The Psychophysiological Correlates of Emotion Processing in Dysphoria

by

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Abstract

The most recent extension of the cognitive vulnerability model of depression suggests that people with mild symptoms of depression (i.e. dysphoria) will show cognitive biases primarily at early information-processing stages, while people with severe symptoms of depression (i.e. clinical depression) will show cognitive biases at late information-processing stages. To date, however, few studies have empirically explored early cognitive biases in dysphoric samples. Here, I manipulated task-relevance to functionally dissociate implicit and explicit emotional processing and used scalp electroencephalograms (EEG) to look at information-processing stages in dysphoric participants. High-density EEG was recorded during the traditional task used to study cognitive biases, the emotional Stroop task (experiment 1), and an emotional word categorization task (experiment 2). Then, in my analyses, unlike previous studies, I focused particularly on early (< 300 ms) frontal ERP effects that differentiated a group with dysphoria from a comparison group with few depression symptoms. I found that early ERP components over frontal scalp were significantly amplified in the dysphoric group, while common measures of late stage processing, such as the emotion-related late posterior positivity (LPP) and reaction time, did not differentiate groups, regardless of task. Next, to show that these effects could be replicated with non-word stimuli, I used emotional faces. Emotional faces are commonly used in ERP studies of attention and emotion, and are the most common stimuli used in neuroimaging studies of depression. As such, by using LORETA source analyses, I was able to tie my ERP findings into a wider literature. This work therefore lends support to the recent extension of the cognitive vulnerability model of depression, and contextualizes the previous cognitive bias results in the wider attention, emotion and depression literatures. This dissertation concludes with a suggestion that future studies carefully differentiate between-group and within-group effects, use different paradigms to dissociate “fast” vs. “slow” effects, and address the usefulness of early biases to predict the onset of depression through longitudinal studies.

Keywords: Depression; Event-related potentials; Emotion; Task-relevance; LORETA
Dedication

To the love of my life,

David R.M. Thompson
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1. General Introduction

The ancient Greeks divided the mind into three independent mechanisms—cognition, emotion, and motivation (Lazarus, 1999). We now believe that these mechanisms are interdependent (for recent review see Pourtois et al., 2013), and can influence each other. For instance, cognition can be biased by both emotional bottom-up exogenous factors, such as emotional stimulus content (Lang, et al., 1997; Öhman et al., 2001), and top-down endogenous motivational factors, such as an individual’s affective style (Davidson et al. 1998).

Theoretically both exogenous and endogenous factors influence cognition through “associative networks” (Beck et al., 2008; Bower, 1981; Lang, 1979). For instance, when an exogenous emotional event occurs, such as the word “gun” on a computer screen, it activates network nodes related to the representation of guns, their function and purpose, the potential consequences of their use, and their motivational value (Bower et al., 1981). Also, the activation of a node causes the priming of all other nodes within its associative network. This gives a processing advantage for all subsequent stimuli that are related to the primed nodes (Disner et al., 2011).

Genes are proposed to mediate many endogenous factors. For instance, healthy children and adolescents are thought to have nodes primed through biological preparedness to respond to negative stimuli (e.g., snakes; Öhman, 2001), and positive stimuli (e.g., erotic pictures; for review see Pessoa & Ungerleider, 2004). These nodes coalesce into negative or positive templates (i.e. schemas) that help people quickly respond to biologically relevant events, improving their evolutionary fitness (for review see Cacioppo & Bernston, 1994).

The extremely influential cognitive model of affective disorder vulnerability (Beck et al., 2008; Clark & Beck, 2010; Disner et al., 2011) proposes that individuals at risk of developing depression have aberrant genes that predispose some of their nodes to
respond to disorder-related stimuli (e.g., events related to sadness), and coalesce into dysfunctional disorder-related schemas. These dysfunctional schemas then bias the allocation of cognitive resources towards disorder-related stimuli and away from neutral and positive stimuli. Currently there is very little overlap between the cognitive model of depression vulnerability (Clark & Beck, 2010) and neurobiological models of emotion processing and depression.

LeDoux (2000) has provided the most prominent model of emotion processing. Using rats, LeDoux (2012) developed a model suggesting that emotion, motivation, and reward-response are all related to survival circuits. These survival circuits have been conserved across mammalian species, and mediate functions that contribute to the organism’s defence, energy and fluid supplies, thermoregulation and reproduction. Survival circuits can be activated by either innate stimuli, or learned stimuli, and once activated focus attention on the relevant external and internal stimuli, increase arousal, engage motivational systems, prioritize particular responses and influence learning and memory formation.

The majority of LeDoux’s work (1999, 2000, 2012) focuses particularly on the survival circuit related to the detection of threat. In rats, information is thought to reach the amygdala through a fast direct route, from sensory pathways to thalamus to amygdala. The amygdala then sends signals to the hypothalamus, increasing arousal and the periaqueductal grey, which outputs to motor control regions and directly influences behavioural responses. Notably, this theory posits that this direct route uses subcortical areas to coarsely process threat stimuli, bypassing cortical areas entirely (LeDoux, 1996).

Armoury and LeDoux (1997) contrasted this direct route with an indirect route. The indirect route flows from the thalamus to the primary sensory cortex, the association cortices, and finally the amygdala, which then again influenced a wide range of downstream systems. Armoury and LeDoux (1997) hypothesize that this thalamo-cortico-amygdala route is longer and slower, but is able to provide a much more accurate and detailed representation of the emotional stimulus.
Aronmy & LeDoux (1997), also suggest that the prefrontal cortex, particularly the ventromedial prefrontal and/or medial orbitofrontal cortex are likely involved in monitoring and inhibiting responses that are no longer appropriate by down-regulating amygdala response, and thus reducing the fear response.

Vuilleumier (2005) further extended Armony and LeDoux’s two-pathway model by suggesting dorsal prefrontal cortical structures may be involved. Referred to as the two-pathway hypothesis Vuilleumier’s direct route is very similar to Armony & LeDoux’s (1997), starting with the superior colliculus and pulvinar nucleus of the thalamus, which send signals directly to the amygdala. Vuilleumier (2005) suggests that the direct route is related to the early event-related potential (ERP) effects that are occasionally reported in response to fearful stimuli within 150 ms of stimulus onset.

The indirect route in Vuilleumier’s two-pathway model (2005) is much more extensive than previous models. In Vuilleumier’s model the indirect route begins with the initial feed-forward visual sweep (V1 to V2/V4 to inferior temporal cortex to amygdala), but there are also early feedback signals from the amygdala that influence visual processing as it occurs. Additionally, rapid magnocellular inputs to the frontal-parietal network guides visual attention during each iterative sweep. This allows top-down signalling and control of ongoing processing (see also Corbetta & Shulman, 2002).

In the neuroimaging literature it has been noted that brain areas used in basic emotional information-processing (for reviews see Adolphs et al., 2002; Fusar-Poli et al., 2009; Lindquist et al., 2012; Murphy et al., 2003; Phan et al., 2002; Pourtois et al., 2013; Vytal & Hamman, 2010) and brain areas implicated in the pathogenesis and maintenance of anxiety and depression overlap (for reviews see Drevets, 1998; Koenigs & Grafman, 2009; Liotti & Mayberg, 2001; Mayberg, 1997, 2007; Phillips et al., 2003a, 2003b, 2008).

The importance of prefrontal regulation in the response to emotional stimuli is also highlighted by Mayberg’s limbic-cortical network model of depression (1997; 1999; 2003) where network dysfunction is thought to underpin both unipolar and bipolar depression (Mayberg 2007). In this model there is decreased activity in dorsal neocortical regions (e.g. dorsolateral prefrontal cortex, inferior parietal cortex, dorsal
anterior cingulate cortex) and a relative increase in ventral limbic and paralimbic regions (e.g. insula, subgenual anterior cingulate cortex, ventral prefrontal cortex, and orbital frontal cortex, parahippocampal gryus). In this model dorsal and ventral regions reciprocally inhibit each other. As such, during sad mood, the ventral limbic-paralimbic regions are activated and the dorsal regions are simultaneously deactivated or suppressed. When a person recovers from depression, the dorsal regions become more active and inhibit the activity of the ventral structures.

Fairly recently, Beevers (2005) has postulated a model which might be used to bring the cognitive and biological models of depression into alignment (Disner et al., 2011). Called the dual process model, Beevers suggests that depression vulnerability is related to initial dysfunctional associative networks (e.g. an unreasonable initial response to depression related stimuli), whereas the later onset of depressive symptoms is related to the failure of inhibition mechanisms.

Beevers model is an attractive extension to Beck’s model of depression (Beck, 2008; Clark & Beck, 2010; Disner et al., 2011), because although the cognitive vulnerability model has proven to be extremely useful in clinical practice, very few empirical studies have shown cognitive biases in depression (for reviews see Beck et al., 2008; Epp et al., 2012). To test Beevers’ dual process model, however, studies need to probe early stages of information-processing in participants at risk of developing depression, and determine if cognitive biases exist at this point is disease development, prior to the failure of the inhibition mechanisms related to the indirect route (as envisioned by Vuilleumier, 2005) and clinical depression.

The paragraphs below summarize the different ways that researchers have functionally disassociated the direct and indirect routes. The first method involves varying the speed at which stimuli are presented. In covert conditions the emotional stimuli are presented, often in passive tasks, at subliminal speeds (~10 ms; e.g., Williams et al., 2007). These covert stimuli are thought to capture attention automatically through the activation of the direct route and ventral “affective” structures (Pessoa & Ungerleider, 2004; Vuilleumier, 2005).
The covert presentation method was not used in this dissertation because subliminal processing rarely differentiates depressed samples from healthy controls (for review see Mathews & Macleod, 2005). Attentional biases in dysphoric and depressed populations are far more common at long stimulus exposure times (500 - 1000 ms, e.g., Bradley et al., 1997; Gotlib et al., 2004; Joormann & Gotlib, 2007; Mogg et al., 1995). Thus, this dissertation focuses on supraliminal presentations, and the dissociating the direct and indirect pathways through the manipulation of task-relevance.

It is quite common to manipulate task-relevance in studies of emotion (e.g., Critchley et al., 2000; Hariri, et al., 2000, 2003; Klumpp et al., 2013; Williams et al., 2006a). In implicit conditions, participants are asked to focus on an aspect of the stimulus that is non-emotional (e.g. the text color of emotional words), making the emotional content of the stimulus task-irrelevant. Increased reaction time latencies to emotional stimuli compared to neutral stimuli are thought to be the result of attention being occupied by task-irrelevant emotional content (Epp et al., 2012; Yiend, 2010). The neurobiological models of emotion suggest that implicit processing is largely dependent on the direct route, and thus the amygdala (Critchley et al., 2000; Hariri et al., 2000; Whalen et al., 1998), although again amygdala activity is not always seen (Pessoa & Adolphs, 2010).

The implicit task is usually contrasted against an explicit task, where, for instance, stimuli are categorized based on their emotional content (for review see Williams et al., 2006a), making emotion task-relevant. Most researchers believe that cognitive control is required to direct attentional resources away from task-irrelevant information (Goldin et al., 2008; Joormann et al., 2007; Klumpp et al., 2012; Vuilleumier et al., 2001). Such cognitive control is exerted by structures related to the indirect route, such as the dorsolateral prefrontal cortex (Bishop, 2009).

Measures that can provide high-resolution timing information, such as event-related potentials (ERPs), have rarely been used to study cognitive biases in depression, perhaps because the direct route is critically dependent on the amygdala (for review see Pessoa & Adolphs, 2010), and the amygdala’s size, location, and closed electrical fields make its activity hard to observe at the scalp (LaBar & Warren, 2009). Outside of the depression literature, however, ERPs have been used extensively to study emotional
information processing in healthy controls (for review see Olofsson et al., 2008). This basic emotion literature can be used to contextualize the results of the few depression studies that have been done and direct future studies.

Therefore the purpose of this introduction is to discuss how ERPs have been used to study emotional information-processing in individuals with and without symptoms of depression, how these results have been interpreted, and how they could be interpreted in the context of the broader emotion literature and new models of depression vulnerability, such as Beevers’ dual processing model (2005). To this purpose, the introduction begins with a brief overview of the symptoms and prevalence of depression, and then reviews the cognitive models of depression vulnerability and cognitive bias in depth. Next it moves on to describing the extensive emotion ERP literature in healthy controls and depressed participants, before focusing on what little work has been done on cognitive biases in depression. This chapter will highlight the need to contextualize the depression-related cognitive bias literature in the wider emotional literature, and ultimately hypothesizes that Beevers’ model is correct—that early stages of emotional processing (< 300 ms post stimulus onset) may be biased by depression risk while later markers of emotional processing (< 300 ms) are not.

1.1. An overview of depression

Depression is a common mental illness, affecting 20% of women and 11% of men at some point in their lives (Kessler et al., 2003, 2005; Kessler & Wang, 2009). The first episode of depression usually occurs during mid-puberty (Angold, et al., 1998), and is followed by a cycle of remission and relapse, with episodes becoming more frequent and intense if the disorder is left untreated (Frank & Thase, 1999; Kessler & Wang, 2009; Solomon et al., 2000).

Several predictors of first-onset depression have been established, including parental history of depression (Goodman, 2007), prior depressive symptoms (Pine, et al., 1999), and neuroticism (Kendler, et al, 2006). However, our knowledge of vulnerability markers is incomplete—the best-fitting predictive model of depression
(Kendler et al., 1993, 2002) does not account for more than 50% of the variance. Thus, we have little ability to predict the onset of depression.

A potentially fruitful direction for the discovery of new and useful predictive vulnerability markers is the study of brain mechanisms involved in emotional information processing and the development of depression using neuroimaging methods, particularly fMRI. For instance, although it has yet to be implicated in the development of depression (Pizzagalli, 2010), activity in the rostral anterior cingulate cortex (ACC; Cg24a) has been shown to separate medication responders from non-responders (Mayberg et al., 1997). If a similar risk-marker could be found it could improve our ability to predict the onset of depression (Frank & Thase, 1999; Mayberg, 2004, 2007; Pizzagalli, 2010).

In search of a predictive marker of risk, symptom provocation paradigms are commonly used to probe the dysfunctional brain mechanisms thought to underlie affective diseases. Individuals with a particular psychiatric disorder are exposed to disorder-congruent and neutral stimuli, and then the resulting brain activity is compared across conditions (for a review across many disorders see Shin et al., 2001). In depression the most common way of probing dysfunctional mechanisms is the study of cognitive bias, often using the emotional Stroop paradigm, which is thought to probe the direct route, because emotion is task-irrelevant. Cognitive biases and the emotional Stroop are thus explored below.

1.2. An overview of cognitive biases in depression

The purpose of this section is to give a comprehensive overview of cognitive biases in depression. Beck’s original cognitive model of depression (1988) rests in a diathesis-stress framework that posits that adverse early-life events (e.g., parental loss) cause an individual to develop negative “associative networks” (Bower, 1981) or “schemas” (Beck, 2008). These schemas become entrenched in dysphoria, increasing attention to negative stimuli in the environment and the interpretation of neutral or ambiguous stimuli in a schema-congruent way (Teasdale, 1988; Clark & Beck, 2010). This leads to a cognitive vulnerability to all future negative events.
As the negative schema bolsters the perceived arousal of all future negative events, it distorts how these events are interpreted and encoded at later information-processing stages and leads to a feedback cycle, and eventually a major depressive episode (Ingram, 1984; Teasdale, 1988).

It should be noted that Beck’s original model (1988) hypothesized that biasing occurred equally across all information-processing stages. It seemed evident to later researchers, however, that this could not be the case (for review see Mogg & Bradley, 2005). Research at that time suggested that anxious individuals exhibited early attention biases for concern-congruent (i.e. threat-related) information, while depressed individuals were thought to exhibit later elaboration and memory biases for concern-congruent (i.e. depression-related) information.

Williams and colleagues, therefore, suggested that there were at least two information-processing stages influenced by cognitive biases (1988, 1997)—a priming stage and an elaboration stage. The Williams’ model led to a general theoretical consensus among researchers that anxious participants should exhibit strong preconscious effects, such as attention capture by subliminally presented threatening stimuli, and inconsistent elaboration and memory biases. In contrast, participants with depression should not show preconscious biases, but strong elaboration and memory biases (for review see Mogg & Bradley, 2005). As empirical work continued, however, researchers began to realize that these proposed biases did not occur consistently in either anxiety (Bar-Haim et al., 2007) or depression (Epp et al., 2012).

There are a number of possible explanations for the inconsistent empirical results. The first explanation is that the word “bias” does not have a consistent definition. Bar-Haim and colleagues (2007) have pointed out that biases are sometimes defined as (1) increased attention to concern-congruent versus neutral stimuli within experimental subjects, and sometimes as (2) increased attention to concern-congruent stimuli between clinical and healthy participants. Anxiety studies have reported both effects as biases of attention, and as supportive of the cognitive vulnerability model of anxiety (Beck & Emery, 1985). Depression studies, alternatively, have interpreted only the within-group bias as supportive of the cognitive vulnerability model of depression.
(Beck, 1988), and have therefore found, overall, less support for Beck’s model of depression.

Another explanation for the inconsistent cognitive bias results is that the most common measure of cognitive bias is reaction time (RT). Some theorists now recognize that cognitive biases do not affect all information processing stages equally, and that multiple stages may be affected in both anxiety (Bar-Haim et al., 2007; Bishop, 2009) and depression (Epp et al., 2012; Yiend, 2010). For instance, both attention capture and maintained attention seem to be affected in depression (Koster et al., 2005). Therefore, RT may be a poor measure of cognitive biases, as RT is the cumulative result of multiple information-processing stages (Sternberg, 1969, 2011, 2013; Pachella, 1973), and particularly dependent on later information processing stages (Falkenstein, 1993). These later processing stages may only be related to current symptom burden, as suggested by Beevers’ model (2005) and Epp and colleagues’ results (2012).

The final explanation for the inconsistent cognitive bias results is that the cognitive biases within a person may change as the disease develops. Epp and colleagues (2012) reported in a meta-analysis of emotional Stroop studies that within-group (negative-neutral) reaction time biases were positively correlated with the number of depression symptoms at the time of testing. This is a particularly important result, and after a description of the emotional Stroop task the Epp study is discussed at length below.

1.2.1. The Emotional Stroop

The original Stroop task (1935) asked participants to read lists of color words (‘red’, ‘green’, ‘yellow’, and ‘blue’), printed in four different ink colors (red, green, yellow, and blue). In the congruent condition the words matched their ink color (e.g., ‘red’ was written in red). In the incongruent condition the words did not match their ink colour (e.g., ‘red’ was written in blue). Stroop found that it took longer to name the colors in the incongruent condition than the congruent condition. This phenomenon is now referred to as the Stroop interference effect or Stroop effect. The most prominent explanatory model of the Stroop effect is Cohen’s Parallel Distributed Processing framework (PDP; Cohen et al., 1990). The PDP framework proposes that color naming and semantic
meaning are processed in two separate information-processing pathways. The two pathways each consist of input nodes (representing color or meaning), intermediate nodes, and output nodes. Attention modulates this system by altering the responsiveness of the nodes according to task demands. The pathways interconnect across multiple units, and activity in one pathway may thus interfere with or facilitate the processing in the other pathway. Because the reading pathway is dominant when these two pathways are activated simultaneously, color reading interferes with color naming, producing the Stroop effect.

Gotlib and McCann (1984) were the first researchers to use emotional words in a Stroop task, and therefore can be credited with creating the first true emotional Stroop. They selected participants that scored high (> 9) or low (< 4) on the Beck Depression Inventory (Beck et al., 1988, 1996), and asked participants to name the ink color of 50 neutral, 50 depressive, and 50 manic words presented by tachistoscope. They found that the valence of the word did not affect the control group, but participants with mild depression were slower (23 ms) to respond to the color of depressive words than to manic or neutral words, a phenomenon dubbed the emotional Stroop interference effect.

This study led to a plethora of emotional Stroop studies in healthy controls (Williams et al., 1996; Yiend, 2010), and participants with affective disorders such as anxiety (Bar-Haim et al., 2007) and depression (Epp et al., 2012). Williams and colleagues (1996) reviewed the results and concluded that Cohen’s PDP model could be used as a framework for modeling the emotional Stroop effect as well, suggesting that, like in the cognitive Stroop, there was an interaction between the color naming and semantic meaning pathways, that these pathways shared nodes, and could influence each other.

Again, it was a common misconception in the literature that only anxious individuals exhibited early attentional biases, while depressed individuals only exhibited later interpretational and memory stage biases (Gotlib & Joormann, 2010). As noted above, recent models of both anxiety (Bishop et al., 2004; Bishop, 2009) and depression (Beevers, 2005) suggest that there are multiple information-processing stages biased in these disorders, and that these biases may change throughout the course of the disease (Epp et al., 2012). In support of this, Epp and colleagues (2012) conducted a large
meta-analysis of all emotional Stroop studies conducted in healthy individuals induced into a sad mood, with dysphoria, and participants with severe depression as assessed through clinical interview. They found large and robust depression-related within-subjects emotional Stroop RT effects in clinical depression versus controls ($g = .98$, $p < .001$), but only a medium sized effect in dysphoric samples versus controls ($g = .55$, $p < .01$), and the smallest effect in sad-mood versus neutral-mood controls ($g = .20$, $p < .05$).

One explanation for these results is that emotional Stroop reaction time results may not be related to early information-processing biases, but primarily to a late stage within-group bias related to the reallocation of attention (de Ruiter & Brosschot, 1994; Epp et al., 2012; MacLeod et al., 1986), cognitive inhibition (Joormann et al., 2004, 2007; Joormann & Gotlib, 2007; Gotlib & Joormann, 2010) or response inhibition (de Ruiter & Brosschot, 1994).

Bair-Haim and colleagues (2007) proposed an emotional information-processing model of vulnerability to anxiety where there may be deficits at multiple information-processing stages. A similar model can be proposed for depression, with the extension that early stage biases may be present in vulnerable individuals, but late stage biases may only develop with clinical depression. This model, with multiple information processing stages affected, would fit with the recent extension of the cognitive vulnerability model (Beevers, 2005), and suggest that individuals at risk of developing depression, such as those with dysphoria, will show early information-processing stage biases, while individuals with clinical depression will show late stage processing biases.

In summary, to move forward, and build on the extensive emotional Stroop literature already gathered in depression, we must (1) differentiate between within-group (i.e. negative versus neutral) and between-group cognitive biases (diseased versus healthy), (2) do a better job of parsing the different information-processing stages involved and (3) acknowledge that cognitive biases may not influence all stages of information-processing equally.

Therefore, in this work: there is a conscientious effort to distinguish between within and between group biases, electrophysiological measures of brain activity are used to observe information-processing on a millisecond-by-millisecond basis, and only
one subgroup of depressive individuals was used—dysphoric individuals with symptoms of depression.

1.3. **A review of event-related potentials (ERPs)**

One way of isolating different information-processing stages is by directly measuring brain activity. This can be done through recording electroencephalograms (EEG), which have excellent temporal resolution as they directly measure the synchronized electrical activity of thousands of cortical pyramidal cells (Luck, 2005). From the EEG, event-related potentials (ERPs) can be derived by time-locking to stimulus onset and averaging over multiple trials.

These ERP waveforms reveal an ordered set of evoked potential components, as well as cognitive and motor responses to the stimuli (Luck, 2000). ERP components are typically distinguished by their polarity and timing (e.g., 100 ms following stimulus onset the “P100” shows as a positive deflection and is thought to index very early attention processes which have been localized primarily to the extrastriate cortex). Emotion is thought to enhance cortical responses at all stages of visual stimulus processing (for review see Kissler et al., 2006).

Note that it is common in the emotion literature to divide early and late at the 300 ms post stimulus mark (Kissler et al., 2006). Electrophysiological studies of brain activity have consistently demonstrated ERP differences for emotional compared to neutral visual stimuli at early (< 300 ms) information-processing stages (Schupp et al., 2006), and late information-processing stages (Cacioppo et al., 1994; Crites, et al., 1995; Hajcak et al., 2010).

1.3.1. **ERP effects elicited by emotional stimuli**

The following section will summarize the existing research on visually presented emotional stimuli in both healthy individuals and individuals with affective disorders such as anxiety and depression. Then the existing ERP research in depression will be summarized. This will be followed by a summary of the emotional Stroop ERP literature, in both healthy and depressed individuals.
*ERP effects elicited by emotional stimuli in healthy participants*

Below the influence of emotion on the ERP waveform is discussed in the chronological order that the effects occur. The earliest, and most under-reported, emotion-related ERP effect is a very early frontal positivity (< 150 ms post stimulus onset) over frontal scalp. ERP studies from Carretié’s lab (2004, 2006) and Eimer’s lab (2002, 2007, 2009) have found early electrophysiological responses over frontal scalp during this very early time window, and source localization has suggested neural generators in the orbital frontal cortex (OFC). Supporting this finding, Jaspers-Fayer and colleagues (2012), using simultaneously recorded EEG and functional magnetic resonance imaging (fMRI), have described an ERP effect with similar timing in response to threatening auditory stimuli. This ERP effect was correlated with orbital frontal cortex (OFC) BOLD activity. Furthermore, single-cell recording experiments have also suggested that the OFC is the source of this activity (Kawasaki et al., 2001; Pourtois et al., 2010), and that this activity is related to the activation of the threat-detection system (Adolphs, et al., 1995; LeDoux, 1996), in both healthy adults to threatening stimuli (Carretié et al., 2004, 2006; Jaspers-Fayer et al., 2012) and individuals with hyper-vigilance disorders, such as anxiety (Taake et al., 2009).

Next, a posterior visual N2 occurs over occipito-parietal scalp (e.g., Sass et al., 2010), peaking at approximately 200 ms. The modulation of the N2 by emotion is referred to as the early posterior negativity (EPN; Junghöfer et al., 2001; Schupp et al., 2006). The EPN occurs on a trial-by-trial basis, 200-300 ms after stimulus onset with an enhanced negativity over temporal-occipital scalp to emotional words, faces and scenes, compared to neutral stimuli. The EPN has been interpreted as an index of attention to emotional stimuli, where emotional stimuli are selected for further and more elaborate processing from the milieu of surrounding neutral stimuli (Oloffson et al., 2008).

Notably, there have been a number of reports of a frontal positivity occurring at the same time as the EPN. In studies using emotional words and pictures (Asmaro et al., 2012; Carolan, et al., 2013; Taake et al., 2009) this effect has been referred to as the early anterior positivity (EAP). There is debate around whether or not the EAP and EPN are separate effects, or if the EAP is the polarity-reversal of the EPN, sharing the same underlying neural generators (Junghöfer et al., 2006; Schupp et al., 2006). A point in
favour of there being different neural generators involved in the EPN versus the EAP is that the EPN is generally thought to be effected by task-relevance, and the EAP is thought to be independent of task-relevance. Note, however, that Junghöfer and colleagues (2006) have suggested that the EAP and EPN originate from the same neural sources, and that the different effects reported by individual studies are actually a consequence of the reference montage chosen by the researchers. An average mastoid reference, which is common in the emotion literature, highlights emotion-related frontal positivities, while an average reference is more likely to display emotion-related posterior negativities during the 200-300 ms time-window. This dissertation will use the average mastoid reference, which is the most common reference used in the emotion literature (Olofsson et al., 2008).

By far the most common emotion-related effect reported in the literature is the late posterior positivity (LPP), which is enhanced for emotional compared to neutral stimuli (Cacioppo et al., 1996; Cuthbert et al., 2000; Foti et al., 2009; Hajcak et al., 2010; Olofsson et al., 2008; Schupp et al., 2000). The LPP typically begins in the same time range as the P3b (300-500 ms; Carretié et al., 2001; Cuthbert et al., 2000), although it is distinct from the P3b, and can continue for up to a second or more after stimulus offset (Hajcak & Olvet, 2008). LPP amplitude is task-dependent (Fischler & Bradley, 2006; Ito & Cacioppo, 2000; Ito et al., 1998; Kayser et al., 1997; Naumann et al., 1992, 1997; Schupp et al., 2000) with the largest voltage in response to task-relevant, highly arousing versus task irrelevant stimuli and versus low arousal stimuli (for review see Olofsson et al., 2008).

It has been proposed that the visual LPP may index the activity of an inhibitory feedback loop between frontal limbic systems and the extrastriate visual system (Albert et al., 2012; Lang & Bradley, 2010; Lui et al., 2012; Moratti et al., 2011; Sabatinelli et al., 2007, 2013; Jaspers-Fayer et al., in preparation). This mechanism inhibits neutral stimuli, which results in the selective survival of activity associated with the processing of emotional stimuli (Brown et al., 2012). Notably, Hajcak and colleagues (2010) have given support for this theory by showing that stimulation of the dIPFC in a depressed sample leads to reduced LPP, perhaps through connections that disrupt the ongoing elaboration process. Hajcak’s group (Foti et al., 2010) has also shown a decreased LPP
in a depressed sample in response to emotional faces, as have others (Deldin et al., 2000; Kayser et al., 2000).

**ERP effects elicited in individuals with depression**

The first pronounced depression-related ERP effect in response to emotional words (Kemp et al., 2009) is an exaggeration of the frontal P2 (150-275 ms) during cognitive paradigms, such as the oddball (Vandoolaeghe et al., 1998; c.f. Deldin et al., 2000; Kayser et al., 2000). At later stages of processing, the P3 has been studied extensively in depressed populations using oddball paradigms with neutral stimuli. By far the most established and replicated ERP findings in depression are related to the reduced amplitude (Blackwood et al., 1987; Diner et al., 1985; Gangadhar, et al., 1993; Roth et al., 1981), and delayed latency (Bruder et al., 2009; Kalayam & Alexopoulos, 1999; Vandoolaeghe et al., 1998) of the P3b or later parietally distributed components. The P3b is thought to reflect selection and evaluation of targets embedded in streams of distractors. Its amplitude is affected by target frequency and salience (Polich, 2007). Animal studies have associated the P3 to the firing rate of the locus coeruleus-norepinephrine (LC-NE) system. Norepinephrine projections to the neocortex can affect cortical arousal levels and signal-to-noise tuning relevant to the selective processing of targets (for review see Nieuwenhuis et al., 2005).

**ERPs elicited by the emotional Stroop**

While the temporal course of the color Stroop has been studied extensively (Duncan-Johnson & Kopell 1981; Liotti et al., 2000b; West & Alain, 1999; West, 2003), only minimal work has been done on the emotional Stroop in healthy adults (Asmaro et al., 2012; Carolan et al., 2013; Franken et al., 2009; Frühholz et al., 2011; Taake et al., 2009; Thomas et al., 2007). Healthy participants often show an increased electrophysiological response to emotional stimuli during both early (Thomas, 2007; Frühholz et al., 2011) and late time windows (Thomas et al., 2007).

The emotional Stroop has been used extensively as a laboratory measure to study cognitive bias in a number of affective disorders, including anxiety, PTSD, phobias, depression and obsessive compulsive disorder (e.g., Kolassa, et al., 2005; Metzger, et al., 1997; Taake et al., 2009; Thomas, et al., 2007, 2013; Sass et al., 2014).
For instance, Taake and colleagues (2009) recorded high-density EEG during an emotional Stroop task recorded in participants with sub-clinical anxiety. A left-lateralized EAP occurred for concern-congruent (i.e. threat-related words; 200-300 ms) compared to neutral words. As well, although this effect was not reported, the ERP figures show an obvious anxiety-related amplification of the P2. Effects in this time range are theorized to index early automatic stimulus discrimination and selection (for review of emotion-related ERP effects see Olofsson et al., 2008).

Few studies report early ERP effects in clinically depressed participants (Fisher et al., 2010; McNeely et al., 2008; Vanderhasselt & De Raedt, 2009; c.f. Dai & Feng, 2010), and only one recent study (Sass et al., 2014) has looked at early effects in dysphoric participants. Sass and colleagues, used an emotional Stroop to elicit ERPs in response to emotional versus neutral words in a dysphoric sample. They did not report group modulations of the ERP waveform (i.e. Bar-Haim et al.’s between subjects effects), and did not report frontal effects. Potentially as a result of this, they did not find evidence for early cognitive biases in dysphoria.

Some studies have reported later effects. McNeely and colleagues (2008) found that individuals with major depressive disorder had larger N450 amplitudes over parietal sites to both negative and positive words compared with neutral words. Dai and Feng (2010), found a similar depression-enhanced N450. Both the McNeely and Dai groups concluded that this finding reflected abnormal involvement of control mechanisms, due to an increased need to suppress the task-irrelevant emotional content of the emotional words. In both instances these results support the two-pathway model of depression vulnerability (Beevers, 2005), which suggests that the strongest effects for a clinical population will occur at later stages of information-processing.

1.4. Research goals

The primary aim of this work is to use electrophysiological measures to study early and late emotional information-processing stages that could differentiate dysphoric participants from participants with no symptoms of depression. This is the first study to
look at early anterior ERP effects is a dysphoric group, in addition to early posterior ERP effects and late stage effects (i.e. the LPP).

Chapter 2 begins with an emotional Stroop task (experiment 1) in participants with dysphoria and a comparison group without symptoms of depression. The ERPs elicited by negative and neutral words are contrasted, and both the early and late time-windows are assessed to determine how information-processing is biased both by emotional stimulus content and by an individual's depression symptoms. Based on the aforementioned studies it was hypothesized that effects during the P2 time-window would be enhanced by the emotional content of the stimuli (Carretié et al., 2004, 2006) and would differentiate groups (Taake et al., 2009). The results of this study suggested that not only did early ERP effects differentiate groups, but furthermore that only early ERP effects differentiate the experimental groups, as later (> 300 ms) effects were only influenced by emotional condition, and not by depression status.

Next, the hypothesis that these effects were automatic, and only present in the implicit emotional Stroop task was tested. Task-relevance has been shown to influence ERP effects as early as 200-300 ms post-stimulus onset (Potts & Tucker, 2001). Therefore another main objective was to determine if task-relevance could be used to functionally dissociate the early anterior positivity (EAP), which is thought to be relatively pre-attentive and automatic (Taake et al., 2009), from the early posterior negativity (EPN), which is influenced by task-relevance (Oloffson et al., 2008). If this were the case, it would give proof for the existence of different underlying neural generators. Conversely, if the EAP and EPN have the same underlying neural generators they should respond in a similar way to the task-relevance manipulation.

In chapter 3, the results of the chapter 2 were replicated and extended through the use of task-relevant and task-irrelevant emotional faces. Most neurobiological studies of emotion and depression have used emotional faces (for review see Stuhrmann et al., 2011). Low resolution electromagnetic tomography (LORETA) analyses were conducted on the significant ERP effects to determine if my results were in agreement with these neuroimaging studies.
2. Emotional Words

2.1. Abstract

Cognitive biases for concern-specific words are potential markers of depression vulnerability, and are theoretically implicated in the etiology and maintenance of depressive episodes. Although previous literature has suggested that anxiety is related to early information-processing stage biases and depression is related to later stage biases, recent quantitative literature reviews have shown the situation is more complex. In this chapter we review the theory that mild symptoms of depression (i.e. dysphoria) are related to early (< 300 ms) information-processing biases, but not late (> 300 ms) information-processing stages. To date, no study has used a technique with high temporal resolution to test this hypothesis. Thus, event-related potentials (ERPs) were recorded during an emotion-irrelevant Stroop task (experiment 1) and an emotion-relevant word categorization task using the same stimuli (experiment 2), to determine if and under what circumstances ERP effects could distinguish between participants with and without mild depression. **Methods:** Mass screening of over 400 undergraduate students was done using the Beck Depression Inventory (BDI), allowing us to identify dysphoric participants with mild-to-moderate depression symptoms (n = 15) and a comparison group (n = 16) with few symptoms of depression. High-density electroencephalograms were recorded while participants completed the tasks. **Results:** In both tasks, dysphoric participants exhibited an amplified and left-lateralized N1, followed by an amplified frontal P2, regardless of emotional condition. The early anterior positivity (EAP) and late posterior positivity (LPP) distinguished between negative vs. neutral emotional words in both tasks, but these effects did not interact with group membership. LORETA analysis of the grandaverage difference waves suggested that group differences were related to fusiform gyri and insular maxima in the emotion-irrelevant task. In contrast, the emotion-relevant task was related to maxima in the fusiform gyri, insula and ACC, perhaps because this task was more difficult.
Conclusion: These results suggest that ERP components reflecting early between-group differences may be better markers of cognitive biases in depression than later ERP components (i.e. the LPP) and reaction time measures. These results support the most recent version of the cognitive vulnerability model of depression, which suggests that early information stages are influenced by depression-risk, while later biases are related to cognitive elaboration.

Keywords: Dysphoria; Event-related potentials; Emotion; Task-relevance; LORETA

2.2. Introduction

Beck’s cognitive model of depression vulnerability (1988, 2008) posits that people at risk of developing clinical depression have cognitive biases for depression-congruent (e.g., sad) information. These biases are thought to boost the emotional salience of sad events, regardless of their task-relevance, distorting how they are interpreted, and remembered (Bower, 1981). Furthermore, these biases create a feedback cycle that can cause and maintain a depressive episode (Teasdale, 1988; for recent review see Yiend, 2010).

Although Beck’s cognitive model has been widely accepted by clinicians, empirical support has been sparse (Beck, 2008). This may be because cognitive biases have primarily been studied using the emotional Stroop task (for review see MacLeod & Mathews, 1991), which does not differentiate different information-processing stages (Williams et al., 1996). In this task, concern-congruent words are presented on a computer screen and the participant is asked to respond to the task-irrelevant work colour of the word. The traditional emotional Stroop interference effect occurs when the reaction time (RT) for concern-congruent emotional words is longer than for neutral control words. In previous studies, emotional Stroop interference has been considered an accurate index of cognitive bias (Yiend, 2010).

Historically anxiety has been associated with attentional biases, such as increased attention capture, whereas depression has been associated with later stage cognitive bias, such as elaboration and memory biases (Mogg & Bradley, 1998, 2005). We now realize, however, that this model is too simplistic, as meta-analyses of both
anxiety (Bar-Haim et al., 2007) and depression (Disner et al., 2011; Epp, 2012) have shown biases at multiple information processing stages.

It is now theorized that early stage biases are related to depression vulnerability, whereas later biases are strongly correlated with depression severity (Beevers, 2005), and there is strong empirical support for the notion that individuals with mild depression symptoms, or dysphoria, often do not show reaction time emotional Stroop interference effects (e.g., McNeely et al., 2008) whereas clinically depressed patients often do (Epp et al., 2012).

To determine if participants with mild symptoms of depression show early stage biases we need to use a method that will allow us to parse the information-processing stream into early and late stages. Event-related potentials (ERPs) offer a temporal resolution of 1 millisecond or better (Luck, 2005), and can give timing information about emotional events (Olofsson et al., 2008). ERP studies of emotion have reliably shown ERP differences for emotional compared to neutral stimuli at both early (Schupp et al., 2006) and late (Cacioppo et al., 1996; Hajcak et al., 2010) stages of information-processing. The current study therefore uses ERPs to determine if early (< 300 ms), and late (> 300 ms) changes in the ERP waveform differentiate participants with and without mild symptoms of depression.

To the authors’ knowledge, only five ERP studies of the emotional Stroop have been conducted using participants with symptoms of depression (Dai & Feng, 2010; Fisher et al., 2010; McNeely et al., 2008; Sass et al., 2014; Vanderhasselt & De Raedt, 2009), but none of these studies reported early (< 300 ms) ERP components, or, in fact, common emotion-related components such as the late posterior potential (LPP). Thus, these studies do not speak directly to whether or not early biases can distinguish between experimental groups, and do not tie neatly into the wider emotion literature.

Early information processing biases were hypothesized as a number of studies have now shown that valence can influence the ERP waveform during the P1-N1 time-window (Bayer et al., 2012; Ortique et al., 2004; Rabovsky et al., 2011; for review see Kislter et al., 2006) before lexical access (Conrad et al., 2011; Kissler et al., 2006) if the task is blocked.
Temporally, the second emotion-related modulation is the early posterior negativity (EPN; 200-300 ms; Schupp et al., 2007), which is seen as a negative deflection over temporal-occipital electrode sites for emotional stimuli compared to neutral stimuli. The EPN may be the inverse of the early anterior positivity (EAP; Taake et al., 2009), which occurs in the same time window, in response to similar manipulations of emotion (Junghöfer et al., 2006). There is some evidence that these effects have different underlying neural generators, as Wambacq and colleagues (2004) reported that the EAP only occurs when emotion is task-irrelevant, while the Olofosson and colleagues (2008) suggest that the EPN is usually larger in emotion-relevant tasks. Here, task-relevance was manipulated to determine if the EPN and EAP could be disassociated in this way.

The final effect of emotion usually occurs after 300 ms for all emotional stimuli compared to neutral stimuli. Called the late posterior positivity, the LPP effect for emotional versus neutral words occurs in healthy controls, often even when emotion is task-irrelevant (Schupp et al., 2007). Visually this effect is seen as a positivity over centro-parietal scalp, approximately 300 to 600 ms post-stimulus (Cacioppo et al., 1996; Cuthbert et al., 2000; Schupp et al., 2000; Hajcak et al., 2010), and is larger when emotion is relevant to the task (Batty & Taylor, 2003; Oloffson et al., 2008). The LPP has been shown to be both increased (Shestyuk & Deldin, 2010) and decreased in depression (Hajcak et al., 2010), and like other measures of late stage information processing, such as reaction time, these results may be due to heterogeneous samples.

2.3. Experiment 1 – The Emotional Stroop

High-density electroencephalograms (EEG) were recorded while participants completed an emotional Stroop task. There was a dysphoric group, defined as in previous studies (Bradley et al., 1997; Joormann et al., 2004, 2008; Joormann & Gotlib, 2007; Shane & Peterson, 2007; Krompinger & Simons, 2009; Koster et al., 2010), as healthy participants with mild-to-moderate depression symptoms.
These depression symptoms were measured by the Beck Depression Inventory-Second Edition (BDI-II; 1996). Note that the BDI acts as a screening measure in this instance, and does not give a clinical diagnosis of dysphoria (i.e. chronic persistence of depression symptoms not reaching the severity or number of symptoms of a major depression episode).

A comparison group of healthy participants that scored in the normal range on the BDI-II. Dysphoric participants were used because dysphoria is thought to be predictive of later clinical depression in college samples (Hankin, et al., 1998). Also, these participants would show early ERP bias and not late ERP biases, which would lend empirical support to current model of depression vulnerability (Beevers, 2005; Clark & Beck, 2010). Both fear and sad words were included, to determine if emotion-related modulations of the ERP waveforms were depression-congruent or related to negative words in general.

The following hypotheses were formed: (1) In line with previous behavioural emotional Stroop studies in dysphoria, RTs would not differentiate the experimental groups; (2) Negative words would elicit a negativity over occipital scalp very early after stimulus onset during the P1-N1 time window; (3) Negative words would elicit a positivity over frontal scalp during the EAP time window, and this effect would be larger in the dysphoric group, (Taake et al., 2009); (4) Significant group effects would be localized to limbic cortico structures, similar to the significant emotion-related effects; (5) Finally a centroparietally distributed LPP would be elicited for negative compared to neutral words. It was unknown if this effect would be related to group status.

2.3.1. **Methods**

**Participant screening**

Over two trimesters 451 undergraduate students in first and second year psychology courses (286 women, Age = 19.13, $SD = 4.64$) completed an online screening session for course credit. After giving informed consent, participants completed a demographics questionnaire (developed in the Laboratory for Affective and Developmental Neuroscience; LADN) and the BDI-II (Beck, et al., 1996), which is a reliable and valid measure of depression symptom severity in college (Oliver & Burkham,
1979), community, and patient samples (Beck, et al., 1988, 1996). The BDI-II is a 21-item self-report questionnaire that assesses the severity of depression on a Likert scale. The following cut-offs were used: 0-9 indicated minimal depression; 10-20 indicated mild depression; 21-30 indicated moderate depression; and scores greater than 30 indicated severe depression (Kendall, et al., 1987). Thirty percent of screened participants met our criteria for at least minimal depression (> 9; 30.30% of the men and 29.00% of the women sampled). As Posner and Snyder (1975) determined that Stroop effects are dependent on quick and automatic reading, approximately half were excluded because they did not speak English as their first language. A dysphoric group (BDI-II score > 9) and a comparison group [matched on gender, education, and handedness with minimal depression scores (≤ 9)] were recruited.

Although they were screened based on the BDI, and English fluency, the participants also completed the Spielberger State-Trait Inventory (STAI; Spielberger et al., 1983). This questionnaire has 20 items that assess state anxiety and 20 that assess trait anxiety. State anxiety items include, “I am worried”, and trait anxiety items include, “I worry too much over something that really doesn’t matter”. All items are rated on a 4-point scale (e.g., from “Almost Never” to “Almost Always”). Higher scores indicate greater anxiety, with a score above 35 on the state items indicative of state anxiety, and a score over 40 on the trait items indicative of trait anxiety.

Before screening and before ERP recording, participants were fully informed about all aspects of the study and signed consent forms, in compliance with the guidelines of the Simon Fraser University Research Ethics Board.

**EEG participants**

All participants used in the study reported normal or corrected-to-normal visual acuity, normal color vision, no history of neurological or psychiatric disorders, no history of drug or alcohol abuse, and no learning disabilities. The final sample included 15 participants with mild depression symptoms [12 women; average age = 18.73 (SD = 1.58); 1.5 years of post-secondary education (SD = 0.86); all right-handed]. These dysphoric participants were matched to sixteen comparison individuals with few depression symptoms [< 4; 11 women; average age = 19.14 (SD = 1.56); 1.92 years of post secondary (SD = 1.19); all right-handed].
Stimuli and apparatus

Word stimuli were selected from the MRC Psycholinguistic Database (http://www.psy.uwa.edu.au/MRCD DataBase/uwa_mrc.htm), and all emotional conditions (fear, sad, happy, neutral) were matched based on number of letters, Kucera-Francis written frequency in the English language (Wilson, 1988) concreteness, and common part of speech (verb, noun, or adjective). The results for the happy condition will be reported elsewhere, as happy information processing is quite distinct from that of negative emotions (Epp et al., 2012).

Figure 2.1. Sequence of events during the emotional words task

Words (happy, fear, sad and neutral) were presented in one of four colors (blue, red, green, and yellow) on a black background for 200 ms. Each word was followed by a jittered inter-stimulus interval (ISI; 1700 to 2300 ms). Presentation of the stimuli was pseudorandom such there were no more than three stimuli with the same emotion or color presented in a row.

See Figure 2.1 for a schematic representation of the Emotional Stroop task. Words were presented by dedicated psychological testing software (Presentation by Neurobehavioral Systems, Albany, CA, USA) in one of four colors (blue, red, green, and yellow) on a black background for 200 ms, followed by a jittered inter-stimulus interval (ISI) of 1700 to 2300 ms, during which time there was only a fixation-cross shown on the screen. Words subtended visual angles from 2.77° to 11.94° in width, and had a standard height of 1.39°. Presentation occurred in a pseudo-randomized order,
constrained so that no more than three stimuli with the same emotion or color were presented in a row.

All participants started with a practice block and had to reach an 80% accuracy rate before advancing. In the emotional Stroop, where emotion is task-irrelevant, participants were asked to respond to the color of the word. Participants completed four blocks. There were 100 stimuli per block, and a 30 second break between the blocks, to reduce fatigue.

**Procedure**

High-density EEG was recorded while participants completed the behavioral task in a sound-attenuated room with standardized low ambient lighting. The CRT monitor presenting the stimuli was positioned 60 cm away from the participants’ nasion and responses were made using the shoulder buttons on a gamepad controller (Logitech, Romanel-sur-Morges, Switzerland). In order to control for a hand laterality-effect, the emotions were counter-balanced across hands. In order to limit eye-movements, participants were asked to keep their eyes on a central fixation-cross throughout the experiment, and to blink during the intervals between trials. All participants were asked to favor accuracy over speed.

**Electrophysiological recording**

The ActiveTwo BioSemi electrode system (BioSemi; Amsterdam, Netherlands) was used to record continuous EEG from 137 Ag/AgCl electrodes (see Figure 2.2). A detailed description of the referencing and grounding conventions used by the BioSemi active electrode system appears on-line (http://www.biosemi.com/faq/cms&drl.htm). Briefly the BioSemi is an active electrode system and replaces the conventional “ground” electrode with two separate electrodes: the Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode both place at midline sites over parietal scalp. With the BioSemi system there is no conventional reference electrode; a mono-polar signal is stored for each active electrode and must be re-referenced after acquisition to obtain optimal signal. Four electrodes were applied to the face with stickers to monitor eye-movements: two electrodes were placed at the bilateral outer canthi to measure horizontal eye-movements (L1/2) and two electrodes were
placed under each eye to monitor vertical eye-movements and blinks (l1/2). A water-soluble conductive electrode gel (SignaGel) was used to improve electrical contact. The quality of electrode contact for each electrode was measured by DC offset, and was always kept below ± 25 mV during acquisition. The signals were digitized at 512 sps with an open pass-band from DC to 150 Hz. The amplifier gain was fixed for each active electrode channel at 32x.

Electrophysiological brain data were analyzed using Brain Electric Source Analysis (BESA 5.3, MEGIS Software GmbH, Germany). The HEOG channels were referenced to each other (L1-L2) to optimize horizontal ocular artifact rejection. Then the EEG was low-pass forward filtered at 0.01 Hz (6 dB/oct). After low-pass filtering each trial was time-locked to stimulus onset, and aligned to a 200 ms pre-stimulus baseline. Subject averages were made for each condition (-1000 to 2000 ms), with trials automatically excluded if an erroneous response was given or if the difference between the maximum and minimum amplitude in one of the electrodes surrounding the eyes (FP1, FPz, FP2, HEOGs, & VEOGs) exceeded ± 120 μV during the time-window of interest (−200 to 800 ms). The BioSemi system does not use a conventional reference electrode, a monopolar signal is stored for each active electrode and all re-referencing is done in software after acquisition. To get optimal signal all channels were re-referenced to the average mastoid. Also, for visualization and analyses, a high-pass 30 Hz (24 dB/oct) filter was applied. In order to examine our effects, grandaverage ERP waveforms for each group (dysphoric, comparison) in each condition (fear, sad, neutral) were created.
Figure 2.2. Electrode Scalp Regions of Interest (sROI)

The BioSemi and international 10-20 system electrode sites for the scalp regions of interest (SROIs).

Please see Figure 2.2 for BioSemi system and equivalent international 10-20 system electrode sites for the electrodes used in the analyses. The visual N1 was scored at bilateral parietal-occipital electrode sites during the 150-170 ms time-window. Both the parietal-occipital EPN and the anterior-frontal EAP were scored over the 200-230 ms time-window using scalp regions of interest (sROIs) similar to those used by previous studies (e.g., Taake et al., 2009; Schupp, et al. 2006). The LPP was scored during the 340-450 ms time-window over the classic centro-parietal electrode sites (Hajcak et al., 2010).
Analyses

All analyses were performed in IBM SPSS Statistics (version 20). To avoid skewed reaction time (RT) results, the average RTs were calculated and trials with an extreme latency (top and bottom 1%) were excluded, as done in previous studies (Jaspers-Fayer et al., 2012). The RT and percentage of correct trials were used as dependent variables in two separate mixed (2x3) ANOVAs. For both of these behavioural analyses the between-subjects factor was Group (dysphoric, comparison), and the within-subjects factor was Emotion (fear, sad, neutral).

In the analyses of the ERP components the average voltage of N1, P2, and LPP was used as dependent variables in separate mixed (2x2x3) ANOVAs. The between-subjects factor was Group (dysphoric, comparison), and the within-subjects factors were Hemisphere (right, left) and Emotion (fear, sad, neutral).

For all analyses, the Greenhouse-Geisser correction to the degrees of freedom was used if there was a significant effect of Emotion or interaction with Emotion, regardless of whether or not tests of non-sphericity were significant, as ERP data has been shown to often violate this assumption (Jennings et al., 1987).

The significance threshold was set at $\alpha = .05$, and partial eta squared ($\eta_p^2$) was reported as a measure of effect size for all ANOVAs (small = .1; medium = .3; large = .5; Cohen, 1977). When the omnibus test was significant, post hoc repeated measures t-tests were used for multiple comparisons. Again the significance threshold was set at $\alpha = .05$, and in this instance Cohen’s $d$ was reported as a measure of effect size (small = 0.2, medium = .5, and large = 0.8; Cohen, 1977), and Bonferroni corrections were used to account for family-wise error.

Source Localization

Source localization was performed with LORETA (low resolution electromagnetic tomography; http://www.uzh.ch/keyinst/loreta.htm; Pascual-Marqui et al., 2002) on the grandaverage so that our results could be related to the neuroimaging literature and current neurobiological models of depression (Phillips et al., 2008; Disner et al., 2011).
The neural generators of significant early ERP effects were estimated using CLARA ("Classical LORETA Analysis Recursively Applied"), in BESA (version 5.3). LORETA (Low resolution brain electromagnetic tomography) calculates the weighted current density at each point in a cubic grid spanning the whole brain volume (voxel size in Talairach space = 7 mm). LORETA assumes that neighbouring neural sources will display similar activity, a phenomenon that has been observed in vivo in the literature (Llinas, 1988; Gray et al., 1989; Silva et al., 1991), and tackles the inverse problem by choosing the solution with the smoothest distribution of activity across grid points. CLARA applies the LORETA algorithm twice iteratively, with each iteration smoothing the image and then setting any grid point with amplitude below 1% of the maximum activity to zero. A new LORETA image is then computed using the weighted amplitudes at each voxel. Reported labels are from the Talairach daemon (www.talairach.org; Lancaster et al., 1997; Lancaster et al., 2000) and are within +/- 5 mm of the reported maxima.

2.3.2. Results

Demographic results

The comparison group did not differ significantly from the dysphoric group on any of the matched variables (sex, education, handedness, and age), but did differ significantly on average BDI-II score (comparison group average = 2.56, \(SD = 2.94\); dysphoric group average = 12.60, \(SD = 3.76\); \(t(29) = 8.24, p = .000, d = 2.975\)).

The dysphoric group scored above the cut-off (> 35) on the state anxiety measure (39.00, \(SD = 9.77\)), whereas the comparison group did not (28.73, \(SD = 6.63\); \(t(29) = - 3.37, p = .002, d = 1.230\)). Additionally, the dysphoric group scored above the cut-off (> 40) on the STAI-trait measure (dysphoric = 45.00, \(SD = 9.59\)), whereas the comparison group did not (31.87, \(SD = 7.64\); \(t(29) = - 4.173, p = .000, d = 1.514\)). Inline with large-scale studies conducted on these measures in undergraduate students (e.g., Gotlib, 1984) the BDI was strongly correlated with the STAI-trait (\(r = 0.77, p = .000, d = 2.41\)), and also correlated with the STAI-state (\(r = 0.52, p = .003, d = 1.218\)).
Behavioural results

There was no significant RT differences between groups, $F(1, 29) = 1.194, p = .284, \eta^2_p = .040$, or emotions, $F(2, 58) = 2.43, p = .109, \eta^2_p = .077$, and no Group x Emotion interaction $F(2, 58) = 0.25, p = .737, \eta^2_p = .008$. This is likely because the majority of trials were correct (fear = 97%; sad = 96%, neutral = 96%), and there were no significant differences in the percentage of correct responses between groups, $F(1, 29) = 0.104, p = .749, \eta^2_p = .004$, or Emotion, $F(2, 58) = 1.189, p = .309, \eta^2_p = .039$, and no Group x Emotion interaction, $F(2, 58) = .376, p = .688, \eta^2_p = .013$. These results support the previous findings (McNeely et al., 2008; Frühholz et al., 2011; Epp et al., 2012) that the emotional Stroop is unable to discriminate between groups when the experimental group has sub-clinical symptoms.

Event-related potential (ERP) results

Early ERPs elicited by the emotional Stroop

The N1 (150-175 ms) elicited by the Emotional Stroop task showed a significant Group x Hemisphere interaction, $F(1, 29) = 7.89, p = .009, \eta^2_p = .214$, such that dysphoric group displayed greater negativity for all words on the left (-4.37 $\mu$V) than the right (-1.38 $\mu$V; $F(1, 14) = 13.83, p = .002, \eta^2_p = .497$), and displayed a greater negativity on the left (-4.37 $\mu$V), than the comparison group (-1.92 $\mu$V; $F(1, 29) = 4.99, p = .033, \eta^2_p = .141$). In contrast, there was no significant difference between groups on the right (dysphoric = -1.38 $\mu$V; comparison = 1.77 $\mu$V; $F(1, 29) = 0.13, p = .721, \eta^2_p = .004$). No other N1 effects or interactions were significant ($p < 0.05$).

Next, the P2 (200-230 ms) showed a significant effect of Group, $F(1, 29) = 7.13, p = .012, \eta^2_p = .197$, such that the dysphoric group (5.34 $\mu$V) displayed greater voltage than the comparison group (2.58 $\mu$V). Unlike the N1, this effect did not interact with Hemisphere ($p < 0.05$). Instead there was a main effect of hemisphere, such that across groups there was a slight increase on the left (4.27 $\mu$V vs. right = 3.66 $\mu$V; $F(1, 29) = 11.98, p = .002, \eta^2_p = .292$). Also unlike the N1, the emotional modulation of the P2, the EAP, distinguished between negative and neutral emotions, $F(2, 58) = 5.02, p = .016, \eta^2_p = .148$, such that fearful words showed a significant positivity [4.18 $\mu$V; $t(30) = 2.78, p = .009, d = 0.167$] and sad words showed a marginally [4.26 $\mu$V; $t(30) = 2.34, p = .026, d = 0.276$] compared to the neutral words (3.30 $\mu$V). Given that there was no significant
difference ($p > 0.05$) between the fearful and sad words, these conditions were collapsed. Although visual inspection (see Figure 2.3) suggests that negative-neutral difference was larger in the comparison group, this result was not significant ($p > 0.05$). In contrast to the EAP, the EPN (200-230 ms) showed a significant right-lateralization, $F(1, 29) = 9.83$, $p = .004$, $\eta_p^2 = .253$, but this could be the result of the earlier lateralization of the N1 (Luck, 2005). There were no significant main effects of Group or Emotion, and no interactions ($p > 0.05$).
Figure 2.3. Early ERP results for the emotional Stroop

A) Topographical maps of the dysphoric-comparison group difference to all words during the N1 (160 ms) and the EPN/EAP (215 ms). B) Waveforms displaying the N1, EAP and EPN (see grey boxes) at frontal (AF5′/6′) and occipital electrode sites (PO8′/P09′) for negative and neutral words in both the dysphoric and comparison groups. *The dysphoric group exhibited a greater N1 ($p < .05$) over left occipital scalp and a greater bilateral response during the EPN/EAP time window ($p < .05$) over frontal scalp. †Additionally the EAP showed a significant difference between the negative and neutral words.
**Late ERPs elicited by the emotional Stroop**

The LPP (340-450 ms) elicited by the emotional Stroop was larger for all negative compared to neutral words, for all participants, main effect of emotion, $F(1, 29)$, $F(2, 58) = 10.32$ $p = .000$, $\eta_p^2 = .0263$. This occurred because both fearful [8.53 μV; $t(30) = 3.98$, $p = .000$, $d = 0.385$] and sad words elicited a greater positivity [8.35 μV; $t(30) = 3.26$, $p = .003$, $d = 0.353$] than neutral words (6.94 μV). Again, there was no depression-related specificity, as there was no difference between the fearful and sad conditions ($p > .05$), so these conditions were collapsed. Although visual inspection of the topographical maps and waveforms (see Figure 2.4) suggested a reduced LPP in the dysphoric group, this effect did not reach significance, $F(1,29) = 0.79$, $p = .382$, $\eta_p^2 = .026$, and the interaction between Group and Emotion was not significant, $F(2, 58) = 1.25$, $p = .294$, $\eta_p^2 = .041$. 
Figure 2.4. Late ERP results for the emotional Stroop

A) Topographical maps of the negative-neutral difference in the dysphoric (left) and comparison (right) groups. B) ERP waveforms at electrode CPz, with a grey box indicating the 340-450 ms time-window used in the analysis. †Both the dysphoric and comparison groups showed the traditional LPP effect, such that negative words elicited a greater positivity than neutral words. There was no significant difference between groups (p > .05).

LORETA estimates of significant early emotional Stroop ERP effects

Based on the significant early ERP findings, source localization was conducted on the grandaverage group difference during the N1 (160 ms) and P2 (215 ms) time-windows (Figure 2.5; Appendix A Supplementary Tables, Table A.1), and the significant emotion difference during the N1 (160 ms) and EPN/EAP (215 ms) time-window (Figure 2.5; Table A.2) using CLARA (Classical LORETA Analysis Recursively Applied).
The LORETA results suggest that the dysphoric group’s left-lateralized N1 was related primarily to a maximum in the left fusiform gyrus, and to a lesser extent, bilateral insular maxima. During the EPN/EAP time window the group difference wave was localized to bilateral insula and the posterior cingulate cortex (PCC)/precuneus. Finally, the EPN/EAP emotion difference wave was localized to the right superior temporal gyrus (STG)/insula, the left ACC, and the right fusiform gyrus.
Figure 2.5. **LORETA localization of significant ERP results elicited by the emotional Stroop**

A) Group differences during the N1 time-window were localized to the fusiform gyrus (FG), and bilateral insular maxima.  B) Group differences during the EAP time-window were localized to bilateral insular maxima and the posterior cingulate cortex (PCC).  C) Emotion differences during the EPN/EAP time-window were localized to the right superior temporal gyrus (STG) and insula, as well as the anterior cingulate cortex (ACC) and the right FG.
2.4. Interim discussion

In experiment 1, dysphoric and comparison participants completed a computerized version of the emotional Stroop task while high-density EEG was recorded.

The N1 elicited by the emotional Stroop

The first notable ERP effect was an amplification and left-lateralization of the N1 component in the dysphoric group. This effect occurred for all words, regardless of emotional condition (fearful, sad, or neutral). In this context, it is possible that the dysphoric group allocated more attention to all stimuli during the emotional Stroop task. Greater N1 amplitudes for emotional stimuli have been shown for emotional versus neutral faces (Carretié et al., 2004) and pictures (Foti, et al., 2009), and left-lateralized N1 have been found in response to emotional pictures (Righart & de Delder, 2006, 2008), but this is the first study to show such early effects in a sample of participants with symptoms of depression, and not in healthy controls. Based on the LORETA analysis and previous literature, the left-lateralization can be interpreted as modulation of ongoing visual processing by endogenous, perhaps insula and amygdala-initiated, gain mechanisms in the prefrontal cortex (Luck et al., 2000; Vuilleumier, 2005, Pourtois et al., 2013; although see Dima et al., 2011). Thus, the lateralized N1 may reflect feedback connections between “affective” regions and visual cortices, allowing for the enhancement of sensory processing (Halgren et al., 1994a; LeDoux, 1996). The early P2 amplification will be discussed in more detail below.

The EAP and EPN elicited by the emotional Stroop

The EAP showed a significant effect of emotion, but this did not interact with group. As mentioned in the introduction, although some studies report earlier findings, many studies suggest that the earliest trial-by-trial differentiation of emotion occurs during the P2-N2 time (Palomba, et al., 1997). Palomba and colleagues interpreted their result as the result of enhanced semantic of processing of words with emotional content in depression (for review see Klumpp et al., 2010).

There was an independent amplification of the P2 that was related to dysphoria. This result was similar to a result found by Shimizu et al., (2006) who found an increased
frontal P2 in response to emotional words during a modified lexical decision task in dysphoric participants. Both the amplified N1 and P2 could be present because the prospect of seeing emotional words, and particularly concern-specific words, is more arousing to the experimental group than the comparison group.

**The LPP elicited by the emotional Stroop**

Like previous studies there was a greater LPP in response to emotional words compared to negative words (Olofsson et al., 2008). As the LPP is anticipated to be much larger in the emotion-relevant task, a more in-depth discussion of the LPP effects will occur in the final discussion and conclusion section of this chapter (chapter 2).

**The LORETA results**

The LORETA results were conducted on the grandaverage difference waves and must be interpreted with some caution. The N1 group effect was localized primarily to the fusiform gyrus, suggesting that the dysphoric group responded to the task as a whole by allocating more attentional resources to all stimuli, perhaps through a gating mechanism (Hillyard & Anllo-Vento, 1998). During both the N1 and P2 time-windows dysphoric group effects were also localized in the insula.

### 2.5. Experiment 2 – Task-relevant emotional words

The emotional Stroop paradigm presents emotion as task-irrelevant. Researchers (e.g., Etkin et al., 2006) often modify the emotional Stroop by asking participants to ignore the color of the word and categorize it based on semantic meaning. Emotion-relevant tasks theoretically engage “cognitive” neocortical areas rather than “affective” limbic areas such as the amygdala and insula (Hariri, 2000). Additionally, it is possible the EAP and EPN effects reported in the literature can be differentiated based on a task-relevance manipulation, as noted in the introduction. Therefore, in experiment 2 participants were asked to categorize the same stimuli based on their semantic meaning. The hypotheses were that: (1) as in experiment 1, reaction time would not differentiate the dysphoric and comparison groups; (2) an electrophysiological response would appear over occipital scalp in response to negative vs. neutral words (i.e. the EPN), while the frontal response (i.e. the EAP) remained, as
both the direct and the indirect routes should be activated by the emotion-relevant task; Finally (3) during a later time-window (> 300 ms) a classic LPP effect would be present (Hajack et al., 2010) for all participants. This effect, based on previous research, may be smaller in the dysphoric group than the depressed group (Foti, 2010).

2.5.1. Methods

The same participants that took part in experiment 1 took part in experiment 2, but recording artifacts caused the exclusion of 2 datasets (1 dysphoric and 1 comparison) from the analyses, leaving 14 participants in the dysphoric group and 15 participants in the comparison group. The stimuli and procedure were the same as in experiment 1, but the task was altered so that emotion was task-relevant. Thus, instead of responding to the stimuli based on the color, participants categorized stimuli based on the semantic meaning of each word (fear, sad, happy, or neutral). Again, the results of the happy condition will be reported elsewhere. The behavioral analyses were conducted in the same way as in experiment 1. In regards to the ERP data, the acquisition, processing and analyses were all the same as in experiment 1.

2.5.2. Results

Behavioural results

As in experiment 1 there was no effect of Group, \( F(1, 27) = 0.00, p = .964, \eta_p^2 = .000 \), and no interaction of Emotion x Group, \( F(2, 54) = 0.34, p = .684, \eta_p^2 = .013 \). In contrast to the earlier study, however, there was a significant difference in RT between emotions, main effect of emotion, \( F(2, 54) = 21.87, p = .000, \eta_p^2 = .448 \), as both fearful (879 ms; \( t(28) = 6.33, p = .000, d = 0.967 \)) and sad words (863 ms; \( t(28) = 5.06, p = .000, d = 0.741 \)) produced increase RT latencies when compared to neutral words (801 ms). There was no significant difference between fearful and sad words, \( t(28) = 0.95, p = .351, d = .106 \).

Similar results were found for the percentage of correct trials. Again there was no effect of Group, \( F(1, 27) = 0.133, p = .719, \eta_p^2 = .000 \), and no interaction of Emotion x Group, \( F(2, 54) = 4.81, p = .330, \eta_p^2 = .012 \). There was an effect of Emotion, \( F(2, 54) = 12.81, p = .000, \eta_p^2 = .322 \) (fear = 76%; sad = 86% neutral = 92%;), with post hoc paired
t-tests showing that the fearful condition, \( t(28) = 4.36, p = .000, d = 1.129 \), and the sad condition, \( t(28) = 2.37, p = .025, d = 0.598 \), kept significantly fewer trials than the neutral condition.

**Event-related potential (ERP) results**

*Early ERPs elicited by emotional word categorization*

Please refer to Figure 2.6, which displays topographical voltage maps of the group difference (panel A) and ERP waveforms (panel B) in response to emotional word categorization. The early (< 300 ms) ERP results were very similar to the results found in experiment 1. Again, there was a significant interaction Group x Hemisphere, \( F(1, 27) = 5.83 p = .023, \eta^2_p = .178 \), such that the N1 elicited by emotional word categorization was left lateralized in the dysphoric group (left = - 4.29 μV; right = - 1.25 μV; \( F(1, 13) = 11.45 p = .005, \eta^2_p = .468 \)). As such the amplitude on the left in the dysphoric group was much greater than the amplitude on the left in the comparison group, \( F(1, 27) = 4.827, p = .037, \eta^2_p = .158 \).

Also again, the P2 during the EAP time-window differentiated the experimental groups, \( F(1, 27) = 5.30, p = .029, \eta^2_p = .164 \), such that negative stimuli elicited greater voltage in the dysphoric group (6.13 μV) than the comparison group (3.51 μV). Again the N2 was not significantly different between groups (\( p > .05 \)).
Figure 2.6. Early ERPs for emotional word categorization.

A) Topographical maps of the dysphoric-comparison group difference to all words. B) Waveforms displaying the N1, EAP and EPN (see grey boxes) at frontal (AF5′/6′) and occipital electrode (PO8′/P09′) sites for negative and neutral words in both the dysphoric and comparison groups. * The N1 elicited by emotional word categorization was-left lateralized the dysphoric group versus comparison group. Also again, the P2 during the EAP time-window differentiated the experimental groups, such that negative stimuli elicited greater voltage in the dysphoric group. EPN was not significantly different between groups (p> .05).
Late ERPs elicited by emotional word categorization

Please refer to Figure 2.7, which shows the topographical voltage maps of the group difference (panel A), and ERP waveforms (panel B) in response to emotional word categorization at late (> 300 ms) time points. As in experiment 1, there was no significant difference between groups during the LPP time-window. The test of the LPP showed a significant effect of Emotion, $F(2, 54) = 30.90, p = .000, \eta_p^2 = .534$, such that participants responded to fearful (8.78 μV; $t(15) = 6.57, p = .000, d = 0.734$) and sad words (8.39 μV; $t(28) = 7.32, p = .000, d = 0.673$) with greater voltage than to the neutral words (5.65 μV). Again, there was no significant effect of Group or interaction with of Emotion x Group ($p > 0.5$).
Figure 2.7. Late ERPs for emotional word categorization

A) Topographical maps of the negative-neutral word difference in the dysphoric and comparison groups. B) ERP waveforms for electrode CPz, (grey box indicates 340-450 ms the time-window used in the analysis). The test of the LPP showed a significant effect of Emotion, with a greater positivity to negative than neutral words.

LORETA estimates of significant emotional word categorization ERP effects

LORETA was used again to localize the significant early effects. Source analysis was conducted on grandaverage group difference waves during the N1 and P2 time-windows (160 ms & 215 ms; Figure 2.8; Table A.3), and the negative-neutral difference wave during the EAP time-window (215 ms, Figure 2.8; Table A.4) using CLARA (Classical LORETA Analysis Recursively Applied).
The LORETA results again estimated that the dysphoric group’s left-lateralized N1 was primarily related to a maximum in the fusiform gyri, and cerebellum. As a secondary finding the bilateral insular maxima were not seen, and instead a maximum was localized to the ACC. Next, the results for the LORETA analysis of the P2 time-window again showed bilateral insular maxima, and a maximum in the posterior cingulate cortex. However, unlike the emotional Stroop, the source localization of the significant group difference also showed a maximum in the anterior cingulate cortex (see Figure 2.8, panel B). Finally, the LORETA analysis of the significant EAP emotion effect estimated frontal generators in the superior temporal gyrus (STG) and insula. Additionally, there was a maximum in the left ACC.
Figure 2.8. **LORETA localization of significant ERP results elicited by the emotional word categorization**

A) Group differences during the N1 time-window were localized primarily to the left fusiform gyrus (FG), and anterior cingulate cortex (ACC). B) Group differences during the P2 time-window were localized to bilateral insular maxima, the posterior cingulate cortex (PCC), and the anterior cingulate cortex (ACC). C) Emotion differences during the EPN/EAP time-window were localized to the superior temporal gyrus (STG) and left ACC.
2.6. Discussion and Conclusion

In experiment 2, dysphoric and comparison participants completed a computerized emotional Stroop task where emotion was task-relevant. The primary finding of experiment 2 was that the manipulation of task-relevance did not change the ability of early ERP effects (the N1 and P2) to differentiate between the experimental groups, and that it did not improve the ability of the LPP or behavioural measures to differentiate between groups. An additional finding was that making emotion-task relevant did not produce an EPN for negative versus neutral words, or influence the LORETA results.

**Early group effects**

Both the N1 and P2 differentiated group, with source analyses suggesting maxima in the insular cortex, which is part of the ventral “affective” system (Eckert et al., 2009) that is involved in the processing of emotional salient events (Taylor et al., 2009). Imaging studies of depressed patients have implicated this area before (Drevets, 1998; Mayberg et al., 1999; Phillips et al., 2003a, 2003b; Phillips et al., 2008) including studies of concern-congruent reaction time biases (Elliott et al., 2002), but this is one of the first studies to suggest that these effects are caused by early information-processing stages.

Shestyuk and Deldin (2010) also recently proposed that a depression-word related frontal P2 modulation might be a useful correlate of negative biases. Shestyuk and Deldin used ERPs as a measure of neural engagement during specific information processing stages, which they derived from emotional self-referential material that was presented to participants with current depression, remitted depression, and healthy controls. The task was an emotion-relevant task, as participants were asked to judge the words as applicable or not to themselves. Greater P2 and LPP component amplitudes occurred in response to negative items relative to positive self-referent items in individuals with current symptoms. The P2 was interpreted as an index of automatic processing, and the LPP as an index of effortful encoding. They suggested that both the early and late processing abnormalities (as indexed by the P2 and LPP), provided evidence for *integrative theories of cognitive dysfunction in major depression* that suggest that at least two mechanisms are dysfunctional in depression.
Here, the enhanced N1 and P2 effects are interpreted as potential markers of cognitive bias as conceptualized by Beck (e.g., 2008), and that the insula maxima found in this study are an index of increased reactivity to negative stimuli, as a result of inherent schema in the participant with symptoms of depression. Unlike in Shetyuk and Deldin (2010), these results alone do not support the integrative theories of cognitive dysfunction in depression, as we did not use clinically depressed patients and did not find late ERP group effects.

**Early emotion effects**

In relation to the debate surrounding the differentiation of the EAP and EPN, this study found that the manipulation of task-relevance did not influence the occurrence of the EPN. As the EAP and EPN did not responded differently to the experimental manipulation, it cannot be claimed that there are different underlying neural generators (Picton et al., 2000; Luck, 2005), supporting the theory of Junghöfer and colleagues (2006) that the EPN and EAP are inverse effects of the same dipole.

**Late emotion effects**

Also of note, later emotional stages, related to the conscious elaboration of emotional events, appeared to be unaffected by group membership, at least in this study, possible because dysphoric participants only had mild depression symptoms. The ERP waveform discriminated between emotional conditions in the emotion-relevant task, collaborating a large body of literature that has shown that the LPP is influenced by task-relevance (for review see Olofsson et al., 2008). Although measures of late stage processing, such as RT latency and the LPP, did not discriminate experimental groups in this study, they often do not differential the experimental and control groups in depression studies (McNeely et al., 2008, for review see Epp et al., 2012), and conceptually this may be because dysphoric participants do not have cognitive biases related to elaboration and inhibition (Beevers, 2005).

**Limitations**

The primary limitation of these experiments was that task-relevance was confounded with task difficulty, and as such the two tasks could not be compared directly. This confound is present in many studies of emotional processing (e.g.,
Critchley et al., 2000; Frühholz et al., 2011; Hariri, et al., 2000, 2003; Klumpp et al., 2013; Williams et al., 2006a), but should be avoided in future by matching task-difficulty, at least in the comparison group.

Also note, in both the task-relevance and task-irrelevant experiments there appears to be an earlier P1 effect (although the stimuli used in both tasks were exactly the same). Testing did not reveal significant results. However, responses in this time window may have carried over to affect the N1 time-window downstream.

A third limitation of this study was that the dysphoric sample was not compared directly to a clinically depressed sample, and in fact few studies have directly compared dysphoria to depression (Gotlib & Joormann, 2010). These results therefore should not be generalized to clinically depressed patients, and can only speak indirectly to how cognitive biases may change with the development of depression (Beevers, 2005).

A fourth limitation is that the results must be interpreted with caution because there was no non-emotional task. Therefore, it is possible that the dysphoric group may always show larger amplitude responses, even during non-emotional tasks.

A final limitation is that there were no concern-specific effects. Gotlib (1984) conducted a large-scale study (n = 443) of common screening measures used in undergraduate populations, including the BDI, and the STAI trait and state measures. He found that the STAI measures strongly correlated with the BDI, and suggested that both the BDI and STAI may simply measure general psychology distress in college students rather than separate, distinct constructs (i.e. anxiety and depression).

Conclusion and future directions

A recent literature review of cognitive impairments in depression (Castaneda et al., 2008), found that although young adults with depressive symptoms had no major cognitive impairments when compared to healthy peers, they did exhibit a minor difference in verbal attention and memory. It is possible that our results are related to this impairment, rather than a cognitive biases working on early stages of information-processing. Chapter 3, therefore, switches to using emotional faces, which have been
shown to be more emotionally salient than words (Adolphs, 2002), and are not dependent on verbal attention or memory.
3. Emotional Faces

3.1. Abstract

Both early (< 300 ms) and late (> 300 ms) stages of information-processing can be affected by cognitive biases in depression. Previous theoretical (for review see chapter 1) and empirical work (chapter 2) has suggested that early event-related potentials (ERPs) can differentiate people with mild symptoms of depression (i.e. dysphoria) from healthy controls. The primary aim of the current study was to build on this work, which was done in an emotional word Stroop, by using emotional faces, which are more emotionally salient. **Methods:** Over four hundred undergraduates were screened for mild-to-moderate depression symptoms, as measured by the Beck Depression Inventory (BDI). Dysphoric participants (n = 15) were compared to matched healthy controls (n = 16). High-density electroencephalograms (EEG) were recorded while participants completed the tasks. **Results:** The dysphoric group showed an amplified and left-lateralized N170, and a higher amplitude frontal P2 in response to all faces, regardless of emotional condition. The grandaveraged group differences were source-localized to the insula in both cases, but also to the posterior cingulate cortex (PCC)/precuneus during the P2 time-window. When emotion was task-relevant an anterior cingulate cortex (ACC) maxima was also found. Measures of late stage processes such as the late posterior positivity (LPP) and RT did not differentiate the experimental groups, although they did show the classic emotion effects. **Conclusion:** Overall, these findings suggest that participants with dysphoria over-recruited left posterior and right frontal brain regions, regardless of relevance of emotion to the task. Additionally, during the emotion-relevant task they over-recruited the ACC. Results are discussed in the context of the lateralization models of emotion processing and the two-pathway models of depression vulnerability.
3.2. Introduction

Depression is a serious mental illness with changes in mood and cognition (American Psychiatric Association, 2013). Theorists posit that depression is the result of innate biases for depression-congruent information (e.g., events related to sadness; Clark & Beck, 2010). The exact timing of these biases, and their influence over various information processing stages, however, is under considerable debate (for review see Yiend, 2010). Compton (2003) theorizes that there are two ways in which emotional significance can effect information processing, it can effect pre-attentive or “automatic” attention very early in the information processing stream, and it can effect the selective attention given to the stimulus later in the processing stream.

Previous work (chapter 2) has shown that individuals with symptoms of depression (i.e. dysphoria) show early information-processing biases (< 300 ms) during an emotional word Stroop task, but not late stage biases (> 300 ms) or reaction time (RT) latency effects, when compared with healthy controls. These results are consistent with the hypothesis that early stages of information-processing can differentiate dysphoric from healthy participants, while late stage biases only develop with major depressive disorder (for meta-analysis of empirical results see Epp et al., 2012; for theory see Beevers, 2005).

In chapter 2 emotional words were used so that our results could be compared to the extensive emotional Stroop literature in depression (Epp et al., 2012). Words, however, are not the best stimuli for studying automatic attention to emotion, or selective attention to emotion, as the emotional salience of words is symbolic (for review see Kissler et al., 2006), and thus must be extraction before decisions regarding biological significance can be made (Adolphs et al., 2002; Halgren, 1994a, 1994b; c.f. Kissler et al., 2007; Schact & Sommer, 2009). Here we have chosen to use faces, as the results can be easily integrated into the much broader emotional face literature in both healthy controls (for reviews see Adolphs, 2002, 2003; Palermo & Rhodes, 2007), and depression (for reviews see Gur 1992, 2002; Leppänen, 2006; Stuhrmann et al., 2011).

Chapter 2 also showed that event-related potentials could be used to determine if the information-processing stages involved in the processing of task-relevant and -
irrelevant face stimuli supported the two-phase model of cognitive vulnerability to depression (Beevers, 2005; Clark & Beck, 2010), which proposes that individuals with mild symptoms of depression (i.e. dysphoria) have disorder-related early stage biases, and that in moderate to severe depression these biases become secondary to disorder-related elaboration and memory biases.

Cognitive and neurobiological models of face perception propose there are at least two processing stages involved, one involved in the processing of identity, and the other involved in the processing of emotion (Bruce & Young, 1986; Haxby et al., 2000, 2002). The processing of identity involves the lateral fusiform gyrus, and anterior temporal regions. The processing of emotion involves the superior temporal sulcus (STS; Haxby et al., 2000) and potentially the threat-detection mechanism directed by the amygdala (Öhman, 2002; Vuilleumier, 2002).

In regards to anticipated event-related potential (ERP) effects, the most common face-related ERP component is the N170 ms, which is measured over the occipito-temporal scalp (Bentin et al., 1996). Until recently, most studies of the N170 have shown no effect of emotion in healthy controls (Carretié & Iglesias, 1995; Eimer & Holmes, 2002; Herrmann et al., 2002; Holmes, et al., 2006; Schupp, et al., 2004; c.f. Batty & Taylor, 2003). Righart and Gelder (2006, 2008), however, have found that the N170 becomes left-lateralization when emotional faces are placed in emotional scenes, such as ones from the IAPS database, and there are frontal ERP effects in the same time window which have been shown to discriminate between fearful and neutral faces (Eimer & Holmes, 2002; Holmes et al., 2003).

Emotion more reliably influences the ERP waveform after 200 ms. For instance; the early posterior negativity (EPN; Junghöfer et al., 2001, 2006; Kissler et al., 2009; Schupp et al., 2004, 2006, 2007) is commonly reported approximately 200–300 ms after stimulus onset for emotional stimuli compared to neutral stimuli. This effect is thought to index the increased attention allocated to the visual processing of emotional faces over neutral faces (Sato et al., 2001) and may be caused by re-entrant projections from the amygdala and the threat detection mechanism (Olofsson et al., 2008; Chapter 1). The EPN co-occurs with a frontal positivity to emotional compared to neutral stimuli (Eimer & Holmes, 2002, 2007; Eimer et al., 2008; Sato et al., 2001), sometimes referred to as the
early anterior positivity (EAP; Taake et al., 2009). Previous work (chapter 2; Junghöfer et al., 2006) suggests that the EPN and EAP have the same neutral generators.

A number of other depression studies have shown late stage effects of emotion (> 300 ms; Cavanagh & Geisler, 2006; Diner et al., 1985; Gangadhar, et al., 1993; Roth et al., 1981), such as the late posterior positivity (LPP; Foti et al., 2000), but the exact influence of depression-status on the LPP is under-debate. Work by Hajcak’s lab (2010; Foti et al., 2010) suggests that the LPP should be reduced in depression.

The primary aim of the current study was to determine if early stage ERP differences could be found in response to emotional faces in participants with dysphoria (i.e. mild symptoms of depression) compared to healthy controls (i.e. few symptoms of depression). A secondary aim was to determine if task-relevance influenced the ability of late stage effects to differentiate the experimental groups when the stimuli were more biologically relevant. Towards this aim the N170/VPP, P2 (including the EPN and EAP), and the LPP were studied. Based on the results of chapter 2, it was hypothesized that there would be an effect of group over frontal scalp during the N170 and P2 time windows, but that later stages of information-processing (> 300 ms) would only show emotion-related differences.

3.3. Experiment 1 – Task-irrelevant emotional faces

3.3.1. Methods

Screening and EEG participants

Fifteen of the dysphoric participants who completed the experiments in chapter 2 were able to complete the experiments below (12 women; average age = 19.29 ± 1.82; 2.0 ± 1.21 years of post-secondary education; all right-handed). The comparison group was composed of the 17 participants included in chapter 2, plus two additional participants [n = 19; 13 women; average age = 18.89 ± 1.57); 1.72 ± 0.96 years of post secondary education; all right-handed]. All participants reported normal or corrected-to-normal visual acuity, normal color vision, and no history of neurological or psychiatric disease.
Stimuli, apparatus and procedure

This experiment used colored photographs of faces taken from the Karolinska stimuli set (13 male, 15 female; 4 emotions: fear, sad, happy, and neutral; Goeleven et al., 2008). The faces were set on a black background and altered using Photoshop (version 10.0.1) to obscure the hairline and create identical facial contours. Then each face had a colored square (red, blue, green, or yellow) superimposed on the nose. Faces were presented for 200 ms, followed by a fixation-cross presented for a jittered inter-stimulus interval (ISI) of 1700 to 2300 ms.

Figure 3.1. Sequence of events for the emotional faces task

Emotional faces (fear, sad, happy, and neutral) were presented with a square superimposed on the nose in one of four colors (blue, red, green, or yellow). Stimuli were presented for 200 ms, followed by a jittered inter-stimulus interval (1700-2300 ms). Presentation was pseudo-random, with no more than three stimuli with the same emotion, color or gender, presented sequentially.

Participants completed a practice block, and were required to reach an 80% criterion before advancing to the actual trials. Stimuli were pseudo-randomized, constrained so that no more than three stimuli with the same emotion or color were presented in a row. Stimuli were further constrained to ensure that no more than three stimuli of the same gender were presented in a row.

There were 100 stimuli per condition, and four emotional conditions, for a total of 400 stimuli presented during the experiment. As emotion was task-irrelevant
participants were asked to indicate the color of the square on the nose. The experiment was divided into four blocks, and ran for approximately 20 minutes. Participants were permitted to rest for approximately 30 seconds between blocks to reduce fatigue.

**Procedure**

The participants completed the behavioural task while high-density EEG was recorded. Participants were positioned 60 cm from a cathode ray tube (CRT) monitor displaying the stimuli. Responses were made using the shoulder buttons on a gamepad controller (Logitech, Switzerland). To control for a laterality effect the emotions were counter-balanced across hands. In order to limit eye-movements participants were asked to keep their eyes on a fixation-cross throughout the experiment, and to blink during the interval between trials. All participants were asked to favor accuracy over speed.

**Electrophysiological recording**

The ActiveTwo BioSemi electrode system (BioSemi; Netherlands) was used to record continuous EEG from 137 Ag/AgCl electrodes (see Figure 3.2). All external electrodes were placed on the outer canthi to measure horizontal eye-movements (L1/2) and under each eye to monitor vertical eye-movements and blinks (I1/2). SignaGel was used to improve electrical contact. The quality of electrode contact was always kept below ± 25 mV during acquisition. The signals were digitized at 512 sps from DC to 150 Hz. The amplifier gain was fixed for each active electrode channel at 32x.

Brain Electric Source Analysis (BESA 5.3, MEGIS Software GmbH, Germany) was used to analyze the EEG data. The outer canthi channels were referenced to each other (L1-L2 and L2-L1) to improve horizontal ocular artifact rejection. EEG was low-pass forward filtered at 0.01 Hz (6 dB/oct). After low-pass filtering each trial was time-locked to stimulus onset, and aligned to a 200 ms pre-stimulus baseline. Subject averages were made for each condition (-1000 to 2000 ms), with trials automatically excluded if an erroneous response was given or if the difference between the maximum and minimum amplitude in the channels beside the eyes (FP1, FPz, FP2, HEOGs, & VEOGs; see Figure 3.2) exceeded ± 120 μV during the −200 to 800 ms window of interest. Excluding the bipolar ocular channels, all channels were re-referenced to the
average mastoid. For visualization and analyses, a high-pass 30 Hz (24 dB/oct) filter was applied. In order to examine our effects, grandaverage ERP waveforms for each group (dysphoric, comparison) in each condition (fear, sad, neutral) were created.

**Figure 3.2. Electrode Scalp Regions of Interest (SROIs)**

The BioSemi and international 10-20 system electrode sites for the scalp regions of interest (SROIs).

Please see Figure 3.2 for conversions from the BioSemi system to the international 10-20 system. Based on visual inspection of the grandaverage and difference waveforms, five effects of interest were tested. The N170 was scored at bilateral temporal-occipital sites (150-175 ms) and the N170-inverse (i.e. VPP), was scored at central sites during the same time-window. The EPN was scored at bilateral parietal-occipital sites, and the EAP was scored at bilateral anterior frontal sites, both...
during the 220-240 ms time-window. Finally, the LPP was scored at the 420-470 ms time-window at traditional central-parietal sites.

**Analyses**

Analyses were performed in IBM SPSS Statistics (version 20). As in previous studies (chapter 2; Jaspers-Fayer et al., 2012), to avoid skewed reaction times (RTs), trials with extreme latencies (top and bottom 1%) were excluded before averaging. The RT and percentage of correct trials were used as dependent variables in two separate 2x3 mixed ANOVAs. For both of the behavioural analyses the between-subjects factor was Group (dysphoric, comparison), and the within-subjects factor was Emotion (fear, sad, neutral).

For the electrophysiological analyses, the average voltage of the N170, VPP, EAP, EPN, and LPP were used as dependent variables in separate (2x2x3) mixed ANOVAs. The between-subjects factor was Group (dysphoric, comparison), and when appropriate the within-subjects factors were Hemisphere (right, left) and Emotion (fear, sad, neutral).

For all analyses, the Greenhouse-Geisser correction to the degrees of freedom was used (Jennings et al., 1987), and the significance threshold was set at $\alpha = .05$. Partial eta squared ($\eta^2_p$) was reported as a measure of effect size for all ANOVAs (small = .1; medium = .3; large = .5; Cohen, 1977). When the omnibus test was significant, post hoc repeated measures t-tests were used for multiple comparisons. In this instance Cohen’s $d$ was reported as a measure of effect size (small = 0.2, medium = .5, and large = 0.8; Cohen, 1977), and Bonferroni corrections were used to account for family-wise error.

**Source Localization**

Source localization was performed with LORETA (low resolution electromagnetic tomography; Pascual-Marqui et al., 2002) on the grandaverages so that our results could be related to the neuroimaging literature on emotion and current neurobiological models of depression (Mayberg, 2007; Phillips et al., 2003a, 2003b, 2008; Disner et al., 2011). The neural generators of significant early ERP effects were estimated using CLARA (“Classical LORETA Analysis Recursively Applied”), in BESA. The benefit of a
distributed source model, like LORETA, over discrete models (such as the equivalent dipole analysis available in BESA), is that by using regional sources instead of dipoles, LORETA does not have to specify the number of sources in advance. Reported labels are from the Talairach daemon (www.talairach.org; Lancaster et al., 1997; Lancaster et al., 2000) and are within +/- 5 mm of the maxima estimated by LORETA.

3.3.2. Results

Demographic results

The dysphoric group did not differ significantly from the comparison group on any of the matched variables (sex, age, education, or handedness), but did differ significantly on average BDI-II score (dysphoric group average = 12.60, SD = 3.76; comparison group average = 2.56, SD = 2.94; t(32) = 8.24, p = .000, d = 2.975).

The dysphoric group score above the cut-off (> 35) on the STAI-state measure (38.93, SD = 9.85), while the comparison group did not (30.06, SD = 6.95; t(32) = -2.93, p = .005, d =1.041), and that the dysphoric group scored above the cut-off (> 40) on the STAI-trait measure while the comparison group did not (dysphoric = 46.25, SD = 9.80; comparison = 33.83, SD = 8.18; t(32) = -3.63, p = .002, d = 1.371, where 40 is the traditional cut-off score). Also, the BDI was strongly correlated with the STAI-trait (r = 0.72, p = .000, d = 2.08), and also correlated with the STAI-state (r = .51, p = .003, d = 1.186).

Behavioural results

There were no significant RT differences between groups, F(1, 32) = 2.77, p = .106, ρ² = .080, or emotional condition, F(2, 64) = 0.12, p = .891, ρ² = .003, and no Group x Emotion interaction, F(2, 64) = 0.54, p = .579, ρ² = .017. Additionally, the vast majority of responses were correct (fear = 97%; sad = 96%, neutral = 97%);, and no significant difference between the groups, F(1,32) = 0.00, p = .957, ρ² = .000, or between emotions, F(2, 64) = 2.41, p = .098, ρ² = .070, was found. Finally there was no significant Group x Emotion interaction, F(2, 64) = 2.14, p = .127, ρ² = .063.
**Event-related potential (ERP) results**

*Early ERPs elicited by task-irrelevant emotional faces*

Please see Figure 3.3. The N170 (150-175 ms) elicited by task-irrelevant emotional faces showed no significant main effects, but did show a significant Group x Hemisphere interaction, $F(1, 32) = 11.74, p = .002, \eta_p^2 = .268$, such that the dysphoric group displayed a greater negativity, $F(1, 14) = 7.02, p = .019, \eta_p^2 = .334$, on the left (-3.76 $\mu$V) than the right (-1.11 $\mu$V). In contrast, the comparison group showed a marginally significant right-lateralization of the N170 (right = -2.76 $\mu$V; left = -1.28 $\mu$V; $F(1, 16) = 4.17, p = .056, \eta_p^2 = .188$). As such the group difference on the left was significant, $F(1, 32) = 6.08, p = .019, \eta_p^2 = .160$.

The N170-inverse, or vertex positive potential (VPP; 150-175 ms), showed a main effect of Group, $F(1, 32) = 4.14, p = .050, \eta_p^2 = .115$, with the dysphoric group displaying greater voltage (5.26 $\mu$V) than the comparison group (2.55 $\mu$V). There was also an additive effect of Emotion, $F(2, 64) = 9.76, p = .000, \eta_p^2 = .234$, with both fearful [4.04 $\mu$V; $t(32) = 3.80, p = .001, d = 0.283$] and sad faces [4.34 $\mu$V; $t(32) = 3.47, p = .001, d = 0.360$] displaying greater voltage than neutral faces (2.85 $\mu$V). There was no significant difference between negative emotions ($p > .05$), and so these conditions were collapsed.

The P2 (220-240 ms) showed a significant effect of Group, $F(1, 32) = 5.19, p = .030, \eta_p^2 = .139$, such that the dysphoric group (-1.40 $\mu$V) displayed a more positive P2 than the comparison group (-4.06 $\mu$V). There was also a significant effect of Emotion, $F(2, 64) = 7.00, p = .002, \eta_p^2 = .179$, such that both fearful [-2.66 $\mu$V; $t(32) = 2.14, p = .039, d = 0.170$] and sad faces [-2.23 $\mu$V; $t(32) = 3.47, p = .001, d = 0.276$] displayed a relative positive compared to the neutral faces (-3.30 $\mu$V). Again, the Group x Emotion interaction was not significant ($p > .05$), and there was no difference between negative emotions ($p > .05$) and so the negative conditions were collapsed. The posterior N2 (220-240 ms) elicited by the task-irrelevant faces showed a significant interaction of Group x Hemisphere, $F(1, 32) = 4.72, p = .037, \eta_p^2 = .128$, such that the dysphoric group displayed greater amplitude on the right (5.34 $\mu$V) than the left (3.26 $\mu$V; $F(1, 14) = 9.33, p = .009, \eta_p^2 = .400$). No other effects were significant ($p > .05$).
Figure 3.3. Early ERPs to task-irrelevant emotional faces.

A) Topographical maps of the dysphoric-comparison difference to all face stimuli during the N170/VPP (160 ms) and EPN/EAP (240 ms) time-windows. B) Waveforms displaying the N170 (PO8’/P09’), VPP (Cz), EPN (PO8’/P09’) and EAP (AF5’/6’). Grey boxes indicate the time-windows used in the analyses.

*Indicates group effects, †Indicates emotion effects. There was a significant left-lateralization of the N170 and right-lateralization of the EPN in the dysphoric group. The N1 (160 ms) and P2 (240 ms) were both significantly amplified by dysphoric group membership and negative emotion.

Late ERPs elicited by task-irrelevant emotional faces

The LPP (420-470 ms) elicited by task-irrelevant emotional faces showed no main effect of Group, $F(1, 32) = 0.91, p = .349$, $\eta_p^2 = .027$, or Emotion, $F(2, 64) = 1.72, p$
= .188, $\eta_p^2 = .051$, and no interaction, $F(2, 64) = 0.157$, $p = .848$, $\eta_p^2 = .005$ (See Figure 3.4).

Figure 3.4. Late ERPs to task-irrelevant emotional faces.
A) Topographical maps of the negative-neutral word difference in the dysphoric and comparison groups during the LPP (420-470 ms; see grey box) time-window. B) ERP waveforms for electrode CPz. There was no effect of either Group or Emotion, and no interaction ($p > 0.05$).

LORETA estimates of significant task-irrelevant face ERP effects

Source analyses were conducted on the grandaveraged group difference wave (see Appendix A Supplementary Tables, Table A.5) and negative-neutral difference wave (see Table A.6) during the N1 and P2 time-windows using CLARA (Classical LORETA Analysis Recursively Applied). LORETA estimated the dysphoric group’s left-lateralized N170 originated primarily in the fusiform gyri. The group-related P2 effect was the result of a right-lateralized insular/putamen maximum and a left precuneus maximum (see Figure 3.5). The significant negative-neutral difference over frontal sites during the N170/VPP time-window was source localised to fusiform gyri, precuneus, and anterior
cingulate cortex (ACC) maxima. The significant EAP difference was source localized to
the ACC, and a network of other fronto-parietal structures (see Figure 3.5).
Figure 3.5. **LORETA localization of significant ERP results elicited by the emotional word categorization**

A) Source estimation of group difference during the VPP time-window. Maxima found in the fusiform gyri (FG) and the anterior cingulate cortex (ACC). B) During the P2 time window group differences were found in the right insula and precuneus. C) Source localization of emotion effects during the VPP time-window showed activity in the fusiform gyri, precuneus, ACC and cerebellum. D) Significant emotion effects during the EAP time-window suggested generators in the ACC, right superior temporal gyrus (STG)/inferior frontal gyrus (IFG), precuneus, fusiform gyrus, insula and cerebellum.

### 3.4. Interim Discussion

The most notable effect in experiment 1 was the strong left-lateralization of the N170 in the dysphoric group. This effect is very similar to the left-lateralization of the
visual N1 in chapter 2, and is also similar the results reported by Righart and Gelder (2006, 2008) when emotional faces were presented in emotion-congruent contexts. An in-depth discussion of the theoretical implications of this effect will occur at the end of this chapter.

The next notable effect was an increased P2 over frontal scalp for dysphoric versus comparison participants. These effects did not interact with the emotional amplification of the VPP and P2. These results replicate the previous work by Taake and colleagues (2009) who also found an increase EAP in anxious participants in response to threat stimuli, but do not replicated the results of Eimer and Holmes (2007). Eimer and Holmes found that fearful stimuli presented at attended locations triggered an enhanced positivity over fronto-central scalp, but these effects were eliminated when emotional stimuli were task-irrelevant, suggesting that emotion was not pre-attentively processed, regardless of task. Our results instead suggest that emotion is pre-attentively processed.

There were no late stage ERP effects and no reaction time effects found during the emotion-irrelevant task. Emotion is more likely to affect these measures of information-processing when emotion is task-relevant (for review see Olofsson et al., 2008). Therefore, task-relevance was manipulated to determine if (1) emotion-related differences could be elicited in these samples; (2) if group differences could be elicited at late stages of information processing.

3.5. Experiment 2 – Task-relevant emotional faces

Based on the higher emotional salience of emotional faces (Adolphs et al., 2002), it was hypothesized that: (1) There may be a group RT difference, and (2) there may be a late stage ERP group difference. Note, however, that Epp and colleagues (2012) suggests that these late stage biases do not occur in dysphoric samples.

3.5.1. Methods

The same participants and stimuli use in chapter 3, experiment 1 were used in chapter 3, experiment 2. The procedure was changed, however, such that participants
were asked to respond to the emotion that each face displayed (fear, sad, happy, or neutral). Thus emotion was task-relevant. Again, the results of the happy condition will be reported elsewhere. The behavioral analyses were conducted in the same way as in chapter 3, experiment 1. The data acquisition, processing, and analyses were all held constant.

3.5.2. Results

Behavioural results

There was a significant effect of Emotion, \( F(2, 64) = 23.78, p = .000, \eta_p^2 = .426, \) on RT, such that emotional conditions [fear (916 ms; \( t(33) = 8.38, p = .000, d = 1.008 \)); sad (880 ms; \( t(33) = 3.76, p = .000, d = 0.542 \)] produced longer RT latencies than neutral faces (838 ms). These RTs latencies are on par with the RTs found in other emotional face discrimination tasks (e.g., Wong et al., 2009). There was no effect of Group however, \( F(1, 32) = 3.534, p = .069, \eta_p^2 = .100, \) and no interaction of Emotion x Group, \( F(2, 64) = .265, p = .768, \eta_p^2 = .008. \)

In the percentage of correct trials there was a significant main effect of Emotion, \( F(2, 64) = 10.71, p = .000, \eta_p^2 = .251, \) as many more errors were made during the emotional-relevant faces task (fear = 87%; sad = 89%; neutral = 94%), with paired t-tests revealing that the fear, \( t(33) = 5.92, p = .000, d = 0.905, \) and sad \( t(33) = 3.43, p = .002, d = 0.789 \), conditions kept significantly fewer trials than the neutral condition. There was no effect of Group, \( F(1, 32) = .405, p = .529, \eta_p^2 = .013, \) and no interaction with Group, \( F(2, 64) = 0.35, p = .942, \eta_p^2 = .001. \)

Event-related potential (ERP) results

Early ERPs elicited by task-relevant emotional faces

See Figure 3.6 for topographical maps and waveforms. The N170 (150-175 ms) elicited by emotion-irrelevant faces showed the same significant Group x Hemisphere interaction, \( F(1, 32) = 7.91, p = .008, \eta_p^2 = .198, \) as the earlier experiment (chapter 3, experiment 1). Again, the dysphoric group displayed a greater negativity on the left (-3.76 \( \mu \)V) than the right (-1.11 \( \mu \)V), although the test within the dysphoric group in this instance was only marginally significant, \( F(1, 14) = 2.99, p = .106, \eta_p^2 = .176. \) The
comparison group showed the opposite effect (left = -0.63 μV; right = -2.33 μV; $F(1, 18) = 5.45, \ p = .031, \ \eta^2_p = .232$), with the N170 significantly right-lateralized. In this instance, however, the group difference on the left was only marginally significant, $F(1, 32) = 2.067, \ p = .160, \ \eta^2_p = .061$.

The VPP (150-175 ms) results were also consistent with the earlier experiment (chapter 3, experiment 1), showing a significant group difference over central scalp during the 150-175 ms time-window, $F(1, 32) = 4.38, \ p = .044, \ \eta^2_p = .120$, with the dysphoric group displaying a greater positive deflection (5.22 μV) than the comparison group (2.95 μV). Also paralleling the emotion-irrelevant faces task there was a significant effect of Emotion, $F(2, 64) = 21.50, \ p = .000, \ \eta^2_p = .402$, such that both fearful [4.39 μV; $t(33) = 4.59, \ p = .000, \ d = 0.307$] and sad faces [5.16 μV; $t(33) = 5.79 \ p = .000, \ d = 0.470$] showed a greater positivity than neutral faces (3.10 μV). As there was no significant difference between fearful and sad faces ($p > 0.05$) these conditions were collapsed (see Figure 3.6, section B, electrode Cz).

The EAP (220-240 ms) again showed a significant effect of Group, $F(1, 32) = 5.05, \ p = .032, \ \eta^2_p = .136$, such that the dysphoric group again showed a positivity (.842 μV) compared to the comparison group (-2.15 μV). Also again, there was a significant effect of Emotion, $F(2, 64) = 10.62, \ p = .000, \ \eta^2_p = .249$, such that both fearful [-.29 μV; $t(33) = 3.94, \ p = .000, \ d = 0.299$] and sad faces [-.13 μV; $t(33) = 2.87, \ p = .007, \ d = 0.315$] displayed more positive voltage relative to the neutral faces (-1.55 μV). Again, as there was no difference between negative emotions ($p > .05$), these conditions were collapsed. In the same time-window (220-240 ms) over occipital sites, unlike in the emotion-irrelevant task, the EPN showed no significant main effects and no significant interactions.
Figure 3.6. Early ERP effects elicited by emotion-relevant faces.

A) Topographical maps of the dysphoric-comparison group difference to all face stimuli during the N170/VPP (160 ms) and EPN/EAP (240 ms) time-windows. B) Waveforms displaying the N170 (PO8'/P09'), VPP (Cz), EPN (PO8'/P09') and EAP (AF5'/6'). Grey boxes indicate the time-windows used in the analyses. *Indicates group effects. † Indicates significant emotion effects. There was a significant left-lateralization of the N170. The VPP and EAP were both significantly amplified by dysphoric group membership and negative emotion.
Late ERPs elicited by task-relevant emotional faces

The LPP (420-470 ms) elicited by the emotion-relevant emotional faces showed a significant effect of Emotion over central-parietal scalp, $F(2, 64) = 8.92, p = .001, \eta_p^2 = .218$, such that both fearful $13.57 \mu V; t(33) = 2.5, p = .017, d = 0.210$ and sad faces $[13.96 \mu V; t(33) = 4.83, p = .000, d = 0.267]$ faces elicited greater positivity than neutral faces (12.35 $\mu V$). There was no significant difference between fearful and sad faces ($p > .05$), so these conditions were collapsed. Although visual inspection suggests that there may be a group difference, the test of this effect did not reach significance, $F(1, 32) = 1.16, p = .290, \eta_p^2 = .035$. 
Figure 3.7. The LPP elicited by emotion-relevant faces.

A) Topographical maps of the negative-neutral word difference in the dysphoric and comparison groups during the LPP (420-470 ms; see grey box) time-window. B) ERP waveforms for electrode CPz. *There was a significant effect of emotion, such that negative faces elicited a greater positive voltage than neutral faces ($p < 0.05$).

LORETA estimates of significant task-relevant face ERP effects

LORETA was used again to localize the significant early ERP findings. Source analysis was conducted on both the grandaverage dysphoric-comparison group difference and the negative-neutral difference during the N170/VPP (160ms; see Table A.7) and P2 (240 ms; see Appendix A Supplementary Tables, Table A.8) time-windows using CLARA (Classical LORETA Analysis Recursively Applied). Again, the LORETA
results suggest that the dysphoric group’s left-lateralized N1 is related to activity in the fusiform gyri, and prefrontal cortex. The EAP group difference was again related to a network of frontal maxima, and a maximum in the precuneus. The LORETA analyses of the emotion-related effects suggested that the N170/VPP emotion effect was related to a network made up of the fusiform gyri, insula, ACC, and precuneus. The EAP emotion-related effect was estimated to originate from the ACC, insula, parahippocampal gyri, and the cerebellum, although again, as these analyses were conducted on the grandaverage group difference wave they must be interpreted with caution.
Figure 3.8. LORETA localization of significant ERP results elicited by the task-relevant emotional faces

B) Source estimation of group difference during the VPP time-window showed maxima in the fusiform gyri (FG), anterior cingulate cortex (ACC) and cerebellum. B) During the P2 time-window group differences were localized to the precuneus, and ACC. C) Source localization of the significant emotion effects during the VPP time-window showed activity in the fusiform gyri, superior temporal gyrus (STG)/insula, ACC, precuneus, and cerebellum. D) Significant emotion effects during the EAP time-window were localized to ACC, insular, Parahippocampal gyri and the cerebellum.
3.6. Discussion and Conclusion

This work investigated the effect of manipulating task-relevance on the processing of emotional in participants with and without dysphoria. Compton (2003) has proposed that emotional significance is assessed through two separate attention mechanisms: one that evaluates the emotional significance pre-attentively or “automatically” and another that gives significant stimulus priority in the competition for selective attention.

This study provides support for the early, automatic processing of emotional stimulus by dysphoric participants who, regardless of task, responded with a strongly left-lateralized N1. In non-emotional circumstances the N170 is right-lateralized in healthy controls (Bentin et al., 1996), and was right-lateralized in our controls. Righart and de Gelder (2006, 2008) however, have shown that when emotional stimuli are presented in surrounding emotional context (e.g., a fearful face in a fear-inducing scene) the N170 can be left-lateralization even in healthy subjects. Righart and de Gelder concluded that their subjects were using the environmental context (i.e. the scene), to rapidly discriminate/categorize the faces at early information-processing stages. Although the environmental context is an exogenous factor, and dysphoric symptoms are an endogenous factor, it is possible that a similar interpretation could be used here. Perhaps the dysphoric group used an internal context (their depression-related schema), to bias the early stage processing of all stimuli in the task.

The early left-lateralization of emotion-processing in this study does not fit easily into decades of emotion-lateralization research. Historically negative emotion has been shown to predominately be processed in the right hemisphere, in both healthy and diseased populations (for reviews see Killgore & Yurgelun-Todd, 2007; Shenale et al., 2003). As such, the right-hemisphere models of emotion processing (Borod et al., 1986, 1998) have suggested that the right hemisphere is predominantly used in the recognition of facial emotion, and the valence-specific models of emotion processing (Adolphs, 2001; Demaree et al., 2005), have suggested that the right hemisphere specializes in negative affect.
Killgore and Yurgelum-Todd (2007), however, recently proposed an extension of these classic models. Although the right hemisphere is predominately involved in the processing of facial expression, it now seems that bilateral anterior brain areas also recruit the left posterior hemisphere when the task involves sadness. This model is corroborated by a number of studies in depression that show greater left, relative to right, hemisphere involvement in emotion processing (Compton et al., 2003; David & Cutting 1990; Mikhailova, et al., 1996; but c.f. Davidson et al., 1990, 1992). The current study suggests that the left posterior hemisphere is recruited during emotional processing by the dysphoric participants because of the sad stimuli used in the study.

**Amplified VPP and P2 in dysphoric participants**

In line with studies using emotional faces (e.g., Eimer & Holmes, 2007), and the extensive research into depression using the oddball paradigm (e.g., Kemp et al., 2009) depression status was related to an exaggerated VPP and P2 for all stimuli, regardless of task or emotional condition. These findings are in line with those of Kemp and colleagues (2009), who also found an exaggerated P2 in the depressed group that was source localized to the fusiform gyri and ventral prefrontal regions.

Given the results presented above, it is possible that the fusiform maxima are related to activity along the “direct” route for the rapid detection of emotion. This route travels from the fusiform gryus (FG; Haxby et al., 2000; 2002; Hoffman & Haxby, 2000), to the amygdala, which has been linked to the processing of negative emotions, particularly fear (Adolphs, 1995; LeDoux, 1996). In contrast to the fusiform maxima, the maximum often found in the ACC in the above experiments may be related to the indirect route, as it was most present in the emotional-relevant task, and may be related to a more detailed evaluation of stimuli and their contextual significance (Iidaka et al., 2001; Ochsner & Gross, 2005).

**Late stage effects do not differentiate dysphoric and healthy comparison subjects**

At late stages the late posterior positivity (LPP) discriminated between emotional conditions in the emotion-relevant task, corroborating a large body of literature that has shown that the LPP is influenced by task-relevance (for reviews see Hajcak et al., 2010; Olofsson et al., 2008). It is important to note that measures of late stage processing,
such as RT latency and the LPP did not differentiate the experimental groups, in support of many other studies done in dysphoria (e.g., McNeely et al., 2008).

Limitations

The primary limitation of these studies is that the emotion-relevant and emotion-irrelevant tasks could not be compared directly, as task-relevance was confounded with task difficulty. Future work should use paradigms that are task-matched for difficulty, at least in the comparison group.

Additionally, as in chapter 2, there appears to be a significant P1 group difference, at least on the left. Again, this effect was not significant, but may carried over to the N1 time-window downstream.
4. General Discussion

The most influential model of depression (Beck, 1967, 1987, 2008) has been the cognitive model of affective disorders (Clark & Beck, 2010). This model posits that people at risk of developing depression acquire depression-related schema that bias the allocation of cognitive resources in favor of depression-congruent events and against neutral and positive events.

The last thirty years has seen a burgeoning interest in studying cognitive biases with behavioural, psychophysiological and neuroimaging methods. For decades there has been a consensus among many researchers that individuals with symptoms of anxiety exhibit early, automatic biases for threat-related information, whereas individuals with symptoms of depression exhibit later encoding and memory biases for depression-related information (e.g., Clark & Beck, 2010; Dalgleish & Watts, 1990; Mathews & MacLeod, 1994; Mineka & Sutton, 1998; Mogg & Bradley, 1998, 2005). Recent meta-analyses, however, have shown that multiple information-processing stages can be biased in both anxiety (Bar-Haim et al, 2007; Bishop, 2009) and depression (Epp et al., 2012), that the cognitive biases reported in the literature are extremely inconsistent.

As noted in the introduction, three explanations for the inconsistent cognitive bias results can be identified: (1) researchers rarely distinguish between between-subjects biases and within-subjects biases (Bar-Haim et al., 2007); (2) studies tend to use gross measures of cognitive bias, such as reaction time (RT), instead of fine measures such as event-related potentials (ERPs); and (3) studies have not taken into account that biases likely change as the disease progresses with late stage differences becoming more apparent as the participant develops clinical depression (Epp et al., 2012).

To address these issues, the current work differentiated between-subject and within-subject biases, used event-related potentials (ERPs) to provide a fine-grained measure of information-processing stages, and concentrated on a fairly homogenous
group of participants (Henrich et al., 2010) with only mild symptoms of depression (i.e. dysphoria).

The primary aim of this work was to study early and late stages of emotional (word and face) information-processing in participants with and without symptoms of depression. A secondary aim was to determine if the early stages were automatic, and processed along the “direct route”.

**Group differences**

Based on the work presented in this dissertation the strongest neural markers of depression vulnerability in a dysphoric sample are the between-subjects ERP biases at early (< 300 ms), but not very early (<150 ms) information processing stages. The very early effects are traditionally found in participants with anxiety, and may be related to a hyper-responsive threat-detection system centered on the amygdala (Mathews, et al., 1997) and orbital frontal cortex (Jaspers-Fayer et al., 2012).

**Early group differences**

The earliest, and most prominent ERP modulation related to depression symptoms, and reported here for the first time, is a significant and replicable occipital N1 amplification and left-lateralization to all stimuli during an emotional task for dysphoric participants compared to participants with few symptoms of depression. This N1 amplification and left-lateralization is potentially the result of negative schema, which boosts processing, particularly in the left visual cortices during emotional tasks (Killgore & Yurgelun-Todd, 2007).

One argument against the interpretation of the amplified and left-lateralized N1 as a good measure of cognitive bias in depressive samples is that the effect was not concern-specific (depression-related) but occurred for all stimuli. Perhaps the early between-subject ERP-based biases in dysphoria do not occur on a trail-by-trial basis because, regardless of whether or not the gating mechanism is mediated by the direct or indirect routes, it is likely a tonic gating mechanism, similar to the classic attention-gating mechanism hypothesized by Hillyard and Anllo-Vento (1998).
In addition to the N1 effects there was also an amplified P2 in the dysphoric versus comparison participants. This result had a similar latency and topography to basic attention results reported by Potts (2004). Potts conducted an ERP study of attention and task-relevance using a visual oddball paradigm with three conditions: passive (no response), overt (key press) condition, and covert (silent counting). He found a task effect during the N1-P2 time window, which occurred on top of the typical oddball target effect, for the overt and covert conditions compared to the passive condition. The dysphoric group’s amplified P2 can, therefore, also be related to a tonic affect-related gating mechanism, which does not respond on a trial-by-trial bases.

It is hard to say where the dysphoric N1 and P2 modulations are related to modulation of early visual processing by the direct route (e.g., the amygdala), or the indirect (e.g., dorsal frontoparietal areas), because the task-relevance manipulation did not provide a double-dissociation of these two mechanisms. A recent study by Dima and colleagues (2011) using fMRI suggests that both routes are activated. Although this is speculation, it is possible that the two routes are active at different times. The LORETA results must be interpreted with caution because the analysis was conducted on the grandaverage, but there was a consistent difference in the estimate neural generators underlying the dysphoric-N1 compared to the dysphoric-P2. Unlike the N1, the dysphoric-P2 was consistently related to a maximum in the precuneus. These maxima hint that, at least by the P2-range, there is some involvement of dorsal stream structures, suggesting that the dysphoric-P2 is related to the indirect route, as described by Vuilleumier (2005).

It is notable that the group effect is not occurring on a trial-by-trial basis. One potential explanation for this is that, although participants were selected based on their BDI score, the dysphoric participants also had above-average trait and state anxiety score on the State-Trait Anxiety Inventory (STAI; Spielberger, 1983). As such, perhaps both the sad words and the fearful stimuli were more emotionally salient than the neutral stimuli.

In future work it may be desirable to look at subscales within the BDI-II. The BDI-II has two subscales, an “affective” subscale (e.g. mood) and a “somatic” subscale (e.g. loss of appetite; Steer et al., 1999; Storch et al., 2004). The affective subscale contains 8
of the 21 items: pessimism, past failures, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, and worthlessness. It is possible that if only the “affective” subscale was used there would be less of a response to the fearful stimuli. The somatic subscale contains the other thirteen items: sadness, loss of pleasure, crying, agitation, loss of interest, indecisiveness, loss of energy, change in sleep patterns, irritability, change in appetite, concentration difficulties, tiredness, and/or fatigue and loss of interest in sex. Many of the somatic subscales overlap with symptoms of anxiety. Thus, it is not uncommon for the BDI and STAI to be highly correlated in pre-clinical undergraduate samples (for review see Endler et al., 1992). Gotlib (1984) has suggested that both the BDI and STAI State Anxiety scale may simply measure “general psychological distress” in college students, rather than separate, distinct constructs (i.e. anxiety and depression). This would fit well with the cognitive vulnerability model of affective disorders (Clark & Beck, 2010; Disner et al., 2011), which suggests that the same type of dysfunctional cognitive mechanism underlies both anxiety and depression.

Late group differences and potential results in acute depression

Notably there were no significant group differences during the LPP time range. However, the LPP results are inline with the most recent formulations of the cognitive vulnerability model of affective disorders (Clark & Beck, 2010; Disner et al., 2011), which incorporate Beevers’ (2005) suggestion that there are at least two phases in the development of depression: an early phase when only early information-processing stage biases of the associate network should be seen; and a later phase, when late information-processing biases and clinical depression develop (e.g., Joormann et al., 2004, 2007; Koster et al., 2010, 2011).

Although not tested directly in this series of experiments, previous research suggests that measureable late stage processing biases emerge with clinical depression (McNeely et al., 2008; Foti et al., 2010) when cognitive control likely becomes erratic (Foti et al., 2009), and there is a decrease in the ability of the dorsolateral prefrontal cortex to respond to disorder-congruent stimuli on a trial-by-trial basis (Bishop, 2009).
Emotion differences

As noted in chapter 1, one of the most common methods used to disentangle the direct and indirect routes in the neuroimaging literature is the manipulation of task-relevance. In this series of ERP experiments task-relevance was likewise manipulated to determine if different processes would unfold. It was found that regardless of task, there were early emotion-related modulations of the ERP waveform (e.g., EAP). These effects were source localized to limbic areas implicated in the automatic processing of emotion (Hariri 2000, 2003), such as the insula.

It is extremely hard to determine if emotion was processed automatically through the “direct” route in this series of experiments. This study is similar to a study by Vuilleumier and colleagues (2001) who asked participants to match the identity of either a pair of task relevant emotional faces, ignoring task-irrelevant houses, or to match the houses and ignore the emotional faces. Like in our study, the elicited brain response did not change between task-relevance and -irrelevant conditions, suggesting that the direct route (and amygdala) were activated regardless of the task. Pessoa and colleagues (2002), however have suggested that the matching houses task used by Vuilleumier was not attention demanding enough, and may have allowed attentional resources to “spill over” and process the facial expressions (see the attentional load theory, Lavie, 1995). The same argument could be leveled here—attentional resources may have been allocated to the emotional content, even when emotion was not task-relevant.

Future researchers need to consider task difficulty and resulting attentional load. As noted in the limitations sections of chapters 2 and 3, the emotion literature has a pervasive task-difficulty confound, where “deep” emotion categorization (i.e. semantic discrimination) tasks are often compared to “shallow” discrimination (i.e. orthographic discrimination) tasks, or even passive reading tasks. Future work should use paradigms that are task-matched for difficulty, at least within the comparison group.

Emotion and the EAP versus the EPN

The emotion ERP literature often reports an emotion-modulated N2, with increased voltage amplitudes in response to emotional compared to neutral stimuli over occipital sites, and effect which has been called the early posterior negativity (Schupp et
al., 2006). In the experiments included in the present work, an averaged mastoid reference was used, and only an early frontal P2-amplification was found (the early anterior positivity; EAP), replicating previous results reported by our lab (e.g., Taake et al., 2009). No EPN was found, event when emotion was task-relevant (Olofsson et al., 2008). These results support Junghöfer and colleagues (2006) hypothesis that the EPN and EAP originate from the same set of neural generators.

The EAP may be driven by a different mechanism than the dysphoria-related amplification of the P2 amplification. Looking again at the basic attention experiment reported by Potts in 1996, in addition to an amplified P2 related to task-relevance, there was trial-by-trial amplification of the P2 for targets compared to standards. He hypothesized, based on previous work with his colleagues (1996), that whereas the posterior N2b is related to perceptual processing, the anterior P2 is related to a trial-by-trial allocation of attention and working memory. A similar interpretation can also be suggested here, with emotion acting as a “target” and causing a trial-by-trial increase in attention to negative compared to neutral words.

Late emotion differences

In contrast to the early task-independent ERP effects, measures of later stage information-processing, including the LPP and behavioural reaction time, were not significantly affected by group membership, and instead were only affected by emotion and task-relevance.

There is an important caveat to make here—the LPP is a distributed effect that spans a large number of centro-parietal electrode sites, and can last for many seconds (Hajcak et al., 2010). Although this study used a traditional set of LPP electrodes (e.g. CPz and surrounding sites) and time window (within the 300-500 ms time range), future studies may wish to define the LPP in their datasets using data-driven techniques.

Summary and Future Directions

This work provides evidence in support of the current cognitive model of depression vulnerability (Clark & Beck, 2010), which incorporates Beevers (2005) suggestion that early stages of information-processing are more likely to show biases than later stages of information processing. A number of issues however, must be
empirically addressed to move forward. For instance, we must find a better way of
distinguishing between the direct and indirect routes, and we must conduct longitudinal
studies to understand biases across the development of affective disorders.

In regard to the first point, a recent literature review in healthy adults (Phaf &
Kan, 2007) suggested that emotional interference is only seen in healthy controls if the
emotional stimuli are presented in a blocked design. This has lead to a theory of “slow”
vs. “fast” emotional interference effects. The fast effect is dependent on early automatic
attention processing biases, while the slow effect is related to the slow disengagement of
attention from highly salient emotional stimuli. The fast effect does not contribute as
much to the cumulative reaction time (RT) measures as the slow effect. One direction
that may be particularly illuminating is to determine if both slow and fast effects can be
found in participants with an induced sad mood, dysphoria and clinically assessed
depression. This may be a better way than task-relevance to dissociate the direct and
indirect routes, and may lead to a better understanding of which routes are affected at
different points in the development of clinical depression.

In regard to the second point, only future longitudinal studies studying the
influence of cognitive biases at difference stages of information processing will allow us
to find reliable markers of depression risk – and only these studies will allow us to
explicitly test the diathesis-stress framework of depression, on which so many of the
models of depression are based.

**Positivity biases**

Although the depression is often thought of as a disorder of negative affect (i.e.
increased sadness), a number of recent studies suggest that there are alterations in the
neural system underlying positive affect as well, particularly early in the course of the
illness (for theoretical review see Forbes et al., 2004). In his review of behavioral and
neuroimaging findings, Leppänen (2006) notes that depression is associated with both
attention biases towards negative stimuli and away from positive stimuli. This *positivity
bias* is related to a diminished neural activity in emotion-related brain areas (e.g. the
amygdala and ventral striatum).
The positivity bias has also been studied using event-related potentials. For instance, Shestyuk and colleagues (2005) found that participants with depression showed a reduced LPP in response to positive or neutral stimuli.

These results tie well into the burgeoning literature on reward insensitivity in depression. Multiple studies by one group (Bress et al., 2013; Foti & Hajcak, 2009; 2010) has shown that the feedback negativity (FN) is decreased in participants with symptoms of depression. This result is interpreted in the context of the anhedonia hypothesis (Dunlop & Nemeroff, 2007), which suggests that there is diminished dopaminergic neurotransmission in depression. The anhedonia hypothesis is supported by recent deep brain stimulation work that has shown that stimulation of the nucleus accumbens can alleviate depression symptoms (Schlaepfer et al., 2008).
References


Appendices
Appendix A.

Supplementary Tables

Table A.1. Source localization of emotional Stroop group differences found during the N1 (160 ms) and P2 (215 ms) time-windows.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Atlas Label</th>
<th>Brodmann Area</th>
<th>Talairach co-ordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 group difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FG</td>
<td>37</td>
<td>x = -39</td>
<td>y = -52</td>
</tr>
<tr>
<td>Right Cerebellum/FG</td>
<td>n/a</td>
<td>32</td>
<td>-52</td>
</tr>
<tr>
<td>Right MTG/Insula</td>
<td>21/13</td>
<td>39</td>
<td>-3</td>
</tr>
<tr>
<td>Left MTG/Insula</td>
<td>21/13</td>
<td>-39</td>
<td>-3</td>
</tr>
<tr>
<td>P2 group difference</td>
<td></td>
<td>13/47</td>
<td>32</td>
</tr>
<tr>
<td>Right Insula/IFG</td>
<td>13/47</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Left Insula/IFG</td>
<td>13/47</td>
<td>-32</td>
<td>4</td>
</tr>
<tr>
<td>PCC/Precuneus</td>
<td>31</td>
<td>-11</td>
<td>-45</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>n/a</td>
<td>18</td>
<td>-52</td>
</tr>
</tbody>
</table>

Note: FG = Fusiform gyrus; IFG = Inferior frontal gyrus; MTG = Middle temporal gyrus; PCC = Posterior cingulate cortex.

Table A.2. Source localization of emotional Stroop emotion difference found during the EAP/EPN (215 ms) time-window.

<table>
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<tr>
<th>Atlas Label</th>
<th>Brodmann Area</th>
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<tr>
<td>EAP Negative-Neutral difference</td>
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<td>x = 39</td>
</tr>
<tr>
<td>Right STG/Insula</td>
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<td>-25</td>
</tr>
<tr>
<td>Left MFG/ACC</td>
<td>n/a</td>
<td>18</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior cingulate cortex; FG = Fusiform gyrus; Medial frontal gyrus; STG = Superior temporal gyrus.
Table A.3. Source localization of emotional word categorization group differences found during the N1 (160 ms) and P2 (215 ms) time-windows.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Atlas Label</th>
<th>Brodmann Area</th>
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<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>N1 group difference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FG/Cerebellum</td>
<td>37</td>
<td>-32</td>
<td>-59</td>
</tr>
<tr>
<td>Right FG/Cerebellum</td>
<td>37</td>
<td>39</td>
<td>-52</td>
</tr>
<tr>
<td>MFG/ACC</td>
<td>10/32</td>
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<td>46</td>
</tr>
<tr>
<td><strong>P2 group difference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Insula</td>
<td>21/13</td>
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<td>-3</td>
</tr>
<tr>
<td>Right Insula</td>
<td>21/13</td>
<td>39</td>
<td>-3</td>
</tr>
<tr>
<td>PCC/Precuneus</td>
<td>31</td>
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</tr>
<tr>
<td>ACC</td>
<td>32</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>n/a</td>
<td>4</td>
<td>-52</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior Cingulate cortex; FG = Fusiform gyrus; MFG = Middle frontal gyrus; MTG = Middle Temporal Gyrus, PCC = Posterior Cingulate Cortex.

Table A.4. Source localization of emotion word categorization differences found during the EAP/EPN (215 ms) time-window.

<table>
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<tr>
<th>Atlas Label</th>
<th>Brodmann Area</th>
<th>Talairach co-ordinates</th>
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<tr>
<td></td>
<td></td>
<td>x</td>
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<tr>
<td><strong>EAP Negative-Neutral difference</strong></td>
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<td></td>
</tr>
<tr>
<td>Right Insula</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>Left STG</td>
<td>22</td>
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<tr>
<td>Left ACC</td>
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<td>-18</td>
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<tr>
<td>Left FG/PG</td>
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<td>-39</td>
</tr>
<tr>
<td>Right Cerebellum</td>
<td>n/a</td>
<td>32</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior Cingulate cortex; FG = Fusiform gyrus; PG = Parahippocampal Gyrus; STG = Superior Temporal Gyrus.
### Table A.5. Source localization of task-irrelevant emotional face group differences found during the N170 (160 ms) and P2 (240 ms) time-windows.

<table>
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<th>Effect</th>
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<th>Talairach co-ordinates</th>
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<td><strong>N170/VPP group difference</strong></td>
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<td></td>
<td></td>
</tr>
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<td>Left FG</td>
<td>37</td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Right FG/Cerebellum</td>
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<td>-52</td>
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<td>Left ACC/MFG</td>
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<td>39</td>
</tr>
<tr>
<td><strong>P2 group difference</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Right Insula/ Putamen</td>
<td>n/a</td>
<td>25</td>
<td>18</td>
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<td>PCC/Precuneus</td>
<td>31</td>
<td>-18</td>
<td>-59</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>n/a</td>
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<td>-52</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior cingulate cortex; BA = Brodmann Area; FG = Fusiform gyrus; MFG = Middle frontal gyrus.

### Table A.6. Source localization of task-irrelevant emotional face differences during the N170/VPP (160 ms) and EPN/EAP (240 ms) time-windows.

<table>
<thead>
<tr>
<th>Atlas Label</th>
<th>Brodmann Area</th>
<th>Talairach co-ordinates</th>
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<tbody>
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<td><strong>N170/VPP Negative-Neutral difference</strong></td>
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<td>Right FG</td>
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<td>39</td>
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<td>Right STG/Insula</td>
<td>38/13</td>
<td>39</td>
</tr>
<tr>
<td>Left Insula</td>
<td>13</td>
<td>-39</td>
</tr>
<tr>
<td>Paracentral Lobule/Precuneus</td>
<td>5/31</td>
<td>25</td>
</tr>
<tr>
<td>MFG/ACC</td>
<td>10/32</td>
<td>-4</td>
</tr>
<tr>
<td>Right FG</td>
<td>20/37</td>
<td>39</td>
</tr>
<tr>
<td>Left Cerebellum</td>
<td>n/a</td>
<td>-25</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior cingulate cortex; Fusiform gyrus; IFG = Inferior frontal gyrus; MFG = Middle frontal gyrus; PG = Parahippocampal Gyrus; PL = Parcentral Lobule; STG = Superior temporal gyrus.
Table A.7. **Source localization of emotion-relevant faces task group differences found during the N170/VPP (160 ms) and P2 (240 ms) time-windows.**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Atlas Label</th>
<th>BA</th>
<th>Talairach co-ordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N170/VPP group difference</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left MFG</td>
<td>11</td>
<td>-39</td>
</tr>
<tr>
<td></td>
<td>Right FG</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>ACC/MFG</td>
<td>32/9</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>n/a</td>
<td>4</td>
</tr>
<tr>
<td><em>P2 group difference</em></td>
<td>Right STG/Insula</td>
<td>38/13</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Precuneus/PCC</td>
<td>7/31</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Left ACC/BG</td>
<td>n/a</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>n/a</td>
<td>25</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior cingulate cortex; BA = Brodmann area; BG = Basal Ganglia; FG = Fusiform gyrus; MFG = Middle frontal gyrus.

Table A.8. **Source localization of task-relevant differences during the N170/VPP (160 ms) and EPN/EAP (240 ms) time-windows.**

<table>
<thead>
<tr>
<th>Atlas Label</th>
<th>Brodmann Area</th>
<th>Talairach co-ordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N170/VPP Negative-Neutral difference</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum/Right FG</td>
<td>n/a</td>
<td>32</td>
</tr>
<tr>
<td>Cerebellum/Left FG</td>
<td>37</td>
<td>-39</td>
</tr>
<tr>
<td>STG/Insula</td>
<td>22/13</td>
<td>-46</td>
</tr>
<tr>
<td>ACC/MFG</td>
<td>32</td>
<td>-11</td>
</tr>
<tr>
<td><em>EAP Negative-Neutral difference</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right BG/Insula</td>
<td>n/a</td>
<td>25</td>
</tr>
<tr>
<td>Left PG/Insula</td>
<td>34</td>
<td>-32</td>
</tr>
<tr>
<td>Right PG</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Left PG</td>
<td>n/a</td>
<td>-32</td>
</tr>
<tr>
<td>Right Cerebellum</td>
<td>n/a</td>
<td>32</td>
</tr>
<tr>
<td>Left Cerebellum</td>
<td>n/a</td>
<td>-18</td>
</tr>
</tbody>
</table>

Note: ACC = Anterior Cingulate cortex; BG = Basal Ganglia; FG = Fusiform gyrus; MFG = Middle frontal gyrus; PG = Parahippocampal Gyrus; STG = Superior temporal gyrus.