis models.

For each ETB task, sensitivity analyses were conducted to further exclude participants who reported technical difficulties or had timeouts affecting more than 25% of the task. Specifically, in these sensitivity analyses:

- ECAT: one participant's EOS assessment data was excluded
- FERT: four participants' EOS assessment data were excluded
- EREC: no sensitivity analyses were planned
- EMEM: no sensitivity analyses were planned.

As changes in emotional processing bias are central to the neuropsychological model of antidepressant drug action, we also explored timepoint-related changes in our task endpoints in this chapter, to check whether these mirror clinical findings discussed in Chapter 3. These analysis models used for this purpose were identical to the ones described above, except for the fact that they included timepoint (Baseline, End of Study) as an additional specified factor, instead of Baseline scores being included as a covariate.

4.3 Results – Facial expression recognition task (FERT)

4.3.1 Facial expression recognition accuracy by valence

The mean percentage accuracy for identifying positive (happiness, surprise) and negative (sadness, fear, anger, disgust) facial expressions on the FERT at Baseline and EOS assessment is illustrated in Figure 4.1, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

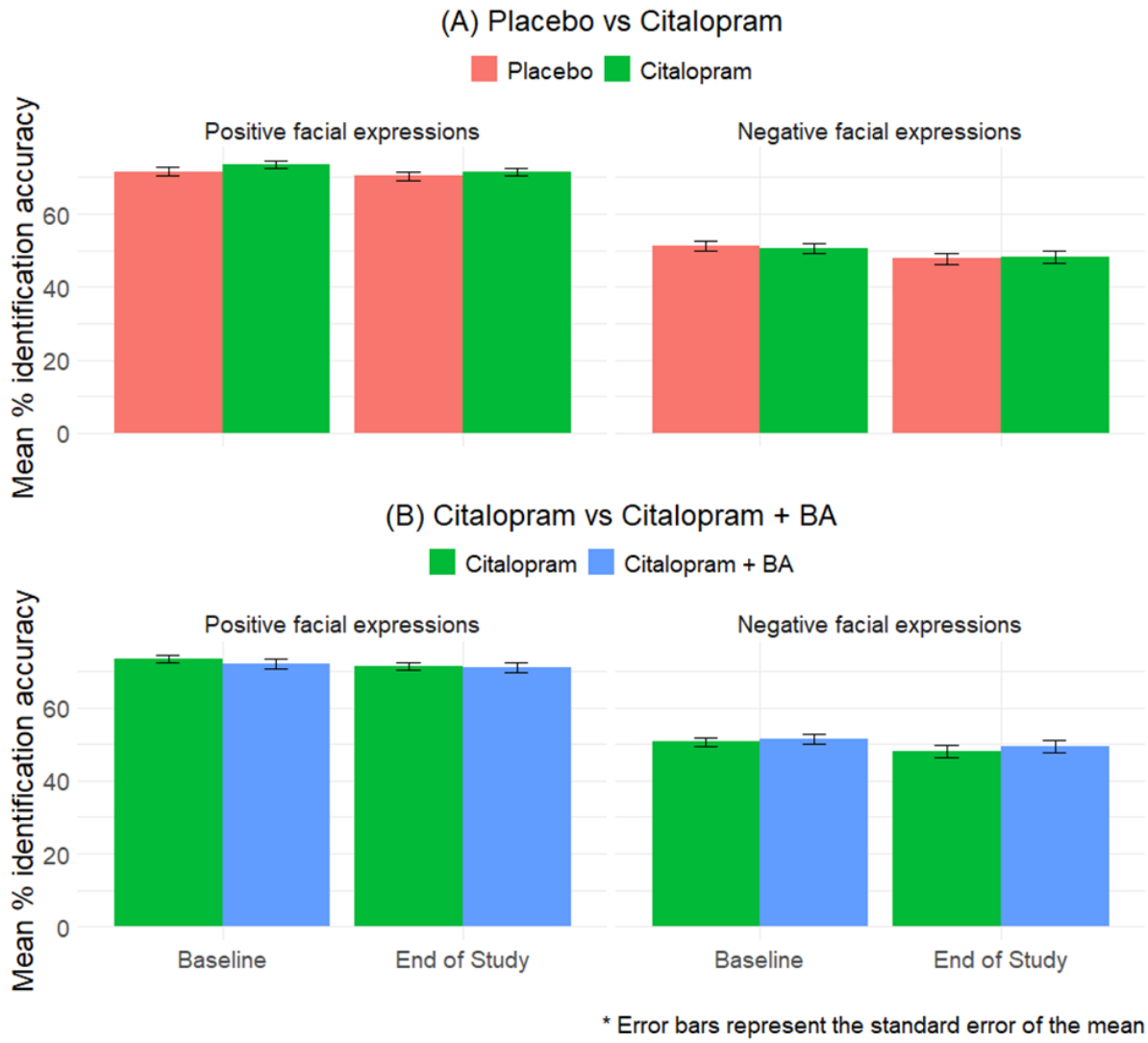


Figure 4.1. Mean percentage identification accuracy for positive and negative facial expressions on the Facial Expression Recognition Task (FERT) at Baseline and End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

4.3.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on facial expression recognition accuracy at EOS assessment ($F(1, 78.13) = 0.15$, $p = 0.700$), nor a significant treatment group and valence interaction ($F(1, 79.92) = 0.58$, $p = 0.449$). The main effect of facial expression valence was statistically significant ($F(1, 160.94) = 11.36$, $p < 0.001$), with positive facial expressions (model-adjusted mean accuracy = 62.1%, SE = 0.96, 95% CI: 60.2% to 64.0%) recognised more accurately than negative facial expressions (model-adjusted mean accuracy = 56.8%, SE = 0.96, 95% CI: 54.9% to 58.7%) across both treatment groups.

4.3.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on facial expression recognition accuracy at EOS assessment ($F(1, 79.71) = 0.14$, $p = 0.712$), nor a significant treatment group and valence interaction ($F(1, 81.19) = 0.0003$, $p = 0.986$). The main effect of facial expression valence was statistically significant ($F(1, 153.67) = 16.40$, $p < 0.001$). As before, positive facial expressions (model-adjusted mean accuracy = 63.3%, SE = 1.02, 95% CI: 61.3% to 65.3%) were recognised with higher accuracy than negative facial expressions (model-adjusted mean accuracy = 54.7%, SE = 1.02, 95% CI: 54.7% to 58.7%) across both treatment groups.

4.3.2 Facial expression recognition accuracy by emotion

The mean percentage accuracy for identifying each facial expression on the FERT at Baseline and EOS assessment is illustrated in Figure 4.2, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

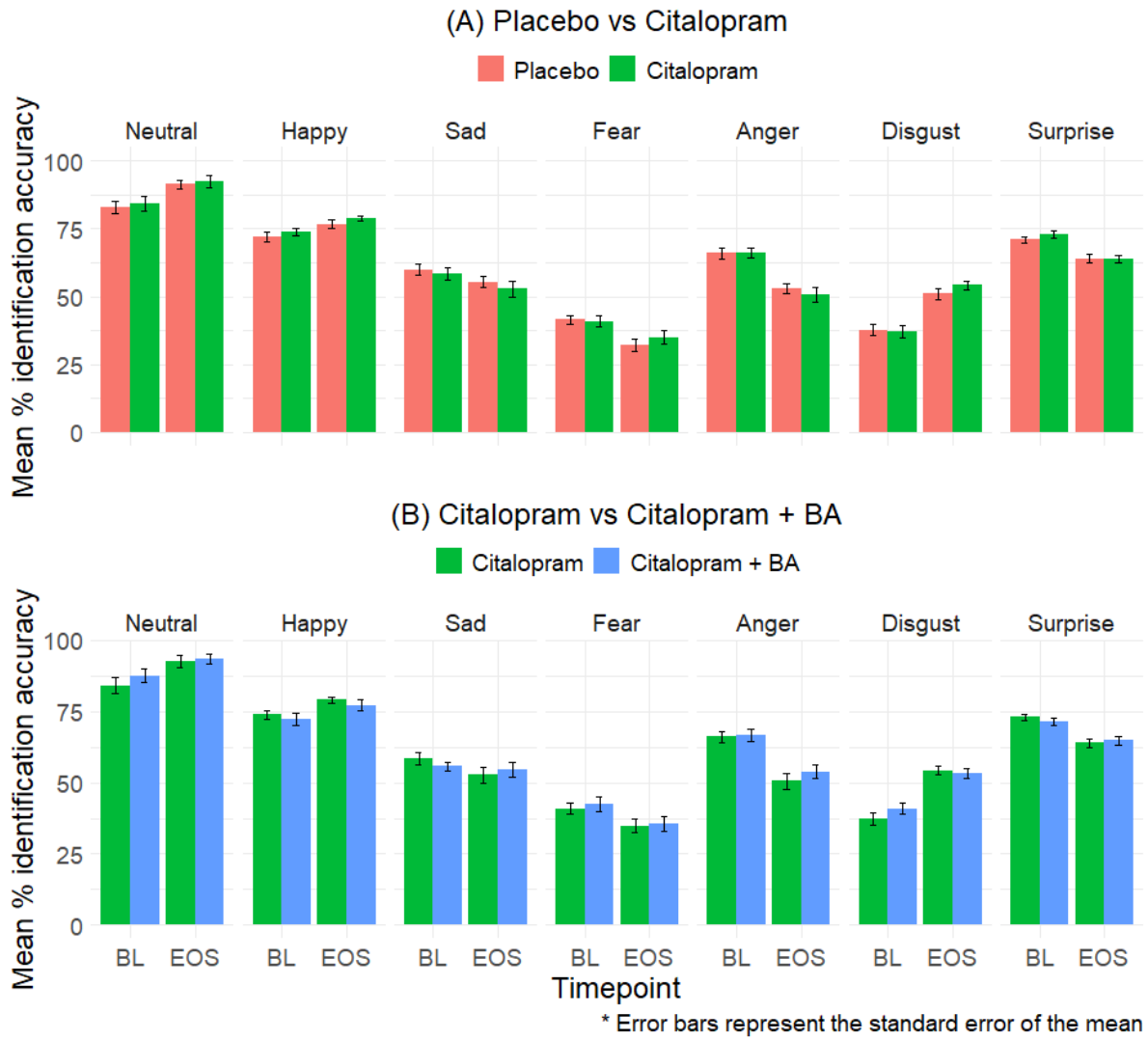


Figure 4.2. Mean percentage identification accuracy for each facial expression on the Facial Expression Recognition Task (FERT) at Baseline and End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.3.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on facial expression recognition accuracy at EOS assessment ($F(1, 81.85) = 0.36$, $p = 0.552$), nor a significant treatment group and emotion interaction ($F(6, 516.94) = 1.24$, $p = 0.282$). The main effect of emotion was statistically significant ($F(6, 526.51) = 114.05$, $p < 0.001$), indicating recognition accuracy rates differed for the seven different expressions. Neutral facial expressions were best identified (model-adjusted mean accuracy = 80.2%, SE = 1.36, 95% CI: 77.6% to 82.9%), while fearful facial expressions were worst recognised (model-adjusted mean accuracy = 44.6%, SE = 1.34, 95% CI: 42.0% to 47.2%) across both treatment groups.

4.3.2.2 Citalopram vs Citalopram + BA comparison

We did we did not observe a significant main effect of treatment group on facial expression recognition accuracy at EOS assessment ($F(1, 83.12) = 0.01$, $p = 0.912$), nor a significant treatment group and emotion interaction ($F(6, 518.46) = 1.11$, $p = 0.355$). The main effect of emotion was statistically significant ($F(6, 528.77) = 87.19$, $p < 0.001$), indicating recognition accuracy rates differed for the seven different expressions. As before, neutral facial expressions were best identified (model-adjusted mean accuracy = 79.7%, SE = 1.48, 95% CI: 76.8% to 82.6%), while fearful facial expressions were worst recognised (model-adjusted mean accuracy = 46.8%, SE = 1.43, 95% CI: 44.0% to 49.6%) across both treatment groups.

4.3.3 Unbiased hit rate

The mean Unbiased Hit Rate (UBHR) for each facial expression at Baseline and EOS assessment is illustrated in Figure 4.3, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

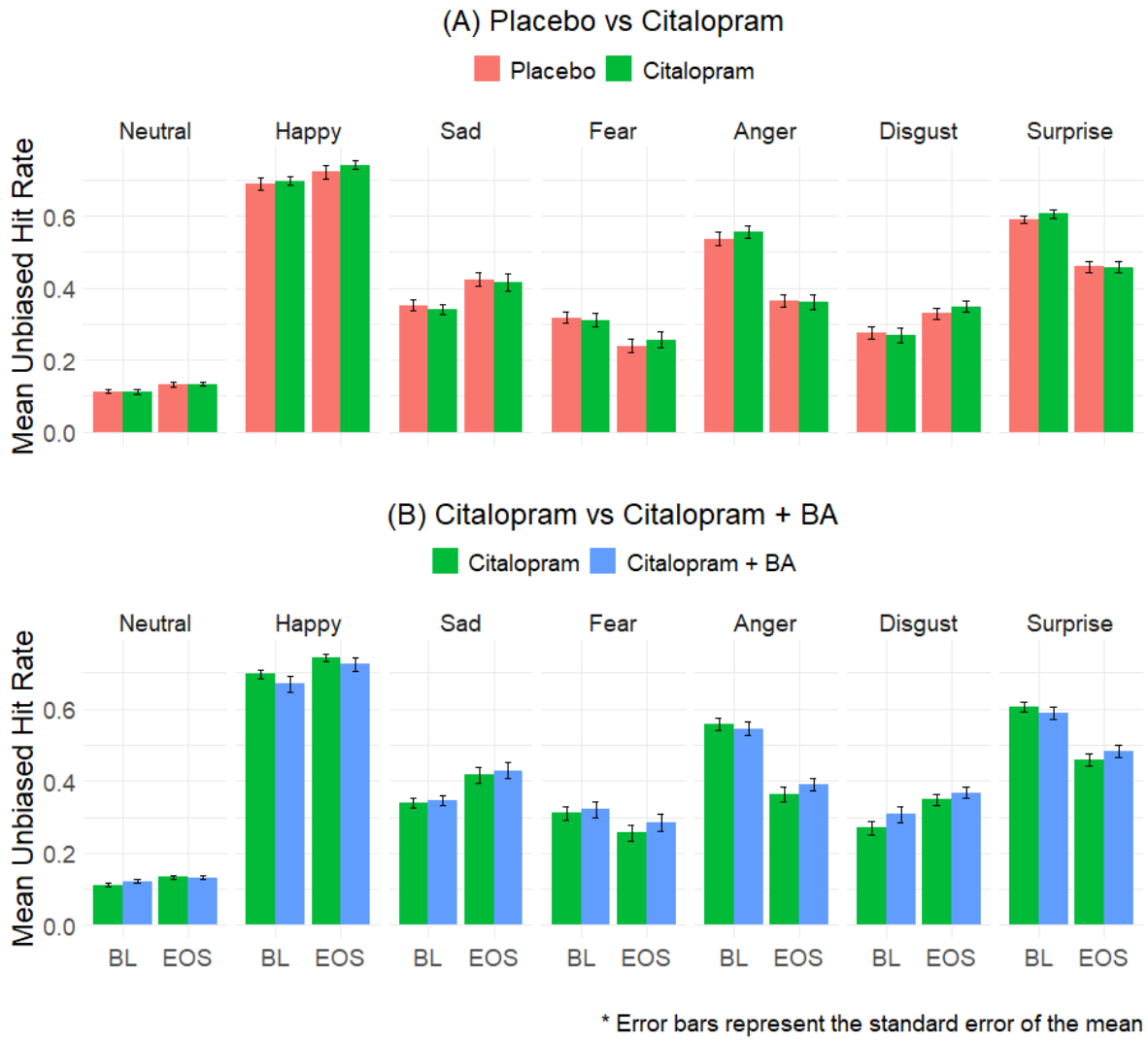


Figure 4.3. Mean Unbiased Hit Rate (UBHR) for each facial expression on the Facial Expression Recognition Task (FERT) at Baseline and End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.3.3.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on unbiased hit rates at EOS assessment ($F(1, 77.91) = 0.31$, $p = 0.580$), nor a significant treatment group and emotion interaction ($F(6, 512.67) = 0.60$, $p = 0.733$). The main effect of emotion was statistically significant ($F(6, 530.78) = 134.36$, $p < 0.001$), indicating unbiased hit rates varied for the different emotions. Happy facial expressions had the highest unbiased hit rates (model-adjusted mean UBHR = 0.62, SE = 0.02, 95% CI: 0.59 to 0.65), while neutral facial expressions had the lowest unbiased hit rates (model-adjusted mean UBHR = 0.25, SE = 0.02, 95% CI: 0.22 to 0.29) across the two treatment groups.

4.3.3.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on unbiased hit rates at EOS assessment ($F(1, 79.47) = 0.52$, $p = 0.475$), nor a significant treatment group and emotion interaction ($F(6, 513.75) = 0.78$, $p = 0.584$). The main effect of emotion was statistically significant ($F(6, 531.27) = 116.52$, $p < 0.001$), indicating unbiased hit rates varied for the different emotions. As before, happy facial expressions had the highest unbiased hit rates (model-adjusted mean UBHR = 0.63, SE = 0.02, 95% CI: 0.60 to 0.66), while neutral facial expressions had the lowest unbiased hit rates (model-adjusted mean UBHR = 0.25, SE = 0.02, 95% CI: 0.22 to 0.28) across the two treatment groups.

4.3.4 Misclassifications by emotion

The mean number of misclassifications (the number of times an emotion was identified without being present, i.e., a false positive) of each emotion made on the FERT at Baseline and EOS assessment is illustrated in Figure 4.4, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

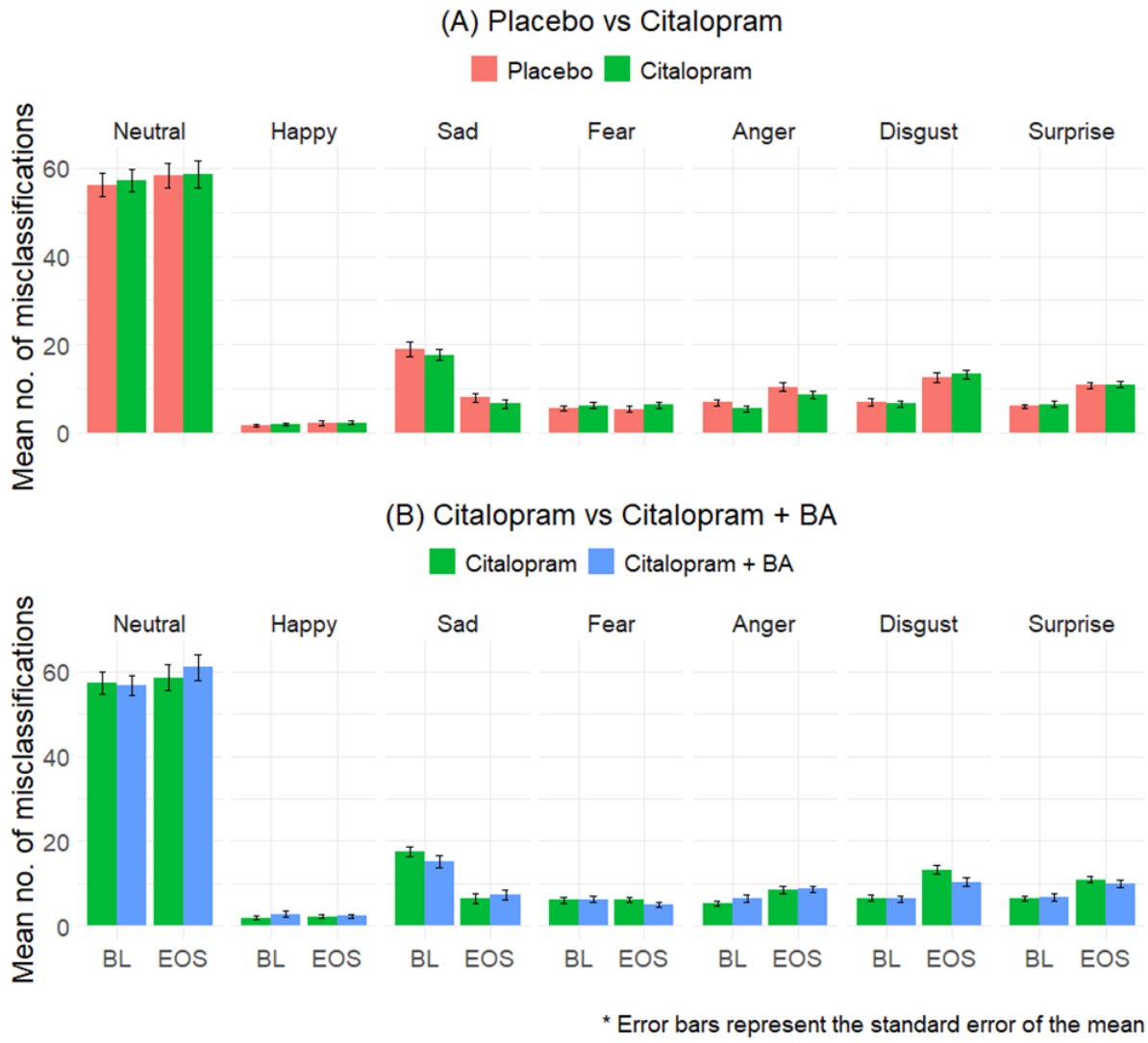


Figure 4.4. Mean number of misclassifications of each facial expression on the Facial Expression Recognition Task (FERT) at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.3.4.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on misclassifications made at EOS assessment ($F(1, 607) = 0.08$, $p = 0.777$), nor a significant treatment group and emotion interaction ($F(6, 607) = 0.20$, $p = 0.977$). The main effect of emotion was statistically significant ($F(6, 607) = 817.82$, $p < 0.001$), indicating that participants mislabelled some emotions more frequently than others. Participants mistakenly assigned the label “neutral” most often (model-adjusted mean no. misclassifications = 27.16, SE = 1.47, 95% CI: 24.28

to 30.05) and the label “sad” least often (model-adjusted mean no. misclassifications = 4.43, SE = 0.69, 95% CI: 3.08 to 5.78) across both treatment groups.

4.3.4.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on misclassifications made at EOS assessment ($F(1, 607) = 0.21$, $p = 0.646$), nor a significant treatment group and emotion interaction ($F(6, 607) = 1.85$, $p = 0.09$). The main effect of emotion was statistically significant ($F(6, 607) = 702.69$, $p < 0.001$), indicating that participants mislabelled some emotions more frequently than others. As before, participants mistakenly assigned the label “neutral” most often (model-adjusted mean no. misclassifications = 29.04, SE = 1.74, 95% CI: 25.62 to 32.46) and the label “sad” least often (model-adjusted mean no. misclassifications = 5.43, SE = 0.75, 95% CI: 3.95 to 6.92) across both treatment groups.

4.3.5 Reaction times for correct responses by emotion

The mean reaction times for correctly identifying each facial expression on the FERT at Baseline and EOS assessment are illustrated in Figure 4.5, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

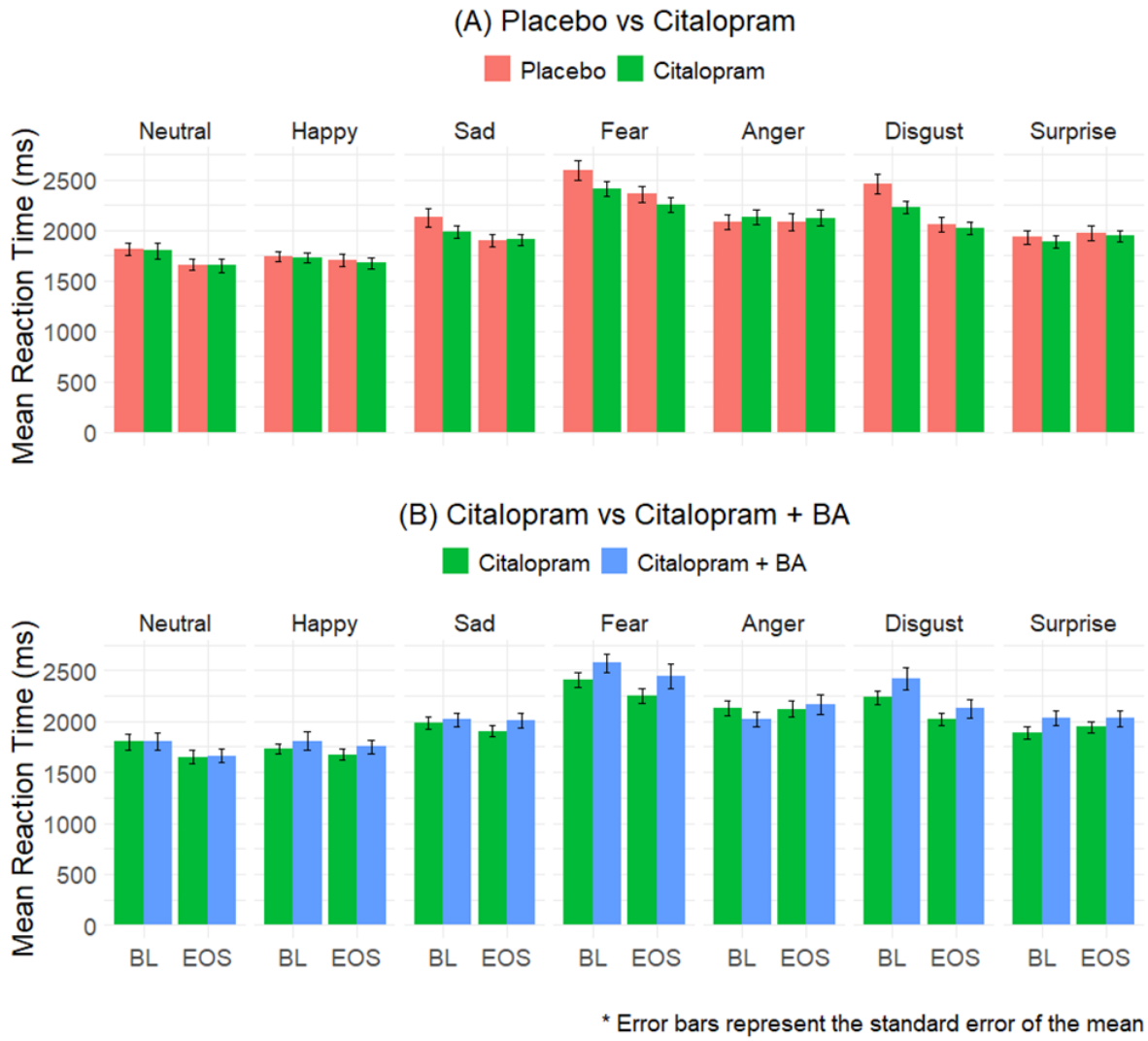


Figure 4.5. Mean reaction times (in milliseconds) for correct identifications of each facial expression on the Facial Expression Recognition Task (FERT) at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.3.5.1 Placebo vs Citalopram comparison

We did not we did not observe a significant main effect of treatment group on reaction times for correct responses at EOS assessment ($F(1, 75.59) = 0.001$, $p = 0.975$), nor a significant treatment group and emotion interaction ($F(6, 510.26) = 0.42$, $p = 0.863$). The main effect of emotion was statistically significant ($F(6, 520.70) = 21.06$, $p < 0.001$), indicating reaction times differed for the seven different expressions. Participants were quickest to correctly identify neutral expressions (model-adjusted mean RT = 1735 ms, SE = 41.0, 95% CI: 1655 ms to 1816 ms), and slowest to correctly identify fearful expressions (model-adjusted mean RT = 2166 ms, SE = 42.8, 95% CI: 2082 ms to 2251 ms) across both treatment groups.

4.3.5.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on reaction times for correct responses at EOS assessment ($F(1, 77.27) = 1.04$, $p = 0.310$), nor a significant treatment group and emotion interaction ($F(6, 511.27) = 0.46$, $p = 0.841$). The main effect of emotion was statistically significant ($F(6, 520.29) = 19.63$, $p < 0.001$), indicating reaction times differed for the seven different expressions. As before, participants were quickest to correctly identify neutral expressions (model-adjusted mean RT = 1755 ms, SE = 44.8, 95% CI: 1666 ms to 1843 ms), and slowest to correctly identify fearful expressions (model-adjusted mean RT = 2181 ms, SE = 46.6, 95% CI: 2089 ms to 2273 ms) across both treatment groups.

4.3.6 Sensitivity analysis

The sensitivity analysis revealed the results to be robust, with no changes to the significance of treatment group effects and interactions, after excluding data from five participants experiencing internet outages (one at Baseline assessment and four at EOS assessment).

4.3.7 Timepoint analysis

When including timepoint as a factor in the analysis models, several findings emerged. For the UBHR measure, we observed significant interactions between timepoint and emotion. This was true for both the model comparing the Placebo and Citalopram groups ($F(6, 1131) = 67.01$, $p < 0.001$), as well as the model comparing the Citalopram and Citalopram + BA groups ($F(6, 1129.98) = 53.68$, $p < 0.001$). The three-way interaction between group, timepoint and emotion was not statistically significant in either model (Placebo vs Citalopram: $F(6, 1131) = 0.52$, $p = 0.797$; Citalopram vs Citalopram + BA: $F(6, 1129.98) = 0.68$, $p = 0.662$), indicating changes in expression recognition from pre- to post-treatment did not differ between treatment groups.

As illustrated in Figure 4.6, recognition of happy, sad and disgust expressions significantly improved, while recognition of anger, surprise, and fear decreased.

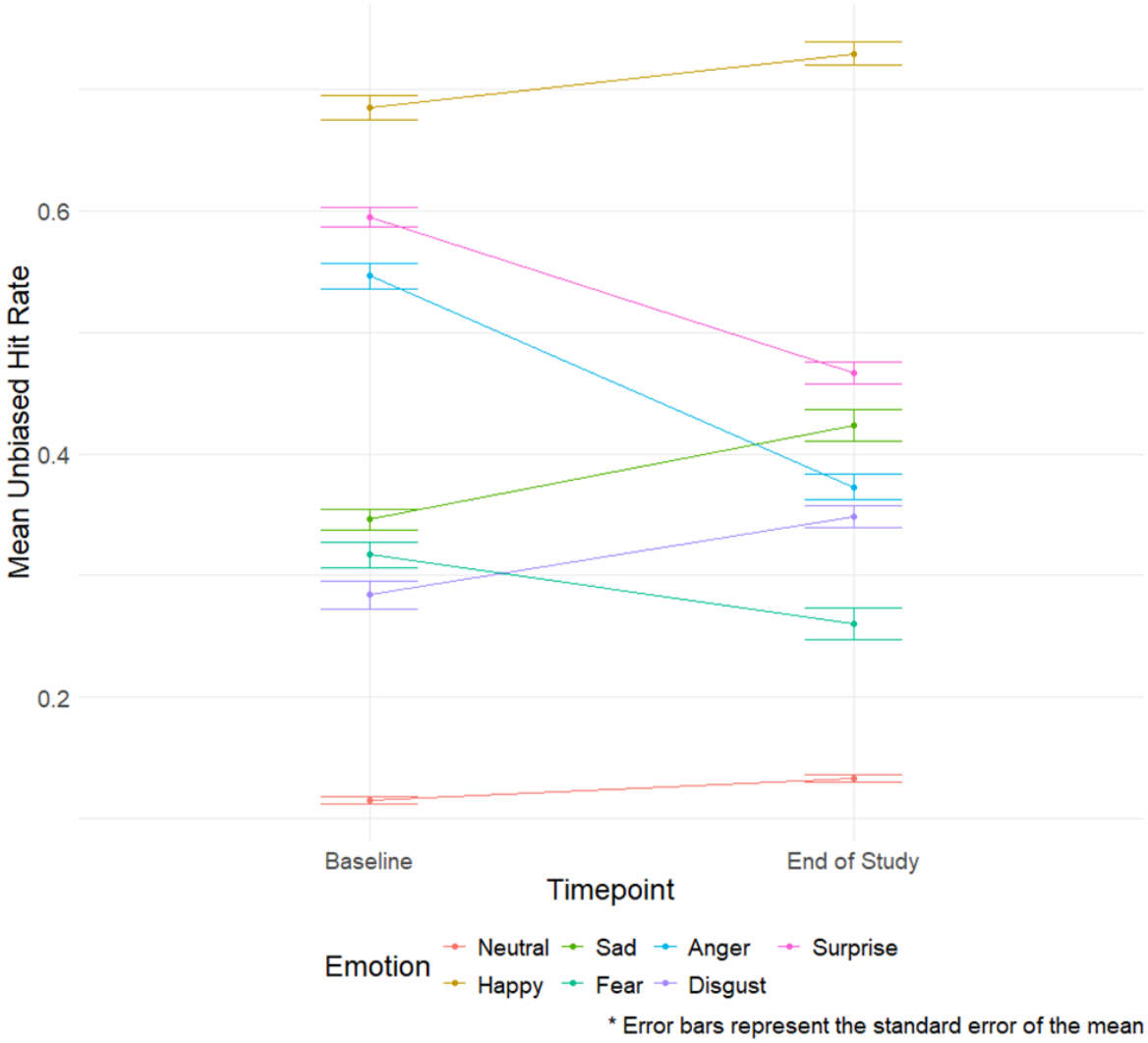


Figure 4.6. Changes in mean Unbiased Hit Rate (UBHR) for each facial expression on the Facial Expression Recognition Task (FERT) from Baseline to End of Study assessment, averaged across treatment groups

Similarly, we observed significant emotion and timepoint interactions for reaction times (Placebo vs Citalopram: $F(6, 1131) = 6.69$, $p < 0.001$; Citalopram vs Citalopram + BA: $F(6, 1130.02) = 4.89$, $p < 0.001$) and misclassifications (Placebo vs Citalopram: $F(6, 1131) = 19.52$, $p < 0.001$; Citalopram vs Citalopram + BA: $F(6, 1131) = 15.56$, $p < 0.001$), in the absence of significant three-way interactions with treatment group (for RT: Placebo vs Citalopram $F(6, 1131) = 0.77$, $p = 0.593$, Citalopram vs Citalopram + BA $F(6, 1130) = 0.63$, $p = 0.703$; for misclassifications: Placebo vs Citalopram $F(1, 1131) = 0.05$, $p = 0.999$, Citalopram vs Citalopram + BA $F(6, 1131) = 0.82$, $p = 0.554$).

Figure 4.7 illustrates changes in reaction times for correct identifications. RTs for correct identifications of most negative emotions were significantly faster at EOS assessment compared to Baseline (with the exception of angry expressions, and sad expressions when only considering the two active treatment groups), while RTs for correct identifications of positive expressions (happy and surprise) remained constant.

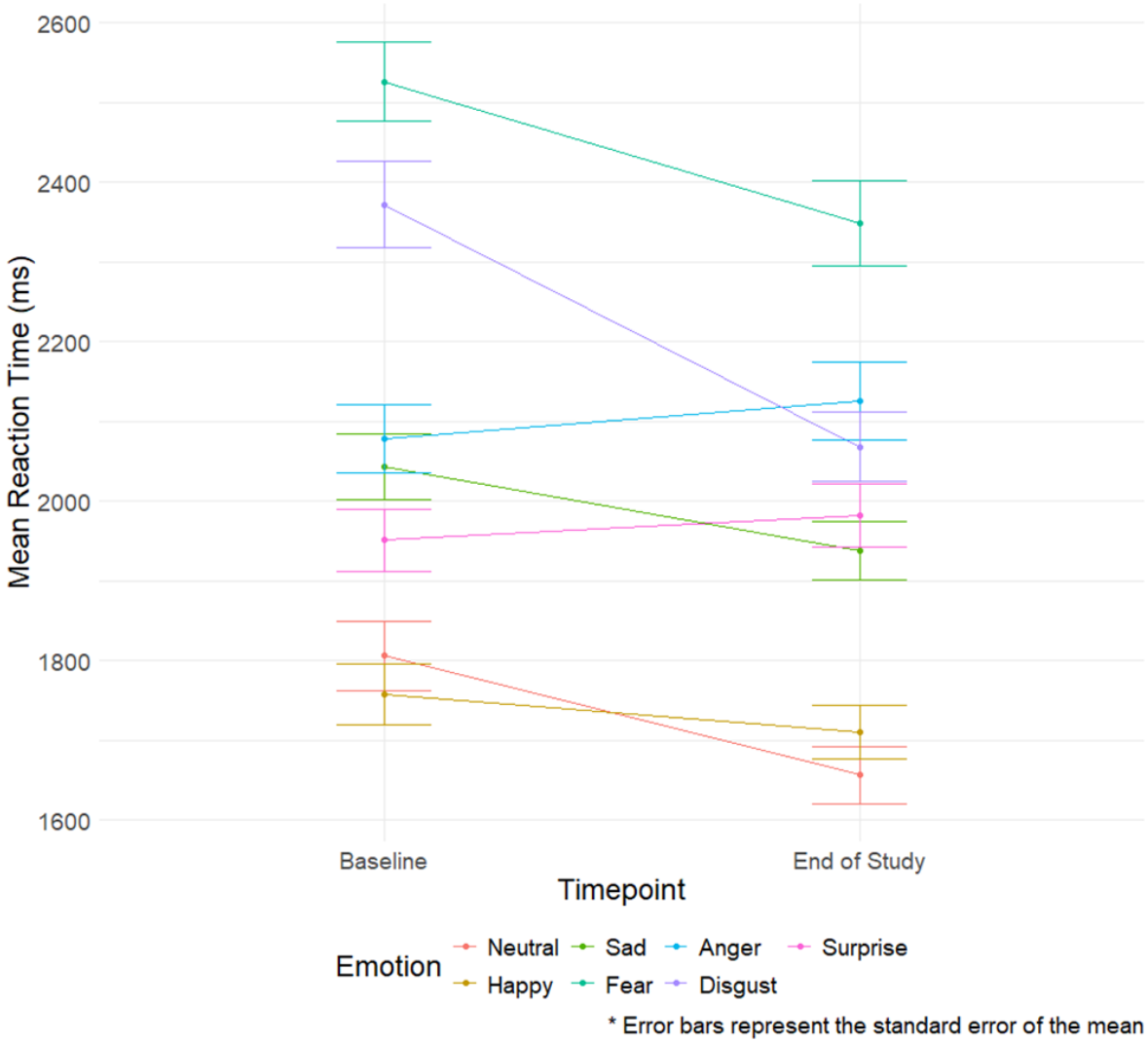


Figure 4.7. Changes in mean reaction times (in milliseconds) for correct identifications of each facial expression on the Facial Expression Recognition Task (FERT) from Baseline to End of Study assessment, averaged across treatment groups

Figure 4.8 illustrates changes in misclassifications. For both group comparisons, misclassifications of other emotions as disgust and surprise significantly increase between Baseline and End of Study assessments, and sad misclassifications decrease most dramatically.

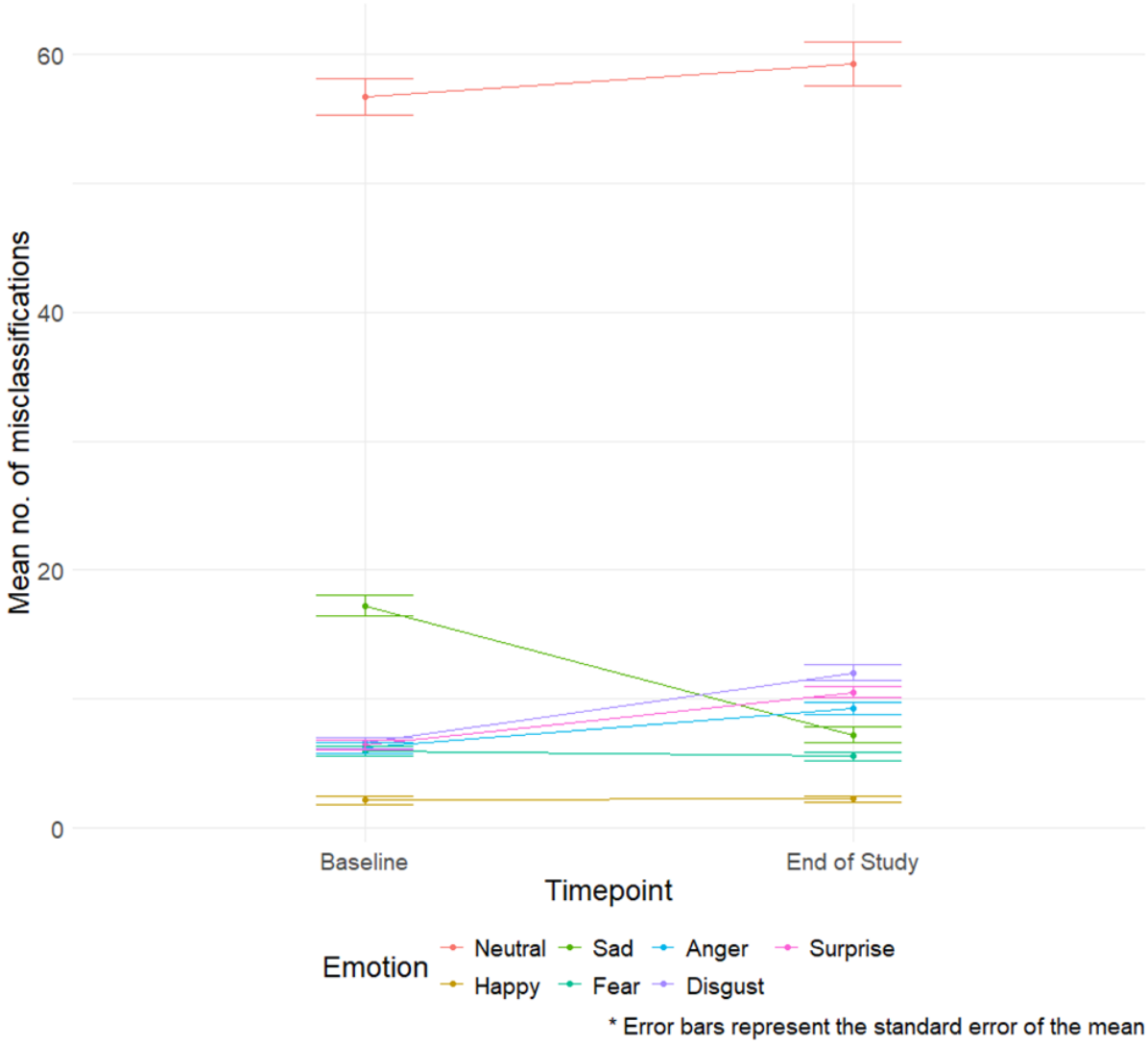


Figure 4.8. Changes in the mean number of misclassifications of each facial expression on the Facial Expression Recognition Task (FERT) from Baseline to End of Study assessment, averaged across treatment groups

4.4 Results – Emotional Categorisation Task (ECAT)

In line with expectations, we observed ceiling effects for positive/negative word categorisation accuracy on the ECAT, across both assessments (Mean accuracy = 95.52%, SE accuracy = 0.24). Participants were very good at indicating they would “like” being referred to as positive personality descriptors and “dislike” being referred to as negative personality descriptors.

4.4.1 Reaction times for correct responses

Mean reaction times for correct identifications of positive and negative personality descriptor words on the ECAT at Baseline and EOS assessment are illustrated in Figure 4.9, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

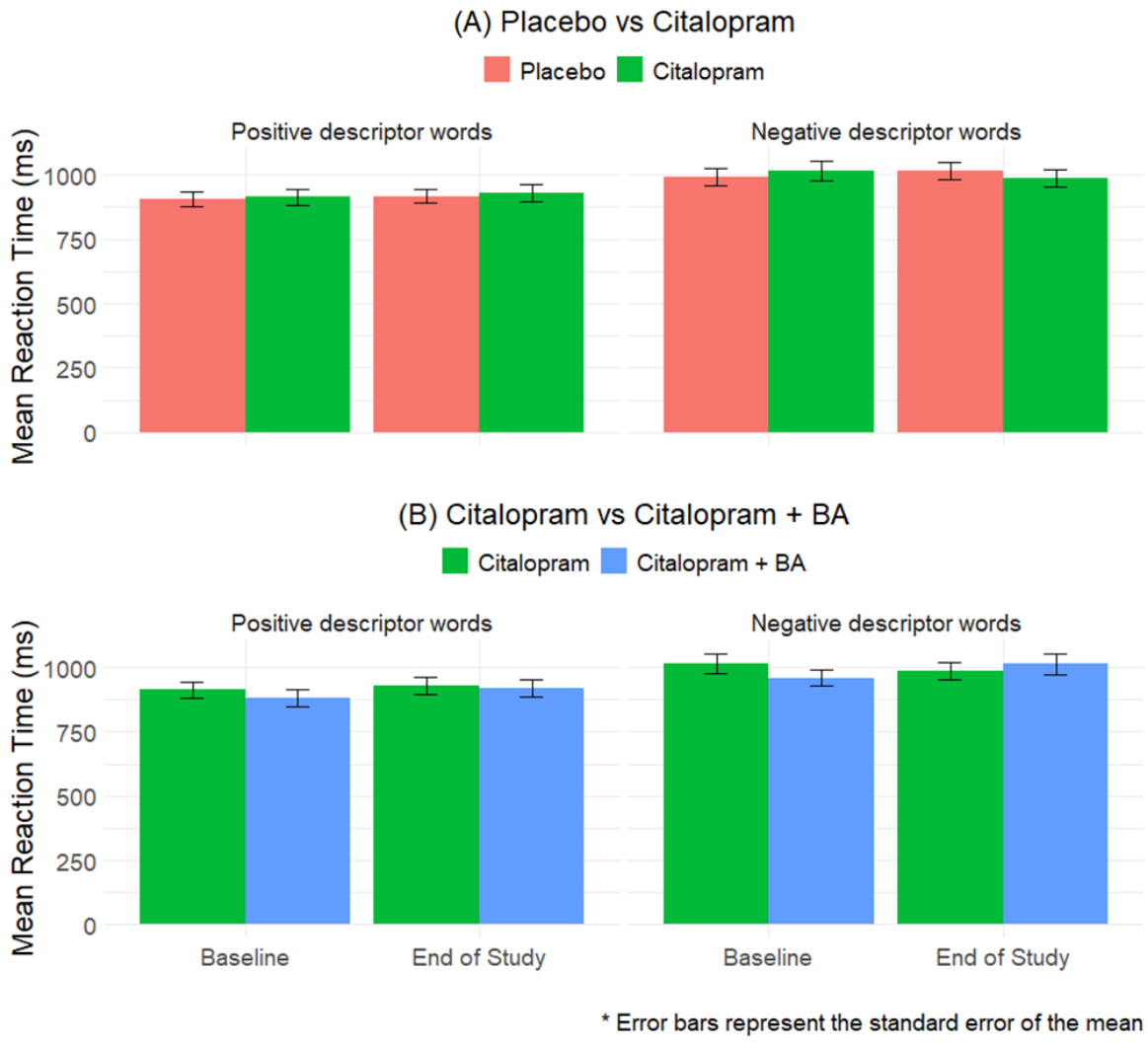


Figure 4.9. Mean reaction times (in milliseconds) for correct identifications of positive and negative personality descriptor words on the Emotional Categorisation Task (ECAT) at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

4.4.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on reaction times for correct responses at EOS assessment ($F(1, 80.91) = 0.14$, $p = 0.708$). However, the treatment

group and word valence interaction approached significance (F(1, 82.20) = 3.67, p = 0.059), suggesting the influence of treatment on reaction times may depend on the emotional valence of the word stimuli.

Follow-up contrasts revealed no significant differences between groups in reaction times in response to either positive (p = 0.687) or negative (p = 0.275) personality descriptor words. The within-group contrast between positive and negative words was not significant for the Citalopram group (p = 0.847), but was significant for the Placebo group (p = 0.017). Thus, participants in the Placebo group were faster to correctly categorise positive words (model-adjusted mean RT = 947 ms, SE = 24.0, 95% CI: 900 ms to 995 ms) compared to negative words (model-adjusted mean RT = 994 ms, SE = 23.9, 95% CI: 947 ms to 1041 ms).

4.4.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on reaction times for correct responses at EOS assessment (F(1, 76.42) = 0.90, p = 0.346). However, the main effect of word valence approached significance (F(1, 97.09) = 3.29, p = 0.073) and was further qualified by a trend-level treatment group and word valence interaction (F(1, 77.26) = 3.81, p = 0.055).

Follow-up contrasts revealed no significant differences between groups in reaction times in response to either positive (p = 0.776) or negative (p = 0.134) personality descriptor words. The within-group contrast between positive and negative words was not significant for the Citalopram group (p = 0.968) but was significant for the Citalopram + BA group (p = 0.009). Participants in the combined treatment group were faster to correctly categorise positive words (model-adjusted mean RT = 957 ms, SE = 27.4, 95% CI: 903 to 1012 ms) compared to negative words (model-adjusted mean RT = 1006 ms, SE = 27.1, 95% CI: 952 ms to 1060 ms).

4.4.2 Sensitivity analysis

The sensitivity analysis revealed the results to be robust, with no changes to the reported treatment group effects or interactions. After excluding data from one participant who experienced timeouts affecting >25% of the task at EOS assessment, the main effect of word valence in the model comparing the Citalopram and Citalopram + BA groups became statistically significant ($F(1, 98.03) = 4.23$, $p = 0.042$), having previously only reached trend-level. Across both treatment groups, participants were faster to correctly categorise positive words (model-adjusted mean RT = 940 ms, SE = 18.2, 95% CI: 904 ms to 976 ms) compared to negative words (model-adjusted mean RT = 967 ms, SE = 18.2, 95% CI: 931 ms to 1003 ms).

However, the interaction between treatment group and word valence was still significant at trend level ($F(1, 78.69) = 3.35$, $p = 0.071$), suggesting that the influence of word valence on reaction times may depend on treatment allocation. As before, only the Citalopram + BA group showed a significant difference in categorisation speed between positive (model-adjusted mean RT = 938 ms, SE = 26.0, 95% CI: 886 ms to 989 ms) and negative words (model-adjusted mean RT = 988 ms, SE = 25.6, 95% CI: 937 ms to 1039 ms; $p = 0.007$), while no such difference was observed in the Citalopram group ($p = 0.768$).

4.4.3 Timepoint analysis

When including timepoint as a factor in the analysis models, we did not observe significant effects of timepoint or significant timepoint and valence interactions for either group comparison (Placebo vs Citalopram effect of timepoint: $F(1, 258.17) = 0.29$, $p = 0.590$), timepoint and valence interaction: $F(1, 257.22) = 0.43$, $p = 0.514$); Citalopram vs Citalopram + BA effect of timepoint: $F(1, 257.76) = 3.61$, $p = 0.059$, timepoint and valence interaction: $F(1, 256.93) = 0.37$, $p = 0.546$).

For the Citalopram vs Citalopram + BA comparison, we observed a significant timepoint and treatment group interaction ($F(1, 257.76) = 4.55$, $p = 0.034$). Follow-up contrasts revealed no

significant differences between groups in reaction times at either Baseline (p = 0.434) nor End of Study assessment (p = 0.690). However, the within-group contrast between Baseline and End of Study assessment was not significant for the Citalopram group (p = 0.870) but was significant for the Citalopram + BA group (p = 0.005). The combined treatment group appears to have increased their correct categorisation times overall, irrespective of the valence of the words (model-estimated RT at Baseline assessment = 922 ms, SE = 32.1 ms, 95% CI = 859 ms to 986 ms; model-estimated RT at End of Study assessment = 974 ms, SE = 32.2 ms, 95% CI = 910 ms to 1038 ms).

4.5 RESULTS – EMOTIONAL RECALL TASK (EREC)

4.5.1 Recall Accuracy

The mean number of positive and negative personality descriptor words correctly recalled on the EREC task at Baseline and EOS assessment is illustrated in Figure 4.10, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

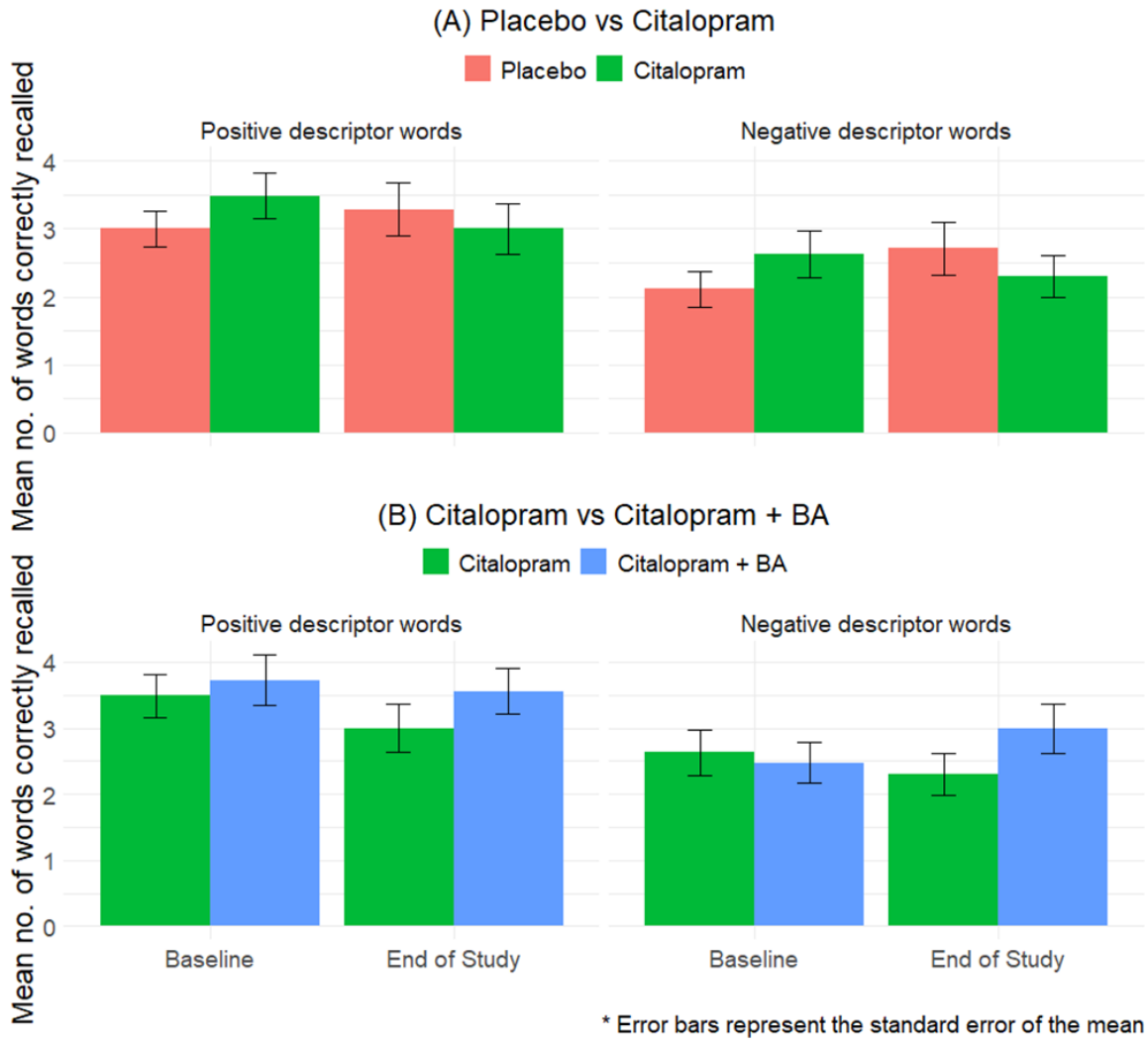


Figure 4.10. Mean number of personality descriptor words correctly recalled on the Emotional Recognition (EREC) task at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

4.5.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on recall accuracy at EOS assessment ($F(1, 82.96) = 0.99$, $p = 0.323$), nor a significant treatment group and word valence interaction ($F(1, 83.07) = 0.06$, $p = 0.809$). The main effect of valence approached significance ($F(1, 89.26) = 3.42$, $p = 0.068$), indicating a trend-level tendency for participants to recall more positive words (model-adjusted mean = 3.03 words, SE = 0.26, 95% CI: 2.52 to 3.54) compared to negative words (model-adjusted mean = 2.59 words, SE = 0.26, 95% CI: 2.07 to 3.10) across both treatment groups.

4.5.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on recall accuracy at EOS assessment ($F(1, 79.13) = 2.24$, $p = 0.138$), nor a significant treatment group and word valence interaction ($F(1, 80.84) = 0.30$, $p = 0.587$).

4.5.2 Intrusions

The mean number of intrusions (words incorrectly recalled which were not part of the original emotional categorisation task) made on the EREC task at Baseline and EOS assessment are illustrated in Figure 4.11, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

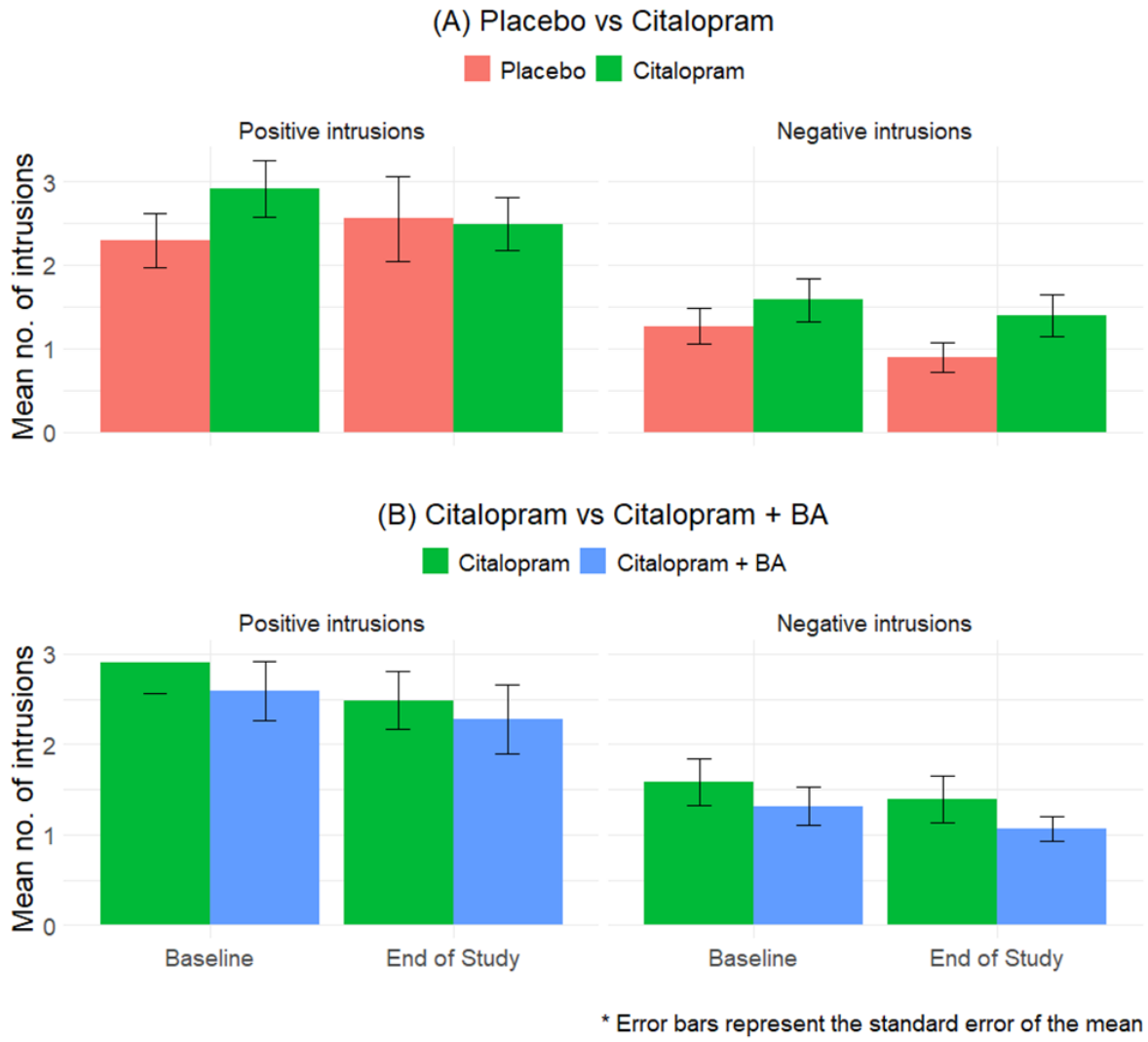


Figure 4.11. Mean number of intrusions made on the Emotional Recall (EREC) task at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

4.5.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on the number of intrusions made at EOS assessment ($F(1, 80.49) = 0.007$, $p = 0.934$), nor a significant treatment group and intrusion valence interaction ($F(1, 81.02) = 1.10$, $p = 0.297$). However, the main effect of valence was statistically significant ($F(1, 90.43) = 6.80$, $p = 0.011$). Participants spontaneously generated more positive intrusion errors (model-adjusted mean = 2.26 intrusions, SE = 0.23, 95% CI: 1.81 to 2.71) than negative intrusion errors (model-adjusted mean = 1.42, SE = 0.23, 95% CI: 0.97 to 1.87) across both treatment groups.

4.5.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on the number of intrusions made at EOS assessment (F(1, 74.56) = 0.21, p = 0.650), nor a significant treatment group and intrusion valence interaction (F(1, 74.87) = 0.05, p = 0.824). The main effect of valence was statistically significant (F(1, 86.67) = 5.31, p = 0.024); as before, participants spontaneously generated more positive intrusion errors (model-adjusted mean = 2.13 intrusions, SE = 0.19, 95% CI: 1.75 to 2.50) than negative intrusion errors (model-adjusted mean = 1.51 intrusions, SE = 0.19, 95% CI: 1.13 to 1.88) across both treatment groups.

4.5.3 Timepoint analysis

When including timepoint as a factor in the analysis models, few novel findings emerged. For the accuracy measure, we did not observe significant effects of timepoint or significant timepoint and valence interactions for either group comparison (Placebo vs Citalopram effect of timepoint: F(1, 259.99) = 0.002, p = 0.961, timepoint and valence interaction: F(1, 257.69) = 0.37, p = 0.542; Citalopram vs Citalopram + BA effect of timepoint: F(1, 255.36) = 0.56, p = 0.455), timepoint and valence interaction: F(1, 252.55) = 1.31, p = 0.253). However, in the model comparing the Placebo and Citalopram groups, we observed a significant timepoint and treatment group interaction (F(1, 259.99) = 5.00, p = 0.026). Follow-up contrasts comparing the two treatment groups were not significant at either timepoint (Baseline assessment p = 0.208, End of Study assessment p = 0.341), nor were contrasts comparing the two timepoints within treatment groups (Placebo group p = 0.102, Citalopram group p = 0.129). However, the direction of the within-group effect appeared to be different, with recall accuracy increasing slightly in the Placebo group from Baseline to EOS assessment (model-estimated number of words correctly recalled at Baseline assessment = 2.57, SE = 0.27, 95% CI: 2.03 words to 3.11 words; model-estimated number of words correctly recalled at End of Study assessment = 3.01, SE = 0.27, 95% CI: 2.47 words to 3.55 words), while a slight decrease is observed in the Citalopram group (model-estimated number of words correctly recalled at Baseline assessment = 3.06, SE = 0.28, 95% CI: 2.51 words to 3.61

words; model-estimated number of words correctly recalled at End of Study assessment = 2.64, SE = 0.28, 95% CI: 2.09 words to 3.19 words), likely driving the interaction effect.

For intrusions on the EREC tasks, both the effect of timepoint and timepoint and valence interactions were not significant in either group comparison (Placebo vs Citalopram effect of timepoint: $F(1, 260.13) = 0.87$, $p = 0.353$, timepoint and valence interaction: $F(1, 257.75) = 0.13$, $p = 0.715$; Citalopram vs Citalopram + BA effect of timepoint: $F(1, 251.77) = 2.36$, $p = 0.126$, timepoint and valence interaction: $F(1, 248.70) = 0.22$, $p = 0.642$). There were no significant interactions with treatment group.

4.6 Results – Emotional recognition memory task (EMEM)

4.6.1 Word recognition accuracy

The mean percentage accuracy recognising positive and negative personality descriptor words on the EMEM task at Baseline and EOS assessment is illustrated in Figure 4.12, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

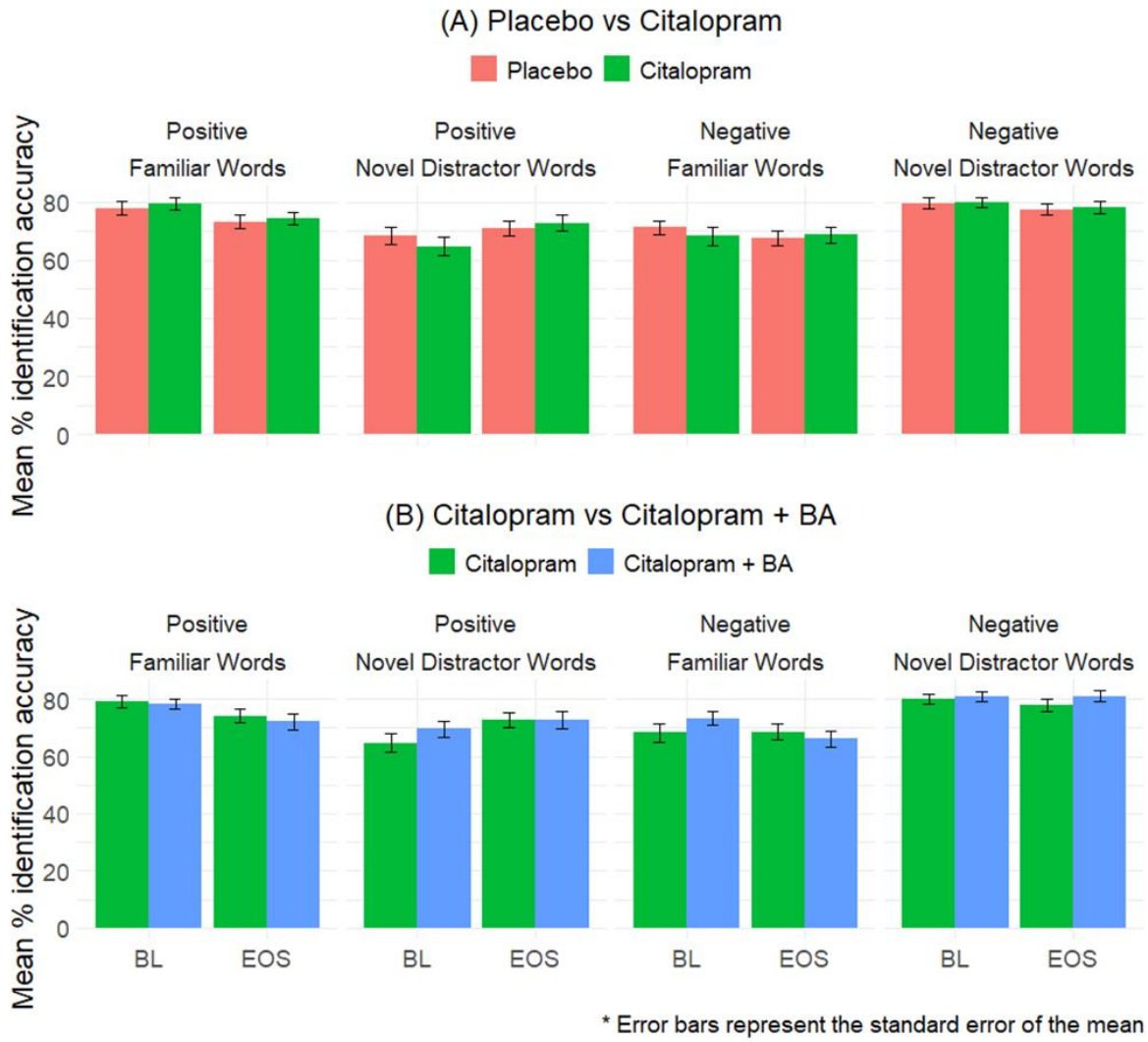


Figure 4.12. Mean percentage recognition accuracy for positive and negative personality descriptor words on the Emotional Recognition Memory (EMEM) task at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.6.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on word recognition accuracy at EOS assessment ($F(1, 314) = 0.58$, $p = 0.447$). The interactions between treatment group and word valence ($F(1, 314) = 0.08$, $p = 0.784$), treatment group and word familiarity ($F(1, 314) = 0.07$, $p = 0.795$), and treatment group, word valence and word familiarity ($F(1, 314) = 0.30$, $p = 0.587$) were also not significant. However, the main effect of word familiarity was statistically significant ($F(1, 314) = 6.26$, $p = 0.013$). Participants were more accurate at identifying novel words (model-adjusted mean accuracy = 75.1%, SE =

1.09, 95% CI: 72.9% to 77.2%) compared to familiar words (model adjusted mean accuracy = 70.6%, SE = 1.09, 95% CI: 68.5% to 72.7%) across both treatment groups.

4.6.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on word recognition accuracy at EOS assessment ($F(1, 72.61) = 0.86$, $p = 0.356$). The interactions between treatment group and word valence ($F(1, 224.74) = 0.15$, $p = 0.703$), treatment group and word familiarity ($F(1, 224.84) = 0.92$, $p = 0.338$), and treatment group, word valence and word familiarity ($F(1, 225.15) = 0.89$, $p = 0.347$) were also not significant. The main effect of word familiarity was statistically significant ($F(1, 224.94) = 15.83$, $p < 0.001$); as before, participants were more accurate at identifying novel words (model-adjusted mean accuracy = 76.4%, SE = 1.19, 95% CI: 74.1% to 78.8%) compared to familiar words (model-adjusted mean accuracy = 70.1%, SE = 1.19, 95% CI: 67.7% to 72.4%) across both treatment groups.

4.6.2 Reaction times for correct responses

Mean reaction times for correct familiarity identifications for positive and negative personality descriptor words on the EMEM at Baseline and EOS assessment are illustrated in Figure 4.13, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

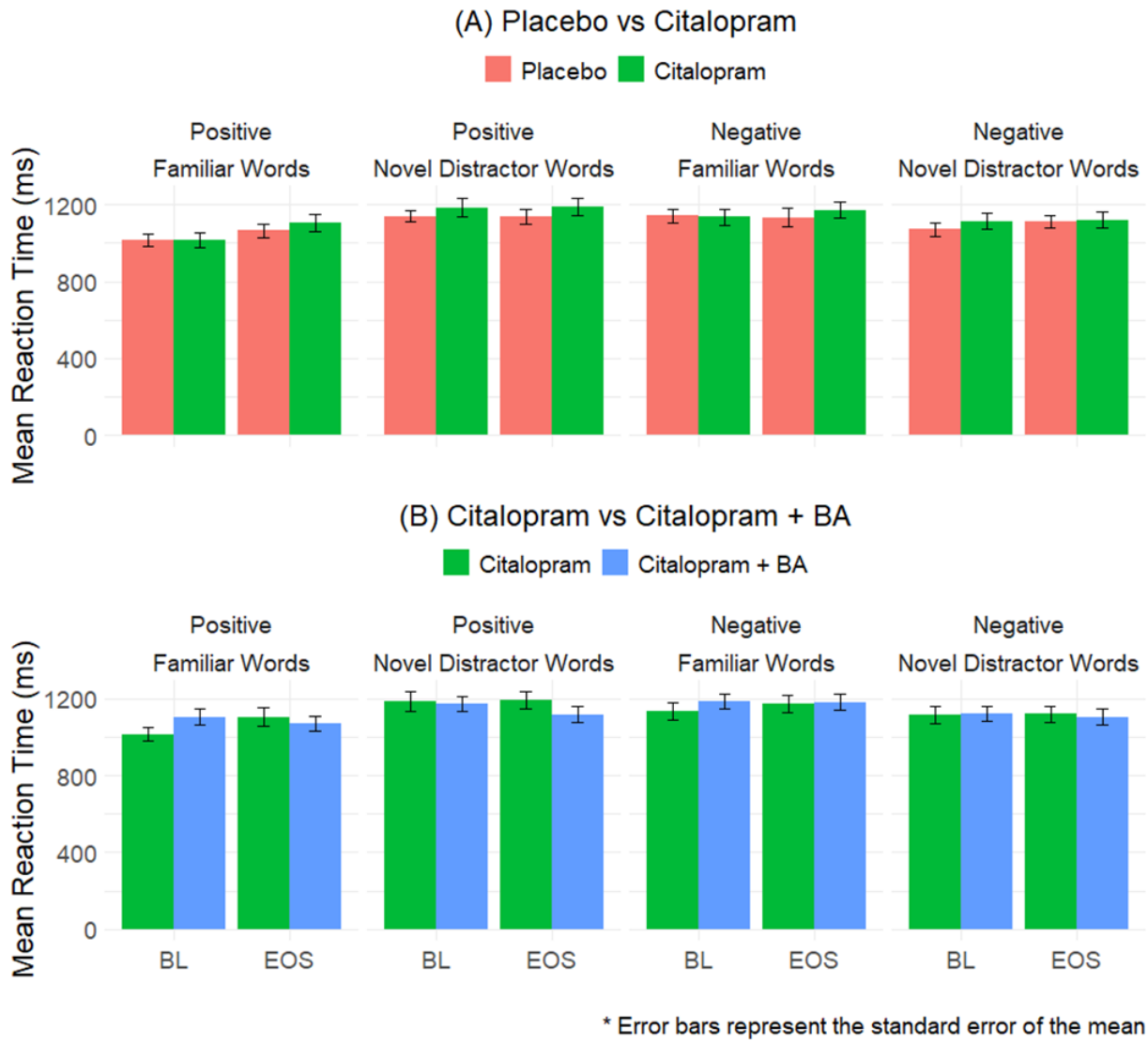


Figure 4.13. Mean reaction times (in milliseconds) for correct familiarity identifications for positive and negative personality descriptor words on the Emotional Recognition Memory (EMEM) task at End of Study assessment, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. BL = Baseline assessment, EOS = End of Study assessment

4.6.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on reaction times for correct word familiarity identifications at EOS assessment ($F(1, 71.62) = 0.17$, $p = 0.686$). The interactions between treatment group and word valence ($F(1, 229.82) = 0.89$, $p = 0.346$), treatment group and word familiarity ($F(1, 230.97) = 1.11$, $p = 0.292$), and treatment group, word valence and word familiarity ($F(1, 229.78) = 1.06$, $p = 0.305$) were also not significant.

4.6.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on reaction times for correct word familiarity identifications at EOS assessment ($F(1, 59.71) = 0.40$, $p = 0.529$). The treatment group and word valence interaction, however, was significant ($F(1, 210.10) = 4.02$, $p = 0.046$), indicating that the influence of treatment on reaction times may depend on the emotional valence of the word stimuli.

Follow-up contrasts revealed no significant differences between groups in reaction times in response to either positive ($p = 0.243$) or negative ($p = 0.968$) personality descriptor words. Within-group comparisons showed that the contrast between positive and negative words was not significant for the Citalopram group ($p = 0.579$), but it was significant for the Citalopram + BA group ($p = 0.021$). Participants in the combined treatment group were faster to correctly categorize positive words (model-adjusted mean RT = 1098 ms, SE = 33.8, 95% CI: 1030 ms to 1165 ms) compared to negative words (model-adjusted mean RT = 1143 ms, SE = 33.9, 95% CI: 1075 ms to 1210 ms), when identifying them as either familiar or novel.

The interactions between treatment group and word familiarity ($F(1, 212.48) = 0.32$, $p = 0.57$) and treatment group, word valence and word familiarity ($F(1, 209.97) = 0.02$, $p = 0.883$) were not statistically significant.

4.6.3 Sensitivity analysis

The sensitivity analysis indicated that the results were robust; excluding data from three participants who experienced timeouts affecting more than 25% of the task (one at the Baseline assessment and two at the EOS assessment) did not alter the significance of any of the effects described above.

4.6.4 Timepoint analysis

When including timepoint as a factor in the analysis models, a couple of novel findings emerged. For the accuracy measure, we observed significant word familiarity and timepoint interactions as well as word valence, familiarity and timepoint interactions, both in the model

comparing the Placebo and Citalopram groups (familiarity and timepoint interaction: *F*(1, 569.63) = 4.65, p = 0.031; valence, familiarity and timepoint interaction: *F*(1, 569.63) = 5.19, p = 0.023), as well as in the model comparing the Citalopram and Citalopram + BA groups (familiarity and timepoint interaction: *F*(1, 554.73) = 9.22, p = 0.003; valence, familiarity and timepoint interaction: *F*(1, 554.73) = 3.88, p = 0.049). The four-way interaction with treatment group was not statistically significant in either model (Placebo vs Citalopram: *F*(1, 569.63) = 1.17, p = 0.279; Citalopram vs Citalopram + BA: *F*(1, 554.73) = 2.08, p = 0.150), indicating the complex changes in recognition accuracy from pre- to post-treatment did not differ between treatment groups.

Figure 4.14 illustrates the three-way interaction, averaged across treatment groups. The distinction in accuracy between positive familiar and positive novel words, initially apparent at Baseline assessment, becomes less pronounced at EOS, while a strong distinction remains in the case of negative familiar versus negative novel words.

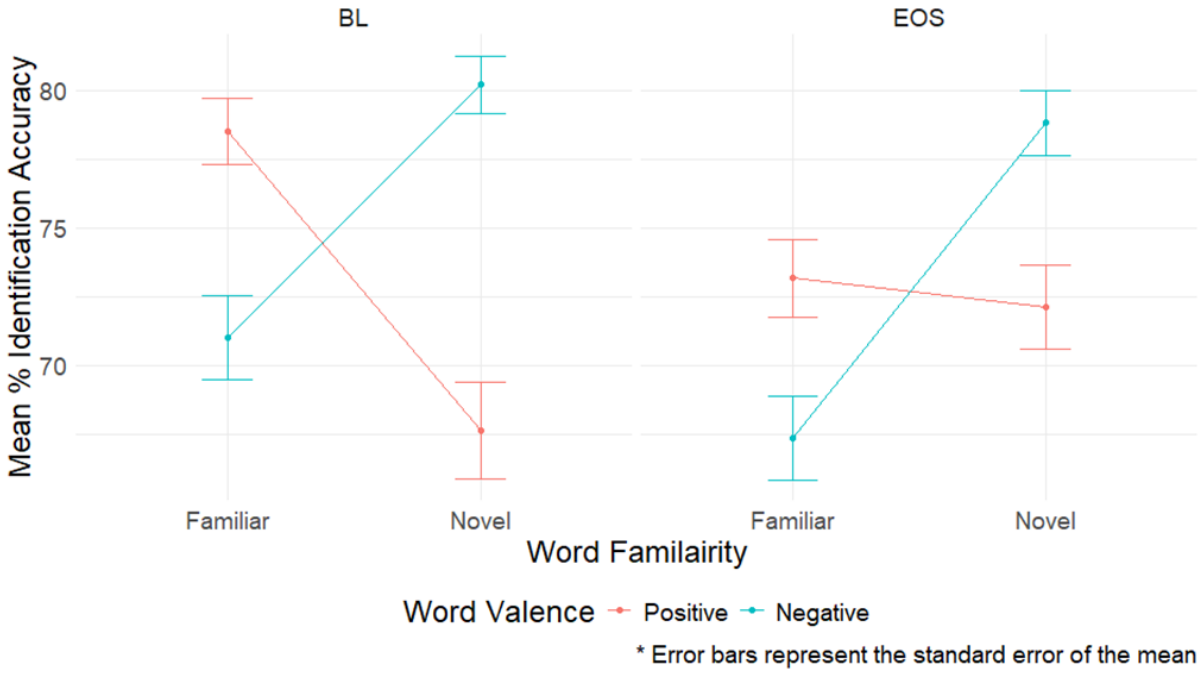


Figure 4.14. Mean percentage identification accuracy on the Emotional Recognition Memory (EMEM) task, by word valence, word familiarity and timepoint, averaged across treatment groups; BL = Baseline assessment, EOS = End of Study assessment

For the reaction time measure, there were no significant effects of timepoint nor interactions between timepoint and word valence or familiarity in either group comparison (all p > 0.056). However, in the model comparing the Citalopram and Citalopram + BA groups, we observed a significant timepoint and treatment group interaction (F(1, 564.00) = 5.62, p = 0.018). Follow-up contrasts comparing the two treatment groups were not significant at either timepoint (Baseline assessment p = 0.367, End of Study assessment p = 0.846), however the within-group difference between timepoints approached significance for the Citalopram + BA group (p = 0.061) but not for the Citalopram group (p = 0.138). For the BA group, reaction times to correct familiar/novel word identifications were marginally faster at EOS assessment compared to Baseline (model-estimated RT at Baseline assessment = 1151 ms, SE = 35.6 ms, 95% CI: 1080 ms to 1222 ms; model-estimated RT at End of Study assessment = 1120 ms, SE = 36.0 ms, 95% CI: 1048 ms to 1191 ms). The opposite was true for the Citalopram group, where reaction times at EOS assessment increased slightly from Baseline, although not significantly so (model-estimated RT at Baseline assessment = 1104 ms, SE = 37.1 ms, 95% CI: 1030 ms to 1178 ms; model-estimated RT at End of Study assessment = 1130 ms, SE = 37.2 ms, 95% CI: 1056 ms to 1204 ms).

4.7 DISCUSSION

To summarise, we were unable to replicate previous findings that short-term SSRI administration induces positive shifts in affective bias compared to placebo. Past studies have consistently reported changes in emotional categorisation, memory, and facial expression recognition with antidepressants (Browning et al., 2007; Harmer et al., 2004, 2008; Walsh, Huneke, et al., 2018), often manifesting as increased processing accuracy and speed for positive-valence stimuli. Based on these results, we hypothesised that environmental enrichment through BA might enhance these effects, particularly if the environment plays a key role in antidepressant drug action. However, our citalopram-only intervention failed to produce the same outcomes reported in the literature, raising questions

about the rest of our findings. Several potential explanations for this surprising result are outlined below.

First, our study employed a repeated-measures design, with participants completing the Emotional Task Battery (ETB) both at baseline and after two weeks of treatment (EOS assessment). In contrast, most previous studies have used a simple between-subjects design, administering the ETB only once, post-treatment (Browning et al., 2007; Harmer, Bhagwagar, Perrett, et al., 2003; Harmer et al., 2004, 2008; Walsh, Huneke, et al., 2018). A repeated-measures design introduces the possibility of practice effects or other factors, such as variability in the test environment and participants' motivation, which could obscure genuine drug effects. In our sample, we observed emotional processing changes over repeat testing and time, but these did not interact with treatment group, or with the valence of task stimuli in most cases. This valid criticism notwithstanding, the ETB has demonstrated good test-retest reliability when different stimulus sets are used for each administration, as in the present study (Thomas et al., 2016), and change-from-baseline measures have been shown to be sensitive to antidepressant effects and predictive of clinical response (Browning et al., 2019; Ruzickova et al., 2023). Importantly, repeated designs are generally advantageous due to their greater statistical power and ability to reduce error variance associated with individual differences, which was a key reason for adopting this approach.

Another potential explanation relates to our method of ETB administration. Previous research to date has used the ETB almost exclusively in-laboratory (Harmer et al., 2004; Murphy, Norbury, et al., 2009; Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018), with participants' medication intake and task performance monitored closely by study researchers. In the CABIN study, we used an online version of the ETB which participants completed at home; this decision was partly motivated by the COVID-19 pandemic to reduce the number of clinic visits required, and partly to increase opportunities for study participation beyond Oxford(shire) residents. While the resulting increases in ecological validity and

participant diversity are particular strengths of the study, it remains that results using the online ETB are not as well-replicated as those using the original laboratory version. Nevertheless, the online ETB has shown sensitivity to differences in emotional processing in participants receiving an online BA intervention compared to a waitlist control group (Ruzickova et al., 2023), and in a large observational study comparing statin users to non-users, ran during the COVID-19 pandemic (Gillespie et al., 2022). Other remote experimental medicine studies employing the online ETB are currently awaiting results (Waters et al., 2023).

An additional limitation of the online ETB is the lack of control we had over the environment and conditions under which data were collected. To minimise the impact of disruption and create (somewhat) standardised conditions for testing, we contacted each participant by telephone prior to each assessment and emphasised the importance of minimising distractibility by silencing their mobile phone and letting other household members know they will be busy for the next one-to-two hours. Nevertheless, one cannot guarantee the complete absence of distractions, which could have decreased the sensitivity of the tasks. Further research using the online ETB will be able to attest its sensitivity under different testing conditions.

Finally, the failure to replicate previous findings with citalopram may also be related to the significant reduction in depression symptoms observed across all treatment groups from baseline to EOS (discussed in detail in Chapter 3). According to the cognitive neuropsychological model of antidepressant drug action, changes in affective bias typically precede self-reported mood improvements (Godlewska & Harmer, 2021; Harmer, Goodwin, et al., 2009; Harmer & Cowen, 2013). However, our timepoint analyses revealed no clear relationships between changes in clinical outcomes and changes in emotional processing one might have expected in the context of the model, such as improvements in speed and/or accuracy for categorising, recognising or memorising positive stimuli across all treatment groups. Indeed, it remains unclear whether the model assumes these changes in affective

bias are maintained after a significant reduction in symptoms, and our study design precluded us from measuring affective bias independent of mood change. It might also mean that the model's assumptions are not universal across all individuals and contexts.

Moreover, fluctuations in depressive symptoms and variability in the persistence of negative schemas among participants could have influenced our findings. The substantial placebo effect, evidenced by the reduction in depression symptoms across all groups, suggests that our sample may not have exhibited the stable negative cognitive models typically targeted by antidepressants. This is difficult to establish as there are no normative data for the ETB we could compare to our Baseline assessment data and represents a major limitation across research utilising the cognitive neuropsychological model. Behavioural activation, in contrast, may exert more top-down, conscious effects on cognition, which could differ from the more automatic effects of antidepressant drugs.

Indeed, some differences in processing speed did emerge between the Citalopram and Citalopram + BA groups, specifically on the Emotional Categorisation (ECAT) and Emotional Recognition Memory (EMEM) tasks. Participants in the combined treatment group showed a tendency to respond faster to positive compared to negative personality descriptor words in both tasks, on trials where they made correct judgements about the nature of the words (i.e., positive/negative, familiar/unfamiliar). In contrast, the Citalopram-only group did not show such differences in categorisation speed between positive and negative words. These differences could suggest more pronounced positive affective biases in the combined treatment group, as initially hypothesised, although it is important to state that no between-group differences in processing speed were observed for either positive or negative valence stimuli.

In the absence of any significant emotional processing differences between the Citalopram-only and Placebo groups, interpreting these findings is challenging. One possibility is that the observed effects reflect changes induced by BA rather than the medication itself. Previous

research has also linked BA to shifts in emotional processing; in their study comparing a four-week online BA protocol with a passive control group, Ruzickova et al. found that participants receiving BA experienced a significantly greater decrease in negative facial expression recognition accuracy from baseline to post-treatment compared to the control group. Moreover, in the BA group, the change in accuracy for positive expression recognition after two weeks of treatment was correlated to participants' depression severity score at the end of the four-week intervention (Ruzickova et al., 2023). While our findings are less robust – likely due to the shorter treatment duration – they align with BA's theoretical framework, which suggests bidirectional effects between cognition and behaviour (Janssen et al., 2020; Myles & Merlo, 2022; Norbury et al., 2024).

Another possibility is that BA-enhanced SSRI therapy resulted in affective processing biases too subtle to detect in the Citalopram-only group. However, without a Placebo + BA group, it remains unclear whether our results reflect a modulation of drug effects through the provision of BA, or if they are attributable to BA alone. Interestingly, our findings contrast with previous research suggesting that combining citalopram with psychological interventions can sometimes enhance negative biases (Browning et al., 2011). In contrast, BA-enhanced treatment in our study appeared to facilitate processing speed for positive compared to negative words. Nevertheless, because we found no significant positive affective biases favouring the Citalopram group over Placebo, it remains a possibility that the effects in the BA group could be spurious or influenced by methodological factors such as task administration and study design. Moreover, our questionnaire data discussed in Chapter 3 suggest that the BA intervention may not have been long enough to meaningfully affect participants' perception of environmental reward frequency, raising questions about whether we adequately tested our initial hypothesis that environmental enrichment might modulate antidepressant effects on affective processing.

In conclusion, while some differences in affective processing speed emerged between the Citalopram and Citalopram + BA groups, the absence of findings consistent with the wider

literature on antidepressant drug action complicates interpretation. Future studies should address the methodological limitations discussed, such as the need for more controlled testing environments and longer intervention length, to clarify whether environmental enrichment enhances antidepressant drug effects on measures of emotional processing. Further exploration of BA's potential to modulate affective biases, both independently and in combination with pharmacological treatments, remains a promising area for future research.

5 CHAPTER 5: THE EFFECTS OF A BEHAVIOURAL ACTIVATION-ENRICHED SSRI INTERVENTION ON REINFORCEMENT LEARNING

5.1 INTRODUCTION

Dysfunctional reward processing is central to the pathophysiology of depression. Alongside a depressed mood, anhedonia is one of two core symptoms required for a diagnosis of Major Depressive Disorder (MDD; American Psychiatric Association, 2021). Although anhedonia has been conceptualised in various ways, a widely accepted definition, which captures its biobehavioural basis, is “a diminished interest or pleasure in response to stimuli that were previously perceived as rewarding” (American Psychiatric Association, 2021). Anhedonia may affect up to 70% of individuals with MDD, though this figure varies depending on the population studied (Cao et al., 2019).

Despite the ubiquity of anhedonia in depression, behavioural impairments show variability across different reward-related processes such as motivation, reinforcement learning, and hedonic capacity. These processes are supported by partially dissociable brain systems, as demonstrated by preclinical and neuroimaging research (Admon & Pizzagalli, 2015; Treadway & Zald, 2011). A consistent finding in depressed populations is an impaired ability to adjust behaviour as a function of reinforcement. For instance, in reward learning tasks like the Probabilistic Reward Task (Pizzagalli et al., 2005), individuals with depression often show a reduced bias toward more frequently rewarded stimuli compared to healthy controls (Halahakoon et al., 2020; Kunisato et al., 2012; Pizzagalli et al., 2008; Steele et al., 2007). Computational modelling of six large datasets suggests that this behaviour may be more closely related to reduced reward sensitivity (lower subjective values assigned to rewards) rather than to impairments in learning itself (Huys et al., 2013), implying that depressed individuals are less sensitive to implicit reward signals.

MDD is also associated with maladaptive responses to negative feedback (Eshel & Roiser, 2010). Some studies have suggested that MDD patients exhibit hypersensitivity to punishment, manifested as a reversal of behaviour patterns when a previous decision led to a negative outcome. For example, Murphy and colleagues (2003) found that depressed individuals, when engaged in a probability reversal learning task, were more likely than controls to switch their choices after receiving non-reward feedback, even after they had learned which stimulus was statistically more advantageous (Murphy et al., 2003). However, other studies suggest that individuals with high depression scores (BDI-II ≥ 13) may simply fail to use negative feedback effectively to improve performance, as evidenced by less frequent adjustments in response to errors compared to those with low depression scores (Holmes & Pizzagalli, 2007). Although rarely studied in parallel, reward and punishment are thought to represent distinct categorical events rather than opposing points on the same continuum (Kubanek et al., 2015). These events trigger distinct behaviours – approach for reward and avoidance for punishment (Huys et al., 2011). Consequently, when evaluating the effects of treatment on reinforcement learning, it is important to consider both reward and punishment processes.

The effects of antidepressant medication monotherapy on reward learning remain debated, with some studies reporting contradictory effects of selective serotonin reuptake inhibitors (SSRIs) on reinforcement learning tasks. While there is evidence that SSRIs increase reward sensitivity (Scholl et al., 2017), and thus reverse an abnormal response pattern seen in depression, other studies show that SSRIs may reduce learning from rewards and increase sensitivity to punishment. Using a gambling task where three different card decks were associated with different probabilities of making a successful gamble, Michely et al. found that a seven-day course of citalopram enhanced computationally derived learning rates based on trials with loss outcomes and reduced learning rates based on trials with gain outcomes, resulting in participants receiving the SSRI making fewer gambles in response to cumulative failure compared to participants receiving a placebo (Michely et al., 2022). In

contrast, other studies have reported decreased sensitivity to both rewards and punishment with chronic SSRI treatment (Langley et al., 2023). Preclinical research suggests that these contradictory effects might stem from SSRIs' indirect modulation of dopaminergic pathways involved in reward processing (Dremencov et al., 2009; Sekine et al., 2007; Shuto et al., 2020; Yoshino et al., 2002).

In contrast to antidepressants, the effects of behavioural activation (BA) on reinforcement learning have received less attention at a behavioural level. Positive reinforcers – stimuli that increase the likelihood of a behaviour – may lose their motivational pull in individuals with depression due to the reinforcement learning deficits discussed above. These deficits could reduce patients' motivation to pursue future rewards and engage in pleasurable activities, potentially exacerbating depressive symptoms. Supporting this idea, experiential sampling studies indicate that individuals with depression engage in fewer activities associated with immediate pleasure and future rewards (Hopko et al., 2003). BA, a treatment designed to encourage engagement in rewarding activities, has proven effective in reducing depressive symptoms (Cuijpers et al., 2007; Ekers et al., 2008, 2014). Although it is unclear whether BA corrects the reward sensitivity deficits typical of depression, neuroimaging studies suggest that brief BA interventions (11–15 sessions) enhance striatal responsiveness to rewards (Dichter et al., 2009) and that brain activation during reward processing may predict response to BA therapy (Carl et al., 2016; Walsh et al., 2017). However, the lack of comparison conditions in many of these studies limits the attribution of these effects specifically to BA.

Both anhedonia (Uher et al., 2012) and associated reinforcement learning deficits (Vrieze et al., 2013) have been linked to poorer prognosis for MDD patients. Notably, anhedonia is not always adequately addressed by existing MDD treatments, whether pharmacological or psychological (Craske et al., 2016; McMakin et al., 2012; Nord et al., 2019). Consequently, this is an area where combining treatments in an evidence-based manner may address this unmet need, potentially improving patient outcomes.

In the CABIN study, we sought to investigate whether BA-augmented SSRI treatment could improve reward and punishment learning in individuals with mild to moderate depression. Participants completed a modified Probabilistic Reward Task (Pizzagalli et al., 2005), involving both monetary gains and losses. We hypothesised that the combined treatment would reverse any blunting of reward sensitivity caused by SSRIs (conceptualised as a lower accuracy in selecting a more frequently rewarded symbol), with BA helping to restore reward responsiveness.

5.2 METHODS

5.2.1 Sample

Participants completed the Probabilistic Instrumental Learning Task (PILT) as part of their online Baseline and End of Study (EOS) assessments. The PILT assesses participants' ability to learn from rewards and punishments by making choices between symbols with different probabilities of leading to beneficial or non-beneficial outcomes. Crucially, the PILT contains an equal number of win and loss trials, presenting different symbol pairs associated with different beneficial and non-beneficial outcomes. On win trials, the beneficial outcome is winning money (20 pence), and the non-beneficial outcome is not winning money (no change). On loss trials, the beneficial outcome is not losing money (no change), and the non-beneficial outcome is losing money (-20 pence). Thus, the optimal choice on any given trial is selecting the symbol with a greater probability (0.7 compared to 0.3) of leading to a favourable outcome (i.e., a 20p win on win trials and no change on loss trials).

All 134 participants completed both assessments; however, we excluded data from eight participants at Baseline (two in the Placebo group, one in the Citalopram group and five in the Citalopram + BA group) and 12 participants at EOS (four in the Placebo group, three in the Citalopram group and five in the Citalopram + BA group) due to very poor performance or evidence of misunderstanding task instructions. After exclusions, the final sample size for analysis was 122 participants (N Placebo = 41, N Citalopram = 41, N Citalopram + BA = 40).

5.2.2 PILT outcome measures

The primary outcome measure for the PILT was choice accuracy, defined as the percentage of trials in which participants chose the advantageous symbol from each pair. This was analysed separately for win trials (where the advantageous symbol was the one with a 0.7 probability of gaining money) and loss trials (where the advantageous symbol was the one with a 0.3 probability of losing money). Performance was assessed over the final 20 trials in each block, as this is where learning typically plateaus (Colwell et al., 2024; Gillespie et al., 2022; Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018).

We also analysed the reaction time to choice (in milliseconds) on trials where the optimal symbol was selected as a measure of decision-making speed. As with choice accuracy, reaction times were assessed over the final 20 trials in each block, separately for win and loss trials.

Lastly, we conducted a 'win-stay/lose-shift' analysis (Iyer et al., 2020) of response patterns over the final 20 trials in each block. We calculated, for each participant, the percentage of 'win-stay' trials, where they stayed with the same choice after an advantageous outcome (n - 1), and the percentage of 'lose-shift' trials, where they shifted their choice after a non-advantageous outcome (n - 1). Since the advantageous and non-advantageous outcomes are different for the win and loss trials in the task (i.e., on a win trial, a no-change outcome is disadvantageous, whereas the opposite is true on a loss trial), the percentage of “win-stay” and “lose-shift” trials were considered separately for each trial type.

5.2.3 Data analysis

Prior to the main statistical analyses, we descriptively explored participants’ choice accuracy and reaction times across the PILT and plotted these for each comparison of interest (Placebo vs Citalopram and Citalopram vs Citalopram + BA). These results are presented in Figures 5.1-5.3. Specifically, we constructed learning curves showing the proportion of participants in each group, on each trial, who chose the symbol associated with a high

probability of loss or gain during the End of Study (EOS) assessment. In addition, we plotted participants' reaction times to choice, separately for win and loss trials and for optimal and non-optimal symbol choices. To construct the plots, trial-by-trial accuracy and reaction time data were averaged across the three blocks of the PILT. Since each block used different stimuli for the win and loss conditions, this averaging provides a comprehensive indication of learning across the entire task. We also describe the average amount of money won by participants in each treatment group when completing the task, during both Baseline and EOS assessments, and present these figures in Table 5.1.

The End of Study (EOS) outcomes of interest, as described in Section 2.2, were entered as dependent variables (DVs) in separate analyses of covariance (ANCOVA). The treatment group (Placebo vs Citalopram or Citalopram vs Citalopram + BA) was used as the between-subjects factor, while the same DV measured at Baseline, along with BDI-II scores at Baseline, were included as covariates to control for pre-existing differences.

A sensitivity analysis was planned which excluded all participants who achieved <50% accuracy across both win and loss trials (five participants at Baseline and two at EOS assessment) and all participants with periods of non-response affecting ¼ of the task or more, across both win and loss trials (one participant at Baseline assessment).

5.3 RESULTS

5.3.1 Descriptives

Learning curves showing the proportion of participants in each group choosing the symbol associated with a high probability of loss or gain during the End of Study (EOS) assessment are presented in Figure 5.1, separately for the Placebo vs. Citalopram and Citalopram + BA group comparisons. High-probability stimuli are advantageous on win trials and disadvantageous on loss trials; thus, a higher choice percentage indicates better learning on win trials, while a lower choice percentage reflects better learning on loss trials.

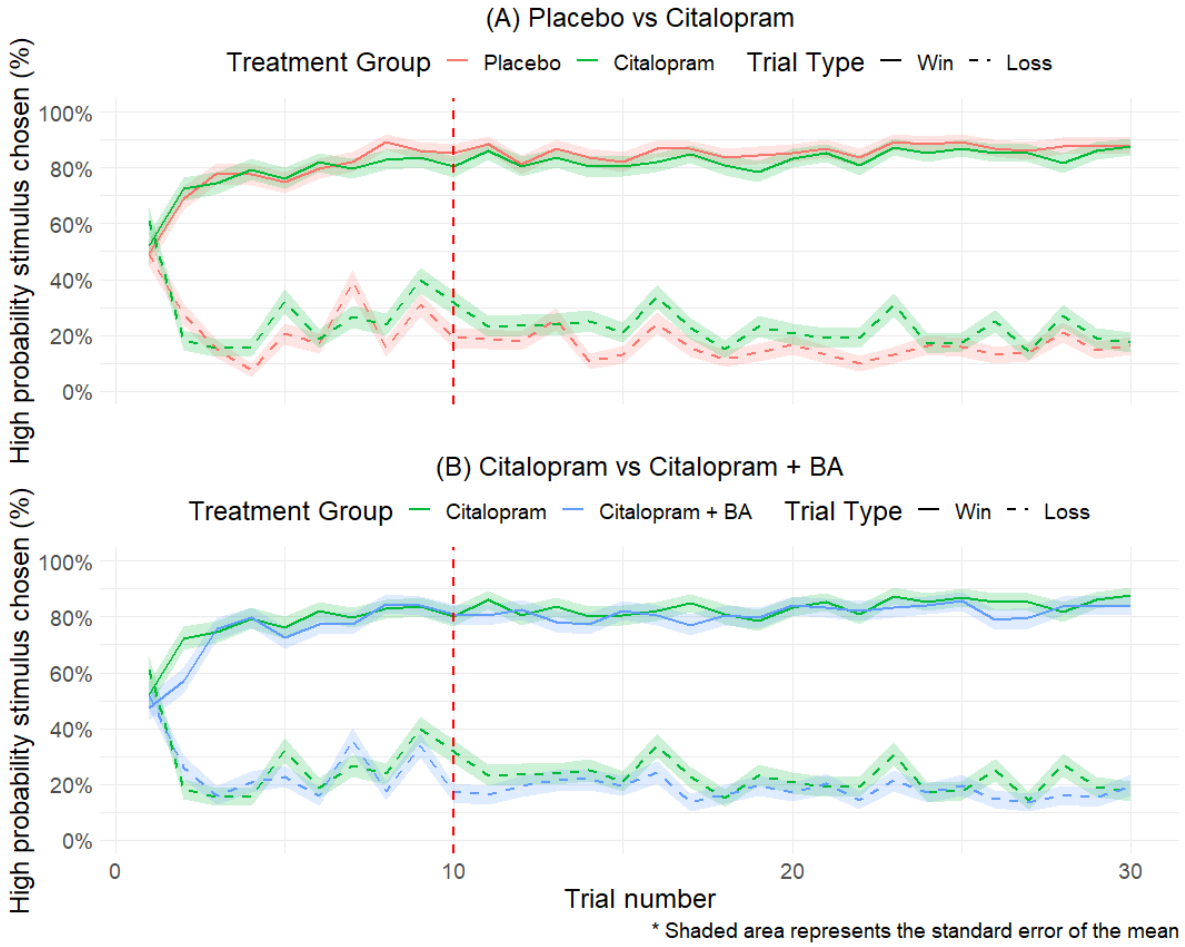


Figure 5.1. Learning curves showing the proportion of participants choosing the high-probability symbol at EOS assessment, trial by trial, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons. High-probability stimuli are advantageous on win trials and disadvantageous on loss trials. The red dotted line indicates the cut-off for trials included in the choice accuracy and reaction time analyses

Figure 5.1 indicates that learning had plateaued by trial 10 in all three treatment groups. This is consistent with previous research using the same task (Colwell et al., 2024; Gillespie et al., 2022; Walsh, Browning, et al., 2018; Walsh, Huneke, et al., 2018) and validates our approach of only considering performance in the last 20 trials of each block to quantify choice accuracy and reaction time to choice. Visual inspection of the learning curves suggested that there were some group differences, with participants in the Citalopram group generally being less accurate on loss trials compared to the placebo group.

Reaction times to choice at EOS assessment are depicted in Figures 5.2 and 5.3, separately for win and loss trials, optimal and non-optimal choices, and the two group comparisons of interest (Placebo vs Citalopram and Citalopram vs Citalopram + BA). Across all treatment

groups, participants were fastest to select optimal choices on win trials, with RTs decreasing across the trials as they learned which symbols were more advantageous. In contrast, on loss trials, participants exhibited more variability in RTs even when making optimal choices, with no clear downward trend. Responses on loss trials were generally slower and less consistent, indicating that participants found these trials more challenging or that the learning process was less straightforward when the task involved unfavourable outcomes. For non-optimal choices, RTs were more variable across both win and loss trials. Non-optimal choices made on loss trials showed the highest variability in RTs across all treatment groups. This variability was particularly pronounced in the latter half of the trials, possibly due to a decrease in the frequency of incorrect responses as participants gained experience with the task. There were some observable differences between the groups, with participants in the Citalopram group tending to respond slightly faster and more consistently across conditions compared to the Placebo group.

PILT task earnings increased slightly from Baseline to EOS assessment in all three treatment groups, indicating a modest effect of pre-exposure to the task. Larger differences in earnings were observed between the Placebo and Citalopram groups than between the Citalopram and Citalopram + BA groups at both assessments.

Table 5.1. Amount of money won on the PILT at each assessment, by treatment group

	Placebo	Citalopram	Citalopram + BA
Baseline assessment	£6.47, SE = £0.26	£5.92, SE = £0.37	£6.33, SE = £0.32
EOS assessment	£7.24, SE = £0.26	£6.61, SE = £0.36	£6.71, SE = £0.40

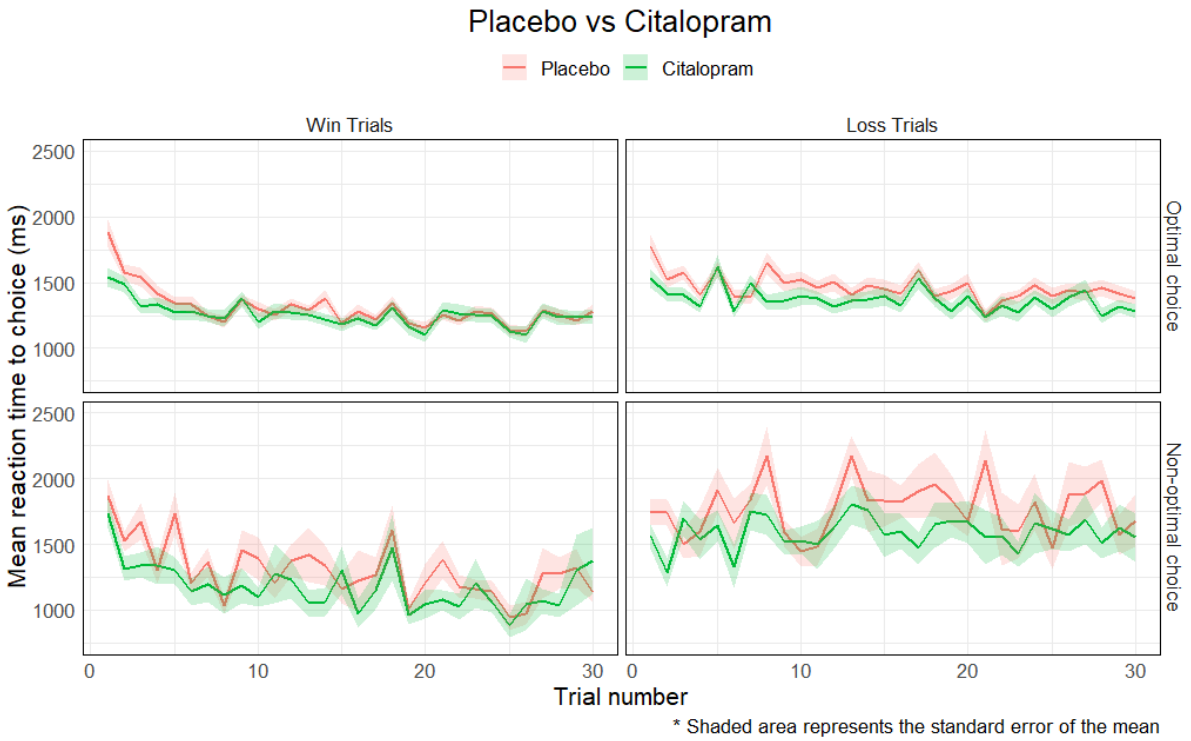


Figure 5.2. Reaction times to choice (in milliseconds) across the PILT at EOS assessment for the Placebo vs Citalopram group comparison, separately for the different trial types (win or loss) and accuracy in selecting the optimal symbol

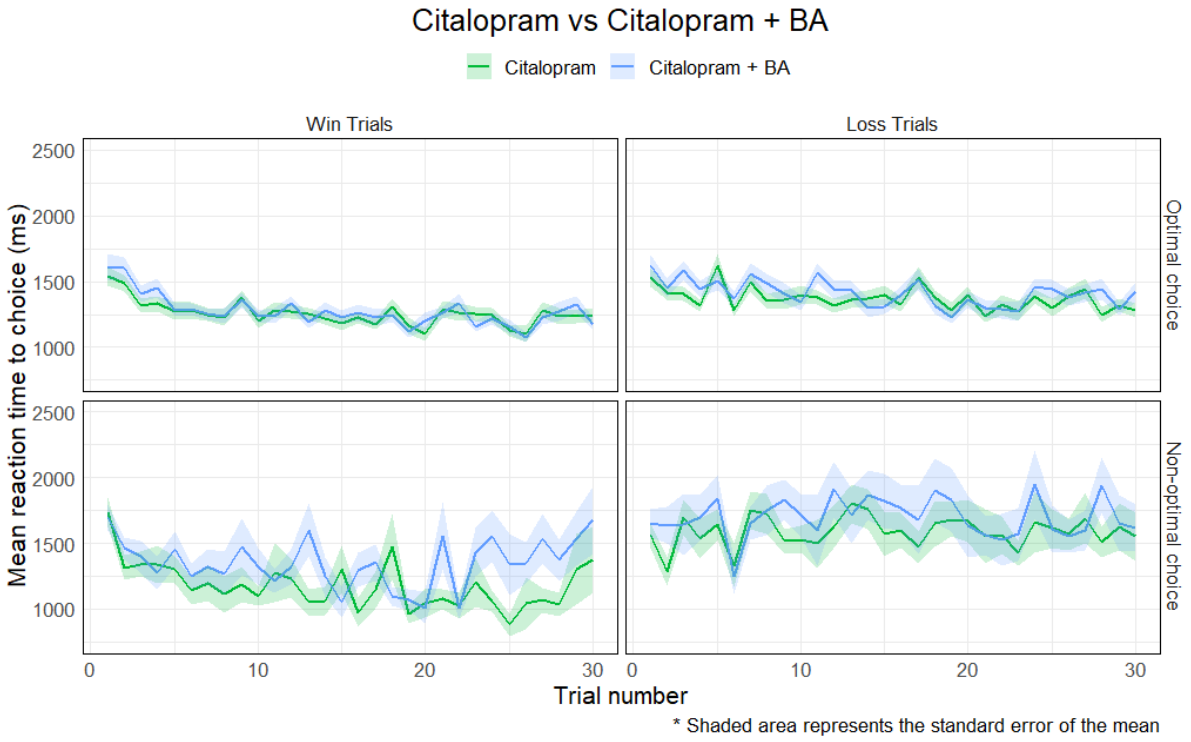


Figure 5.3. Reaction times to choice (in milliseconds) across the PILT at EOS assessment for the Citalopram vs Citalopram + BA group comparison, separately for the different trial types (win or loss) and accuracy in selecting the optimal symbol

5.3.2 Choice accuracy

Mean choice accuracy values across the last 20 trials of the three PILT blocks at EOS assessment are presented in Figure 5.4, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

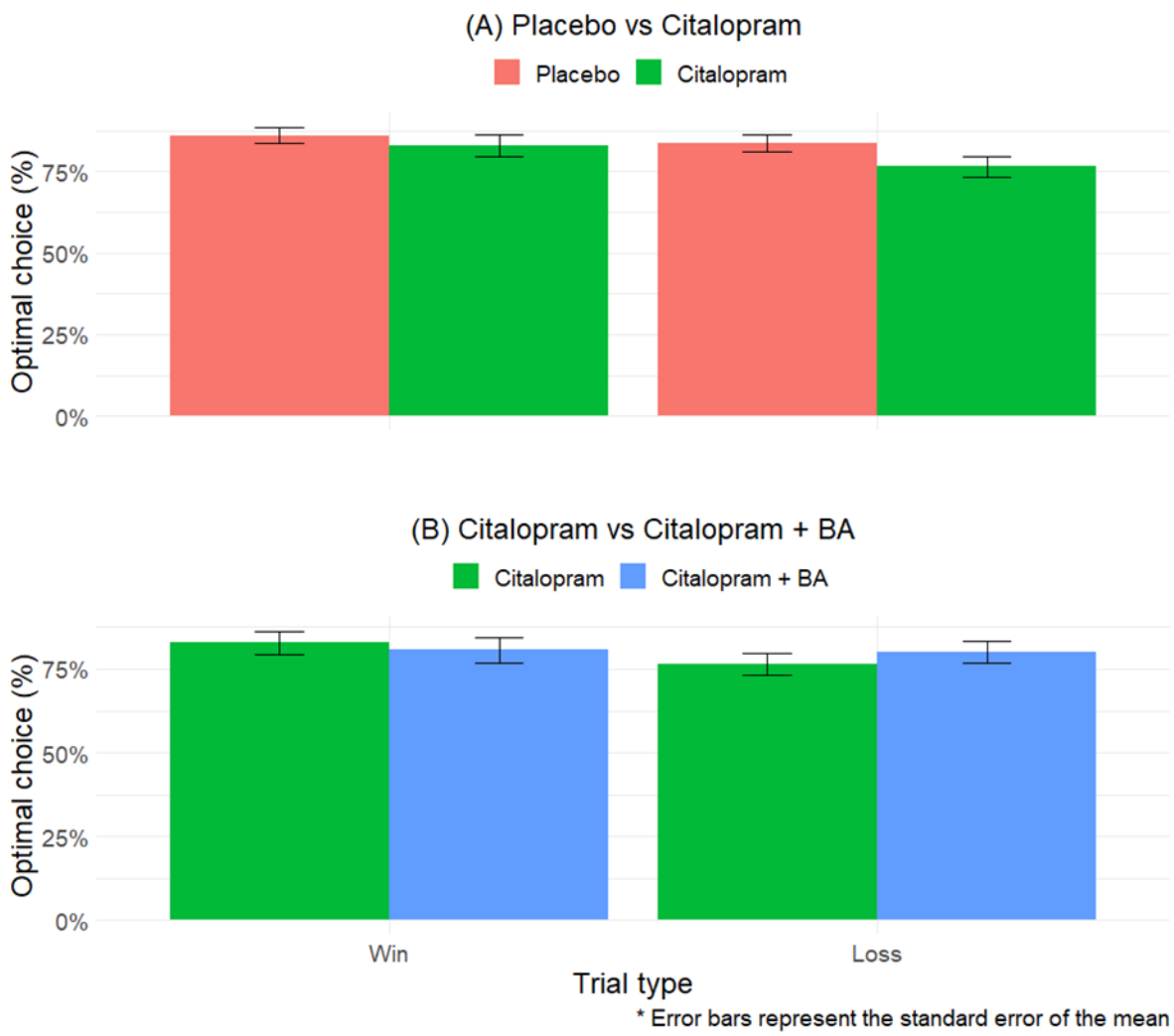


Figure 5.4. Choice accuracy (percentage of trials on which the optimal symbol was selected) averaged over the last 20 trials of the three PILT blocks at EOS assessment, separately for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. Note the optimal choice is different on win and loss trials

5.3.2.1 Placebo vs Citalopram comparison

For win trials in the PILT, we did not observe a significant main effect of treatment group on choice accuracy at EOS assessment ($F(1, 78) = 0.64$, $p = 0.425$). However, the main effect of treatment group on choice accuracy for loss trials was statistically significant ($F(1, 78) =$

4.53, p = 0.036). On loss trials, the Citalopram group selected the optimal, low probability loss choice significantly less frequently (model-adjusted mean = 79.0%, SE = 2.43%, 95% CI: 74.1% to 83.8%) compared to the Placebo group (model-adjusted mean = 81.2%, SE = 2.43%, 95% CI: 76.4% to 86.1%).

5.3.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on choice accuracy at EOS assessment for either win ($F(1, 76) = 0.30$, p = 0.585) or loss ($F(1, 76) = 0.98$, p = 0.325) trials.

5.3.3 Reaction time to optimal choice

Mean reaction times to making an optimal choice across the last 20 trials of the three PILT blocks at EOS assessment are presented in Figure 5.5, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

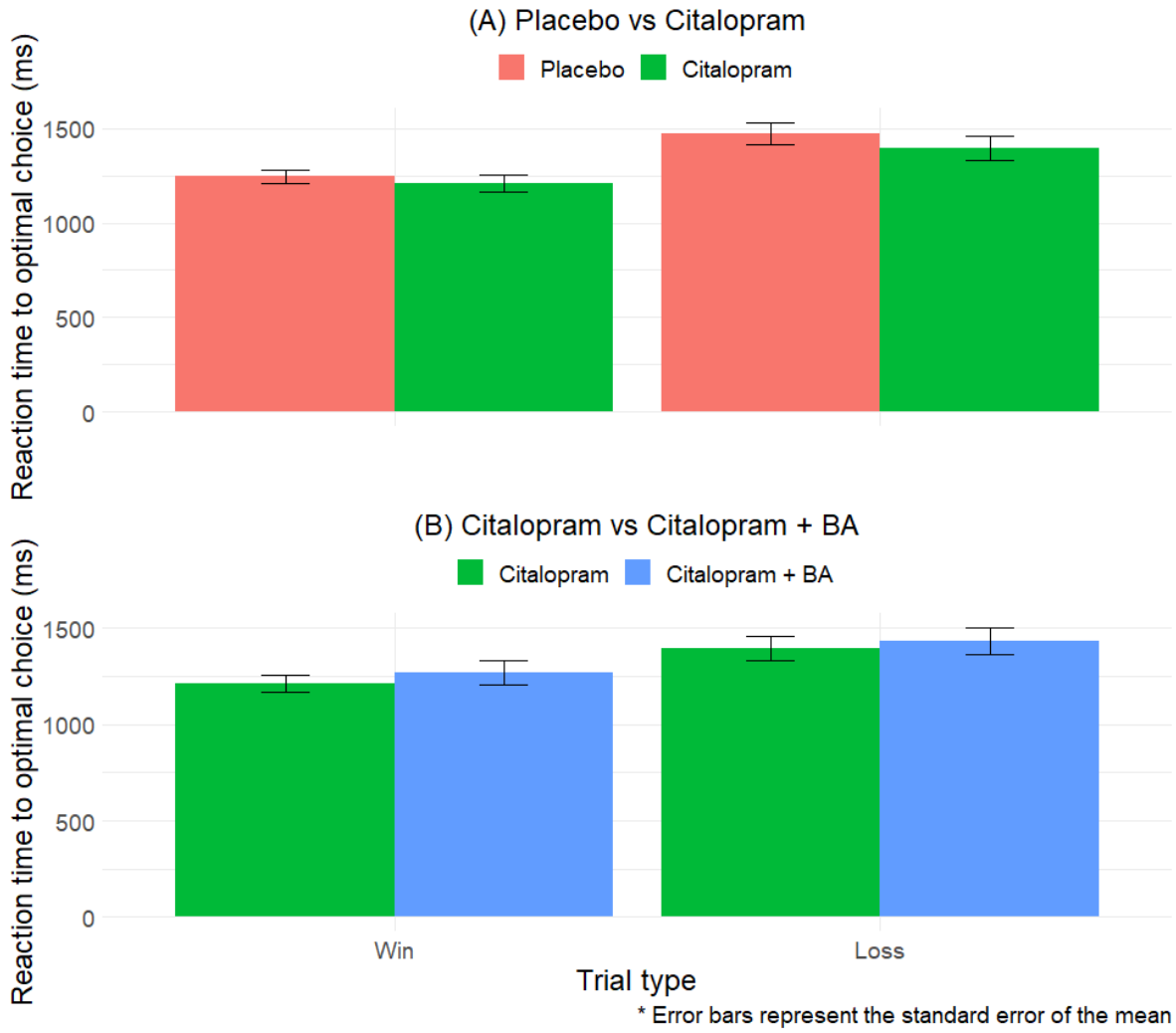


Figure 5.5. Mean reaction times (in milliseconds) to optimal choice selection averaged over the last 20 trials of the three PILT blocks at EOS assessment, separately for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison. Note the optimal choice is different on win and loss trials

5.3.3.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on reaction times to optimal choice selection at EOS assessment for either win ($F(1, 78) = 0.64$, $p = 0.426$) or loss ($F(1, 78) = 1.76$, $p = 0.189$) trials.

5.3.3.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on reaction times to optimal choice selection at EOS assessment for either win ($F(1, 76) = 0.94$, $p = 0.336$) or loss ($F(1, 76) = 0.18$, $p = 0.676$) trials.

5.3.4 Win-stay/Lose-shift

The percentage of win-stay and lose-shift trials across the last 20 trials of the three PILT blocks at EOS assessment are presented in Figure 5.6, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

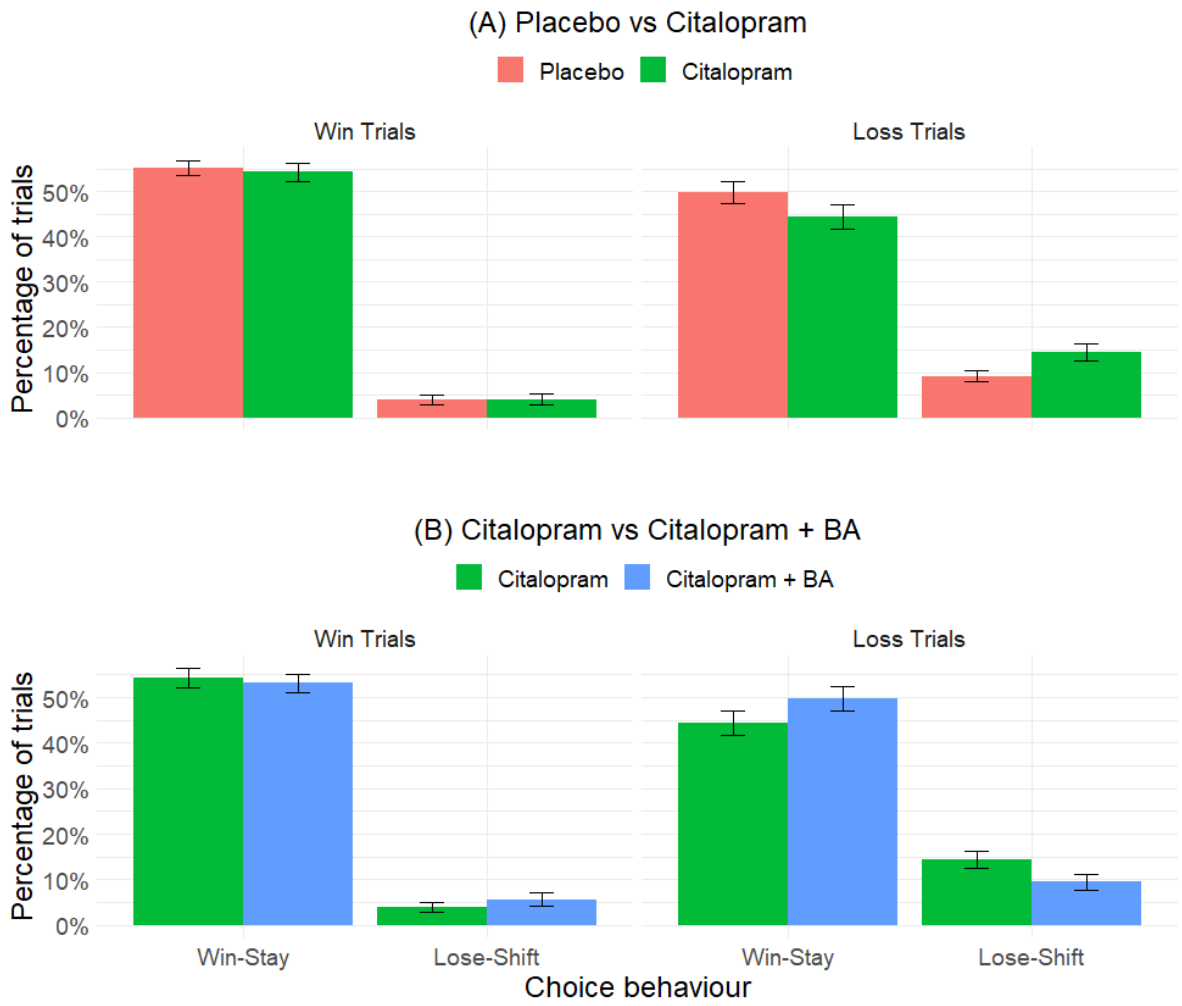


Figure 5.6. Percentage of "win-stay" and "lose-shift" trials across the last 20 trials of the three blocks of the PILT at EOS assessment, presented separately for win and loss trials and (A) the Placebo vs Citalopram comparison and (B) the Citalopram vs Citalopram + BA Comparison

5.3.4.1 Placebo vs Citalopram comparison

For win trials in the PILT, we did not observe a significant effect of treatment group on the percentage of win-stay ($F(1, 78) = 0.15$, $p = 0.697$) or lose-shift ($F(1, 78) = 0.0003$, $p = 0.987$) trials. However, for loss trials, a trend towards significance was observed in the effect of treatment group on the percentage of win-stay trials ($F(1, 78) = 3.69$, $p = 0.059$). Following

an advantageous outcome (no change) on loss trials, the Citalopram group stayed with the same symbol choice less often (model-adjusted mean = 46.8%, SE = 1.97%, 95% CI: 42.9% to 50.7%) compared to the Placebo group (model-adjusted mean = 47.5%, SE = 1.97%, 95% CI: 43.5% to 51.4%).

Additionally, we found a significant effect of treatment group on the percentage of lose-shift trials ($F(1, 78) = 9.78$, $p = 0.002$). Following a disadvantageous outcome (-20p loss) on loss trials, the Citalopram group shifted their symbol choice significantly more often (model-adjusted mean = 13.1%, SE = 1.21%, 95% CI: 10.68% to 15.5%) compared to the Placebo group (model-adjusted mean = 10.5%, SE = 1.21%, 95% CI: 8.06% to 12.9%).

5.3.4.2 Citalopram vs Citalopram + BA comparison

For win trials in the PILT, we did not observe a significant effect of treatment group on the percentage of win-stay ($F(1, 76) = 0.27$, $p = 0.605$) or lose-shift ($F(1, 76) = 1.16$, $p = 0.284$) trials. Similarly, for loss trials, the effect of treatment group on the percentage of win-stay trials was not significant ($F(1, 76) = 2.79$, $p = 0.099$). However, we found a significant effect of treatment group on the percentage of lose-shift trials ($F(1, 76) = 6.48$, $p = 0.013$). Following a disadvantageous outcome (-20p loss) on loss trials, the Citalopram + BA group shifted their symbol choice significantly less often (model-adjusted mean = 10.4%, SE = 1.44%, 95% CI: 7.58% to 13.3%) compared to the Citalopram group (model-adjusted mean = 13.4%, SE = 1.40%, 95% CI: 10.62% to 16.2%).

5.3.5 Sensitivity analysis

When participants who achieved <50% accuracy across both win and loss trials were excluded from the analysis, several changes in the statistical outcomes were observed. The comparison between the Placebo and Citalopram groups for accuracy on loss trials, which was previously significant, shifted to trend-level significance ($F(1, 75) = 3.64$, $p = 0.060$). In the "win-stay, lose-shift" analysis, the comparison between the Citalopram and Citalopram + BA groups for the percentage of win-stay choices on loss trials became statistically

significant ($F(1, 72) = 4.02$, $p = 0.049$), whereas it had not been significant in the initial analysis. Specifically, following an advantageous (no change) outcome on loss trials, the Citalopram + BA group tended to stay with the same symbol choice more often (model-adjusted mean = 49.8%, SE = 2.34%, 95% CI: 45.2% to 54.5%) compared to the Citalopram-only group (model-adjusted mean = 46.7%, SE = 2.22%, 95% CI: 42.3% to 51.2%). No other changes to the previously reported results were observed.

5.4 Discussion

In the CABIN study, we aimed to explore the effects of BA-augmented SSRI treatment on reward and punishment learning in individuals with mild to moderate depression. Our primary hypothesis was that BA would mitigate any potential blunting of reward sensitivity induced by citalopram and improve reward learning. However, contrary to this expectation, we observed no significant differences in reward learning (win trials) across treatment groups. Instead, the most pronounced effects emerged from loss trials, where a two-week course of citalopram appeared to increase punishment sensitivity compared to placebo.

At the EOS assessment, participants in the Citalopram group showed a reduced likelihood of selecting the stimulus associated with a lower probability of loss compared to the Placebo group. They also shifted their symbol choices more frequently following disadvantageous outcomes (losses) compared to both the Placebo and Citalopram + BA groups. Notably, this behaviour was observed during the last 20 trials of each block, a phase when learning was expected to have "plateaued" and participants should have been aware of which stimulus was statistically more advantageous. This finding echoes a previous result in depressed patients, who were more likely than controls to switch their choices after receiving non-reward feedback in a probability reversal learning task, even after they had learned the more advantageous option (Murphy et al., 2003). This may suggest a less stable integration of punishment-related information over trials, as well as heightened sensitivity to negative feedback. The Citalopram group also showed a decreased (albeit not statistically significant)

tendency to stick with the same symbol after an advantageous outcome (no change) on loss trials compared to the Placebo group, further supporting the notion that citalopram may alter loss outcome sensitivity. Such findings align with previous research indicating that SSRIs can alter decision-making in response to aversive outcomes, though the direction and nature of these effects have varied (Langley et al., 2023; Michely et al., 2022).

The observation that participants in the Citalopram group were more likely to switch symbol choices after a disadvantageous outcome and, to a lesser extent, less likely to stick with the same choice after an advantageous outcome may alternatively suggest that citalopram could increase exploratory behaviour in response to negative (loss) or ambiguous (no change) outcomes. This aligns with previous research showing that a one-week course of citalopram enhanced information gathering in a task where stimulus sampling incurred a monetary cost. In that experiment, healthy volunteers chose how many cards to “reveal” before deciding the predominant colour of the deck. In one condition, sampling was cost-free, while in the other, each card reveal cost 10 points from a starting total of 250. Participants randomised to citalopram increased their number of card draws in both conditions compared to those on placebo, even when this reduced their potential earnings. Computational analysis revealed that citalopram decreased the subjective cost of information gathering, making it feel less cognitively effortful (Michely et al., 2023). Importantly, our findings contrast with previous research showing that depressed patients tend to adjust their behaviour less after receiving negative feedback (Holmes & Pizzagalli, 2007). This raises the question of whether citalopram may facilitate behavioural adjustments in response to negative feedback, potentially by reducing the cognitive cost of exploration.

Interestingly, adding BA to citalopram treatment appeared to reverse some of the response patterns observed with citalopram monotherapy. Although no significant differences between the Citalopram and Citalopram + BA groups were found on win trials, the Citalopram + BA group exhibited fewer shifts in symbol choice following a disadvantageous outcome (loss)

compared to the Citalopram group on loss trials. Additionally, they showed a greater tendency to stay with the same symbol after an advantageous outcome (no change), an effect that became statistically significant when excluding poor task performers from the analysis. Despite the lack of a statistically significant difference in overall accuracy between the two groups, these findings suggest that BA may decrease loss outcome sensitivity. This aligns with the broader conceptualization of BA as a treatment that encourages engagement in rewarding behaviours and reduces avoidance (Cuijpers et al., 2007). However, our results also imply that BA may help moderate responses to negative feedback, reducing the likelihood of disproportionate reactions to losses and enabling more stable performance in tasks involving uncertainty or potential punishment. These findings highlight the need to further explore the mechanisms of action for BA, particularly in relation to its effects on reward and punishment learning. Understanding how BA influences these processes could provide valuable insights into its relationship with treatment outcomes and inform more targeted therapeutic approaches.

Contrary to expectations, there were no observable effects of treatment on participants' behaviour during win trials. This finding is surprising given that SSRI administration has been associated with decreased sensitivity to rewarding outcomes in several studies (Langley et al., 2023; McCabe et al., 2010; Michely et al., 2022). Such reduced reward sensitivity has been linked to unwanted SSRI effects, including emotional blunting and reduced efficacy in addressing anhedonia (Vrieze et al., 2013). However, in the CABIN study, participants generally showed improvements in depression and anxiety symptoms in all treatment groups, as well as in their ability to derive rewards from their environment, as measured by the Environmental Reward Scale (EROS) (see Chapter 3). These overall improvements in well-being might explain why we did not observe any detrimental effects on choice accuracy and response patterns on win trials with citalopram.

Another reason we may have failed to replicate previous findings on learning from reward could be due to our task design. Our modified version of the Probabilistic Learning Task (Pizzagalli et al., 2005) emphasises losses as well as wins, which may have masked subtle changes in reward-driven behaviour. Loss trials in our study were more challenging and led to greater variability in participants' behaviour, as evidenced by the learning curves and reaction time (RT) graphs. Another important consideration is the population studied. Much of the cited literature involves healthy volunteers, whereas our sample consisted of depressed participants who might already exhibit abnormalities in reward processing. SSRIs may have different effects in depressed and non-depressed populations, and so further research involving depressed participants is needed to replicate and extend our findings.

Interpreting how performance during reinforcement learning tasks translates to real-life behaviours is challenging. An increase in choice-switching following a detrimental outcome could be adaptive or maladaptive, depending on the context. If this behaviour reflects higher punishment sensitivity, it might be maladaptive, as it suggests a reluctance to sample an action multiple times before deciding its overall benefit. For example, if someone does not enjoy a social gathering with a new group of friends on the first occasion, they may be less likely to accept a second invitation, potentially missing out on future enjoyable experiences. This could lead to decreased participation in activities that are generally rewarding but occasionally have drawbacks – a pattern that BA might help counteract. On the other hand, if increased choice-switching reflects greater information gathering, it might be positive as it could suggest an alleviation of motivational deficits commonly seen in depression (Michely et al., 2023). To better understand these dynamics, computational modelling could be valuable in distinguishing between these possibilities and providing deeper insights into the mechanisms at play.

In conclusion, our findings suggest that punishment learning may be a key mechanism through which BA modulates the effects of SSRI treatment. We observed that citalopram primarily influences punishment learning, leading to less stable decision-making following

negative feedback – a pattern that appears to be reversed with the addition of BA. Further research is needed to determine whether these effects are adaptive or maladaptive and to understand their relationship with treatment outcomes. Additionally, more behavioural studies are necessary to explore the effects of BA on reward learning.

6 CHAPTER 6: THE EFFECTS OF A BEHAVIOURAL ACTIVATION-ENRICHED SSRI INTERVENTION ON DAILY SELF-REPORTED MOOD AND AFFECTIVE VARIABILITY

6.1 INTRODUCTION

Assessing daily self-reported mood alongside the exploratory clinical outcomes discussed in Chapter 3 may offer valuable insights into how BA-enhanced SSRI treatment exerts therapeutic benefits, even in the absence of an effect on emotional processing.

While SSRIs are often described as having a delayed onset of effect in addressing the subjective symptoms of MDD, typically requiring 4–6 weeks for noticeable improvement, evidence suggests that they may exert therapeutic benefits earlier than previously thought. A meta-analysis by Taylor et al. found that treatment with SSRIs, compared to placebo, was associated with clinician-assessed clinical improvement by the end of the first week of use (Taylor et al., 2006). Similarly, another meta-analysis of 76 placebo-controlled studies found that approximately 60% of the mood improvement observed by the end of the trials, in both active antidepressant and placebo groups, occurred within the first 2 weeks of treatment. Furthermore, drug-placebo differences were most pronounced during this early period and diminished in a stepwise manner thereafter (Posternak & Zimmerman, 2005). Daily mood assessments might be more sensitive to such early mood changes induced by antidepressants than traditional clinical scales, which are typically designed to be administered at longer intervals, such as every few weeks.

Furthermore, early improvements in mood have been shown to be predictive of later treatment response. Research indicates that improvements within the first two weeks of treatment are associated with better long-term outcomes (Gorwood et al., 2015; Szegedi et al., 2009). Notably, early improvement does not necessarily refer to reductions in negative affect alone. A study by Gorwood et al. found that an increase in joy after two weeks of treatment with agomelatine was a stronger predictor of response at six weeks than a

decrease in sadness, suggesting that early changes in positive affect may provide important predictive information about treatment efficacy (Gorwood et al., 2015).

SSRIs also influence irritability, a symptom reported by approximately half of adults with MDD (Fava et al., 2010). Findings from the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) study showed greater improvements in irritability with sertraline compared to placebo after eight weeks of treatment, as measured by the 5-item irritability domain of the Concise Associated Symptom Tracking scale (Jha et al., 2020). Importantly, early increases in irritability (during the first six weeks of treatment) can emerge as a side-effect of antidepressant use, along with other symptoms such as anxiety, panic, insomnia, and mania/hypomania – a collection of symptoms referred to as “activation syndrome” (Harada et al., 2008; Jha et al., 2017; Sinclair et al., 2009). When combined with changes in depressive symptoms, these early increases in irritability are predictive of poorer longer-term outcomes (Jha et al., 2017; Minhajuddin et al., 2020).

Lastly, SSRIs are associated with "emotional blunting" in a subset of individuals, which is characterised by a diminished range and intensity of emotional experiences, such as a reduced ability to cry or feel enjoyment (Goodwin et al., 2017). Daily assessment of both positive and negative affect, as well as irritability, could help clarify the onset and extent of the effects described above, providing a deeper understanding of how SSRIs influence emotional experiences during the initial stages of treatment.

Psychological therapy, including cognitive-behavioural approaches, has also been shown to have rapid effects on mood. Research has shown that depression symptoms often improve rapidly between the second and fourth CBT sessions, with the rate of improvement stabilising as more sessions are completed (Cuijpers, Hollon, et al., 2013). As much as 40% of the variance in treatment outcomes can be attributed to changes in symptoms that occur by the third therapy session (Lambert, 2013). Thus, a granular look at affect changes during

CABIN's three-session BA course could be of great interest. Importantly, a focus on day-to-day affect change would be of relevance here, as BA might help transiently increase positive feelings and decrease negative feelings through the completion of daily tasks and goals set by each individual participant. These might become larger or more sustained as participants begin to benefit more from the therapy. BA might also help counter some of the early side effects of citalopram through its beneficial effects on anxiety (Hopko et al., 2016).

Beyond affect in and of itself, affective variability (also referred to as mood instability) in major depression has been of great interest to research due to its association with illness severity (Kuppens et al., 2007; Panaite et al., 2020; Sultson et al., 2024), poor prognosis (Patel et al., 2015) and depression risk (Angst et al., 2003). Mood instability is linked to many symptoms of depression, such as negative affect and neuroticism, and may contribute to maintaining negative cognitive-emotional processing styles (Kircanski et al., 2012; Miller et al., 2009; Miller & Pilkonis, 2006). Consequently, mood instability may additionally distort how individuals interact with their environment and make decisions, often resulting in negative outcomes and stressful life events, which in turn perpetuate negative affect and further mood instability. Therefore, decreasing affective variability might be one avenue through which successful treatment may alleviate these biases and ultimately lead to symptom improvement.

Both SSRIs and behavioural activation (BA) offer potentially contrasting approaches to managing affective variability in depression. SSRIs may initially exacerbate mood instability due to side effects like "activation syndrome" discussed above, particularly in the early stages of treatment (National Health Service, 2021). Additionally, some patients report experiencing emotional blunting within the first few weeks of taking an SSRI (Price et al., 2009), which may have the opposite effect on instability; as mood begins to feel more "flat" and the intensity of both positive and negative emotions is "toned down", affective variability might decrease. While emotional blunting is not experienced by all patients, with estimates suggesting a prevalence of around 46% (Goodwin et al., 2017), it may still contribute to a

reduction in mood variability in some cases. However, given the potential for activation syndrome to increase variability and emotional blunting to decrease it, the net impact of SSRIs on mood variability is likely to be complex and patient-dependent, with the overall effect varying based on individual responses to treatment.

In contrast, BA provides a more proactive approach to mood management, which may help stabilise mood swings by promoting consistent activity and improving coping strategies. BA fosters a sense of control and mastery over daily activities, which can counter feelings of helplessness often associated with mood instability (Scherer, 2022). Moreover, preliminary evidence suggests that BA may be effective in treating depressive symptoms in bipolar disorder (BD), where mood instability and irritability are core features (Weinstock et al., 2016; Wright et al., 2022). Although BA primarily focuses on alleviating depressive symptoms, rather than directly targeting mood fluctuations, its structured approach may contribute to more stable affect over time in patients treated with SSRIs.

New technologies and widespread internet access now allow for sensitive monitoring of affect change and variability. Experience sampling methods (ESM) encompass a variety of research techniques used to collect data on individuals' behaviours, emotions, and experiences in real-time and in their natural environments. Participants are prompted at random or scheduled intervals throughout the day to report on their current state, using tools such as smartphones, diaries, or specialised devices (Myin-Germeys et al., 2018). ESM provide more objective and accurate reflections of early mood changes and mood variability during treatment, avoiding recall biases common in retrospective clinic assessments. In this study, we used an experience sampling questionnaire called the “Mood Zoom” (Tsanas et al., 2016) to measure affective ratings on six positive, negative and irritability-related items over a 21-day period encompassing one baseline week and two treatment weeks.

Based on the literature briefly reviewed above, we hypothesised that BA-enriched SSRI treatment would increase self-reported positive affect and decrease self-reported negative

affect over the two-week treatment period, compared to citalopram alone. We further speculated that BA-enriched SSRI treatment would result in increasingly positive day-to-day mood trajectories, with larger improvements in positive affect emerging between the two groups as the study progresses. Lastly, we hypothesised that BA-enriched SSRI treatment would reduce affective variability – particularly in terms of irritability and possibly in both positive and negative affect – compared to citalopram alone.

6.2 METHODS

6.2.1 "Mood Zoom" questionnaire

The experience sampling questionnaire used in the CABIN study was adapted from Tsanas et al., who developed the "Mood Zoom" out of a need for more precise instruments for longitudinal assessment of mood variability in psychiatric disorders such as BD and Borderline Personality Disorder (Tsanas et al., 2016). The original "Mood Zoom" is comprised of the following six descriptor items, each rated daily on a Likert scale from 1 (not at all descriptive of the participant's mood) to 7 (very much descriptive of the participant's mood): (1) anxious, (2) elated, (3) sad, (4) angry, (5) irritable, and (6) energetic. In the CABIN study, we used the word "happy" instead of "elated" to capture joyful rather than manic feelings, which may be more relevant for depression as described in the introduction to this chapter (Gorwood et al., 2015).

Participants were prompted daily by text message to report their mood, at a pre-specified time convenient for each participant; these times were allowed to span the whole day, although most participants requested an evening text reminder. The text message directly linked to a Qualtrics page displaying the questionnaire (see Figure 6.1), which was optimised for delivery on both desktop and mobile devices.

Daily mood monitoring started on formal inclusion in the study and randomisation at Screening 2 and continued until the day of the participant's End of Study (EOS) assessment. For most participants, this corresponded to a period of ~21 days (three weeks). Where the

recording period was longer (for example, due to more than seven days passing between Screening 2 and Baseline assessment), responses were trimmed such that analyses only encompassed 21 days' worth of data from each participant (the two weeks of active treatment plus the seven "baseline" days directly before treatment start).

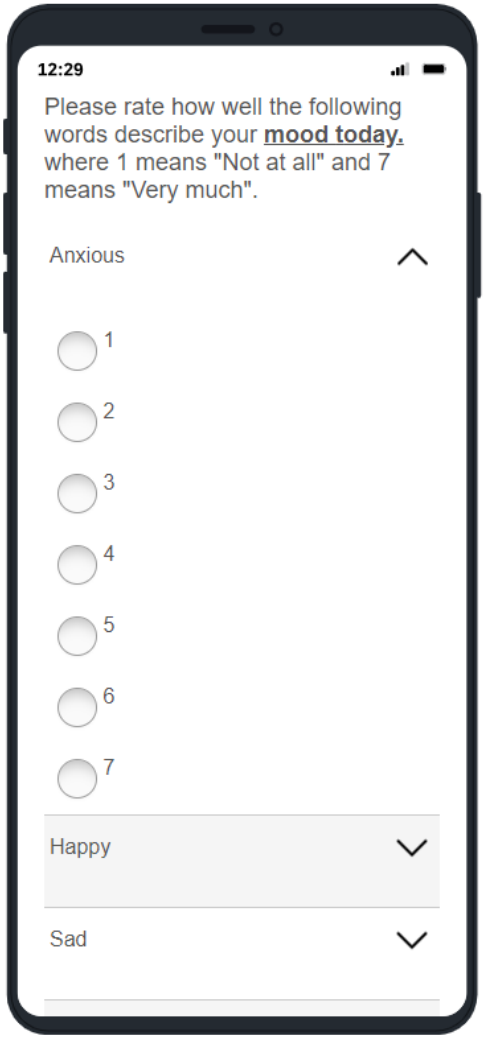


Figure 6.1. The "Mood Zoom" questionnaire used in the CABIN study, shown on a mobile device

6.2.2 Sample and adherence

All 134 subjects participated in "Mood Zoom" data collection.

Adherence was defined as the percentage of prompted "Mood Zoom" responses that were completed. As previously sent links did not expire at the end of each day, participants could, in theory, submit back-dated responses; where the researcher could clearly identify that this

was the case through the participant-inputted date (rather than the system-recorded date), the response was counted and included in the analyses presented in this chapter (approximately 7.5% of data). Although this approach might introduce recall bias into the results, it also maximises data available and thus statistical power. The mean adherence over the course of the study was 91.89% (SD = 7.65). As illustrated in Figure 6.2, adherence was consistently above 75% throughout the study in all treatment groups.

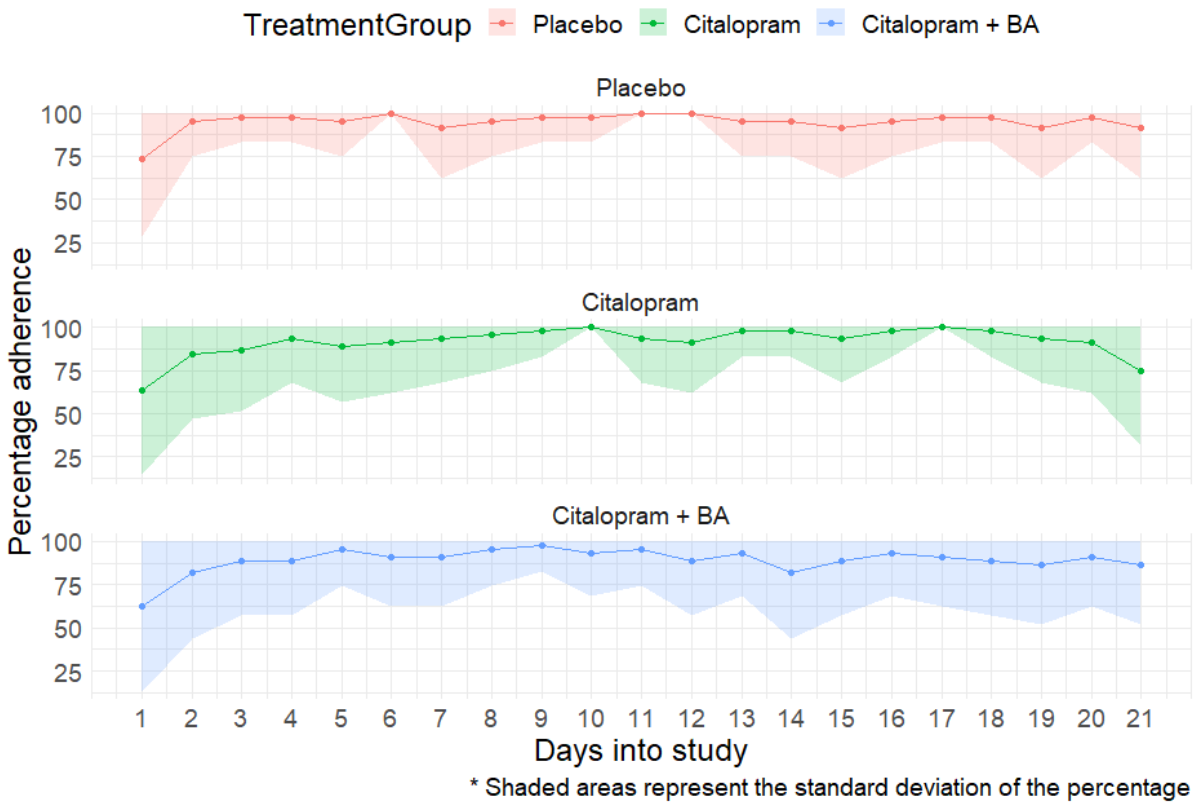


Figure 6.2. Percentage adherence for the "Mood Zoom" questionnaire over the course of the study, by treatment group

To assess the impact of questionnaire adherence on results, sensitivity analyses were conducted to control for the number of days' worth of "Mood Zoom" data available for each participant.

6.2.3 "Mood Zoom" variables

According to the original publication of Tsanas et al., the latent variable structure of the "Mood Zoom" has three components, as follows: positive affect (dominated by the "happy"

and “energetic” items), negative affect (dominated by the “sad” and “anxious” items) and irritability (dominated by the “angry” and “irritable” items) (Tsanas et al., 2016). Thus, for our analyses, we created composite daily scores for positive affect, negative affect and irritability by averaging the scores of the two items making up each “Mood Zoom” component. We then defined “valence” as a within-subjects factor, where each participant's ratings were categorised according to these three components – positive affect, negative affect, and irritability – allowing us to examine how the three treatment conditions influenced these different affective dimensions over time.

To quantify the variability of the time-series, we computed the Root Mean Square of Successive Differences (RMSSD) for each affective dimension, for each participant and for each of the three weeks of ratings considered (Baseline, Treatment week 1, Treatment week 2). The RMSSD is a simple measure of variability that captures day-to-day changes in mood ratings, and has been used previously in similar research (Tsanas et al., 2016). It is calculated by taking the differences between each consecutive day's ratings, squaring these differences, averaging them, and then taking the square root of this average:

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}$$

In calculating the RMSSD, we removed observations collected more than one day apart (3.87% of data), as these do not accurately represent day-to-day changes and could artificially inflate variability. By capturing the RMSSD separately for the three weeks of ratings provided by participants, we can investigate how the three treatment conditions affect mood variability while controlling for a no-treatment baseline. We can also directly test our hypothesis that BA-enriched citalopram treatment might lead to lower mood variability.

6.2.4 Analysis of “Mood Zoom” data

To examine the effect of treatment group on affective change over the two treatment weeks, we first aggregated daily ratings from the baseline week to create baseline scores for

positive affect, negative affect, and irritability. These baseline scores allowed us to control for initial affective states in our analyses.

We then fitted linear mixed-effects models to the "Mood Zoom" data, incorporating both fixed effects (related to treatment group, valence, treatment week, and covariates) and random effects (accounting for individual differences among participants). This approach appropriately handles the longitudinal structure of the data and helps to distinguish between-subject variability from within-subject variability. The primary model used to investigate affective trajectories across the two treatment weeks was as follows:

$$rating \sim (treatment\ group\ x\ valence\ x\ treatment\ week) + average\ baseline\ rating + (1|Participant\ ID)$$

To examine affective trajectories across the 14 days of treatment with greater granularity, we replaced the treatment week variable with measurement day as a within-subjects factor in our model:

$$rating \sim (treatment\ group\ x\ valence\ x\ measurement\ day) + average\ baseline\ rating + (1|Participant\ ID)$$

Measurement days were coded as days 8 through 21 of data collection. This model allowed us to compare groups on each measurement day, providing insight into when during treatment the ratings might begin to diverge.

To analyse the RMSSD values, we employed a similar linear mixed-effects modelling approach as was used for the "Mood Zoom" ratings. The model was specified as follows:

$$RMSSD \sim (treatment\ group\ x\ valence\ x\ treatment\ week) + baseline\ RMSSD + (1|Participant\ ID)$$

In contrast with analyses presented in other chapters, we chose not to control for participants' baseline BDI-II scores in any of these models, due to their high correlation with

the “Mood Zoom” composite scores (correlation with positive affect score: -0.33, $p < 0.001$; correlation with negative affect score: 0.39, $p < 0.001$; correlation with irritability score: 0.187, $p = 0.032$).

Following model fitting, we conducted repeated measures ANCOVAs to further isolate the effects of treatment group (Placebo vs. Citalopram or Citalopram vs. Citalopram + BA) on “Mood Zoom” ratings and their RMSSD, with valence (positive affect vs. negative affect vs. irritability) and treatment week (week 1 vs. week 2) as within-subject factors. We also examined the interaction among treatment group, valence, and study week. This two-step approach enhanced the precision and nuance of our analyses by accounting for daily and/or weekly fluctuations in mood ratings, leading to more reliable estimates of the treatment effects.

If BA-enhanced citalopram treatment leads to more positive mood trajectories compared to citalopram alone, we would expect statistically significant treatment group × valence × study week and treatment group × valence × measurement day interactions. Specifically, we anticipated differences in favour of the BA-treated group on the positive affect dimension, but not the negative affect and irritability dimensions. Additionally, we hypothesised that the slopes of model-estimated “Mood Zoom” ratings would be steeper in the Citalopram + BA group compared to the Citalopram alone group, or that group differences would become more pronounced as treatment progresses.

It is important to note that the ratings for each of the three composite “Mood Zoom” scores and their associated RMSSD values were not normally distributed. However, linear mixed-effects models are robust to non-normality of the raw data, if the model residuals are normally distributed. To verify this assumption, we inspected the residuals using histograms and QQ plots, which confirmed that they approximately followed a normal distribution. Additionally, we performed separate analyses using non-parametric statistical methods,

which yielded results consistent with those from the linear mixed models, reinforcing the robustness of our findings.

Finally, sensitivity analyses were conducted to further control for questionnaire adherence, which was recorded as the number of valid “Mood Zoom” days of data collected from each participant.

6.3 RESULTS

6.3.1 Weekly mood trajectories

Weekly mean composite “Mood Zoom” ratings for positive affect, negative affect and irritability over the three weeks of data collection (baseline, treatment week 1, treatment week 2) are presented in Figure 6.3, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

Upon visual inspection, it is apparent that ratings for negative affect items and irritability items decreased as the study progressed in all treatment groups. In contrast, ratings for positive affect items remained relatively stable throughout the study.



Figure 6.3. Mean weekly ratings for each of the three "Mood Zoom" dimensions, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison; BL = Baseline week, Week 1 = Treatment week 1, Week 2 = Treatment week 2

6.3.1.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on "Mood Zoom" ratings over the two treatment weeks ($F(1, 84.5) = 0.60$, $p = 0.441$), nor a significant interaction between treatment group and valence ($F(2, 3378.2) = 2.40$, $p = 0.090$) or between treatment group and treatment week ($F(1, 3379) = 0.07$, $p = 0.795$). However, the three-way interaction between treatment group, valence, and treatment week was significant ($F(2, 3375.6) = 6.49$, $p = 0.002$).

When analysing each "Mood Zoom" dimension separately, the interaction between treatment group and treatment week was significant for positive affect ($F(1, 1070.79) = 8.72$, $p = 0.003$)

and irritability (F(1, 1069.45) = 5.20, p = 0.023), but not for negative affect (F(1, 1070) = 2.36, p = 0.125). These significant interactions were driven not by differences between the treatment groups, which were not significant at either study week for any valence, but by changes within the Citalopram group during treatment.

Specifically, in terms of positive affect, the Citalopram group experienced a significant increase from the first to the second week of treatment (model-adjusted mean for week 1 = 3.21, SE = 0.10, 95% CI: 3.01 to 3.40; model-adjusted mean for week 2 = 3.57, SE = 0.10, 95% CI: 3.37 to 3.76; p < 0.001), while ratings in the Placebo group remained stable (model-adjusted mean for week 1 = 3.34, SE = 0.09, 95% CI: 3.16 to 3.53; model-adjusted mean for week 2 = 3.39, SE = 0.09, 95% CI: 3.20 to 3.58; p = 0.504).

Regarding irritability, both treatment groups experienced a decrease from the first to the second week of treatment, but this decrease was more pronounced in the Citalopram group (model-adjusted mean for week 1 = 1.96, SE = 0.09, 95% CI: 1.78 to 2.14; model-adjusted mean for week 2 = 1.62, SE = 0.09, 95% CI: 1.43 to 1.80; p < 0.001) compared to the Placebo group (model-adjusted mean for week 1 = 1.93, SE = 0.09, 95% CI: 1.75 to 2.11; model-adjusted mean for week 2 = 1.79, SE = 0.09, 95% CI: 1.61 to 1.97; p = 0.021).

6.3.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on “Mood Zoom” ratings over the two treatment weeks (F(1, 83.6) = 0.001, p = 0.973), nor a significant interaction between treatment group and valence (F(2, 3284.8) = 0.83, p = 0.434) or between treatment group and treatment week (F(1, 3290.1) = 0.23, p = 0.631). However, the three-way interaction between treatment group, valence, and treatment week was significant (F(2, 3279.1) = 10.44, p < 0.001).

When analysing each “Mood Zoom” dimension separately, the interaction between treatment group and treatment week was significant for positive affect (F(1, 1040.85) = 11.23, p < 0.001) and irritability (F(1, 1039.74) = 11.74, p < 0.001), but not for negative affect (F(1,

1038.32) = 1.96, p = 0.162). Like previous results comparing the Placebo and Citalopram groups, these significant interactions were driven not by differences between the treatment groups, which were not significant at either study week for any valence, but by changes within the Citalopram group during treatment.

In terms of positive affect, the Citalopram group experienced a significant increase from the first to the second week of treatment (model-adjusted mean for week 1 = 3.15, SE = 0.10, 95% CI: 2.96 to 3.35; model-adjusted mean for week 2 = 3.51, SE = 0.10, 95% CI: 3.32 to 3.71; p < 0.001), while ratings in the Citalopram + BA group remained stable (model-adjusted mean for week 1 = 3.40, SE = 0.10, 95% CI: 3.22 to 3.59; model-adjusted mean for week 2 = 3.40, SE = 0.10, 95% CI: 3.21 to 3.59; p = 0.943).

In terms of irritability, the Citalopram group experienced a significant decrease from the first to the second week of treatment (model-adjusted mean for week 1 = 2.04, SE = 0.09, 95% CI: 1.87 to 2.22; model-adjusted mean for week 2 = 1.70, SE = 0.09, 95% CI: 1.52 to 1.88; p < 0.001), while ratings in the Citalopram + BA group remained stable (model-adjusted mean for week 1 = 1.82, SE = 0.09, 95% CI: 1.65 to 1.99; model-adjusted mean for week 2 = 1.80, SE = 0.09, 95% CI: 1.62 to 1.97; p = 0.681).

6.3.2 Daily mood trajectories

Daily mean composite “Mood Zoom” ratings for positive affect, negative affect and irritability over the three weeks (21 days) of data collection are presented in Figure 6.4, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

Similar patterns to those observed in the weekly aggregated data are evident upon visual inspection of the daily ratings. Negative affect and irritability show a downward trajectory across the two treatment weeks in all treatment groups. A slight upward trend is observable for positive affect, particularly in the Citalopram group. Additionally, Citalopram treatment appears to be characterised by initial decreases in positive affect and increases in irritability

at the very start of treatment; however, these changes were not sustained throughout the two-week treatment period.

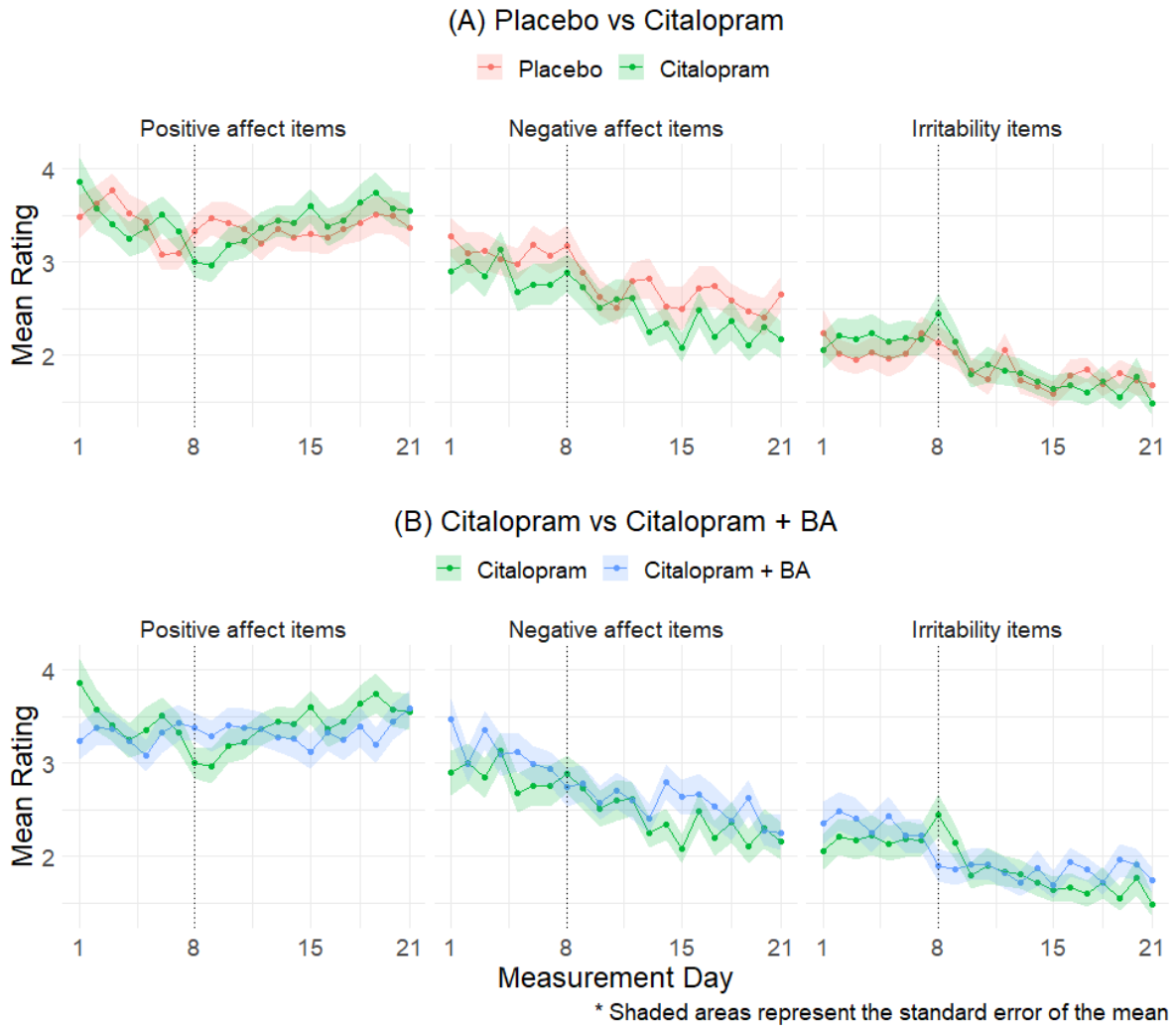


Figure 6.4. Mean ratings for each Mood Zoom dimension over the course of 21 study days, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison; dotted line at day 8 represents the start of the treatment period

6.3.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on "Mood Zoom" ratings over the 14-day treatment period ($F(1, 84.6) = 0.59$, $p = 0.445$), nor a significant interaction between treatment group and valence ($F(2, 3306.1) = 2.58$, $p = 0.076$) or between treatment group and measurement day ($F(13, 3307.5) = 0.34$, $p = 0.986$). However, the three-way interaction between treatment group, valence, and measurement day was significant ($F(26, 3303.7) = 1.56$, $p = 0.036$).

When analysing each “Mood Zoom” dimension separately, the interaction between treatment group and measurement day was marginally significant for positive affect (F(13, 1046.99) = 1.74, p = 0.048), but not for negative affect (F(13, 1046.14) = 1.06, p = 0.390) or irritability (F(13, 1045.57) = 1.33, p = 0.187).

For positive affect, a significant group difference was observed on day 9 of data collection (measurement day = 9), where the Citalopram group showed lower ratings than the Placebo group (model estimated difference = -0.57, SE = 0.23, df = 629, t-ratio = 2.55, p = 0.011). No other group comparisons reached statistical significance.

However, it is important to note that this difference would not survive correction for multiple comparisons (p < 0.0036), indicating that the finding should be interpreted with caution.

6.3.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on “Mood Zoom” ratings over the 14-day treatment period (F(1, 83.7) = 0.002, p = 0.961), nor a significant interaction between treatment group and valence (F(2, 3212.6) = 0.80, p = 0.451) or between treatment group and measurement day (F(13, 3214.7) = 0.60, p = 0.860). However, the three-way interaction between treatment group, valence, and measurement day was significant (F(26, 3207) = 2.04, p = 0.001).

When analysing each “Mood Zoom” dimension separately, the interaction between treatment group and measurement day was significant for positive affect (F(13, 1015.75) = 1.89, p = 0.027) and irritability (F(13, 1014.59) = 2.46, p = 0.003) but not for negative affect (F(13, 1013.17) = 1.45, p = 0.131).

For positive affect, significant differences were observed on measurement days 8 and 9. On day 8, the Citalopram + BA group had higher ratings compared to the Citalopram group (model-estimated difference = 0.53, SE = 0.23, df = 640, t-ratio = 2.32, p = 0.021). Similarly,

on day 9, the Citalopram + BA group again had higher ratings than the Citalopram group (model-estimated difference = 0.52, SE = 0.23, df = 628, t-ratio = 2.29, p = 0.023).

For irritability, significant differences were also observed on measurement days 8 and 9. On day 8, the Citalopram + BA group showed lower irritability compared to the Citalopram group (model-estimated difference = -0.71, SE = 0.20, df = 550, t-ratio = -3.55, $p < 0.001$). On day 9, this difference persisted, although it was less pronounced (model-estimated difference = -0.43, SE = 0.20, df = 538, t-ratio = -2.20, p = 0.028).

No other group differences reached statistical significance. However, it is important to note that only the day 8 difference in irritability would survive correction for multiple comparisons ($p < 0.0036$), indicating that the findings should be interpreted with caution.

6.3.3 Mood variability

Mean variability values (as measured by the RMSSD) for positive affect, negative affect and irritability during the three weeks of data collection (baseline, treatment week 1, treatment week 2) are presented in Figure 6.5, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

RMSSD values for all three “Mood Zoom” dimensions generally decrease over the course of the study, suggesting reduced variability in mood ratings across all treatment groups. While the Placebo and Citalopram groups show more sustained decreases in mood rating variability throughout the entire study period, in the Citalopram + BA group the largest changes appear to occur between the baseline week and treatment week 1, with little changes in mood variability from the first to the second week of treatment.

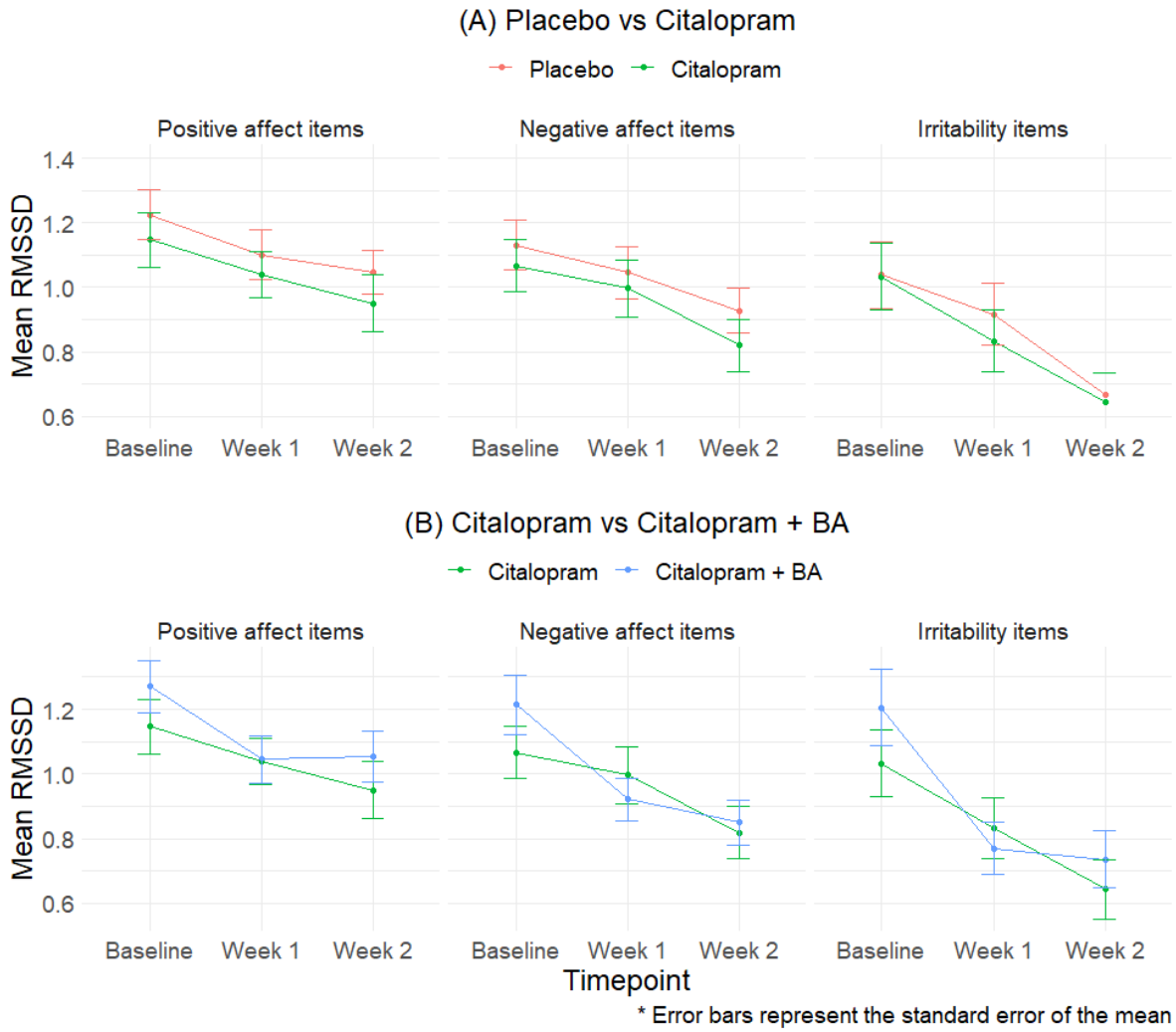


Figure 6.5. Mean weekly RMSSD values for each of the three "Mood Zoom" dimensions, for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison; Week 1 = Treatment week 1, Week 2 = Treatment week 2

6.3.3.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on mood variability over the two-week treatment period ($F(1, 82.65) = 0.67$, $p = 0.416$). Furthermore, the interactions between treatment group and valence ($F(2, 421{,}96) = 0.06$, $p = 0.938$), treatment group and study week ($F(1, 421.87) = 0.0002$, $p = 0.990$), and treatment group, valence and study week ($F(2, 421.87) = 0.15$, $p = 0.862$) were also not statistically significant.

6.3.3.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on mood variability over the two-week treatment period ($F(1, 84.20) = 0.13$, $p = 0.716$). The interactions between

treatment group and valence (F(2, 416.17) = 0.59, p = 0.554), treatment group and study week (F(1, 417.62) = 1.96, p = 0.162), and treatment group, valence and study week (F(2, 416.13) = 0.26, p = 0.769) were also not statistically significant.

6.3.4 Sensitivity analyses

Additionally controlling for questionnaire adherence/data availability did not change any of the above-presented results.

6.4 Discussion

Contrary to our hypothesis, BA-enhanced SSRI treatment did not increase self-reported positive affect nor decrease self-reported negative affect compared to citalopram alone. Average ratings for negative affect items of the "Mood Zoom" decreased throughout the course of the study in all treatment groups, which is in line with the analyses reported in Chapter 3 comparing clinical outcomes reported before and at the end of the treatment period; there, we also found self-reported depression and anxiety symptoms (measured by the BDI-II and STAI-S, respectively) to significantly decrease in all three treatment groups.

Interestingly, citalopram treatment was associated with more pronounced changes in both positive affect and irritability from the first to the second week of treatment, compared to both the Placebo and Citalopram + BA groups. Only the Citalopram group showed a significant increase in positive affect during this period, alongside the most pronounced decreases in irritability. These findings suggest that, while the placebo effect may predominantly manifest in reductions in negative affect (as seen in both the "Mood Zoom" and BDI-II data), active SSRI treatment may have a more targeted effect on increasing positive affect. This aligns with previous research suggesting that antidepressants can enhance positive emotional experiences, which may be critical to full recovery from depression (Gorwood et al., 2015; Wichers et al., 2010).

The absence of a significant increase in positive affect in the Citalopram + BA group, despite seeing it in the Citalopram-only group, is an intriguing result. While BA encourages active engagement and promotes positive affect through behavioural reinforcement, its initial focus is often on reducing avoidance and addressing negative affect. It is possible that, early in the treatment process, BA may have drawn more attention to depressive symptoms or required participants to make behavioural changes that initially dampened the positive affect boost observed with SSRIs alone.

Furthermore, our findings do not support the hypothesis of emotional blunting in the active treatment groups. On the contrary, average ratings for positive affect increased throughout the treatment period in the Citalopram-only group, and there were no significant differences between the Citalopram and Placebo groups at either treatment week. This suggests that emotional blunting, if present, did not manifest as a reduction in positive affect in our sample, reinforcing the idea that SSRIs may enhance positive mood without dampening emotional experiences. However, it is important to note that the observed increase in positive affect with citalopram was relatively small (estimated at 0.36 on a 7-point scale), so these findings should be interpreted with some caution.

Taking an SSRI in an enriched environment did not consistently alter day-to-day changes in affective state over the 21-day study period compared to citalopram alone, with affective trajectories across all treatment groups being broadly similar. However, our analysis of daily "Mood Zoom" ratings revealed some early group differences around the start of treatment (on measurement days 8-9), particularly between the Citalopram and Citalopram + BA groups. Specifically, citalopram treatment was associated with a transient decrease in positive affect and increase in irritability, though this pattern was not sustained and appeared to reverse by the end of the two-week period. Interestingly, the Citalopram + BA group showed more positive affect and less irritability on days 8-9 compared to the Citalopram group. Although only the difference in irritability remained significant after correction for

multiple comparisons, this early pattern coincided with the timing of the first BA session for most participants in the combined treatment group, suggesting a potential short-term effect related to the introduction of BA.

These early group differences may be attributed to both specific and non-specific treatment effects. Firstly, they may reflect non-specific effects of extended contact with the research team in the Citalopram + BA group, a well-documented confounding factor in psychotherapy studies (Cuijpers, Reijnders, et al., 2019). Additionally, they could be driven by participants' expectations regarding their treatment; those receiving the combination treatment may have had specific expectations based on their knowledge of receiving adjunct BA, influencing their early mood responses.

More importantly, they may reflect therapeutic processes that lead to immediate mood improvements following therapy sessions. The first BA session was designed to introduce participants to the purpose and structure of BA and included goal setting for the remainder of the intervention. This hopeful and forward-looking nature of the session could have positively impacted participants' sense of self-efficacy, leading to improvements in positive affect. In contrast, subsequent BA sessions (occurring around days 14 and 19) focused more on problem-solving and may have been perceived as more challenging, which could explain the absence of further positive effects linked to those sessions.

Although we were unable to directly link participants’ engagement in scheduled BA activities with their daily self-reported mood in this study, these findings highlight the importance of incorporating such measures in future research. Monitoring participants' engagement in BA activities could help identify specific behaviours that lead to immediate increases in positive affect. Indeed, a recent study piloted a remote intervention where participants were prompted to practice a series of researcher-taught CBT skills for 28 days after hospital discharge, with affect measured immediately afterward. While there was no difference in subsequent affect change between the different types of CBT skills used, participants

experienced modest reductions in negative affect after engaging in any of the prompted CBT skills practice. Moreover, individuals who reported larger or more consistent effects of previous prompted CBT activities also reported less anger, anxiety, and emotional reactivity at the end of the 28-day study period (Bernstein et al., 2022). This highlights the potential use of ecological momentary assessment tools like the “Mood Zoom” to enhance the delivery of psychological treatment and, in the case of BA, increase environmental enrichment.

Contrary to our hypothesis, the combined treatment did not significantly impact affective variability. Instead, RMSSD values generally decreased across all three treatment groups throughout the study, with the decline being more pronounced for the negative affect and irritability dimensions of the “Mood Zoom.” This could be in part an effect of response fatigue, where participants become more predictable in their answers with repeated exposure. To determine whether our findings reflect true mood stabilisation or merely a habituation effect, future research could employ random sampling times instead of administering the questionnaire at the same time each day or vary the order of the items presented to minimise the formation of response patterns.

Lastly, a limitation of the work presented in this chapter is that we did not examine individual “Mood Zoom” items, focusing instead on the dimensions of positive affect, negative affect, and irritability as described in the original publication (Tsanas et al., 2016). A strength of this approach is its grounding in previous research, as existing studies using experience sampling methods have highlighted the importance of positive-negative affect dynamics in predicting treatment response to psychotherapy and combination therapies (Husen et al., 2016; Wichers et al., 2012). Our results similarly reflect this potential distinction, with all treatments affecting negative but less positive affective states. Additionally, following the latent structure of the questionnaire, as described by Tsanas et al., provides a robust framework for interpreting the data. However, by constructing composite scores, we may have lost some nuance that individual item analyses could provide – especially in

understanding SSRI effects on positive affect, which in our study comprised ratings of "happy" and "energetic." This represents an important area for future research.

7 CHAPTER 7: THE EFFECTS OF A BEHAVIOURAL ACTIVATION-ENRICHED SSRI INTERVENTION ON BIOLOGICAL MARKERS OF CIRCADIAN RHYTHM

7.1 INTRODUCTION

A defining feature of major depressive disorder (MDD) is the disruption of circadian rhythms; alterations in rest-activity rhythms, social rhythms, hormone rhythms and body temperature rhythms have all been observed in patients with MDD (Vadnie & McClung, 2017). In the CABIN study, we explored the possibility that restoring typical circadian rhythms, specifically rest-activity cycles and surges in cortisol in response to awakening, might constitute mechanisms through which behavioural activation (BA) could enhance the effects of Selective Serotonin Reuptake Inhibitor (SSRI) treatment.

The mechanisms that regulate circadian activity patterns involve intricate interactions between environmental cues (such as the light-dark cycle, social interactions, meals, physical activity) and the internal clock located in the suprachiasmatic nucleus of the anterior hypothalamus. Patients with MDD often exhibit alterations in rest-activity patterns as measured through actigraphy, including lower general levels of physical activity (Minaeva et al., 2020), shorter bouts of daily activity (Fasmer et al., 2016), and flattened circadian fluctuations in activity levels (Difrancesco et al., 2022; Lyall et al., 2018; Walker et al., 2020). Symptom severity has been shown to correlate with the complexity of rest-activity patterns (Spulber et al., 2022), as well as with the amount of light and moderate-intensity physical activity performed (Helgadóttir et al., 2015; Morres, Hatzigeorgiadis, Krommidas, et al., 2019). Moreover, physical activity interventions have proven to be effective in reducing depressive symptomatology (Morres, Hatzigeorgiadis, Stathi, et al., 2019). Depression also adversely affects sleep, with core features being increased sleep onset latency, reduced sleep efficiency, and difficulty in maintaining a regular sleep schedule (Nutt et al., 2008; Pye et al., 2021).

The effects of SSRI treatment on objectively-measured activity levels remain largely unexplored, although one large observational study found that SSRI users showed significantly less overall movement over a seven-day period compared to individuals not taking SSRIs, even when controlling for depression severity (Heinz et al., 2022). SSRIs can also have side effects such as dizziness, sedation, and insomnia, especially during the first weeks of treatment, which may impact both rest and activity patterns (Hicks et al., 2002). SSRIs are known to reduce the amount of rapid eye movement (REM) sleep and increase REM sleep onset latency, potentially due to increased levels of synaptic serotonin and stimulation of the 5-HT1A receptor (Wichniak et al., 2017; Wilson & Argyropoulos, 2005). Thus, administered alone, SSRIs might not be as effective in reducing rest-activity disturbances as they are at treating depressive symptoms, particularly in the initial stages of treatment.

On the other hand, BA aims to increase activity levels by encouraging participants to engage in various pursuits, often with a focus on physical exercise as a treatment goal (Pentecost et al., 2015). While some participants may choose to focus on social or hobby-based activities rather than enhancing physical fitness, achieving these goals might still result in (indirect) increases in physical movement (e.g., getting to a painting class implies more movement than if one were to not attend and stay home instead). BA also promotes more regular rest-activity patterns due to the structure it introduces, such as keeping activity diaries and performing tasks at scheduled times. Thus, it would be of great interest to examine if BA-enhanced SSRI treatment results in heightened physical activity compared to an SSRI alone, due to more frequent sampling of the environment, as well as the establishment of more consistent activity routines.

Like rest-activity patterns, hormone rhythms are impacted by depression. In particular, the secretion of cortisol, a glucocorticoid hormone produced by the adrenal cortex, is often disrupted (Vadnie & McClung, 2017). Cortisol plays a critical role in the body's stress response and helps regulate metabolism, immune function, and circadian rhythms. One

specific aspect of cortisol secretion that is often examined is the Cortisol Awakening Response (CAR). The CAR is the rapid increase in cortisol levels 30–45 minutes after waking, with typical levels rising by about 50-60% from awakening, peaking approximately 30-45 minutes later (Pruessner et al., 1997; Stalder et al., 2016). The CAR is distinct from stress-reactive cortisol secretion and reflects the body's natural response to awakening, preparing it for daily activities and stressors. A higher CAR in healthy individuals is associated with attenuated distress responses to daily life stress (Powell & Schlotz, 2012).

Depression has been linked with both increased and blunted CAR. For instance, currently depressed adults have shown a higher CAR compared to healthy controls (Vreeburg et al., 2009), while treatment-resistant depression and high neuroticism have also been associated with heightened CAR (Markopoulou et al., 2010; Portella et al., 2005). Conversely, a blunted CAR has been observed in women with mild-to-moderate depression and in patients with severe MDD (Eikeseth et al., 2019; Stetler & Miller, 2005). An inverted U-shaped relationship has been suggested, where both high and low depression severity are associated with lower CAR compared to intermediate severity levels (Wardenaar et al., 2011).

SSRI administration, specifically citalopram, has been associated with increases in salivary cortisol when administered acutely and over the short term (Bhagwagar et al., 2002; Harmer, Bhagwagar, Shelley, et al., 2003; Nadeem et al., 2004; Pariante et al., 2004). A six-day course of 20mg of citalopram daily resulted in significantly higher cortisol levels 45 and 60 minutes after waking, indicative of a higher CAR (Harmer, Bhagwagar, Shelley, et al., 2003). Citalopram also enhances glucocorticoid-mediated negative feedback of the HPA axis, suggesting that it might normalise HPA axis hyperactivity (Pariante et al., 2004).

BA may enhance SSRI efficacy by increasing physical and social activity, which can influence cortisol rhythms. Increased physical activity levels, such as those promoted by BA, have been associated with a more robust CAR in both children and adults (Drogos et al., 2019; Ogasawara et al., 2022; Wegner et al., 2019), although an intensity dependency has

been noted (Anderson & Wideman, 2017). Additionally, BA's structured approach to activity planning and monitoring might improve coping with daily stressors, potentially resulting in a more robust CAR.

In the CABIN study, we used wrist-worn actigraphy devices to objectively monitor the physical activity and rest-activity patterns of participants. We also used at-home saliva collection kits to measure participants' cortisol secretion as well as CAR in the first half-hour post-awakening. Based on the literature briefly reviewed above, we hypothesised that BA-enhanced SSRI treatment will lead to increased objective levels of physical activity and less variability in daily rest-activity patterns compared to citalopram alone, as denoted by more consistent active/inactive time periods. We also hypothesised that citalopram would increase waking salivary cortisol levels compared to placebo. Additionally, we expected participants receiving the combination treatment to exhibit a more robust Cortisol Awakening Response (CAR) compared to the citalopram-only group, potentially reflecting a better ability to deal with daily stressors.

7.2 METHODS – ACTIGRAPHY

7.2.1 Actigraphy data collection and processing

7.2.1.1 Sample

Out of the 134 participants who completed the CABIN study, 131 consented to being equipped with wrist-worn GENEActiv Original actigraphy watches (ActivInsights Ltd, UK). In addition to the three participants not equipped with an actigraphy watch (two in the Placebo group, one in the Citalopram + BA group), data loss occurred in a further five participants (two in the Placebo group, two in the Citalopram group and one in the Citalopram + BA group), as follows:

- Device loss (two participants)
- Technical problems with recording (one participant)
- Early removal due to skin sensitivity (one participant)

- Error in setting device sampling frequency (one participant)

Therefore, the final sample for analysing rest and activity patterns consisted of 126 participants (N Placebo = 41, N Citalopram = 42, N Citalopram + BA = 43).

7.2.1.2 Device set-up

Participants were set up with their actigraphy device at Screening 2. Devices were configured by the study team using the GENEActiv software for Windows PCs (ActivInsights Ltd, UK), which required each participant's height, weight, and BMI to be entered. Actigraphy watches were given to participants to wear immediately after being configured and recording started immediately. Participants were asked to wear the devices on their non-dominant wrist for 24 hours a day for the duration of their participation in the study, which amounted to approximately 21 days from their Screening 2 visit to their EOS assessment. This specific guidance to wear the device on the non-dominant wrist was given because it typically exhibits less movement during daily activities compared to the dominant hand, thereby limiting unwanted motion artefacts. One ambidextrous participant was instructed to wear the watch on the wrist of the hand they did not use for writing. The wrist side where the watch was ultimately fitted was recorded for all participants.

Participants returned their actigraphy watches to the research team via pre-paid mail after their EOS assessment.

7.2.1.3 Data collection

The GENEActiv watches contain a tri-axial accelerometer measuring raw acceleration in gravitational units, with a range of +/- 8g (1g = 9.8 m/s2). The primary measure of activity is the gravity-subtracted signal vector magnitude of acceleration (Esliger et al., 2011), calculated as:

$$Acceleration\ magnitude = \left(\sum \sqrt{x^2 + y^2 + z^2} - g\right)$$

where x, y, and z are the three raw signals and g (9.8 m/s²) is subtracted to account for acceleration due to gravity. Negative values are rounded to zero, as per the Euclidean Norm Minus One (ENMO) (Hildebrand et al., 2014; van Hees et al., 2014).

To optimise battery life for the approximately three-week study period, the device sampling frequency was set to 25Hz, which kept the device functioning without the need for charge for four weeks.

7.2.1.4 Data pre-processing

Data were extracted from each actigraphy watch upon receipt from the participant, using the GENEActiv PC software. All data were extracted in .bin files and stored securely on university Microsoft OneDrive cloud servers prior to pre-processing.

Data were pre-processed using the *GGIR* package for R Statistical Software version 4.0.3 (Migueles et al., 2019). The *GGIR* non-wear algorithm ensured that any suspected actigraphy watch removals were identified and missing intervals imputed with the average of similar time points from other full days of recording. Any days with more than three hours of missing data were automatically excluded from further analyses due to inability to compute the desired rest and activity outcomes. Because of this, only data included between the first and last midnight of actigraphy recording were analysed for each participant. Appendix 1 provides two examples of actigraphy data quality plots generated by *GGIR*, from two representative participants with and without detected watch non-wear.

Two data files were outputted by the *GGIR* pre-processing package. The first held overall summary data for each actigraphy watch (across a maximum of 28 days), and the second included day-by-day summary measures of rest and activity. For the subsequently presented analyses, we used the day-by-day summary files such that each day could be identified as either part of the baseline week, or as part of the two treatment weeks (either treatment week 1 or treatment week 2). Where recordings where longer than three weeks, data in these files were trimmed such that analyses only encompassed 21 days' worth of recording

from each participant (the two weeks of active treatment plus the 7 days directly before treatment start).

7.2.1.5 Rest and activity variables

Non-parametric circadian rhythm analysis (NPCRA) variables (Van Someren et al., 1999) reflecting the structure of rest-activity patterns were calculated using the *GGIR* algorithm.

For the CABIN study, we were particularly interested in the M10 and L5 outcome measures, which provide key insights into participants' arousal patterns during the day and night. M10 activity quantifies the magnitude of physical movement during the most active 10-hour period of a 24-hour day. M10 values are expressed in milli-g (mg), where 1g represents the acceleration due to Earth's gravity (approximately 9.8 m/s^2), and 1mg equals one-thousandth of a g. This unit reflects the magnitude of body movement, with higher values indicating more vigorous physical activity. M10 onset serves as a phase marker, representing the time at which the most active 10-hour period begins. It is expressed in decimal hours, where, for example, a value of 10.5 corresponds to an onset time of 10:30 AM.

Similarly, L5 activity quantifies the magnitude of movement during the least active 5-hour period of a 24-hour day, also expressed in mg. Higher L5 values suggest more movement during the night, which can indicate less restful sleep. Lower L5 values, on the other hand, typically reflect reduced movement and a more restful sleep state. L5 onset, like M10 onset, is expressed in decimal hours; for example, a value of 22.5 corresponds to an onset time of 10:30 PM. Activity measured in this way is a validated indicator of circadian phase, predicting the rhythm of melatonin secretion (Bonmati-Carrion et al., 2014).

We further quantified the variability of M10 and L5 onsets by calculating the Root Mean Square of Successive Differences (RMSSD) for each participant and each week of actigraphy recording. The RMSSD is described in more detail in Chapter 6, but it is briefly summarised by the equation:

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}$$

In calculating the RMSSD, we removed observations collected more than one day apart (3.53% of data), as these do not accurately represent day-to-day changes and could artificially inflate variability.

Following data pre-processing, each participant had daily values for M10 activity, M10 onset, L5 activity, and L5 onset for each day of data collection (up to a maximum of 21 days). Additionally, each participant had six RMSSD values representing M10 and L5 onset variability for each of the three weeks of data collection.

7.2.1.6 Data cleaning

After consultation with an actigraphy expert, 11 days with M10 values over 150 (0.46% of actigraphy data) and one day with a L5 value over 40 (0.04% of data) were excluded from analysis due to these values being outside of their respective distributions and not commonly observed in actigraphy data.

7.2.2 Analysis of actigraphy data

Prior to the main statistical analyses, we descriptively explored variables with potential relevance to rest-activity patterns and plotted these for each treatment group. Specifically, we investigated the number of days of valid GENEActiv data collected from each participant, the number of days of GENEActiv data collected within each season, participants' season at study entry/randomisation, and the body location where the actigraphy watch was fitted. These variables are presented in Figures 7.1-7.3.

To examine the effect of treatment group on rest and activity patterns over the two treatment weeks, we first aggregated daily summary measures from the baseline week to create baseline scores for M10 activity, M10 onset, L5 activity, and L5 onset. These baseline scores allowed us to control for initial rest-activity patterns in our analyses.

We then fitted linear mixed effects models to the rest-activity data to account for both fixed effects (related to treatment group, treatment week, and covariates) and random effects (related to individual differences among participants). This approach takes into account the longitudinal structure of the data and helps to separate between-subject from within-subject variability. For each of the rest-activity variables (M10 activity, M10 onset, M10 onset variability, L5 activity, L5 onset, and L5 onset variability), we used the following model:

$$rest - activity\ variable \sim (treatment\ group\ x\ treatment\ week) + baseline\ score + baseline\ BDI - II\ score + (1|Participant\ ID)$$

Following this, we conducted repeated measures ANCOVAs to isolate the effect of treatment group (Placebo vs. Citalopram or Citalopram vs. Citalopram + BA) as the between-subjects factor, treatment week (week 1 vs. week 2) as the within-subjects factor, and the treatment group by study week interaction. This two-step approach enhances the accuracy and nuance of our models, accounting for daily and/or weekly fluctuations and patterns, leading to more reliable estimates of the treatment effects.

Sensitivity analyses were performed to further control for seasonality and data availability (recorded as the number of valid actigraphy data days collected from each participant). Additionally, we assessed the impact of excluding three participants who wore the actigraphy watch on their dominant wrist instead of their non-dominant wrist.

7.3 Results – Actigraphy

7.3.1 Descriptives

The median number of days of valid GENEActiv data was 20 for the Placebo group and 19 for the Citalopram and Citalopram + BA groups (see Figure 7.1). On average, participants provided 18 to 19 days' worth of data that could be included in our analyses (Mean Placebo = 18.66, SE = 0.48; Mean Citalopram = 18.07, SE = 0.49; Mean Citalopram + BA = 18.26, SE = 0.52).

A small number of outlying participants were present in all three treatment groups, who provided less than 15 days with valid GENEActiv data. To assess the impact of actigraphy watch non-wear on results, sensitivity analyses were conducted to control for the number of days' worth of actigraphy data available for each participant.

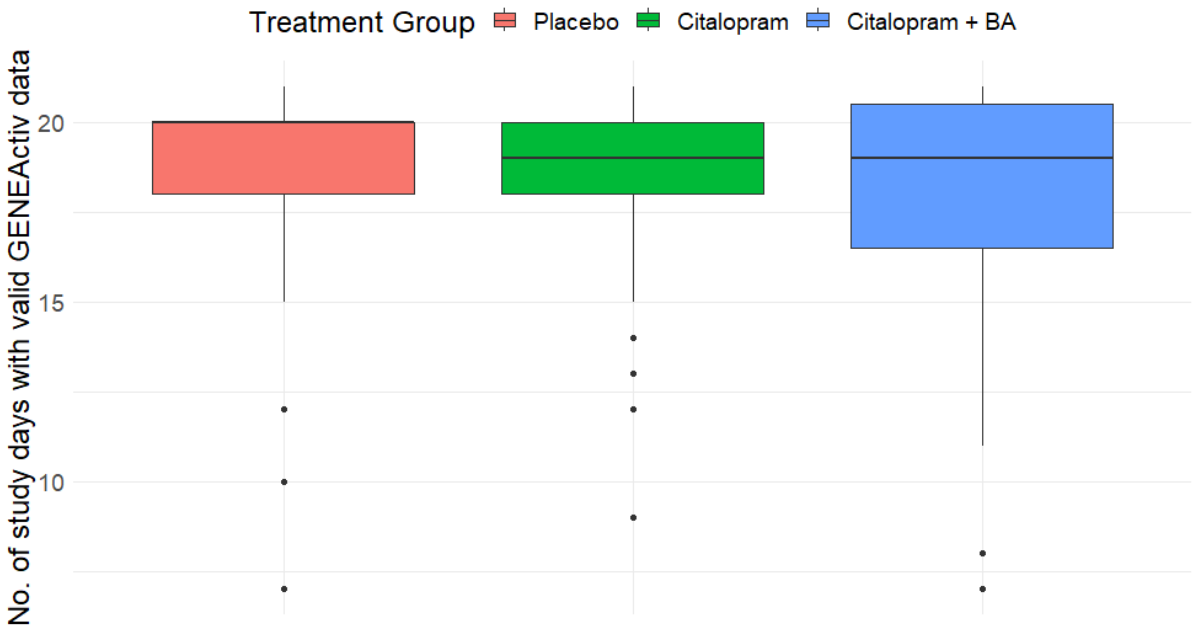


Figure 7.1. Boxplot of data availability per treatment group. Bold lines denote the median number of days with valid GENEActiv data

Seasonal patterns in actigraphy data collection are illustrated in Figure 7.2. As expected in a large study running over the course of several years, participants were randomised and data were collected across all four seasons, with no substantial differences in data seasonality apparent between the treatment groups.

Nevertheless, some seasonal differences in recruitment rates were observed, with the lowest rates in winter (N = 24) and the highest in autumn (N = 38). To account for potential effects of seasonality on our results, sensitivity analyses were conducted to control for these variations in observation timing.

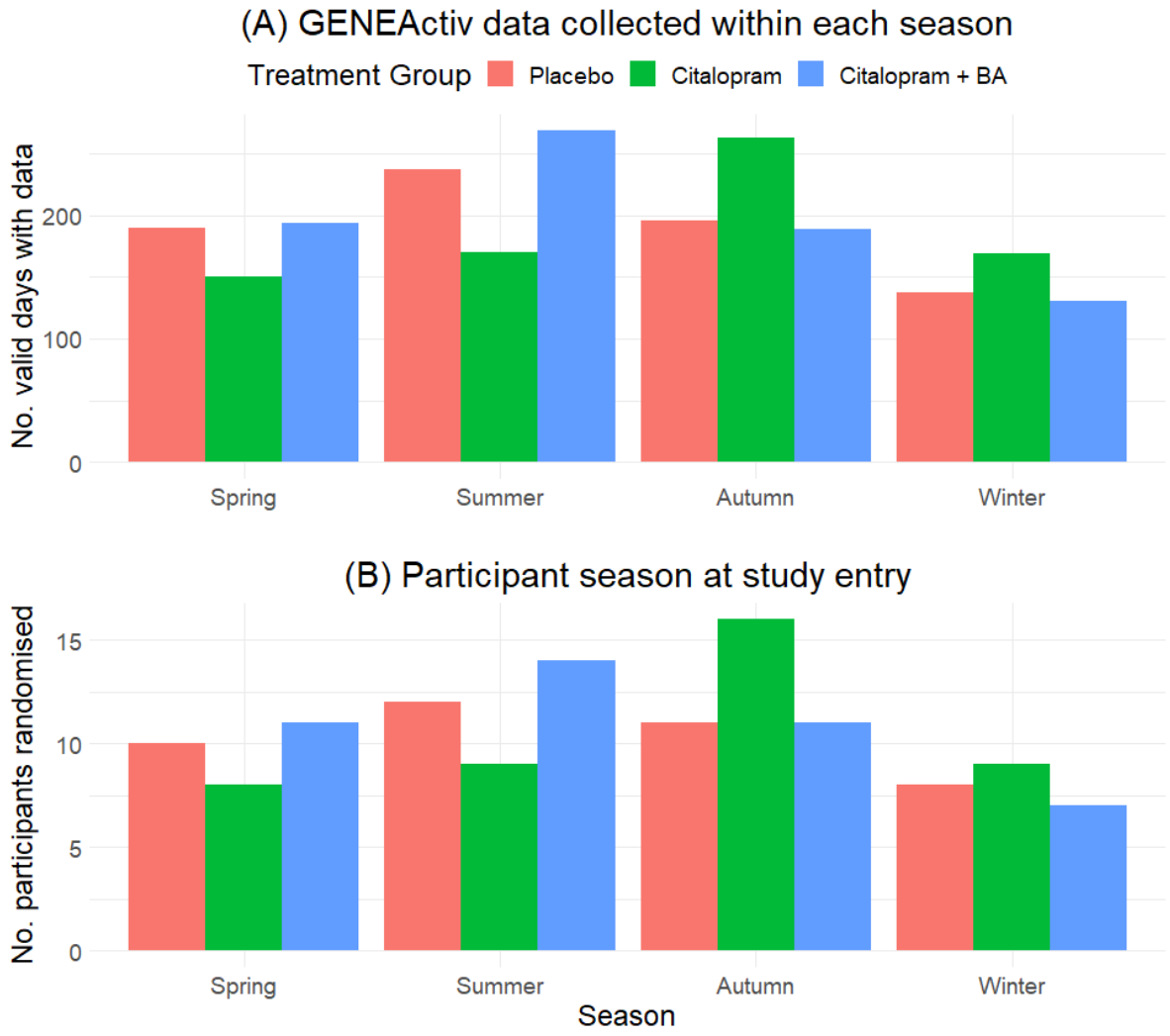


Figure 7.2. (A) number of days with valid GENEActiv data collected within each season, per treatment group and (B) number of participants randomised within each season, per treatment group

Our sample was comprised of more right-handed (N = 104) compared to left-handed (N = 21) participants, hence most participants wore their GENEActiv watch on their left (non-dominant) wrist (N Placebo = 29; N Citalopram = 39; N Citalopram + BA = 34; see Figure 3). Three participants wore the actigraphy device on their dominant rather than non-dominant wrist. As this can introduce unwanted motion artefacts, we planned a sensitivity analysis excluding these participants.

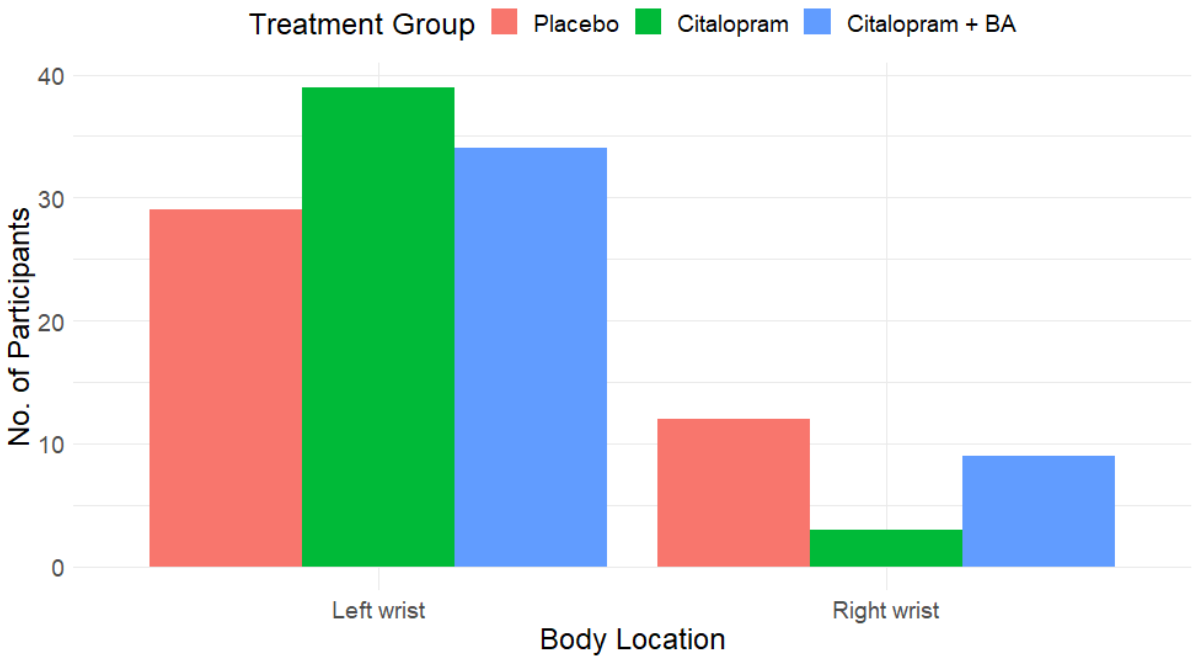


Figure 7.3. Number of participants wearing the GENEActiv watch on each wrist, per treatment group

7.3.2 M10 activity

The weekly mean M10 activity values over the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.4, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

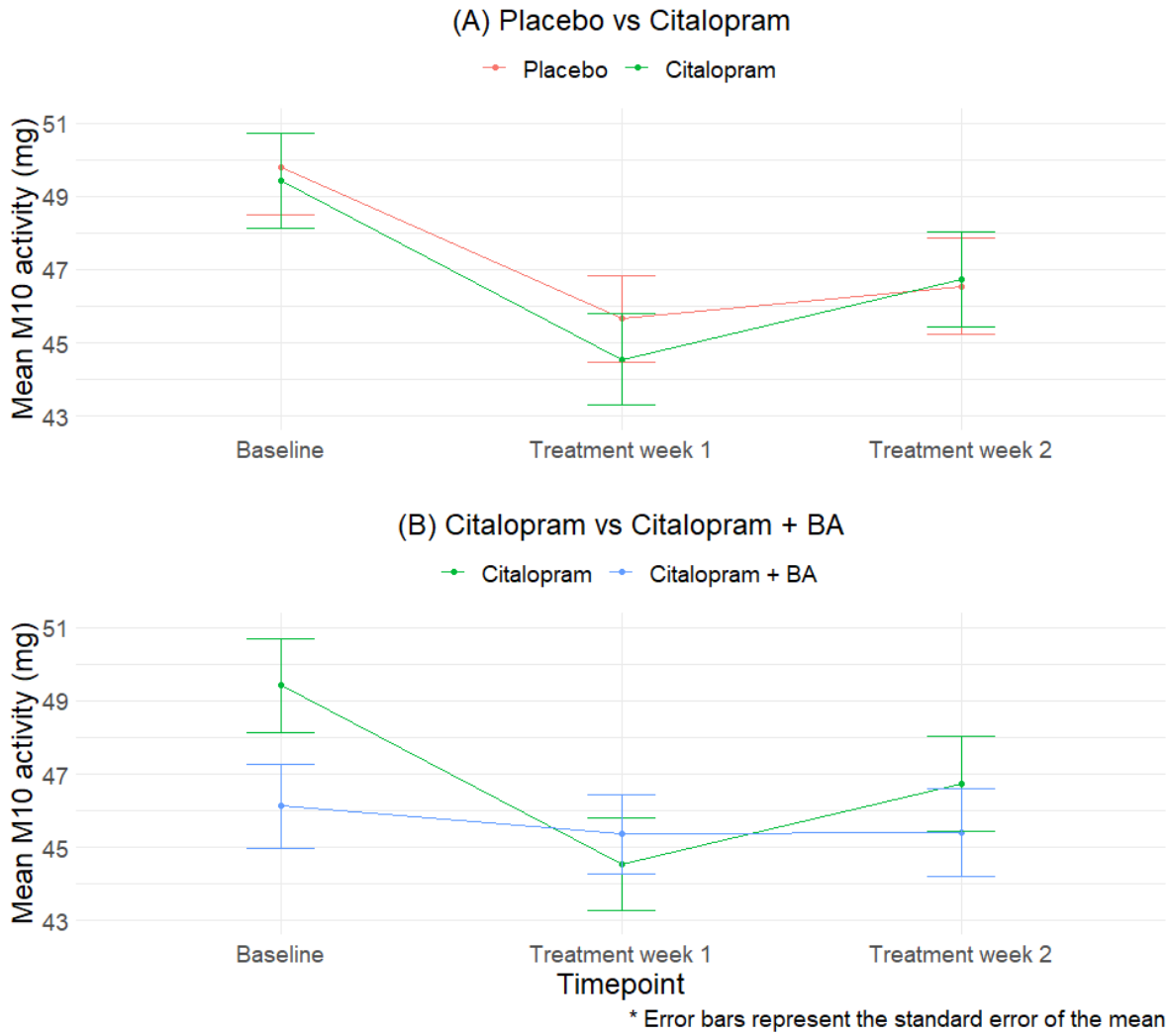


Figure 7.4. Weekly mean M10 activity values across three weeks of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.2.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on M10 activity over the two treatment weeks ($F(1, 72.50) = 0.05$, $p = 0.818$), nor a significant treatment group by treatment week interaction ($F(1, 950.43) = 0.66$, $p = 0.416$).

7.3.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on M10 activity over the two treatment weeks ($F(1, 76.67) = 0.62$, $p = 0.433$), nor a significant treatment group by treatment week interaction ($F(1, 963.54) = 2.47$, $p = 0.117$).

7.3.3 M10 onset

The weekly mean M10 onset values over the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.5, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

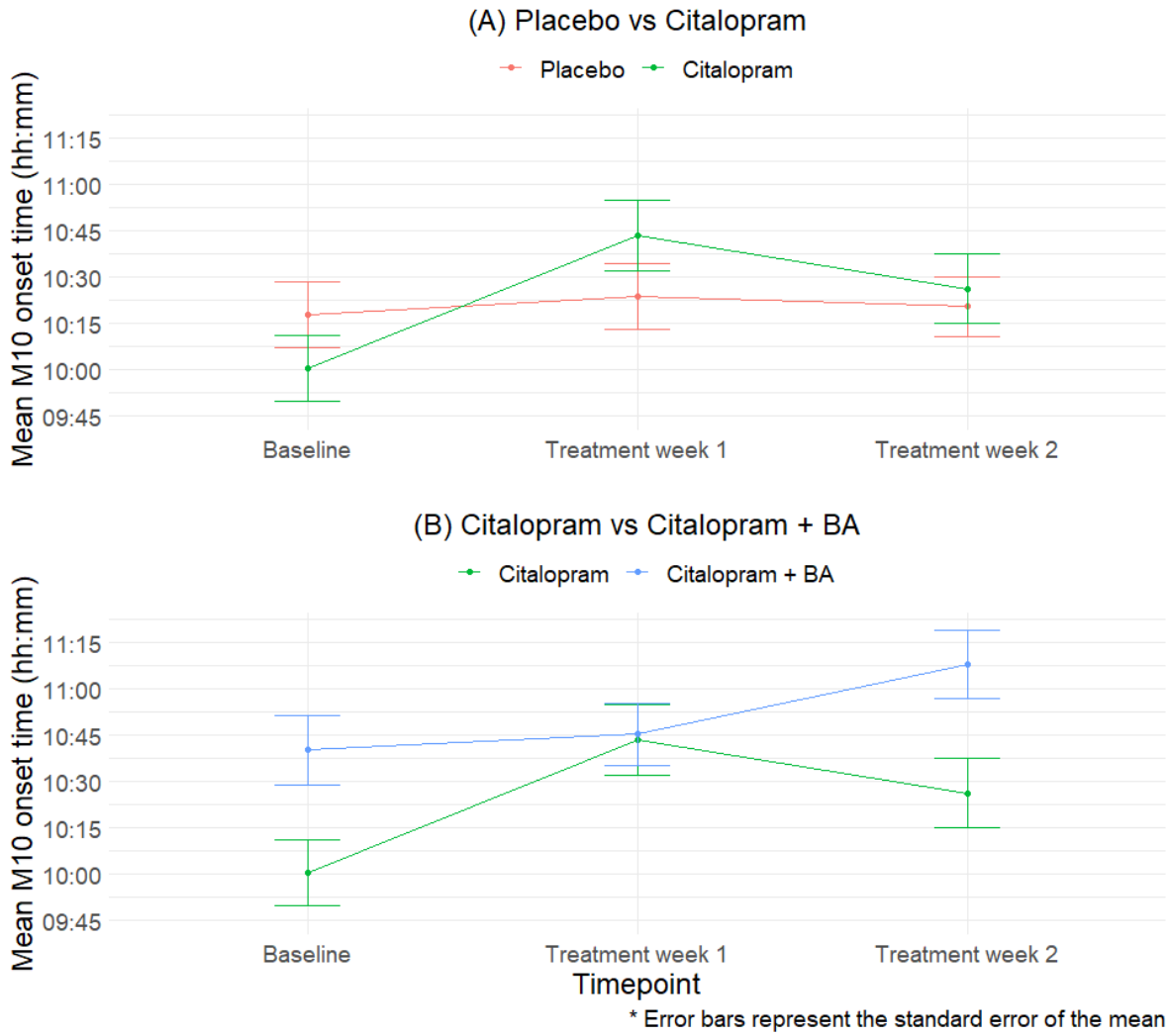


Figure 7.5. Weekly mean M10 onset values across three weeks of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.3.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on M10 onset over the two treatment weeks ($F(1, 74.25) = 0.99$, $p = 0.323$), nor a significant treatment group by treatment week interaction ($F(1, 951.47) = 2.21$, $p = 0.137$).

7.3.3.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on M10 onset over the two treatment weeks ($F(1, 80.14) = 0.01$, $p = 0.904$). However, the treatment group and treatment week interaction was significant ($F(1, 972.18) = 6.02$, $p = 0.014$).

Follow-up contrasts revealed no significant differences between groups at either treatment week 1 (model-adjusted mean for the Citalopram group = 10:54 AM, SE = 12 minutes, 50 seconds, 95% CI: 10:30 AM to 11:24 AM; model-adjusted mean for the Citalopram + BA group = 10:36 AM, SE = 12 minutes, 32 seconds, 95% CI: 10:12 AM to 11:00 AM; $p = 0.256$) or treatment week 2 (model-adjusted mean for the Citalopram group = 10:36 AM, SE = 13 minutes, 8 seconds, 95% CI: 10:12 AM to 11:00 AM; model-adjusted mean for the Citalopram + BA group = 11:00 AM, SE = 12 minutes, 58 seconds, 95% CI: 10:36 AM to 11:24 AM; $p = 0.191$).

However, the within-group contrast between treatment week 1 and treatment week 2 was not significant for the Citalopram group ($p = 0.107$) but approached significance for the Citalopram + BA group ($p = 0.063$). The modest increase in M10 onset time from approximately 10:36 AM to 11:00 AM in the combined treatment group appears to have driven the significant interaction.

7.3.4 M10 onset variability

The mean M10 onset variability during the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.6, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

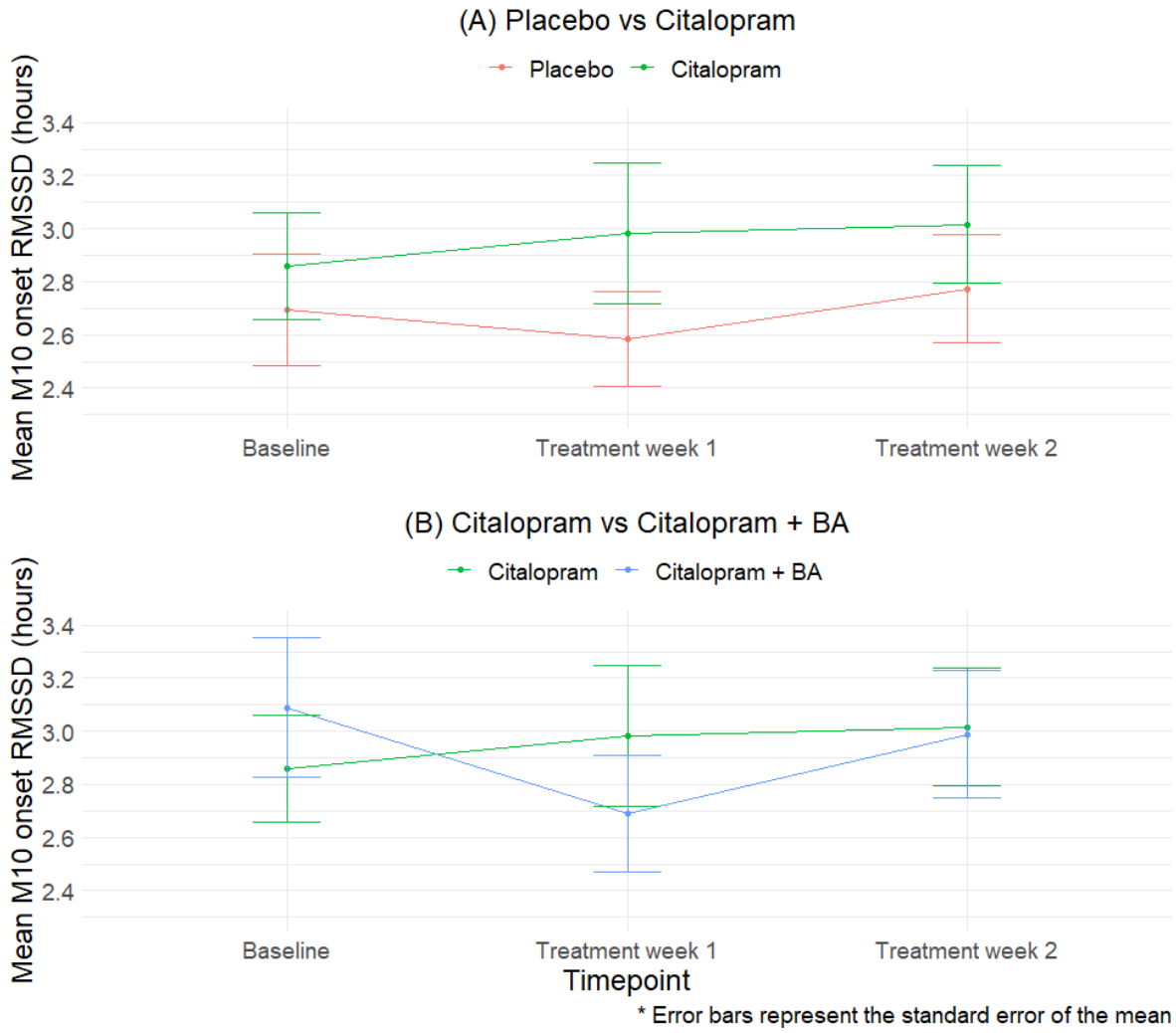


Figure 7.6. Mean M10 onset variability (as measured by the Root Mean Square of Successive Differences) during each week of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.4.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on M10 onset variability over the two treatment weeks ($F(1, 72.79) = 0.92$, $p = 0.341$), nor a significant treatment group by treatment week interaction ($F(1, 73.83) = 0.43$, $p = 0.515$).

7.3.4.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on M10 onset variability over the two treatment weeks ($F(1, 75.42) = 0.77$, $p = 0.382$), nor a significant treatment group by treatment week interaction ($F(1, 75.91) = 0.75$, $p = 0.390$).

7.3.5 L5 activity

The weekly mean L5 activity values over the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.7, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons. Upon visual inspection, it appears that L5 activity decreases progressively in the Placebo group from baseline through to treatment week 2. In contrast, the Citalopram group shows a slight increase in L5 activity between baseline and treatment week 2. By treatment week 2, there may be a potential difference between the two groups, with the Placebo group showing lower levels of activity relative to the Citalopram group. In contrast, there seems to be no noticeable difference between the two active treatment groups at any of the time points, suggesting that the addition of BA to citalopram does not lead to marked changes in L5 activity.

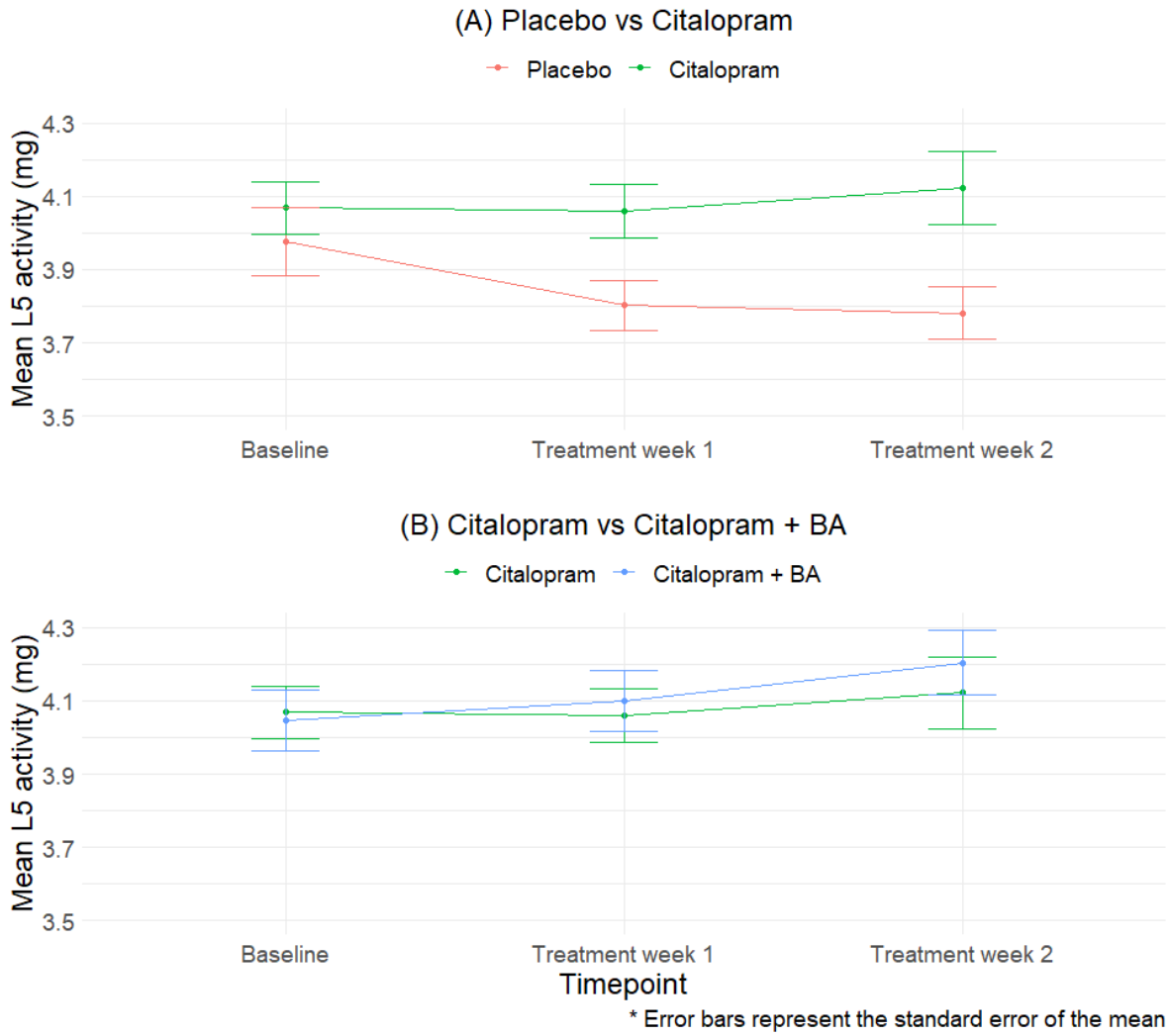


Figure 7.7. Weekly mean L5 activity values across three weeks of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.5.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on L5 activity over the two treatment weeks ($F(1, 76.94) = 2.04$, $p = 0.158$), nor a significant treatment group by treatment week interaction ($F(1, 947.43) = 0.46$, $p = 0.498$).

7.3.5.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on L5 activity over the two treatment weeks ($F(1, 80.16) = 0.02$, $p = 0.879$), nor a significant treatment group by treatment week interaction ($F(1, 965.87) = 0.02$, $p = 0.887$).

7.3.6 L5 onset

The weekly mean L5 onset values over the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.8, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

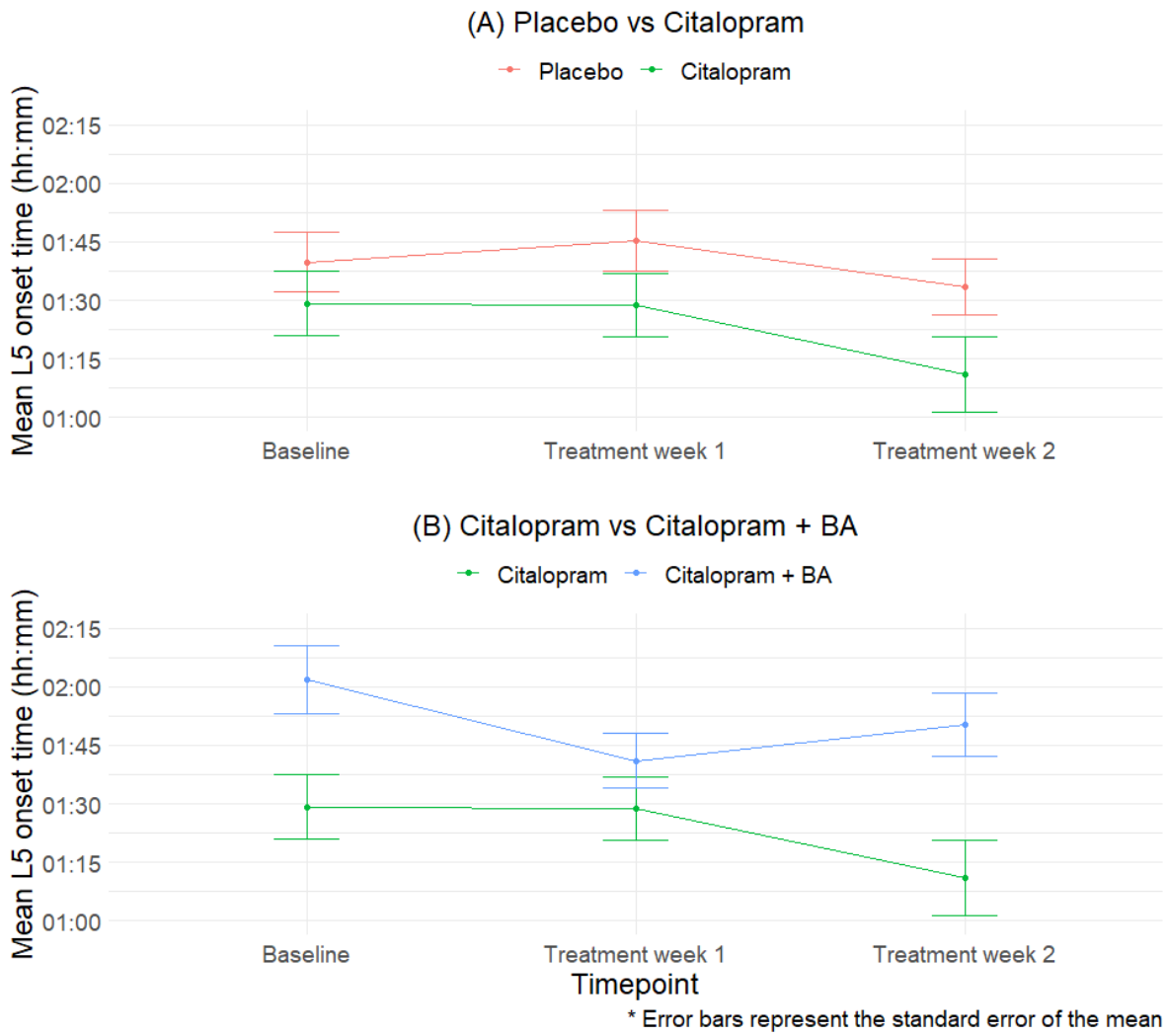


Figure 7.8. Weekly mean L5 onset values across three weeks of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.6.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on L5 onset over the two treatment weeks ($F(1, 78.49) = 1.47$, $p = 0.228$), nor a significant treatment group by treatment week interaction ($F(1, 952.13) = 0.55$, $p = 0.458$).

7.3.6.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on L5 onset over the two treatment weeks ($F(1, 81.69) = 1.20$, $p = 0.276$). However, the treatment group and treatment week interaction was significant ($F(1, 968.64) = 4.78$, $p = 0.029$).

At treatment week 1, L5 onset times were very similar for both the Citalopram and Citalopram + BA groups (model-adjusted mean for both groups = 01:36 AM; Citalopram SE = 11 minutes, 6 seconds; Citalopram + BA SE = 10 minutes, 48 seconds, 95% CI for both groups: 01:12 AM to 01:54 AM), with no significant difference between the groups ($p = 0.971$). In contrast, at treatment week 2, the Citalopram + BA group showed a marginally later L5 onset time compared to the Citalopram-only group, with the difference approaching significance (model-adjusted means: Citalopram + BA = 01:48 AM, SE = 11 minutes, 6 seconds, 95% CI: 01:24 AM to 02:06 AM; Citalopram = 01:18 AM, SE = 11 minutes, 17 seconds, 95% CI: 00:54 AM to 01:36 AM; $p = 0.057$).

Within-group comparisons showed no significant difference between treatment week 1 and week 2 for the Citalopram + BA group ($p = 0.219$). However, for the Citalopram group, the contrast approached significance ($p = 0.064$), with a modest decrease in L5 onset time from treatment week 1 (01:36 AM) to treatment week 2 (01:18 AM).

Thus, the significant interaction between treatment group and treatment week appears to be driven by a modest decrease in L5 onset time in the Citalopram group, as well as the marginally later onset in the Citalopram + BA group by treatment week 2.

7.3.7 L5 onset variability

The mean L5 onset variability during the three weeks of recording (baseline, treatment week 1, treatment week 2) are presented in Figure 7.9, separately for the Placebo vs Citalopram and Citalopram vs. Citalopram + BA group comparisons.

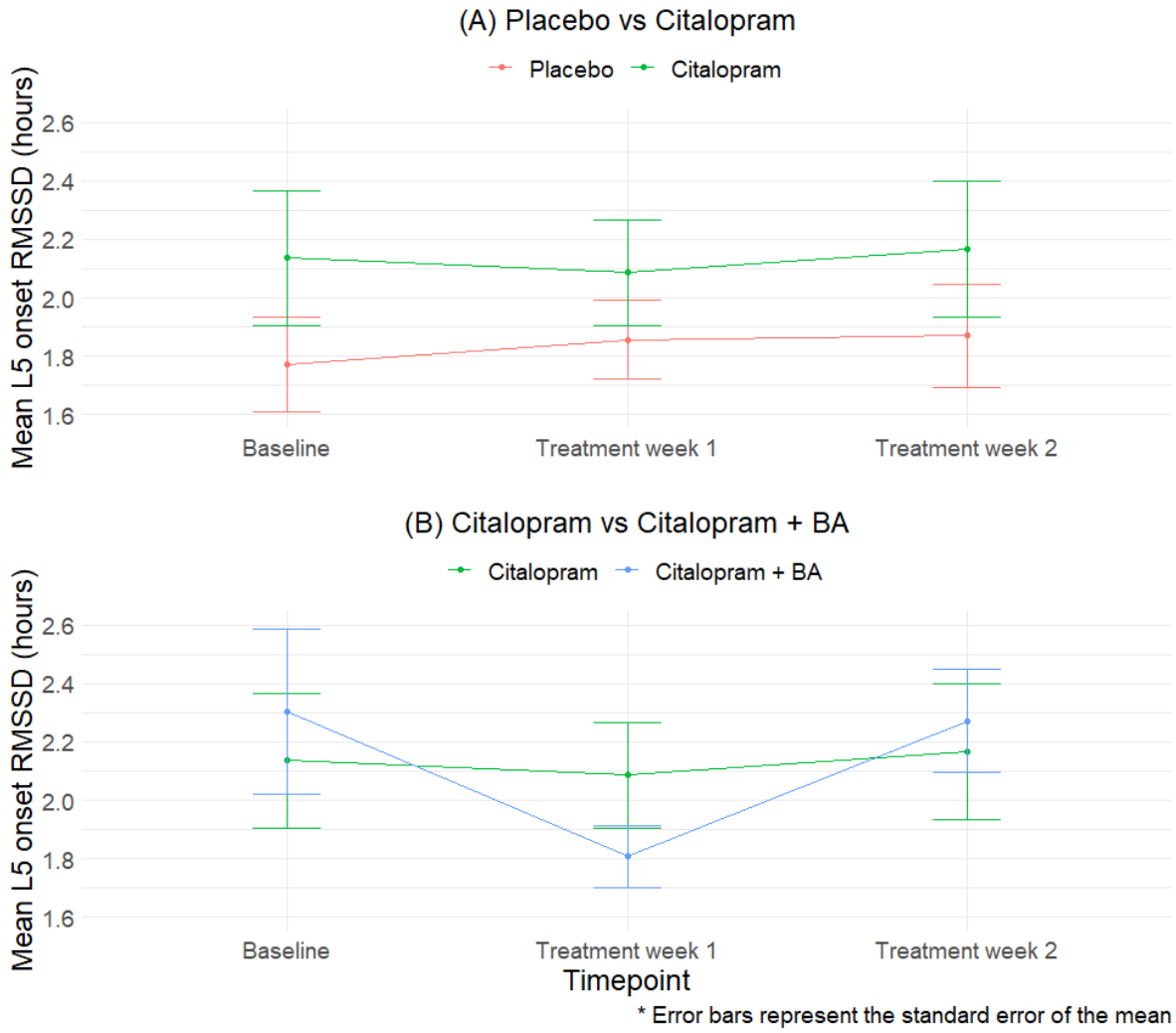


Figure 7.9. Mean L5 onset variability (as measured by the Root Mean Square of Successive Differences) during each week of actigraphy recording for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.3.7.1 Placebo vs Citalopram comparison

We did not observe a significant main effect of treatment group on L5 onset variability over the two treatment weeks ($F(1, 73.26) = 0.56$, $p = 0.456$), nor a significant treatment group by treatment week interaction ($F(1, 74.47) = 0.06$, $p = 0.805$).

7.3.7.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant main effect of treatment group on L5 onset variability over the two treatment weeks ($F(1, 78.44) = 0.73$, $p = 0.394$), nor a significant treatment group by treatment week interaction ($F(1, 79.15) = 1.55$, $p = 0.217$).

7.3.8 Sensitivity analyses

Additionally controlling for the seasonality of observations and participant data availability did not change any of the above-presented results, nor did excluding three participants who wore the actigraphy watch on their dominant rather than non-dominant wrist.

7.4 METHODS – WAKING SALIVARY CORTISOL

7.4.1 Saliva sample collection and cortisol assaying

To measure waking salivary cortisol, participants collected saliva samples pre- and post-treatment, using saliva collection kits provided by the study team. The kits contained six Sarstedt Salivette® tubes for saliva collection, two Royal Mail safeboxes for postage, and a detailed instruction sheet on how to use the equipment provided. Three samples were collected on each occasion: immediately upon waking, 15 minutes after waking and 30 minutes after waking. Samples were mailed to the research team on the day of collection.

The validity of waking salivary cortisol data relies heavily on the temporal accuracy of saliva sample collection across the pre-specified post-awakening period. To verify compliance with the instructions given by the research team, and included within the sample collection kit, we asked participants to report the exact date and time of each sample collected by filling in a label pre-affixed to each tube. This way, we were able to verify that the samples were taken on the days agreed with the study team, and that the 15-minute between-sample interval was adhered to. Where this was not the case, the participant was excluded from subsequent analyses. Nevertheless, this relies on participants accurately reporting their awakening time and not delaying the process of sample collection in relation to the moment of waking, something we were not able to independently verify.

7.4.2 Sample

Out of a total of 134 participants, 14 (three in the Placebo group, six in the Citalopram group, five in the Citalopram + BA group) did not provide all three saliva samples at both timepoints and/or did not take the saliva samples as per protocol (e.g., did not adhere to the 15-minute time intervals between samples). This left a total sample of 120 participants for analysis of waking cortisol levels (N Placebo = 42, N Citalopram = 38, N Citalopram + BA = 40).

7.4.3 Data pre-processing

For each of the six saliva samples and each participant, the average of the two cortisol values resulting from the duplicate assay was used in subsequently presented analyses. Cortisol values were converted from ug/dL to nmol/L, the latter being more often used in the literature.

Cortisol awakening curves where the cortisol concentration in nmol/L was plotted against the sample number were created for each participant and each timepoint, and visually inspected. Example cortisol curves are provided in Appendix 2, illustrating cases with a detectable CAR (increase in salivary cortisol concentration with each successive sample) as well as instances where the curves were flat. However, no exclusions were made on this basis, as it is still unresolved whether there are genuine occurrences of participants not showing a positive cortisol awakening response (Dockray et al., 2008; Smyth et al., 2013).

7.4.4 Waking cortisol response variables

For each participant and each timepoint (pre- and post-treatment), we calculated the delta Cortisol Awakening Response (delta CAR) as: $\Delta CAR = cortisol_{T3} - cortisol_{T1}$, the Area Under the Curve with respect to the increase (AUCi) as: $AUCi = \left(\frac{cortisol_{T2} - cortisol_{T1}}{2} \times 15\right) + \left(\frac{cortisol_{T2} - cortisol_{T1} + cortisol_{T3} - cortisol_{T1}}{2} \times 15\right)$ and the Area Under the Curve with respect to the ground (AUCg) as: $AUCg = \left(\frac{cortisol_{T1} + cortisol_{T2}}{2} \times 15\right) + \left(\frac{cortisol_{T2} + cortisol_{T3}}{2} \times 15\right)$, where:

- $cortisol_{T1}$ is the cortisol level measured immediately upon waking
- $cortisol_{T2}$ is the cortisol level measured 15 minutes after waking
- $cortisol_{T3}$ is the cortisol level measured 30 minutes after waking and is thought to correspond to the peak cortisol response (Wüst et al., 2000) and
- 15 represents the time interval (in minutes) between each measurement.

Delta CAR and AUCi are both measures which capture the rapid increase in cortisol levels that occurs within the first 30-45 minutes after waking, and thus both reflect the reactive component of the Cortisol Awakening Response (CAR), i.e., the specific response of the HPA axis to awakening.

AUCg is a measure that captures the total cortisol secretion over a specified period, in this case over the first half hour post-awakening and is indicative of overall cortisol exposure and HPA axis activity.

7.4.5 Analysis of salivary cortisol data

The post-treatment delta CAR, AUCi and AUCg values were each entered as dependent variables (DVs) into separate analyses of covariance (ANCOVA). Treatment group (Placebo vs Citalopram or Citalopram vs Citalopram + BA) was used as the between-subjects factor and participants' pre-treatment delta CAR/AUCi/AUCg values and BDI-II scores at Baseline assessment were covaried for.

7.5 RESULTS – WAKING SALIVARY CORTISOL

Mean salivary cortisol levels (in nmol/L) for each pre- and post-treatment sample are displayed in Figure 7.10, separately for the Placebo vs Citalopram and Citalopram vs Citalopram + BA group comparisons.

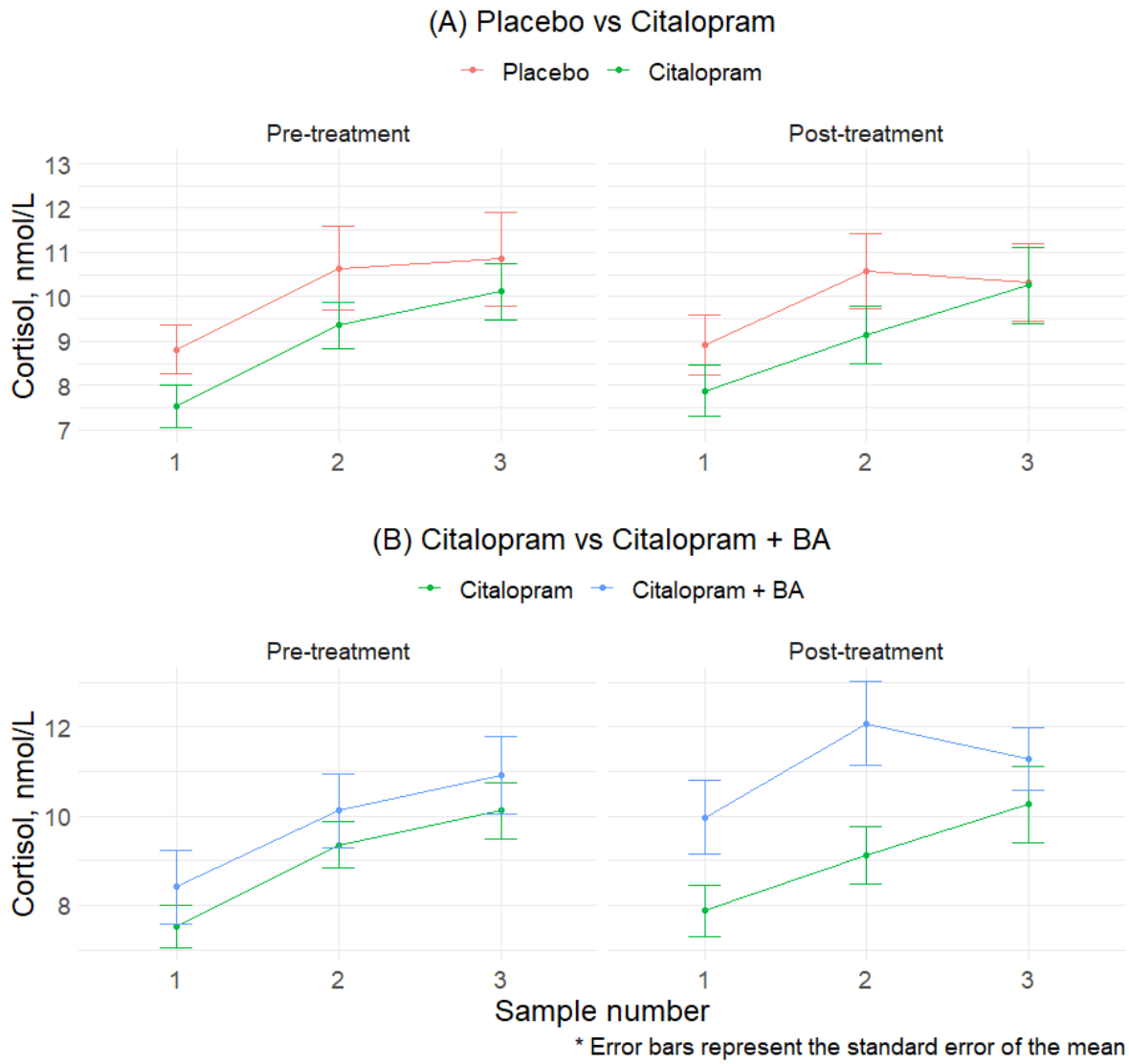


Figure 7.10. Mean salivary cortisol levels (in nmol/L) for each pre-and post-treatment sample, separately for (A) the Placebo vs Citalopram group comparison and (B) the Citalopram vs Citalopram + BA group comparison

7.5.1 Delta CAR

7.5.1.1 Placebo vs Citalopram comparison

We did not observe a significant effect of treatment group on post-treatment delta CAR ($F(1, 76) = 0.94$, $p = 0.336$).

7.5.1.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant effect of treatment group on post-treatment delta CAR ($F(1, 74) = 1.13$, $p = 0.291$).

7.5.2 Area under the curve with respect to the increase (AUCi)

7.5.2.1 Placebo vs Citalopram comparison

We did not observe a significant effect of treatment group on post-treatment AUCi ($F(1, 76) = 0.007$, $p = 0.936$).

7.5.2.2 Citalopram vs Citalopram + BA comparison

We did not observe a significant effect of treatment group on post-treatment AUCi ($F(1, 74) = 0.08$, $p = 0.780$).

7.5.3 Area under the curve with respect to the ground (AUCg)

7.5.3.1 Placebo vs Citalopram comparison

We did not observe a significant effect of treatment group on post-treatment AUCg ($F(1, 76) = 1.33$, $p = 0.253$).

7.5.3.2 Citalopram vs Citalopram + BA comparison

The effect of treatment group was statistically significant ($F(1, 74) = 5.51$, $p = 0.022$). Post-treatment AUCg values were higher in the Citalopram + BA group (model-adjusted mean = 22.1, SE = 1.37, 95% CI: 19.4 to 24.8) compared to the Citalopram only group (model-adjusted mean = 18.8, SE = 1.41, 95% CI: 16.0 to 21.6).

7.6 DISCUSSION

Contrary to our hypothesis, we did not find any evidence that BA-enhanced SSRI treatment increases participants' objective physical activity levels over two weeks of treatment compared to citalopram alone, as measured by the M10 activity index. While this might be a surprising finding given the therapy's focus on increasing activity levels, directly or indirectly, research linking BA to objective increases in physical activity is scarce; most studies report increases in subjective levels of "activation", such as those measured by the Behavioural Activation for Depression Scale (Dimidjian et al., 2017; Hoyer et al., 2020; Richards et al., 2017). Even in such cases, research has failed to consistently demonstrate increases in

activation are significant mediators or predictors of treatment response, casting doubt on this being a mechanistic explanation for BA action (Hoyer et al., 2020; Janssen et al., 2020; Richards et al., 2017).

It is also important to note that our measure of physical activity, the M10, does not distinguish between goal-directed activity versus activity per se. In BA, patients are encouraged not only to increase the number and types of activities they perform, but to choose those activities purposefully e.g., to decrease avoidance or time spent in rumination, or to address a specific personal goal. As such, two groups with the same objective activity levels might experience differing degrees of benefit from said activity, as it is goal-directed activity which is associated with therapeutic gains (Coote & MacLeod, 2012). This explanation, however, is called into question by an absence of a difference between the two groups in BADS scores (discussed in Chapter 3), which would indicate a differentiation in the quality of activities between the groups. It is also possible that our BA intervention, consisting of just three sessions compared to the 8-16 sessions recommended by NICE guidelines (National Institute for Health and Care Excellence, 2022), was not long enough to meaningfully affect participants' levels of activity.

We also found no significant differences between groups in L5 activity, a proxy for sleep quality, although there was a graphical suggestion of higher L5 activity in the Citalopram group compared to Placebo by the second treatment week. Citalopram is known to affect sleep, with common side effects including insomnia and difficulty staying asleep particularly apparent early in treatment (Wichniak et al., 2017; Wilson & Argyropoulos, 2005). It's possible that our study was underpowered to detect differences via actigraphy, as participants in the Citalopram group reported poorer sleep than the Placebo group on the "Change in sleep patterns" item of the BDI-II at the End of Study assessment (Kruskal-Wallis chi-squared = 9.15, df = 1, p = 0.002). Notably, significant improvements in self-reported sleep from Baseline to EOS were observed only in the Placebo group (Friedman chi-squared

= 11.27, df = 1, p < 0.001), while no significant change was reported in the Citalopram (Friedman chi-squared = 1.09, df = 1, p = 0.297) or Citalopram + BA groups (Friedman chi-squared = 2.67, df = 1, p-value = 0.103). Interestingly, L5 activity values were similar in both active treatment groups throughout the study, indicating similar effects of citalopram with and without the addition of BA.

We found weak evidence of activity phase modulation with the addition of BA. The Citalopram + BA group showed a modest increase in M10 onset time between the two treatment weeks, and a marginally higher L5 onset time compared to the Citalopram group by treatment week 2. Interestingly, no group differences were observed at week 1, though visually, the BA group appeared to show a decrease in inactive period onset times compared to baseline. However, this trend shifted by week 2, with onset times increasing instead. Given that these individual effects were not statistically significant, we must interpret them cautiously; however, future studies might explore the possibility of a more gradual shift from sleep to wakefulness (and vice-versa) with BA, potentially mediated by the completion of relevant activities (e.g., preparing for the next day, reading before bed, taking a long morning shower). These findings warrant replication.

Lastly, we found no significant effect of BA-enhanced SSRI treatment on the variability in the onset of active and inactive periods. Given that BA encourages the establishment of structured activities, this lack of effect was unexpected. However, as mentioned earlier, the brief nature of our intervention may have been insufficient to produce meaningful changes in routine.

In terms of waking salivary cortisol, we found no effect of a two-week course of citalopram on the post-treatment delta CAR, AUCi and AUCg compared to placebo. This is surprising considering the strong evidence of increases in morning salivary cortisol with short-term citalopram administration (Harmer, Bhagwagar, Shelley, et al., 2003; Pariante et al., 2004; Ronaldson et al., 2018), as well as increases in salivary cortisol after citalopram is

administered acutely (Bhagwagar et al., 2002; Nadeem et al., 2004). This discrepancy raises questions about participant compliance with the medication or saliva collection procedures, or both.

Regarding medication compliance, we texted participants nightly to remind them to take their study capsule and asked them to reply with the time they had taken it. Of those who had a UK phone number and were able to engage with our texts (129/134 participants), 65.1% confirmed they had taken all 14 capsules and 94.6% sent 10 or more confirmation texts. While these figures reflect good compliance, due to the remote nature of the study, we were unable to independently verify whether the capsules had indeed been ingested.

The absence of an observed effect on waking cortisol with citalopram in our study may stem from at-home sampling inaccuracies. While we excluded all participants who appeared not to follow instructions, we could not objectively verify saliva sampling times. As noted by Stalder and colleagues, the timing of the first sample is particularly important for CAR assessment; delays of 15-20 minutes post-awakening can result in underestimations by missing the cortisol peak, while shorter delays of 5-10 minutes may inflate CAR estimates by artificially creating an earlier peak (Stalder et al., 2016). Future studies might address these limitations by incorporating packaging that records opening times or using actigraphy to monitor exact awakening times, in addition to the start of active periods as used in this study.

Moreover, differences in participant characteristics, such as mental health status, may explain inconsistencies with previous studies, which mostly involved healthy volunteers (Bhagwagar et al., 2002; Harmer, Bhagwagar, Shelley, et al., 2003; Nadeem et al., 2004; Pariante et al., 2004). As noted in the chapter introduction, people with depression exhibit different patterns in waking cortisol and the CAR compared to healthy individuals, and these may be differentially affected by citalopram administration. Long-term SSRI use in depressed patients is not consistently associated with increases in CAR (Manthey et al., 2011; Ruhé et al., 2015), and may lead to decreases in salivary cortisol at the moment of

awakening (Ruhé et al., 2015). Variability in participant routines, such as awakening times, and the absence of data on shift work, which can affect CAR (Federenko et al., 2004; Griefahn & Robens, 2010), further complicate interpretation and should be accounted for in future research.

With these limitations in mind, we did observe a significant difference in post-treatment waking salivary cortisol between the Citalopram and Citalopram + BA groups; the Citalopram + BA group had a higher post-treatment AUCg value, reflective of greater cortisol exposure in the first half hour post-awakening. In the absence of a between-group difference in our CAR measures of delta CAR and AUCi between the groups, this implies that added BA might increase overall cortisol production post-awakening but does not specifically alter the shape of the CAR. This raises interesting questions about the role of BA in modulating overall stress-related physiological processes; the higher cortisol exposure in the Citalopram + BA group could reflect a more robust response to awakening and might indicate partial restoration of circadian rhythm dysregulation often seen in depression (Eikeseth et al., 2019; Stetler & Miller, 2005; Vadnie & McClung, 2017). Taken together with the actigraphy results, which tentatively suggest a phase shift in the start of both active and inactive daily periods with BA, this indicates that BA may help realign circadian rhythms, potentially making the transition from sleep to wakefulness more gradual or effective. Nevertheless, future studies would have to confirm whether the increase in overall cortisol production is beneficial in this case, or indicative of heightened physiological stress.

In conclusion, our results suggest a modest impact of BA-enhanced SSRI treatment on circadian rhythms. Further research is needed to understand their robustness and relationship with treatment outcomes.

8 CHAPTER 8: GENERAL DISCUSSION

The aim of this thesis was to directly test, for the first time in human participants, the hypothesis that the environment plays a critical role in the success of antidepressant treatment for major depression. We hypothesised that the environment could serve as a crucial interface between the early cognitive changes induced by antidepressant drugs and subsequent clinical improvement (Godlewska & Harmer, 2021; Murphy et al., 2021). Specifically, we proposed that environmental enrichment would facilitate changes in information processing biases induced by the SSRI antidepressant citalopram, as measured by the Emotional Task Battery (ETB), compared to the antidepressant alone after two weeks of treatment.

To test this, we conducted a large two-year experimental medicine study involving more than 130 participants with mild-to-moderate depression – the Combined Antidepressant and Behavioural Intervention (CABIN) study. The study compared the effects of a two-week intervention with either placebo, citalopram alone, or citalopram combined with behavioural activation (BA). BA was chosen as a proxy for environmental enrichment due to its strong evidence base and focus on increasing engagement in rewarding activities (Ekers et al., 2014; Richards et al., 2017; Ruzickova et al., 2023).

The thesis also aimed to better characterise the role of the environment in antidepressant treatment and provide insights into when and how environmental change may enhance pharmacotherapy. Several potential mechanisms of action for BA-enhanced SSRI treatment were explored, including facilitating positive affective biases in emotional processing, improving reward learning, reversing abnormalities in circadian rhythms and reducing mood variability.

Across multiple domains, however, results did not support our predictions – neither in the comparison of citalopram alone versus placebo nor in the comparison of citalopram alone versus BA-enhanced SSRI treatment. These findings challenge some of our initial

hypotheses and raise questions about the timing, dosage, and delivery of BA interventions in combination with pharmacotherapy. Possible design limitations and reasons for these results are discussed below.

8.1 SUMMARY OF FINDINGS

8.1.1 Clinical outcomes

All three treatment groups showed significant improvements in depression and anxiety scores from the start to the end of the two-week intervention. The change in Beck Depression Inventory-II (BDI-II) scores, in particular, was estimated to correspond to an approximate 37% decrease in symptoms, a change that is considered clinically relevant from both clinicians' and patients' perspectives (Button, Kounali, et al., 2015; Kounali et al., 2022). No significant differences were observed between placebo and citalopram, or between citalopram and BA-enhanced citalopram treatment, suggesting that placebo or expectation effects may have contributed to the observed improvements.

Given the short duration of the intervention, it is likely that two weeks was insufficient to produce measurable effects on self-reported clinical outcomes in the active treatment groups beyond those observed in the placebo group. Indeed, clinical outcomes were exploratory in nature in this experimental medicine study. Nonetheless, the lack of clear differences between the citalopram-only and combined treatment groups on measures of positive environmental reinforcement, such as the Behavioural Activation for Depression Scale (BADS) and Environmental Reward Observation Scale (EROS), is surprising and contradicts previous findings using a similar BA protocol (Ruzickova et al., 2023). This raises questions about whether our manipulation of environmental enrichment through BA was successful or sufficient to drive the expected changes in markers explored in subsequent chapters.

Additionally, we observed significant between-group differences in depression and anxiety symptoms, with participants in the Citalopram + BA group appearing more unwell than those in the Citalopram-only group. Although baseline BDI-II scores were statistically controlled for

in subsequent analyses, the degree to which they may have influenced the mechanistic outcomes remains uncertain.

8.1.2 Emotional processing

We were unable to replicate prior findings of increased positive or decreased negative affective biases in participants taking citalopram compared to placebo. We found evidence for emotional processing changes over repeat testing and time, but these did not differ between treatment groups or show a clear relationship with task stimulus valence in most cases. However, some modest differences in emotional processing speed emerged post-treatment in the combined treatment group. Specifically, participants in the Citalopram + BA group were faster to correctly categorise positive personality descriptor words as positive compared to categorising negative descriptors as negative in the Emotional Categorisation Task (ECAT). Additionally, they were marginally faster at correctly recognising positive personality descriptors compared to negative personality descriptors as being either familiar or novel in the Emotional Memory Task (EMEM). These within-group valence contrasts were not significant in the Citalopram-only group, suggesting the potential for more pronounced positive affective biases in the combined treatment group. Nonetheless, interpretation of these findings remains challenging due to the absence of significant between-group differences in reaction time to either positive or negative words, and the absence of more robust emotional processing changes in the citalopram-only group relative to placebo across the Emotional Task Battery (ETB).

8.1.3 Reinforcement learning

While we did not observe the expected improvements in reward learning with the BA-enhanced SSRI treatment compared to citalopram alone, the findings related to punishment learning were particularly noteworthy. Citalopram was associated with decreased accuracy in selecting the optimal low-probability loss stimulus compared to placebo post-treatment, suggesting a potential change in how participants processed negative outcomes. Additionally, the citalopram group displayed altered response strategies on loss trials,

characterised by increased shifting of responses following negative (disadvantageous) feedback and, to a lesser extent, less persistence in choosing the same stimulus after neutral (advantageous) feedback compared to placebo. Interestingly, BA appeared to reverse these effects, promoting more consistent response patterns by decreasing “lose-shift” behaviour and increasing “win-stay” responses relative to citalopram alone. However, this adjustment did not result in better overall accuracy on loss trials, as no significant differences were observed between the Citalopram + BA and Citalopram-only groups in this regard.

8.1.4 Daily mood and affective variability

One of our primary hypotheses was that BA would enhance day-to-day mood stability when combined with SSRI treatment. However, we did not observe significant differences in mood variability between the Citalopram + BA and the Citalopram-only groups. Citalopram treatment was associated with improvements in positive affect and reductions in negative affect and irritability over the course of the two-week treatment, but these effects were not amplified by the addition of BA. Interestingly, citalopram was also linked to early decreases in positive affect and increases in irritability at the very start of treatment, which were subsequently reversed over the length of the intervention. In contrast, BA did not lead to sustained improvements across the full treatment period but appeared to buffer against these initial "dips" in mood. This suggests a potential short-term effect related to the introduction of BA, which may reflect therapeutic processes that promote immediate mood improvements.

8.1.5 Biological markers of circadian rhythm

Contrary to expectations, BA-enriched SSRI treatment did not lead to increased objective physical activity (PA) levels during the two-week treatment period compared to citalopram alone, as measured by the M10 activity index. We had hypothesised that BA would increase movement both directly and indirectly, as participants engaged more in rewarding activities including exercise. However, both our results and previous literature cast doubt on PA as a

key mediator of BA's therapeutic effects. Similarly, no significant between-group differences were observed in the L5 activity (a proxy for sleep quality). Instead, we found weak evidence of phase modulation in the Citalopram + BA group, with a modest shift towards a later start in both active and inactive periods, suggesting a potential influence of BA on circadian rhythms.

We also observed a significant increase in post-treatment cortisol production in the first half-hour post-awakening in the Citalopram + BA group compared to the Citalopram-only group, although this was not accompanied by a more pronounced Cortisol Awakening Response (CAR). This suggests BA may promote a more robust response to awakening, but whether this reflects an adaptive response, indicating partial restoration of circadian rhythm dysregulation often seen in depression (characterised by an abnormal CAR), or heightened psychological stress remains unclear. Issues with at-home measurement of cortisol and inability to verify awakening times contribute to the difficulties with data interpretation.

8.2 LIMITATIONS OF THE CABIN STUDY

8.2.1 Experimental medicine approach

Our investigation was grounded in the cognitive neuropsychological model of antidepressant drug action (Godlewska & Harmer, 2021; Harmer, Goodwin, et al., 2009; Harmer & Cowen, 2013), which has been strongly validated by both behavioural and neuroimaging studies over the past two decades. This model posits that serotonergic antidepressants initiate an early shift in emotional processing, which precedes mood improvement and plays a critical role in the clinical response to treatment. While substantial empirical evidence has affirmed the relevance of these affective bias shifts for subsequent treatment response (Browning et al., 2019; Godlewska et al., 2016), it remains unclear whether such changes are *necessary* for antidepressants to produce therapeutic effects.

In the CABIN study, we hypothesised that environmental enrichment provided by BA might facilitate antidepressant effects, leading to more pronounced positive affective biases on

emotional processing tasks compared to citalopram alone – even if BA itself does not directly affect emotional processing (although there is some existing evidence to suggest it does – see Ruzickova et al., 2023). However, alterations in emotional biases are not always present with antidepressants, and their predictive accuracy for clinical response is not absolute. For example, a recent study involving 74 primary care patients with depression assessed performance on emotional processing tasks (emotional categorisation, memory, and facial expression recognition tests) before and after one week of treatment, with treatment response evaluated at 4–6 weeks. The combination of changes in response to the facial emotion recognition task and subjective depression symptoms emerged as the best predictor of response, with 77% accuracy in the training sample and 60% accuracy in an independent validation group (Browning et al., 2019). Whether this level of accuracy is sufficient for clinical utility remains open to debate.

The mood improvement observed in all three treatment groups in the CABIN study, without clear corresponding changes in emotional processing from Baseline to End of Study assessment, raises further questions about the core assumption of the cognitive neuropsychological model – that cognitive changes precede mood improvements. However, this discrepancy does not necessarily invalidate the model's assumptions in our context. It is possible that the measures of emotional processing used in our study were not sensitive enough to detect subtle cognitive shifts or that such changes occurred outside the timeframe or parameters we assessed. Additionally, mood improvements might have been influenced by factors like demand characteristics in self-reported outcomes, rather than genuine therapeutic change rooted in cognitive restructuring. On the other hand, we cannot entirely rule out the possibility that the model's assumptions may not fully apply to all individuals or contexts. For instance, participants' cognitive biases may not have been as negatively skewed at baseline (something difficult to ascertain due to the lack of normative ETB data), or their depressive symptoms might have been more transient, reflecting situational distress rather than a stable negative cognitive model. Testing these possibilities was beyond the

scope of the current study; nevertheless, it remains important for future research to explore these nuances and further evaluate the universality of the model's assumptions.

An alternative approach would have been to use clinical outcome measures as primary endpoints, with emotional processing tasks (such as those in the Emotional Test Battery) as secondary endpoints. However, this strategy would still face its own challenges, such as the risk of demand characteristics in clinical assessments. Moreover, a longer study period – at least 4 to 6 weeks – would have been needed, given this is the typical timeframe in which antidepressant effects are thought to emerge fully.

8.2.2 Remote data collection

The experimental medicine approach in this study relied heavily on biomarkers of treatment response, such as the Emotional Task Battery (ETB). The ETB has been widely used to assess early antidepressant-induced changes in emotional cognition, both as direct measures and as predictors of future clinical improvement (Arnone et al., 2009; Browning et al., 2007, 2019; Harmer et al., 2004, 2008; Walsh, Browning, et al., 2018). However, it has been less frequently employed in studies involving psychological therapies (Ruzickova et al., 2023) or combined treatments, and even fewer studies have used the online version of the ETB, as we did in the CABIN study (Gillespie et al., 2022; Waters et al., 2023). As this online format is less well-validated than the in-clinic version, this may have affected the reliability of our results.

As noted in Chapters 2 and 4, online behavioural testing offers important advantages, such as ease of implementation and the ability to recruit from groups traditionally excluded from clinical research. However, it also introduces variability due to less controlled environments and potential distractions that may have impacted data quality. While we required participants to only use laptops or PCs to access the website hosting the online ETB and applied rigorous data cleaning protocols (as detailed in Chapter 2), differences in participant setup – and, more importantly, engagement with the tasks – may still have influenced outcomes. Such variability in testing conditions may have obscured even medium-to-large

drug effects, potentially explaining why we failed to replicate the well-established finding of positive shifts in emotional processing with SSRI treatment compared to placebo. This also highlights a broader translational gap between controlled research settings and remote, real-world applications, where biomarkers like the ETB may be less useful for monitoring and predicting treatment response outside the clinic.

Other measures used in the CABIN study, such as the waking salivary cortisol assessments, may have also been impacted by the unsupervised nature of data collection, potentially leading to the unexpected lack of replication of a drug effect on waking cortisol levels relative to placebo. Future studies may choose to implement more modern packaging solutions (e.g., tamper-proof or time-stamped containers) which precisely record the time of opening/saliva sample collection.

8.2.3 Length of Intervention

The length of the intervention used in this study is closely tied to the experimental medicine approach, which often involves the rapid screening of promising treatments using validated markers of treatment response, potentially reducing the need for lengthy and costly clinical trials. As a result, intervention durations are typically short, usually a single dose or 1-2 weeks. Although the duration of our BA intervention was informed by previous research using a similar online protocol, which demonstrated reliable differences in behavioural activation by the end of the second week (Ruzickova et al., 2023), our data suggest that the combined intervention did not increase participants' contentedness with their activities (as measured by the Behavioural Activation for Depression Scale) or their frequency of positive environmental reinforcement (as measured by the Environmental Reward Observation Scale) beyond the effects of citalopram alone.

It is possible that a two-week, three-session course of BA was insufficient to lead to meaningful change. The National Institute for Health and Care Excellence (NICE) recommends 8 regular BA sessions for less severe depression and between 12 and 16

sessions for more severe cases. Anecdotally, some CABIN participants found the theory behind BA logical but felt that three sessions were not enough to establish new habits.

Additionally, a limitation of the study was that we did not directly measure engagement in BA beyond session attendance – all participants randomised to the combined treatment condition attended all three BA sessions. Future studies may benefit from measuring not only self-reported environmental reward availability but also the proportion of scheduled BA activities completed, to determine whether there is a relationship between the two.

8.2.4 Absence of a Placebo + BA treatment group

One of the study's most significant limitations is the absence of a Placebo + BA treatment group. This gap makes us reliant on prior literature to estimate the standalone effects of BA and prevents us from distinguishing whether the observed effects in the Citalopram + BA group are purely additive or synergistic. For instance, in the Probabilistic Instrumental Learning Task (PILT), we found that citalopram increased the proportion of lose-shift responses on loss trials compared to placebo, a pattern that was reversed with added BA. Without a Placebo + BA group, however, we cannot definitively establish whether BA alone would have resulted in an even greater decrease in response-shifting in response to loss, or whether BA amplified or modulated the effects of SSRI treatment in a different way than simple additive effects might suggest.

The absence of a Placebo + BA group also limits our ability to accurately estimate the effects of taking the placebo pill – it could be that our placebo comparison induced stronger effects because it still required active engagement in the treatment (i.e., taking a capsule each day). This phenomenon is often observed when comparing psychological treatments to pill placebos rather than to passive waitlist controls (Cuijpers et al., 2014; Prioleau et al., 1983). It would have been particularly interesting to compare a pill placebo with a pill placebo + BA treatment group in this study; if no difference emerged between these groups, it might suggest that engagement in a structured treatment (like taking a pill) already

provides significant therapeutic benefit, making it harder to detect BA's standalone impact in a short-term study.

8.2.5 Lack of complete blinding

Another limitation of the study design is the lack of complete blinding. The primary researcher administered the BA intervention and informed participants whether they would begin BA as early as the Screening 2 appointment, before baseline testing, to accommodate for activity tracking and treatment personalisation ahead of the first BA session. Additionally, the research team was aware that participants receiving BA were also assigned to take citalopram and were only blind to drug allocation in the BA-free groups. This awareness could have influenced expectations about treatment outcomes, particularly in the Citalopram + BA group.

Since participants in the Citalopram + BA group were aware they would begin the psychological intervention before completing the Baseline assessment, expectation effects along with spontaneous recovery between assessments were both concerns. To address this and ensure transparency, we compared BDI-II scores from the Screening and Baseline assessments to check for any expectation effects or spontaneous recovery. Importantly, no significant differences in depression scores were found between Screening and Baseline in any of the treatment groups, indicating that this limitation did not affect our subsequent findings.

Additionally, the potential influence of incomplete blinding on the research team was mitigated by the online data collection protocol, as the primary researcher was not directly involved in the collection of either pre- or post-treatment outcome data. This helped reduce the possibility of researcher bias influencing the results, even though the team was aware of some of the treatment allocations.

8.2.6 Sample

Our sample consisted of participants with self-reported mild to moderate depression symptoms and high levels of anxiety. The sample had several strengths, including well-matched demographic characteristics across the three treatment groups and representativeness of Southeast England in terms of ethnic makeup. However, there were notable limitations. As a volunteer sample, participants may have been particularly motivated to receive (psychological) treatment and may have inflated their symptomatology at baseline in order to meet study eligibility criteria. This could, at least partly, explain the large placebo effect observed among those who did not receive an active form of therapy.

Participants were included in the study based on self-reported BDI-II scores, with mood episodes further assessed through the Structured Clinical Interview for DSM-5, Researcher Version (SCID-5 RV). However, these researcher-led assessments primarily informed exclusion rather than inclusion decisions, as participants were not required to meet the criteria for a major depressive episode at the time of inclusion if they were in the required BDI-II score range. This raises potential concerns, as there may be differences between individuals who meet diagnostic criteria for MDD and those who do not, not only in terms of severity but also in symptom stability and time since depression onset. Research has shown that a shorter time since depression onset, along with younger age and less severe symptoms are associated with higher remission rates with placebo treatment (Nelson et al., 2012; Shinohara et al., 2019). Unfortunately, the lack of formal documentation of time since depression onset in our sample limits our ability to fully contextualise the placebo response observed.

Lastly, there were differences in depression and anxiety symptoms between treatment groups, with the Citalopram + BA group appearing more unwell than the Citalopram-only group, as reflected by higher BDI-II and STAI-S scores across both Baseline and End of Study assessments (see Chapter 3). Although baseline differences in depressive symptoms

were controlled for in subsequent analyses, they may still have influenced our mechanistic outcomes.

8.3 IMPLICATIONS FOR THE COGNITIVE NEUROPSYCHOLOGICAL MODEL OF ANTIDEPRESSANT DRUG ACTION

Our results raise questions about some of the assumptions of the cognitive neuropsychological model of antidepressant drug action, specifically regarding the role of environmental factors in antidepressant efficacy. The failure to replicate previous findings of antidepressant-induced changes in emotional perception, memory or categorisation may suggest that our ETB test battery or study design lacked the sensitivity to detect such changes. Nevertheless, the findings pertaining to reinforcement learning as a related aspect of affective processing are interesting, and prompts us to revisit some of our initial assumptions.

We hypothesised that BA would potentiate the effects of citalopram by amplifying the emotional biases typically induced by the antidepressant alone. In this framework, we envisioned a feedback loop wherein positive affective biases initially induced by citalopram would facilitate positive environmental interactions, which would in turn reinforce these biases, eventually leading to improved mood. However, our findings suggest that environmental enrichment may not operate exclusively through antidepressant-induced cognitive-emotional changes to influence mood.

This is perhaps best evidenced through our reinforcement learning results. Citalopram alone was associated with decreased accuracy in selecting the optimal low-probability loss stimulus and increased “lose-shift” behaviour, suggesting a potential change in how participants process negative outcomes. The finding that citalopram affected performance on loss trials is consistent with the idea that antidepressants modulate affective biases by reducing the salience of negative stimuli, a key component of "hot" cognition (Harmer et al., 2009; Roiser et al., 2012). However, the increased switching after losses seems to indicate

heightened sensitivity to negative feedback, which contrasts with the predictions of the cognitive neuropsychological model. Interestingly, both increased response-shifting after negative feedback (Murphy et al., 2003) and a lack of response adjustment after errors (Holmes and Pizzagalli, 2007) have been documented in depression, perhaps pointing to a general deficit in integrating negative feedback effectively. This raises the question: what exactly do SSRIs remedy in this respect? Do they reduce the emotional impact of negative feedback, alter how feedback is used to guide decision-making, or perhaps increase exploration? Our findings suggest that citalopram may heighten sensitivity to negative feedback in some contexts, but the implications of this for MDD treatment remain unclear.

It is also noteworthy that our findings are not entirely consistent with previous literature on the effects of increased serotonin availability on aversive learning. For example, Colwell et al. (2024) also observed that the selective serotonin-releasing agent fenfluramine reduced the number of optimal choices during loss trials compared to placebo, but this was due to reduced outcome sensitivity for losses rather than an increased impact of negative feedback on choice behaviour (Colwell et al., 2024). This discrepancy could reflect differences in study populations (healthy volunteers in Colwell et al. vs. depressed individuals in the current study). Other healthy volunteer studies have found that citalopram treatment reduced learning from reward and enhanced learning from punishment in terms of a computationally derived learning rate, without meaningfully affecting outcome sensitivity (Michely et al., 2022). Together, these findings suggest that the effects of serotonin modulation on reinforcement learning may depend on both the population studied and the specific task parameters used.

Despite the complexity of our citalopram monotherapy results, environmental enrichment through BA appeared to modulate, but not potentiate, the changes in reinforcement learning induced by the antidepressant. Adjunct BA promoted more consistent response patterns, decreasing “lose-shift” behaviour and increasing “win-stay” responses, effectively counteracting the effects of citalopram. This aligns with BA’s focus on increasing

engagement in rewarding activities and reducing avoidance, though the practical implications of these results have been difficult to interpret.

These findings suggest that, rather than contributing to the emergence of cognitive bias change, environmental enrichment may create a behavioural and cognitive environment that enables antidepressant-induced biases to be differentially expressed. For example, by reducing avoidance behaviours and promoting engagement with positive stimuli, BA may create a cognitive environment more conducive to the expression of positive affective biases, as participants become less preoccupied with negative stimuli and more attuned to positive information. This is consistent with animal research showing that antidepressants taken in adverse environments can potentiate rodent models of depression, with improvements in saccharine preference, inflammation and brain plasticity only observed in the context of positive environmental change (Branchi et al., 2013; Alboni et al., 2017). Thus, BA may create a context where antidepressant-induced changes manifest differently.

This challenges the traditional view that antidepressants and psychological therapies operate through entirely independent mechanisms, instead highlighting the potential for synergistic interactions between pharmacological and environmental factors as predicted by the neuropsychological model. However, we cannot rule out the possibility that BA may also exert “top-down” effects on conscious, goal-directed aspects of cognition, such as goal-setting and causal attribution of events (Norbury et al., 2024). Without a BA + placebo group, we cannot determine whether these effects are synergistic or simply reflect BA’s independent mechanisms.

While our findings contribute to the cognitive neuropsychological model by highlighting the importance of punishment sensitivity as a latent construct in the treatment of depression, several uncertainties remain. For example, it is unclear whether the observed effects on punishment learning are specific to BA or could be achieved through other forms of environmental enrichment. Additionally, the lack of robust changes in reward learning raises questions about the extent to which these interventions differentially influence reward and

punishment pathways. One must also be careful not to over-interpret these results, as no effects were observed on any other task in our battery. This raises the possibility that the observed reinforcement learning effects may be isolated or context-specific, rather than reflecting a broader change in cognitive-emotional processing.

In summary, our findings contribute to the cognitive neuropsychological model by suggesting that environmental enrichment through BA may alter how antidepressant-induced changes in punishment sensitivity are expressed. However, the lack of effects on other tasks and the failure to replicate antidepressant-induced affective bias changes more broadly highlight the need for caution and further investigation.

8.4 CLINICAL IMPLICATIONS

Our results do not support the notion that environmental enrichment through behavioural activation (BA) in the first two weeks of SSRI treatment is critical for antidepressant efficacy. While previous study design limitations notwithstanding, this may also suggest that the early stages of SSRI treatment may not be the optimal time to introduce BA. Anecdotal feedback from participants indicated that SSRI side effects, such as fatigue and disrupted sleep, may have hindered their ability to fully engage in BA activities. Although our formal physical symptom assessments showed no significant differences in side effects between groups, we only examined six domains (agitation, anxiety, dizziness, dry mouth, headache, and nausea). Importantly, we did not assess sleep disturbance as a potential side effect, though BDI-II data revealed that participants in the Citalopram group reported poorer sleep on the "Change in sleep patterns" item at the End of Study assessment, compared to the Placebo group.

Furthermore, BA may not be the most suitable intervention to pair with SSRIs for treating depression. BA benefits from a strong evidence base, but it is a heterogeneous intervention where participants choose their own activities and therapy goals, some of which may not promote the kind of positive environmental exploration thought to enhance antidepressant

drug action (e.g., solitary, home-based hobbies). Alternative interventions, such as exercise, may offer greater benefits. While physical activity (PA) can be a part of BA in some cases, exercise in and of itself can be thought of as a standalone intervention for depression with its own effects on neuroplasticity, inflammation, and the endocrine system. Exercise can directly promote environmental exploration (e.g., running outdoors, taking a class at the gym) and enhances self-esteem, self-efficacy, and social support (Kandola et al., 2019). Participants in exercise interventions often seek assistance from family and friends, which may reduce loneliness and increase levels of environmental reinforcement (Schuch et al., 2016). Indeed, some studies have shown that exercise combined with antidepressant medication may be more effective compared to medication alone (Kvam et al., 2016; Lee et al., 2021).

There is also evidence that the social aspect of the environment may be particularly important for the success of antidepressant treatment. Studies examining environmental moderation of SSRI effects have consistently found that people in supportive social environments respond best to treatment (Chiarotti et al., 2017; Shiroma et al., 2014). In the CABIN study, we measured participants' Baseline levels of social support (using the Multidimensional Scale of Perceived Social Support, MSPSS) and established that, on average, participants benefitted from moderate levels of support from family, friends and significant others, with no apparent differences between treatment groups (Chapter 3). Nevertheless, it is unclear how these levels of social support played out during treatment or if participants were comfortable disclosing their study participation to those who could have supported their BA goals. Interventions which explicitly target social interaction and connection, such as social dance, may from this perspective be better candidates for combining with SSRI treatment.

In their narrative review of dance interventions for mental health, Delattre et al. emphasise that dance-based movement activities with strong social components (e.g., partner or group dance) hold particular promise as primary or supplementary approaches for reducing low

mood and depression (Delattre et al., 2024). These activities may provide a platform for SSRI-induced emotional biases, such as improvements in positive facial expression recognition, to enhance social interactions and, in turn, improve mood. Both exercise and social dance should be explored as alternative interventions in future research.

8.5 FUTURE DIRECTIONS

One practical step that can be taken without the need for new data collection is to develop an understanding of the specific types of activities that may be beneficial when combined with antidepressants early in the treatment course. As mentioned above, BA is a heterogeneous intervention and so individual activities and goals chosen by study participants can vary greatly; this opens the possibility of categorising individual BA goals into specific activity categories (e.g., physical exercise, social activities, skill-building activities), and tentatively explore their relationship with our measures of behavioural activation, environmental enrichment, and emotional cognition. While it is unlikely such investigations would be adequately statistically powered, they could serve as a stepping stone for identifying more targeted environmental enrichment manipulations for future research.

A natural next step might involve conducting a follow-up study which addresses the major limitations of the current research. Key improvements would be extending the duration of BA administration, adopting a four-group design that includes a Placebo + BA treatment group, and incorporating clear measurements of engagement with BA therapy. This could involve tracking the proportion of scheduled BA activities completed alongside the use of validated measures of environmental reward, such as the Environmental Reward Observation Scale (EROS). Based on our exploratory investigation into BA activity categories and other empirical evidence, replacing BA with more suitable manipulations of environmental enrichment – such as exercise or social interventions like partnered dance or group-based movement activities – could also be considered.

Arguably, the most intriguing result from our study concerns reinforcement learning, where significant differences were observed between the citalopram and combined treatment groups, particularly in relation to punishment sensitivity. Our findings suggest that BA may play an important role in stabilising responses to loss, even when citalopram introduces variability in behaviour. Though no significant changes were observed in reward learning, the shifts in punishment learning – such as the between-group differences in the proportion of win-stay and lose-shift responses on loss trials – highlight an area where the interaction between pharmacological and psychological treatments could be better understood. Notably, elements of BA such as goal-setting have also been associated with reductions in effort sensitivity when deciding how to act to gain reward (Norbury et al., 2024). Given the strong association between these reward processing constructs and the anhedonic and amotivational aspects of depression, which are often poorly addressed by current treatments, this is an exciting avenue for future research.

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APPENDIX 1 – EXAMPLE ACTIGRAPHY DATA QUALITY PLOTS

The GENEActiv watches were set to record at a sampling rate of 25Hz, providing a battery life of approximately 28 days, with the first 21 days typically corresponding to the study period included in the analysis. The *GGIR* data processing package's non-wear algorithm detected suspected non-wear periods, with missing intervals imputed using the average of similar time points from other full days of recording. Any days with more than three hours of missing data were automatically excluded from further analyses, as it would not be possible to compute the desired rest and activity outcomes. Below are two examples of actigraphy data quality plots generated by *GGIR*: one from a participant without detected watch non-wear (Figure 1) and one with extensive detected non-wear (Figure 2).

Appendix 1 – Example actigraphy data quality plots

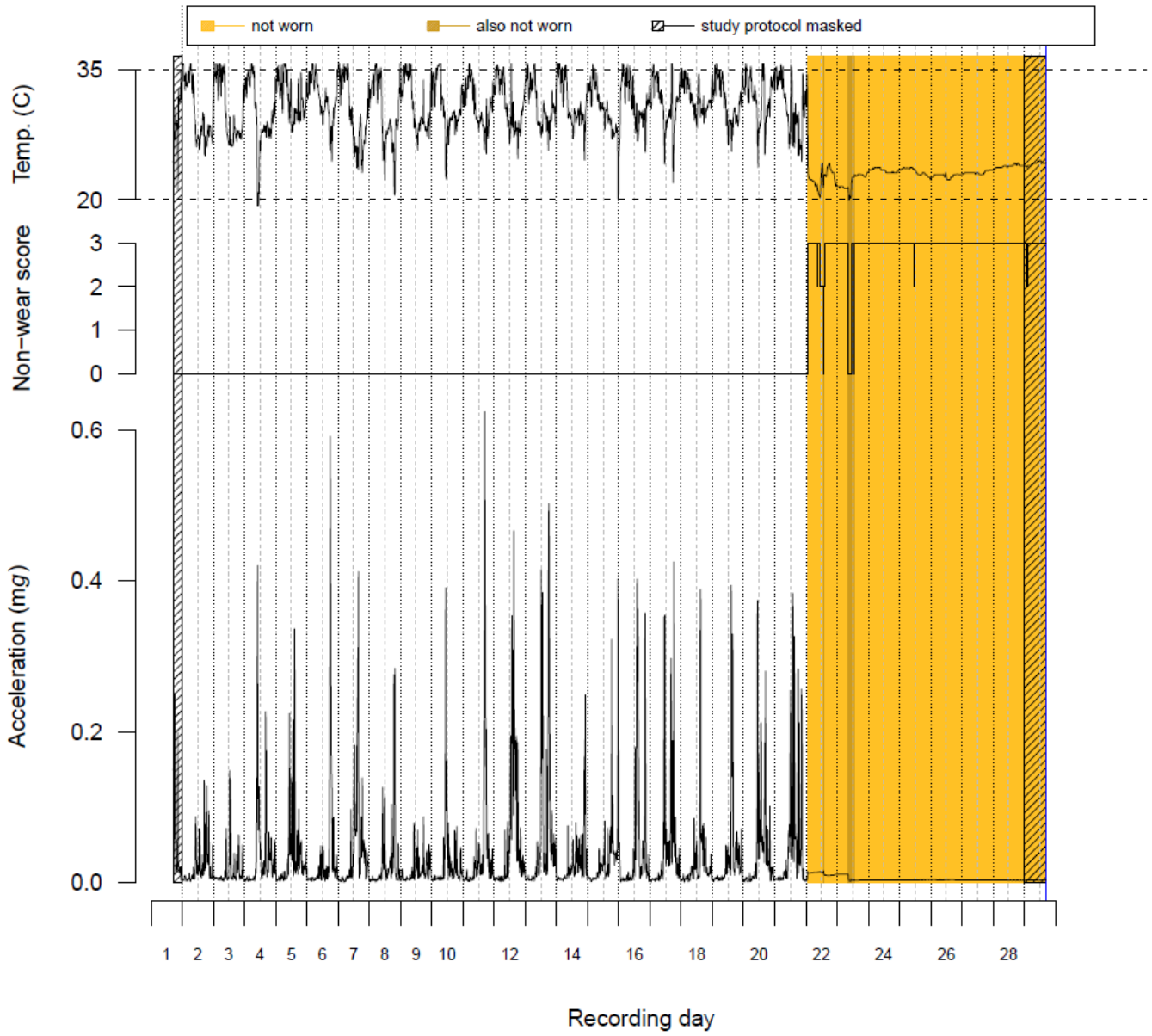


Figure 0.1. Example actigraphy data quality plot for a participant with no detected watch non-wear over the 21-day CABIN study period

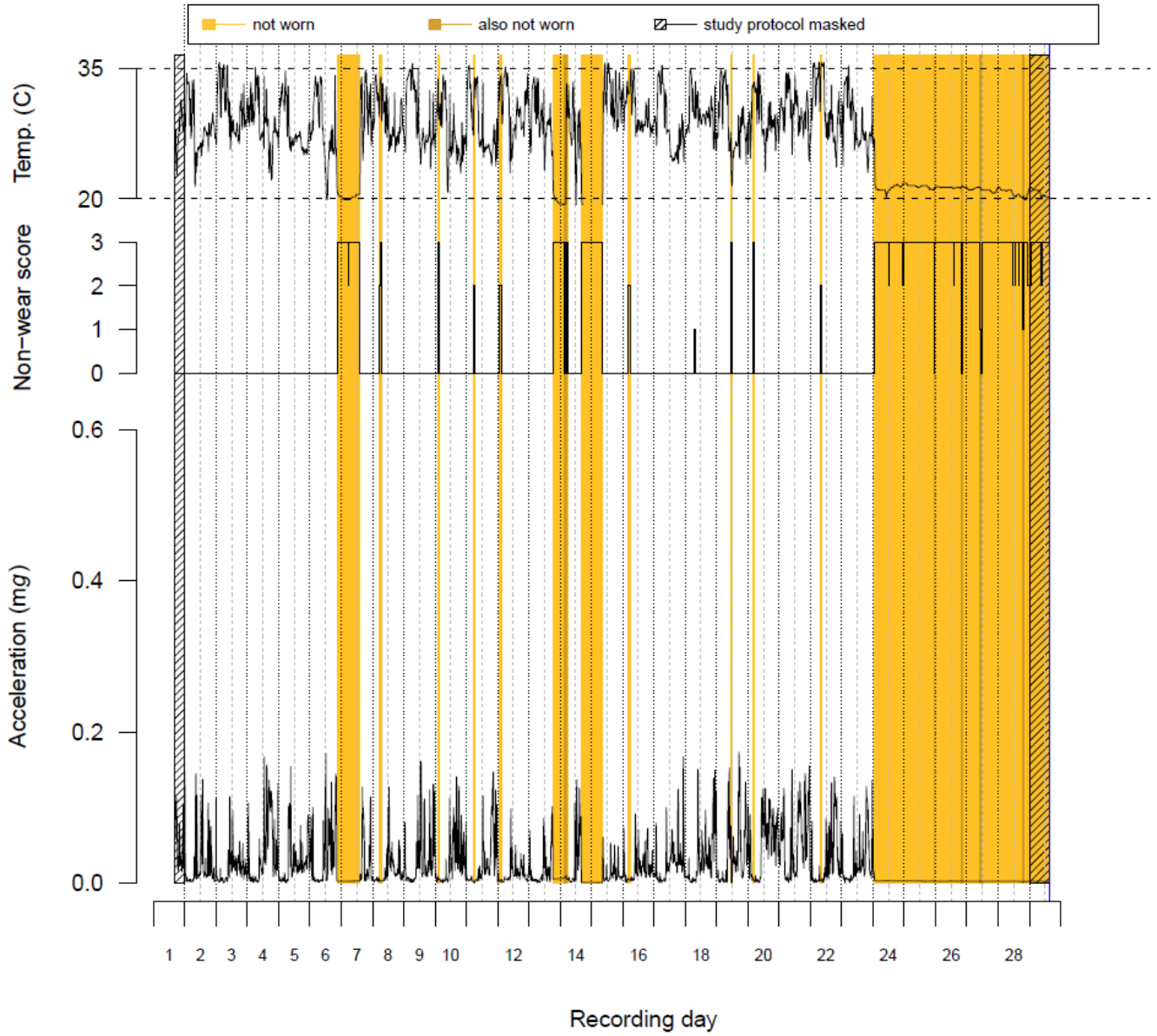


Figure 0.2. Example actigraphy data quality plot for a participant with extensive detected watch non-wear over the 21-day CABIN study period

APPENDIX 2 – EXAMPLE CORTISOL CURVES

Cortisol awakening curves, where cortisol concentration (in nmol/L) was plotted against the sample number, were created for each participant at each timepoint and visually inspected. Below we illustrate example cases with a detectable CAR post-treatment (Figure 1) as well as instances where the cortisol curves were flat (Figure 2). No exclusions were made based on these results, as it remains unresolved whether the absence of a positive CAR represents a genuine phenomenon.

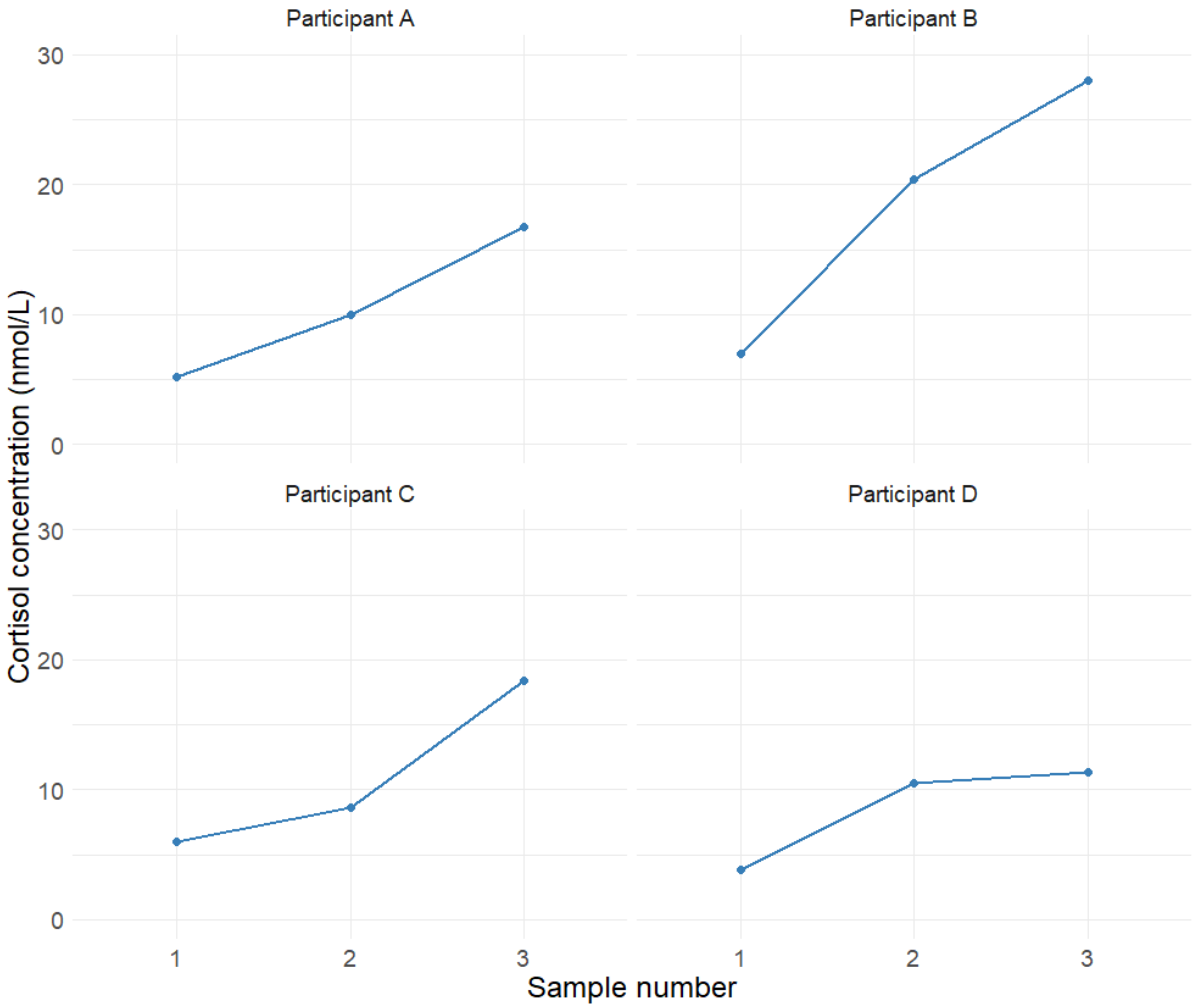


Figure 0.1. Four representative participants with a visually detectable cortisol awakening response post-treatment, where the cortisol concentration (in nmol/L) increases as a function of sample number from awakening (sample 1) to 30 minutes post-awakening (sample 3)

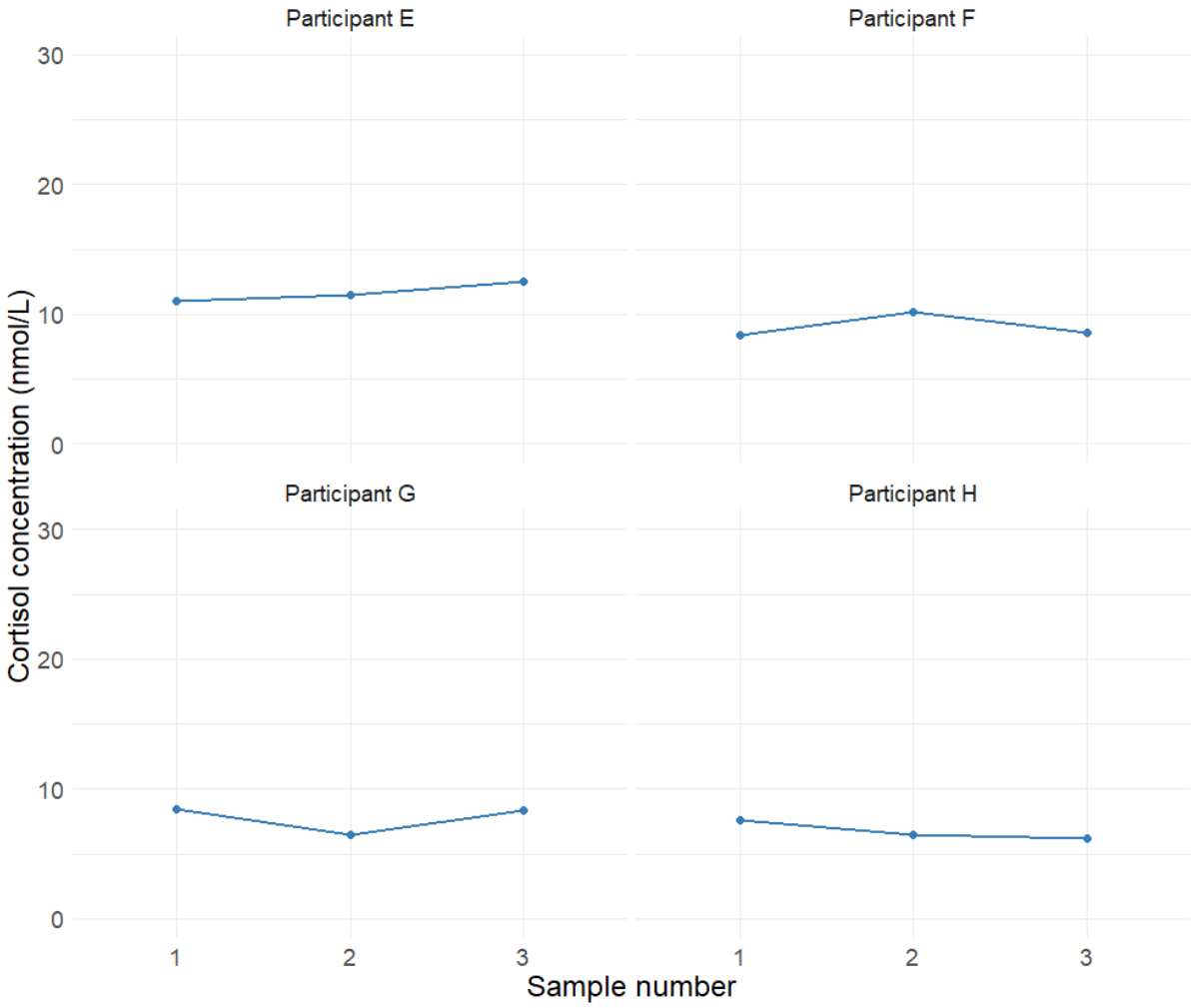


Figure 0.2. Four representative participants without a visually detectable cortisol awakening response post-treatment, where the cortisol concentration (in nmol/L) remained stable as a function of sample number from awakening (sample 1) to 30 minutes post-awakening (sample 3)