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MOTIVATIONAL UNDERPINNINGS OF NEGATIVE AFFECT AS REVEALED BY EMOTIONAL MODULATION OF EEG BANDS

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CONTENTS

OVERVIEW

The studies reported in this thesis pertain to a project aiming at investigating the motivational underpinnings of psychopathologies characterized by negative affect, such as anxiety and depression. Unbalanced or conflicting motivational tendencies can lead to disturbances in emotional responding and ongoing affect, which are often associated with psychopathology. As it will be introduced in the first chapter, motivational drives are thought to be sustained by two main systems in the brain, namely the *appetitive* and the *defensive* motivational circuits. The appetitive system contributes to approach behaviors in response to rewarding and pleasant stimuli. On the other side, the defensive system drives withdrawal from threat and is important for triggering unpleasant emotions. Therefore, emotions can be described as *action dispositions* reflecting basic tendencies to both approach and withdrawal in response to emotional stimuli.

Several models postulated that negative affect in psychopathology arises from an excessive activation of the defensive system, which leads to an increased and dominant tendency to actively withdrawal from potential threats in the environment. Partially contrasting with this theoretical conceptualization, the aim of this thesis was to investigate whether negative affect could also manifest in psychopathologies which are not characterized by a straightforward increase in withdrawal tendencies. In this sense, EEG correlates of motivational tendencies in response to emotional stimuli were investigated in *blood phobia* and in *dysphoria* (i.e., subclinical depression). Accordingly, blood phobia, contrary to other specific phobias, is not associated with an increase in action disposition in response to the feared stimulus. Therefore, negative affect in

these individuals does not seem to arise from a pronounced tendency to actively withdrawal. Depression represents another example of condition in which it is not clear whether negative affect is subtended by a dominance of the withdrawal system or by a lack in appetitive motivation. Accordingly, it is matter of debate whether depressed mood is due to preferential processing of unpleasant stimuli or reduced sensitivity to rewards and positive emotions.

In order to investigate these aspects, three studies were conducted. In study 1, it was chosen to investigate modulation of EEG bands during an emotional Go/Nogo task in blood phobia. The emotional Go/Nogo task, including phobia-related pictures, along with phobia-unrelated unpleasant, neutral and pleasant stimuli, was ideal to investigate the lack of action disposition in blood phobia. Results showed that individuals with blood phobia display a conflicting motivational pattern, characterized by co-occurring tendencies to attend and avoid the feared stimulus, in strong contrast with other phobias. In Studies 2 and 3, modulation of EEG bands during an emotional imagery task in individuals with dysphoria was investigated. The emotional imagery is an active task, in which individuals are requested to actively imagine emotional scenarios; therefore it was well suited to investigate emotional modulation of appetitive and defensive motivational tendencies. Overall, results supported the idea that depressed mood in dysphoria is due to a lack in appetitive motivation, accompanied by a reduction in processing of pleasant stimuli. Again, we found no evidences of increased defensive motivation and tendency to withdrawal in dysphoric individuals.

Finally, our research focused on possible clinical implications of the abovementioned findings, concerning the application of bio-behavioral trainings for the reduction of negative affect. In line with the pertaining literature, results from of our first three studies showed that frontal alpha asymmetry is an informative index of motivational tendencies underlying affect and emotional responses. Therefore, a fourth study was conducted, aimed at evaluating the effectiveness of a frontal alpha asymmetry neurofeedback training in reducing negative affect, anxiety and depressive symptoms in healthy individuals. After five training sessions, healthy individuals succeeded in reducing right compared to left prefrontal activity, through a specific increase in right frontal alpha. In accordance with the role of the right prefrontal cortex in defensive motivation and negative affect, this increase in right frontal alpha power was associated with a significant reduction in negative affect and anxiety.

In conclusion, the present thesis confirms and extends the link between motivational tendencies and negative affect, showing that negative affect is not exclusively associated with an increase in defensive motivation and in active withdrawal disposition. Accordingly, among psychopathologies characterized by negative affect, blood phobia and dysphoria do not display the typically predicted motivational pattern. A first step toward the transition from basic research to clinical application has been proposed, with the implementation of an EEG-based neurofeedback for the reduction of negative affect. Overall, the present work is of potential relevance for a better understanding of the motivational underpinnings of psychopathologies characterized by negative affect, also providing a strong rationale for the application of bio-behavioral trainings.

Keywords: Negative affect; Motivation; Emotion; EEG bands; Psychopathology; Blood phobia; Dysphoria; Neurofeedback

1 EMOTIONS AND THE MOTIVATIONAL BRAIN

1.1 The appetitive and defensive motivational systems

Emotions can be conceptualized in terms of adaptive responses, refined throughout evolution in order to facilitate survival and adaptation to the environment (Lang, Bradley, & Cuthbert, 1998). In particular, experienced emotions are sustained by neural circuits evolved to adaptively respond to external stimuli, which can be either appetitive or threatening for the individual. Accordingly, several authors proposed that two fundamental *motivational systems* exist in the mammalian brain (Davidson, 1992; Dickinson & Dearing, 1979; Gray & McNaughton, 1982; Konorski, 1967; Lang, Bradley, & Cuthbert, 1997; Lang & Bradley, 2013; Lang, 2010): an *appetitive/approach* system, which drives approach behaviors toward rewarding stimuli (e.g., nutrients, sex, social interaction, nurturing), and a *defensive*/*avoidance* system, associated with defensive responses to aversive stimuli (e.g., attack, illness, injury). The trait-like balance between appetitive and defensive dispositions has been referred to as the *affective style* of the individual (Davidson, Jackson, & Kalin, 2000; Davidson, 1998a, 1998b, 2004). Each individual's affective style influences responses to emotional stimuli, being also related to dispositional mood, and vulnerability to psychopathology. Importantly, the appetitive and defensive systems influence behavioral responses to emotional stimuli 1) by modulating perceptual processing and attentional engagement, 2) by prompting physiological responses, functional to energy mobilization, 3) by directly reinforcing specific action patterns. In more details, the appetitive system facilitates preparatory behaviors which reduce the distance from potentially rewarding stimuli, thus increasing the chances of life-sustaining consummatory behaviors (Schultz, 2015).

On the other hand, the defensive system often acts as a “fight or flight” circuit, which mobilizes energy in order to actively face the threat or escape; nonetheless, under some circumstances, the defensive system can also mediate behavioral “freezing” (hiding), increased vigilance**,** and counter-threat displays (LeDoux, 2012). For instance, in a prototypical predator/pray scenario, with the imminence of a physical confrontation (*pre-encounter defensive* behavior) the pray will display 1) augmented vigilance (increasing demand for attentional resources), 2) increasing physiological mobilization, 3) behavioral freezing, but increased action readiness. When the physical confrontation becomes inevitable (*circa-strike defensive behavior)*, action readiness triggers fight or flight behaviors and threat displays (Fanselow, 1994; see Löw, Lang, Smith, & Bradley, 2008 for a laboratory simulation of the predator-prey survival scenario in humans).

In the classical conceptualization, the two motivational systems are thought to be reciprocally related, implying that when one is activated the other is inhibited (Konorski, 1967). However, some authors suggested that the two systems can also be *independently activated*, *co-activated* or *co-inhibited* {Formatting Citation}. This hypothesis was based on pioneering animal studies, which measured the strength of approach and avoidance behaviors in rats respect to a goalbox; the goalbox consisted in a device administering rewards (food) or punishments (schock), alternatively (Brown, 1942, 1948; Figure 1.1). Accordingly to what has been described in the predator-prey scenario, these studies showed that avoidance behaviors prevail over approach when the proximity to the stimulus increases, suggesting a *negative bias* when the motivational activation is high (Y axis in Figure 1.1). On the contrary, when

the stimulus is far, approaching behaviors such as curiosity and exploration are observed, suggesting a *positive offset* in safe and low-activating contexts (Cacioppo & Berntson, 1994; Miller, 1966).

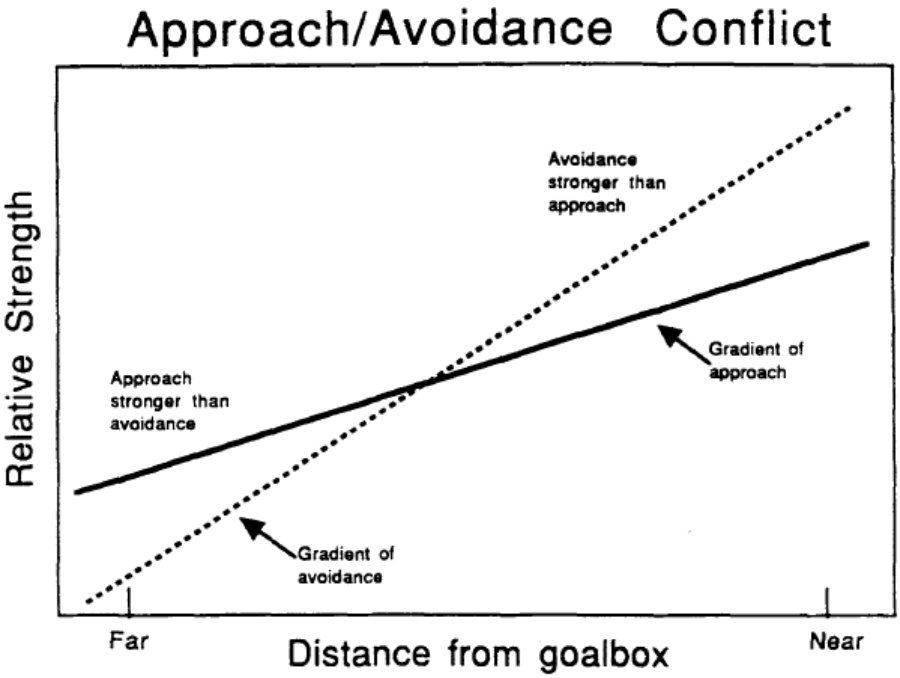

Figure 1.1 Graphic representation of the dynamics of an approach-avoidance conflict. The dashed line represents the avoidance gradient, which is steeper than the approach gradient (solid line). This implies that avoidance behaviors prevail over approach when the proximity to the stimulus increases, while the opposite pattern is elicited when the stimulus is far. At lines' intersection an approach/avoidance conflict arises, resulting in no action, despite motivational activation. Adapted from Miller, 1959.

Supporting evidence for such a relation between the two motivational systems comes from studies on motivated attention in humans. It has been shown that motivated attention in safe conditions is by default oriented toward appetitive stimuli in healthy individuals; nonetheless, with the proximity of a threat source, threat detection mechanisms occasionally interrupt the ongoing attentional and behavioral program, allocating attention toward potential danger (for a review see Frewen, Dozois, Joanisse, & Neufeld, 2008). Accordingly, threatening stimuli are commonly identified

faster among distractors compared to appetitive and neutral ones (Öhman, Flykt, & Esteves, 2001; Öhman, Lundqvist, & Esteves, 2001), suggesting that the avoidance system is functional for quickly identifying threat and organizing withdrawal responses (LeDoux, 1998, 2012).

Intriguingly, as depicted in Figure 1.1, at an intermediate distance from the stimulus an approach/avoidance conflict emerges, since both motivational systems are active (co-activation), and none of them prevails (Cacioppo & Berntson, 1994; Miller, 1966). The co-occurrence of tendencies to attend and avoid a stimulus results in increased motivational activation, but no action. This conflicting activation can be observed in response to emotional stimuli or emotional scenarios in which appetitive and aversive features are contemporary present. Furthermore, the absence of motivated behavior can also result from a failure in the independent activation of the appetitive or the defensive system, as it will be discussed in the course of the present work.

1.2 Emotions as action dispositions: the dimensional model

Under the motivational perspective, emotions are conceived as *action dispositions*, or states of action readiness, defined as the individual's readiness/unreadiness to engage in interaction with the environment (Frijda, 1986, 2007). Accordingly, transient emotional states are frequently perceived and reported as impulses to “move towards”, “move away” and “move against” (Davitz, 1969). Different emotional states can be characterized in terms of the *direction of* the behavior that they trigger (approach/withdrawal), even when they are almost indistinguishable on the basis of their neural and autonomic activation patterns (Lang

& Bradley, 2010). Hence, the direction of the motivational drive is diriment in the characterization of emotion. Furthermore, both approach and withdrawal dispositions can be elicited with greater or less strength and energy mobilization, depending on stimulus' intensity, and on the intensity of the motivational drive (Miller, 1966; Schneirla, 1959). The *direction* and *intensity* parameters of the motivational activation are in a close relation with the emotional *valence* and *arousal*, the two main dimensions which characterize every emotional state, according to the *dimensional model of emotion* (Lang, Bradley, & Cuthbert, 1990; Figure 1.2).

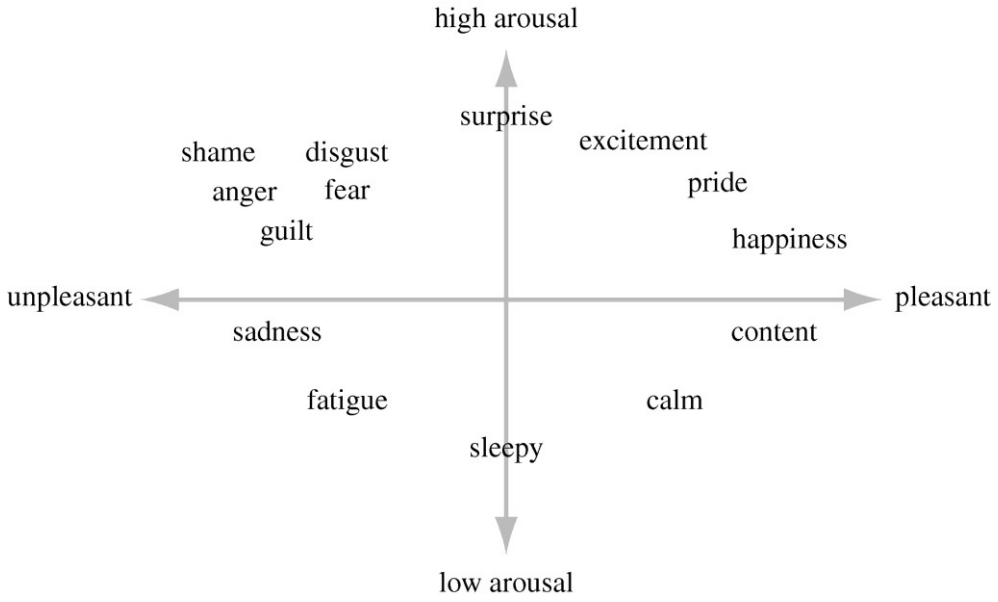

Figure 1.2 The dimensional model of emotion. Emotions are distributed on a bi-dimensional space, along the valence (pleasant/unpleasant) and arousal (low/high, or calm/activated) axes. Adapted from Barrett & Bar, 2009.

Valence refers to the pleasantness/unpleasantness of the experienced emotion, which often corresponds to the direction of the underlying motivational drive. In fact, pleasant and unpleasant emotions are typically activated by the approach and withdrawal systems, respectively. This assumption, however, is not always valid, such as in the case of anger. Anger triggers approach behaviors, in order

to attack, albeit being a negatively valenced emotion, and therefore is a classic example of dissociation between motivational direction and perceived valence. As it will be described in details later, the dissociation between valence and motivational direction is observable also at the neural level (Berkman & Lieberman, 2010; Harmon-Jones, Gable, & Peterson, 2010). On the other hand, the arousal dimension corresponds to the subjective feeling of being calm or aroused/activated, and reflects the intensity of the motivational activation, independently from valence (Bradley & Lang, 1994). As depicted in Figure 1.3, both pleasant and unpleasant stimuli (i.e. those rated with high and low valence scores, respectively) typically elicit higher arousal ratings compared to neutral ones, indicating stronger motivational activation. Importantly, arousal scores also vary within the pleasant and the unpleasant categories, suggesting that emotional stimuli differ in their motivational salience.

Figure 1.3 Valence and arousal: Valence and arousal elicited by different emotional stimuli. Valence and arousal scores were measured through the Self-assessment Manikin (SAM). Adapted from Bradley & Lang, 1994.

1.3 Brain circuits involved in appetitive and defensive motivations

The appetitive and defensive motivational systems rely on evolutionary ancient brain structures, which subserve similar functions in humans and in other mammals. On the other hand, humans further developed control and modulation over primitive impulses, mostly subtended by the prefrontal cortex (Damasio et al., 2000; Ochsner & Gross, 2005). For this reason, human emotional responses are complex, multifactorial, and not predictable in a deterministic way. Nonetheless, primary motivational drives maintain a strong influence on orienting behavior (Damasio & Carvalho, 2013). The main brain structures involved in appetitive and defensive motivations when facing emotional stimuli will be briefly reviewed (Figure 1.4).

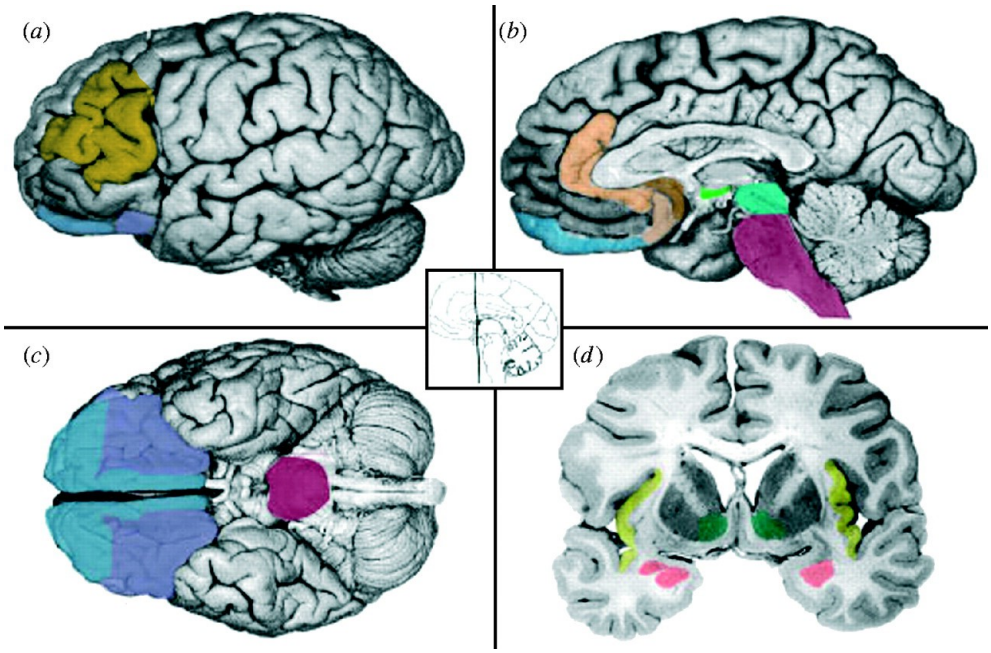

Figure 1.4 Motivational systems in the emotional brain (a-d). The amygdala (pink) and ventral striatum (green) are central in triggering defensive and appetitive responses, being interconnected with the hypothalamus (light green) and autonomic control centers in the midbrain and brainstem (turquoise and maroon). Among cortical regions are counted: the orbitofrontal cortex (OFC), including the ventrolateral prefrontal cortex (vlPFC; light blue) and the ventromedial prefrontal cortex (vmPFC; light purple); the sub/pregenual portions of the anterior cingulate cortex (ACC; brown and salmon, respectively); the agranular insula (yellow); the dorsolateral prefrontal cortex (dlPFC; gold). Adapted from Barrett & Bar, 2009.

1.3.1 Subcortical circuits

Amygdala

A large body of evidence exists regarding subcortical brain structures involved in the production of the defense response to threatening stimuli. The so-called *dual-routes model* claims the existence of a quick subcortical pathway connecting the thalamus directly to the *amygdala*, and a slow one bringing perceptual information to sensory cortices (LeDoux, 1998). In the case of threatening visual stimuli, for instance, the basolateral nucleus of the amygdala receives the sensorial input directly from the thalamus (pulvinar and medio-dorsal nuclei); in parallel, visual information runs on the cortical route from the lateral geniculate nucleus of the thalamus to the visual cortex, which in turn projects back to the amygdala (Carretié, Albert, López-Martín, & Tapia, 2009). Animal studies strongly support the hypothesis that the subcortical route enables rapid and automatic processing of threatening stimuli, functional to quickly organize adaptive responses, more so than the accurate, resource-dependent cortical route (for a review see LeDoux, 2000).

Along the subcortical route, the basolateral nucleus of the amygdala projects in turn the sensorial information to the *central nucleus (CeA)* (LeDoux, 2012). The central nucleus, together with the *bad nucleus of the stria terminalis (BNST)*, represents the core efferent stations for triggering the defense response at the neural, autonomic, hormonal and behavioral level. Accordingly, these structures are connected to several areas within the hypothalamus, the midbrain, the pons and the bulb, as summarized in Figure 1.5.

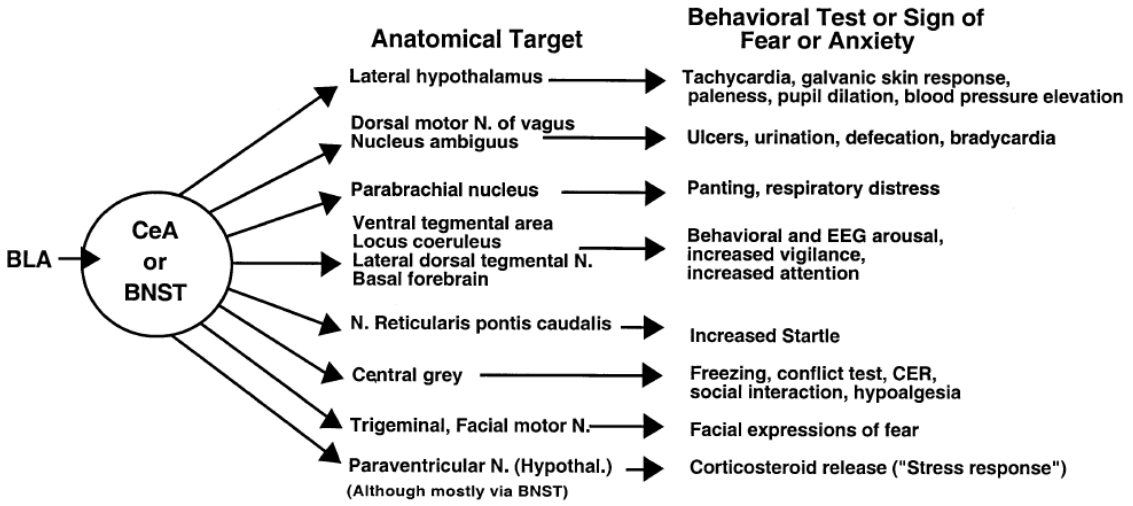

Figure 1.5 The defense response: Detailed efferent projections from the Central Nucleus of the Amygdala (CeA) and the Bed Nucleus of the Stria Terminalis (BNST). On the right, effects on cortical, autonomic, hormonal and behavioral outcomes are reported. N. = nucleus; EEG = electroencephalogram; CER = conditioned emotional responses; Hypothal. = Hypothalamus. Adapted from Walker, Toufexis, & Davis, 2003.

Among the efferent structures, the *periaqueductal gray (PAG)* in the midbrain is crucial in the coordination of coherent physiological and behavioral responses to threat (Holstege & Georgiadis, 2004). On one hand, stimulation of PAG lateral columns elicits tachycardia, increased blood pressure and flow to the face, pupillary dilation, piloerection and analgesia, as well as fight/flight defensive behaviors. On the other hand, the medial subdivisions of the PAG prompts a different defensive response, known as *freezing*, which consists in behavioral immobilization (Gregg & Siegel, 2001). Other structures mediate increases in respiratory rate (*parabrachial nucleus*), blood pressure and heart rate (l*ocus ceruleus*). Sympathetic discharge and autonomic arousal are prompted by the lateral nucleus of the *hypothalamus*, while the paraventricular nucleus increases the release of adrenocorticoids (Gorman, Kent, Sullivan, & Coplan, 2000). Parasympathetic discharge, which facilitates bradycardia and digestive functions, is mediated by amygdala's influence on the dorsal motor nucleus of the vagus and on the nucleus ambiguus. Cortical arousal is also under amygdala's

influence; the central nucleus projects to the ventral tegmental area, the locus coeruleus and the basal forebrain, which release dopamine, norepinephrine and acetylcholine, respectively. These structures are part of the well-known *reticular activating system* (Magoun, 1952; Moruzzi & Magoun, 1949; Steriade, 1996), which is central in the modulation of cortical arousal, reflected in electroencephalographic (EEG) oscillations.

Importantly, due to extensive efferent projections to the sensory cortices, such as the visual cortex, amygdala quickly increases sensorial processing and attention toward motivationally salient stimuli (Freese & Amaral, 2005). Accordingly, several studies reported that the amygdala is often activated not only by threatening but also by rewarding stimuli. Due to amygdala's direct influence on sensorial cortices, emotional stimuli receive preferential perceptual processing and greater attentional allocation compared to neutral ones, as revealed by both behavioral (e.g., Bradley, Cuthbert, & Lang, 1996; Buodo, Sarlo, & Palomba, 2002) and neurophysiological studies (e.g., Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Mini, Palomba, Angrilli, & Bravi, 1996; Palomba, Angrilli, & Mini, 1997; Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997). Importantly, motivated attention on emotional stimuli is functional to acquire information in order to adaptively select a proper response. Therefore, it has been hypothesized that, other than prompting a fast defense response in case of sudden threat, amygdala subserves detection of motivational salience, enhancing motivated attention and cortical arousal in response to both unpleasant and pleasant stimuli (Costa et al., 2010; Wager et al., 2008).

Ventral striatum/Nucleus accumbens

From an evolutionary point of view, "the brain needs to identify the reward value of objects for survival and reproduction, and then direct the acquisition of these reward objects through learning, approach, choices, and positive emotions. […] Rewards induce approach behavior, also called appetitive or preparatory behavior, and consummatory behavior. […] Rewards have the potential to elicit positive emotions. The foremost emotion evoked by rewards is pleasure" (Schultz, 2015, pp. 853-855). Appetitive and positively valenced stimuli, such as food, sex, and social interactions, are thought to activate brain circuits involved in reward. At the subcortical level, the ventral parts of the *striatum*, including the *nucleus accumbens*, *ventral caudate*, *putamen* and *pallidum*, along with *ventral tegmental area* and *lateral hypothalamus* represent a network of regions rich in dopamine and opioid receptors, commonly considered the core motivational circuit supporting approach to rewards (Berridge, 2004; Schultz, 2006). These structures, together with nuclei in the brainstem, such as the *parabrachial nucleus*, represent crucial "hedonic" spots (Berridge & Kringelbach, 2015). In particular, the nucleus accumbens has been associated with anticipation of viewing rewarding stimuli (i.e., "wanting") (Knutson, Wimmer, Kuhnen, & Winkielman, 2008), but also in "liking", or post-goal positive affect (Costa et al., 2010; Sabatinelli et al., 2007), thus representing an important hub for appetitive responses. Nonetheless, it has been suggested that nucleus accumbens may also be involved in avoidance. Accordingly, dopamine neurons and acetylcholine fibers within this nucleus are thought to have opposing roles, with dopamine facilitating approach and acetylcholine fostering avoidance and inhibition (Hoebel, Avena, & Rada, 2009). Therefore, other

than being crucial for driving appetitive behavior toward rewarding stimuli, the nucleus accumbens, along with the mesolimbic dopaminergic system, participates in detection of motivational salience of both appetitive and threatening stimuli.

1.3.2 The role of the paralimbic cortex

At the level of the paralimbic cortex, the *ventro-medial prefrontal cortex* (including the medial orbital cortex and the ventral part of the medial prefrontal cortex) and the affective subdivision of the *anterior cingulate* (Bush, Luu, & Posner, 2000) are part of the mesolimbic dopamine circuit, and have direct projections to the amygdala, hypothalamus and lower brainstem autonomic effectors (Knyazev, 2012). Accordingly, these structures, together with the nucleus accumbens, have been reported to be more activated by pleasant (erotica), compared to neutral (people) and unpleasant (mutilation) stimuli (Sabatinelli et al., 2007; Figure 1.6). Moreover, activation in these regions was highly correlated with reported pleasantness during emotional imagery (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010).

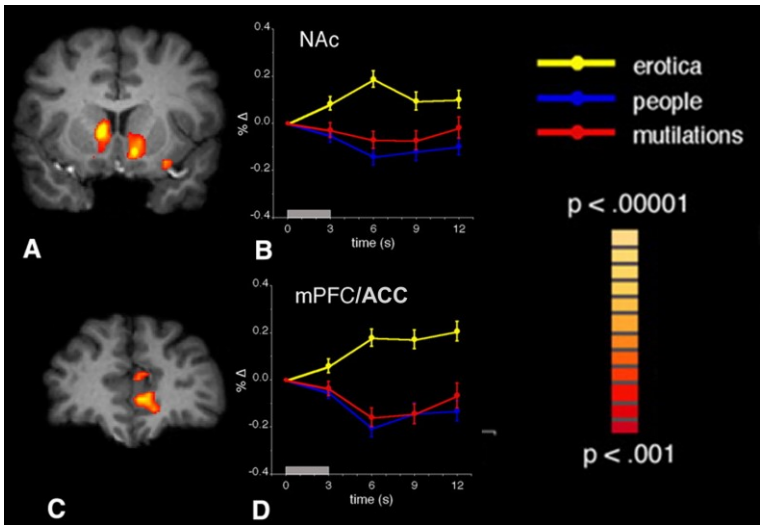

Figure 1.6 Brain responses to pleasant stimuli: Activation in bilateral nucleus accumbens (*A*) and medial prefrontal cortex/anterior cingulate (*C*) is greater for erotic and romantic stimuli compared to unpleasant and neutral stimuli (B; D). Adapted from Sabatinelli et al., 2007.

Interestingly, it has been suggested that sub-regions of the ventral prefrontal cortex are differently involved in processing of pleasant and unpleasant stimuli. O'Doherty and colleagues (2003) reported that subjective rating of attractiveness in emotional faces were positively correlated with activation in the *ventro-medial prefrontal cortex*, and negatively with the *ventro-lateral orbital cortex*, especially at the right side (see also Pizzagalli, Shackman, & Davidson, 2003). More in general, it has been proposed that the ventral prefrontal cortex, including the anterior cingulate, represents an important cortical site of integration of bodily signals and information on visceral activity (Damasio & Carvalho, 2013; Damasio et al., 2000). Together with the *anterior insula*, these structures receive visceral inputs for instance from the heart, lungs, gut and skin, contributing to a feed-back and feed-forward influence from center to periphery, which allows assigning affective value to the stimulus (Bush et al., 2000; Rolls, Kringelbach, & De Araujo, 2003). Therefore, by monitoring the homeostatic processes in the body, these structures are thought to enable individuals to take decisions and orient behavior, based on the emotional properties of the situation (Damasio & Carvalho, 2013; Damasio et al., 2000).

1.3.3 The asymmetrical contribution of the dorsolateral prefrontal cortex

From the data outlined above, it emerges that automatized processing of threatening and appetitive stimuli in the amygdala, the ventral striatum and in the paralimbic cortex represents a primitive and evolutionary preserved mechanism. Although we share with other animals the same tendencies to approach pleasant stimuli and avoid unpleasant ones, several models suggest that in humans approach/avoidance responses to emotional stimuli are under further control from the

dorsolateral prefrontal cortex (dlPFC). In particular, the left and right dlPFC are thought to differently contribute to affect and emotional responses. A model for hemispherical specialization of the dlPFC in emotion is the so called *valence hypothesis*, which argued that the left and right dlPFC subtend pleasant and unpleasant emotions, respectively. On the other hand, posterior regions of the brain, especially at the right side, were hypothesized to subtend emotional arousal (Heller & Nitscke, 1997). The hypothesis that the left and right hemisphere could differentially contribute to pleasant and unpleasant emotions had been initially formulated based on the observation that neurological patients with left-lateralized lesions showed prevalent negative affect and depressed mood, while right-lesioned patients where characterized by general hyperthymia (Goldstein, 1939). Further studies using pharmacologically-induced inactivation of right and left hemispheres supported early reports, with left inactivation causing negative mood and anhedonia, and right inactivation determining euphoric reactions (e.g., Perria, Rosadini, & Rossi, 1961). The first attempt to test the valence hypothesis with functional magnetic resonance (fMRI), directly comparing right and left activation, was conducted by Canli and colleagues (1998). In response to positively valenced stimuli greater left- compared to right-sided activation emerged, while in response to negatively valenced stimuli, the opposite pattern was observed (Figure 1.7).

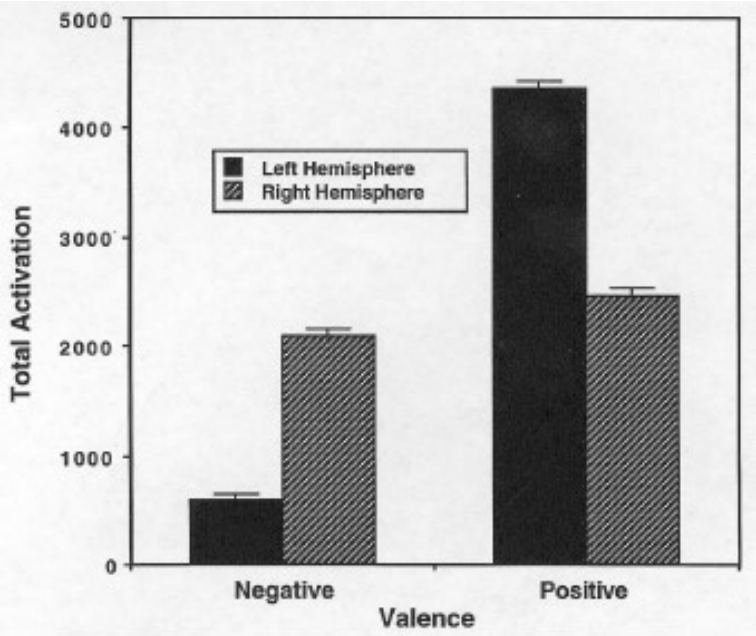

Figure 1.7 Hemodynamic response (i.e. total activation on the Y axis) to positively and negatively valenced pictures in the left and right hemispheres. Adapted from Canli et al., 1998.

In particular, in accordance with the valence hypothesis, positive stimuli significantly activated the left middle frontal gyrus, as well as middle and superior temporal gyri. Significant activation in response to negative stimuli was seen in the right inferior frontal and gyrus rectus. More recently, similar results emerged in the context of an emotional Stroop task using emotional words (Herrington et al., 2005).

The abovementioned results argue in favor of the valence hypothesis. Nonetheless, some authors proposed that hemispheric specialization of the dlPFC can be related to the motivational direction (approach/withdrawal) elicited by emotional stimuli, more than to emotional valence itself (e.g., Harmon-Jones & Allen, 1998). In fact, although it is true that positively valenced stimuli often elicit approach motivation, and that negative stimuli commonly prompt withdrawal, this is not always the case, as introduced in paragraph 1.2. Anger, for instance, is a negative emotion which frequently triggers approach behaviors, evolutionary functional to face a potential opponent or to capture a prey (Harmon-Jones et al., 2010). Furthermore, one

important function of the dlPFC is to control primitive motivational drives automatically elicited by emotional stimuli, re-orienting motivation toward individual's goals, such as in the case of the delay of a reward (Davidson, 2004). Therefore, the valence theory has been refined in the *approach/withdrawal theory* for the hemispherical specialization of the dlPFC, which posits that left and right prefrontal cortex are specialized in driving and maintaining approach and withdrawal motivations, respectively (Davidson, 1992, 2004). The differential activity between the right and left prefrontal lobes is thought to be specifically associated with the affective style of the individual, which, as it has been mentioned above, influences responses to emotional stimuli, dispositional mood, and vulnerability to psychopathology. This model is largely overlapping with the view that 1) the left prefrontal cortex is functional to organize limited resources toward goal-oriented behaviors, predisposing the individual to experience positive affect and emotions; 2) the right prefrontal cortex is an important biological substrate of behavioral avoidance and withdrawal, thus being more often activated in case of threatening, negatively-valenced stimuli (Gray & McNaughton, 1982; Sutton & Davidson, 1997).

Recent studies contributed to the dissociation of the valence and motivation effects on dlPFC asymmetrical activation. Berkman and Lieberman (2010) asked participants to press a button either to decide to "eat" or "don't eat" in response to pleasant and unpleasant food pictures. The participants were instructed to respond pretending to like insects and dislike meat. In this way, participants had to approach (eat) personally disgusting stimuli, and avoid (don't eat) likeable food. Irrespective of pleasantness, approaching responses were subtended by increased activation in left

dlPFC while withdrawing responses elicited greater right-sided dlPFC activation (Figure 1.8), while this laterality effect could not be found in the ventral PFC. Importantly, left dlPFC activation was associated with trait subjective measures of approach motivation.

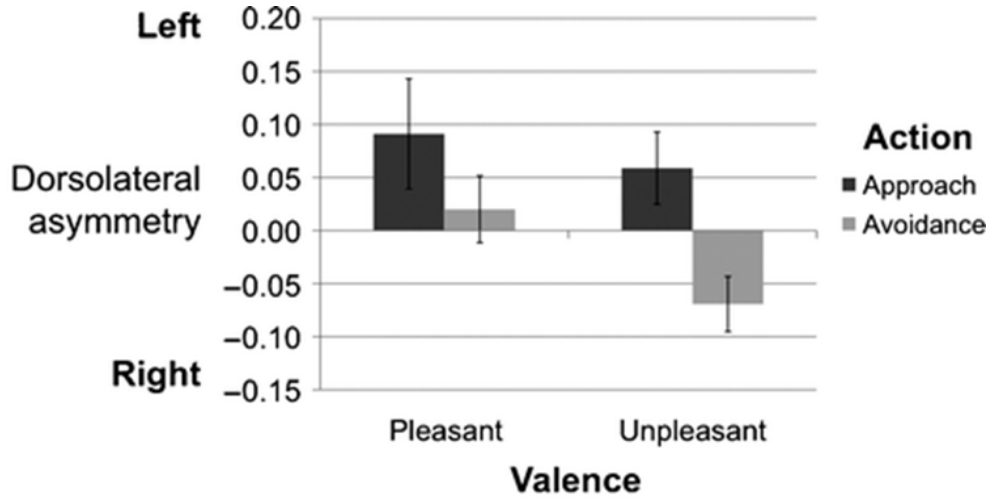

Figure 1.8 Dissociation between valence and approach/withdrawal motivation in the left and right dlPFC. Dorsolateral asymmetry scores were calculating subtracting the average left–right hemodynamic changes from baseline (higher scores = more left-sided activation). The only significant effect resulted to be the main effect of action, showing that approaching responses elicited higher asymmetry scores compared to avoidance, irrespective of valence. Adapted from Berkman & Lieberman, 2010.

Consistent findings on the respective roles of the left and right dlPFC in approach and withdrawal motivations come from another study which employed near-infrared spectroscopy (NIRS) during an approach-avoidance task (AAT) involving both pleasant and unpleasant pictures (Ernst et al., 2013). Left dlPFC was more active when the participants had to approach the stimuli ("pull"), irrespective of their emotional valence, while right dlPFC was always more active for incongruent conditions. It has been proposed that dlPFC maintains and integrates information relevant to approach/avoidance goal pursuits (Davidson, 2004), through its functional connections with the other areas of the motivational network. In line with this hypothesis, it has been shown that when the ongoing motivational goal is challenged, left and right dlPFC exhibit stronger functional connectivity (i.e. correlated patterns of hemodynamic

response) with core regions brain regions involved in instantiating motivational processes, such as the amygdalae, the basal ganglia, the ventromedial prefrontal cortex and the anterior cingulate (Spielberg et al., 2012; Figure 1.9).

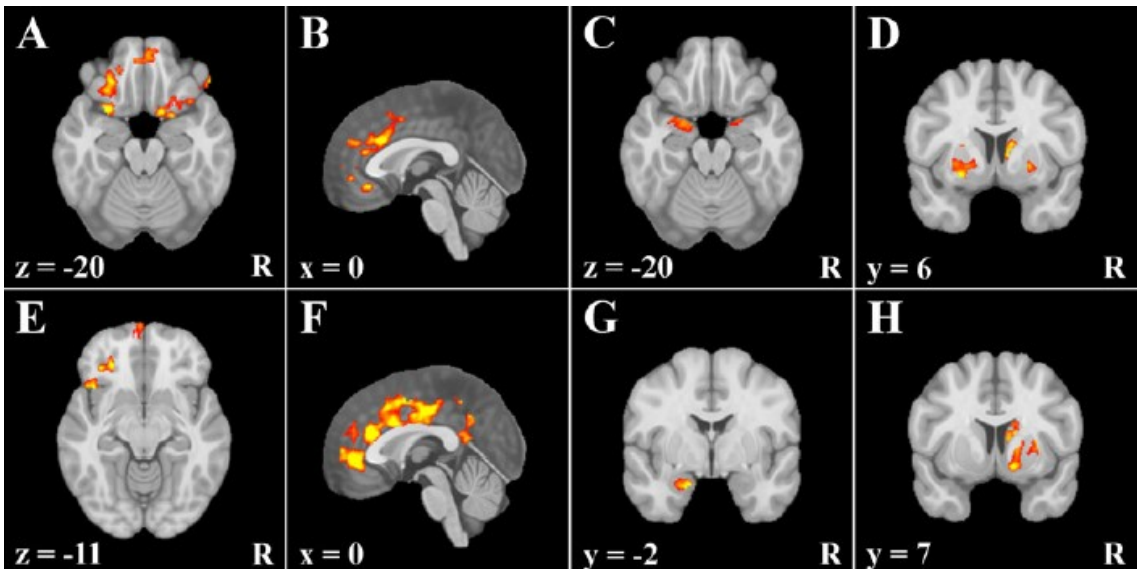

Figure 1.9 Areas exhibiting motivation-dependent correlation with dlPFC: A–D = clusters exhibiting stronger functional connectivity with the left dlPFC cluster associated with approach motivation. E–H = clusters exhibiting stronger connectivity with the right dlPFC cluster associated with avoidance motivation. A = orbitofrontal cortex (OFC); B = anterior cingulate (ACC); C = bilateral amygdala; D = basal ganglia (putamen, pallidus, caudate); E = OFC; F = ACC; G = left amygdala; H = basal ganglia. x, y, and z = coordinates are in MNI 2009a space. Adapted from Spielberg et al., 2012.

Summarizing, there is evidence that 1) responses to emotional stimuli are driven by basic motivational tendencies toward approach or withdrawal, and thus emotions can be conceived as action dispositions; 2) these primitive motivational circuits in the brain are strongly dependent from subcortical and paralimbic structures, in particular the amygdala, the striatum/basal ganglia, the anterior cingulate and the ventro-medial prefrontal cortex; 3) the asymmetrical contribution of the dorsolateral prefrontal cortex represents a mechanism which further modulates motivational tendencies in response to emotional stimuli.

2 ELECTROENCEPHALOGRAPHIC (EEG) BANDS IN THE STUDY OF MOTIVATIONAL RESPONSES TO EMOTIONAL STIMULI

Electroencephalographic (EEG) studies on emotion and the motivational brain received a considerable attention in the field of Affective Neurosciences (Keil, 2013). Accordingly, compared to other neuroimaging techniques, such as functional magnetic imaging (fMRI) or positron emission tomography (PET), EEG provides important complementary information about emotion-related brain processes.

EEG has very high temporal resolution, in the order of milliseconds, thus informing about the brain's activation in the *time* domain (Lopes da Silva, 2013). A precise characterization in time of brain activation is diriment in research on emotion. In fact, the processing of emotional stimuli in the brain occurs within few hundred milliseconds, enabling the organism to rapidly assess their motivational salience and to select the appropriate behavioral response (Lang et al., 1998; Olofsson, Nordin, Sequeira, & Polich, 2008). Therefore, since neural processing of emotional stimuli occurs in a time window which is beyond the temporal resolution of imaging techniques such as fMRI, information provided by EEG are of extreme relevance in the field of emotion (see Figure 2.1).

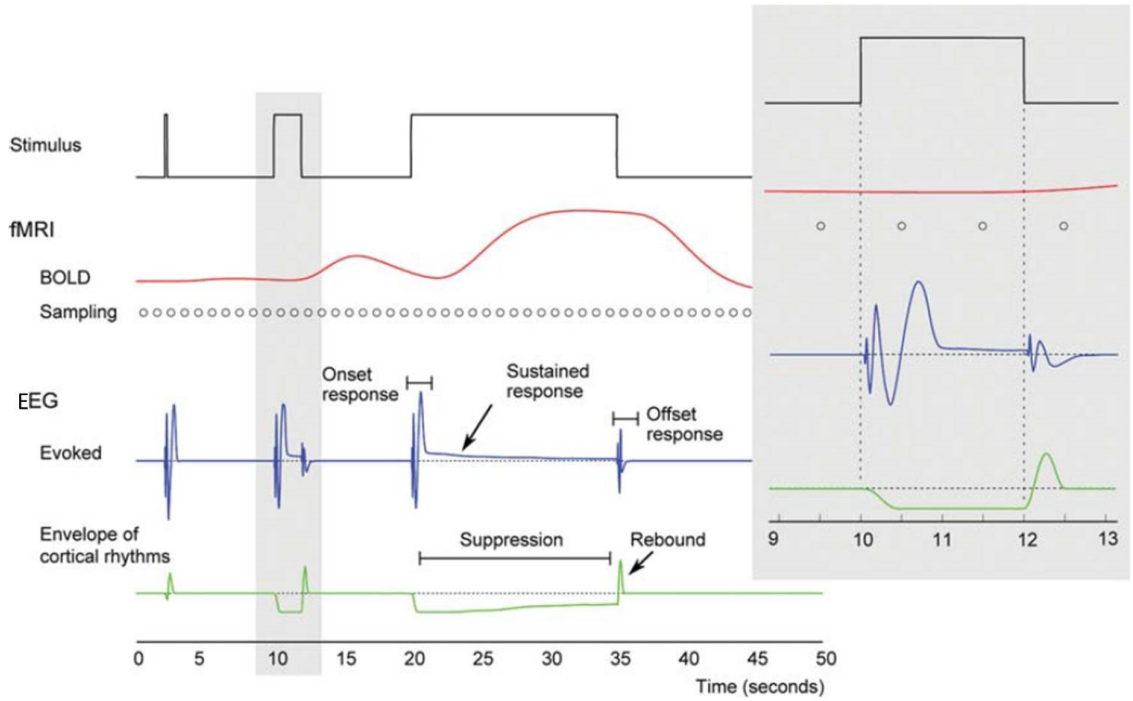

Figure 2.1 EEG signal compared to fMRI BOLD response. The black solid line represents the occurrence of two stimuli, the first one lasting 2 sec and the second one 15 sec. A significant BOLD response (red line) is obtained only when stimulation persists for several seconds (15 sec stimulus). On the contrary EEG evoked responses (blue line) are instantly elicited by stimulus' onset and offset, with possibly a relatively weak sustained response. Envelope of EEG cortical rhythms ranging between 10 Hz and 20-Hz (green line) may undergo suppression and rebound modulation, showing a time course more comparable to that of BOLD. Adapted from Salmelin & Parkkonen, 2010.

Moreover, differently from the hemodynamic response, EEG is a direct measure of brain's activation (Lopes da Silva, 2013). Oscillations of the EEG signal reflect the oscillations in the neurophysiological activity of the underlying neurons, allowing investigating brain responses at specific *frequencies* (or frequency bands). It is intriguing to note that already Hans Berger, the first researcher to conduct EEG recordings on humans between 1910 and 1929, observed that EEG bands were differently influenced by arousal levels (Berger, 1969). He accounted that during states of heightened arousal the oscillatory activity around 10 Hz (i.e., alpha band) tended to fade, while EEG waves in the 25/30 Hz range (beta band) got more abundant. After these early studies, a considerable amount of literature has been produced on how

EEG oscillations are influenced not only by cortical arousal, but also by transient emotional responses and ongoing affect (for a recent review see Güntekin & Başar, 2014). Importantly, since they are modulated by both emotional states and affect, EEG bands represent an additional important source of information on motivational systems in the brain.

EEG has drawbacks too, which should be carefully considered when designing a study and interpreting the results. The major disadvantage of EEG is the low spatial resolution compared to other neuroimaging techniques, such as fMRI (Dale & Sereno, 1993). Since EEG sensitivity is maximal for spatially organized assemblies of neurons (such as the pyramidal cells in the cortex), and since the spatial resolution decreases as a function of the depth of the generators, the lack of spatial accuracy is especially relevant for deep and subcortical sources, which are often of interest in the study of emotion (Hillebrand & Barnes, 2002; Lopes da Silva, 2013; Malmivuo, 2012). Nonetheless, EEG has been largely employed in Affective Neurosciences without explicitly referring to underlying neural generators. Moreover, nowadays the increasing availability of high-density EEG systems, along with computational improvements substantially ameliorated source estimation in EEG (Michel & Murray, 2012).

In the present chapter, after a brief introduction on the EEG signal and methodologies, emotional modulation of EEG bands and its relation to the motivational brain will be reviewed, focusing on research on healthy adults.

2.1 Generators of the EEG signal

Electroencephalography is the graphical representation in time of the difference in voltage between two sites on the scalp (Olejniczak, 2006). An extensive description of EEG sensors and recording instrumentations is beyond the scopes of this paragraph, and comprehensive reviews exist (Luck & Kappenman, 2011; Luck, 2005). Briefly, EEG is safe, non-invasive and silent, it is often recorded through standard electrode caps with multiple sensors applied on the scalp, and a reference electrode must be chosen to measure differences in voltage. Different sources of activity contribute to the EEG signal (including current gradients in glia cells and action potentials) (Lopes da Silva, 2013). Nonetheless, there is a general agreement that the major sources of the signal recorded outside the scalp are the *post-synaptic potentials* (excitatory – EPSP - or inhibitory - IPSP) at the level of the apical dendrites of the pyramidal cells in the cortex (Buzsáki, Anastassiou, & Koch, 2012). For instance, in the case of an EPSP (Figure 2.2, *left*), when the neurotransmitter is released, a flux of positive ions (Na^+ or Ca^{2+}) flows from the extracellular into the intracellular space, producing a local extracellular *sink* (a negative local field potential; LFP). An opposing current goes from the intracellular to the extracellular space along the neuron, in order to maintain electro-neutrality (return current), generating an extracellular *source* (positive LFP). The sink and the source work as an *electrical dipole,* generating current flows both inside and outside the neuron (intra- and extracellular currents).

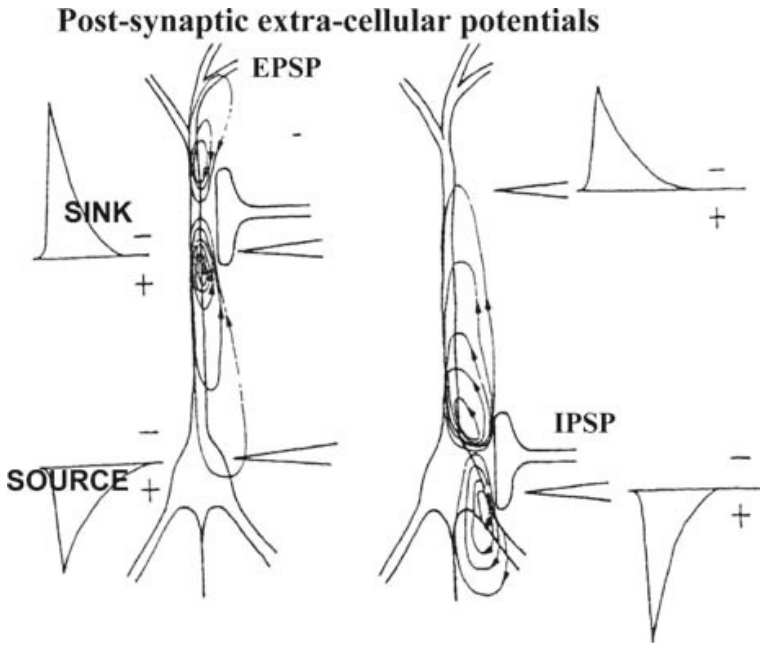

Figure 2.2 EEG dynamics in a pyramidal neuron. A schematic representation of both an excitatory (left) and an inhibitory (right) postsynaptic potential (EPSP/IPSP). During both phenomena, the extracellular local field potentials (LFP), represented by the sharp waves in the figure, have opposite polarities at the sink and the source. This voltage difference makes the current flowing both inside and outside the neuron (intra- and extracellular currents) between the sink and the source. Adapted from Lopes da Silva, 2009.

Albeit the activity at the single cell level would not be strong enough to be recorded at the scalp level, the synchronized and long-lasting activity of an assembly of similarly orientated neurons (i.e., 50.000 cortical cells, see Murakami & Okada, 2006) can sum in a larger dipole, thus being detectable by EEG sensors. In order to reach the sensors, the current has to be conducted through different layers (i.e., brain tissue, cerebrospinal fluid, skull and skin). Volume conduction attenuates and transforms the signal to a considerable extent, due to the different electric conductivities of the layers. Therefore, the sensitivity of EEG decays as the inverse square of the distance of the sources from the sensors (Buzsáki et al., 2012).

2.2 The oscillatory nature of the EEG signal

The raw EEG signal results from the superimposition of oscillations at discrete frequencies, which can be characterized in terms of *amplitude*, *phase* and *period* (see Figure 2.3, *top*). Through oscillations, the brain achieves synchrony in different neural populations, creating the conditions to modulate the membrane potentials of those neurons collectively (Lopes da Silva, 2013). As stated in Buzsáki (2006), this behavior is how the brain manages to detect sudden internal and external changes, while normally preserving its autonomous organization. From the first EEG studies, brain oscillations ranging from very slow (< 1 Hz) to fast (> 30 Hz) were observed and grouped in frequency bands (Figure 2.3). Standard EEG frequency bands are delta (δ, frequency, 0.5–4 Hz; amplitude, > 100-200 μV), theta (θ, frequency, 4-8 Hz; amplitude, 50-200 μV), alpha (α, frequency, 8–13 Hz; amplitude, 30-50 μV), beta (β, frequency, 13–30 Hz; amplitude, <20 μV) and gamma (γ, > 30 Hz; amplitude, <5 μV) (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1974; Figure 2.3, *bottom*).

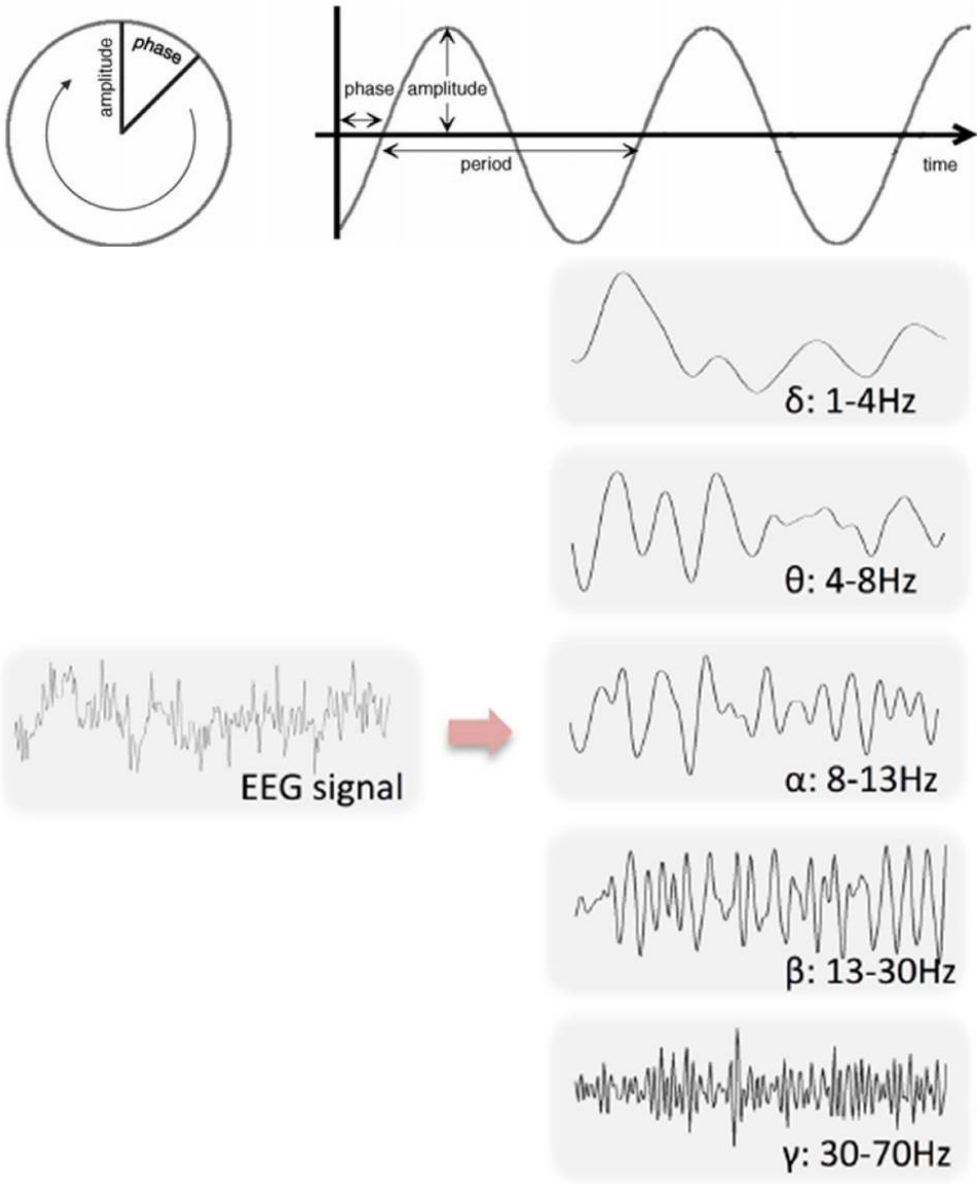

Figure 2.3 *Top:* The *amplitude* is the height from the center line to the peak; the *phase* quantifies how far the function is horizontally to the right of a specific position; the *period* is the length from one peak to the next. *Bottom:* example of raw EEG signal and its underlying band components. Adapted from Buzsáki, 2006 and from Deligianni, Centeno, Carmichael, & Clayden, 2014.

The borders of these bands were somehow arbitrary chosen, based on visual inspection of the raw signal. Nonetheless, recently, by using a factorial analysis of EEG spectral values, clusters of frequency components emerged showing a considerable overlap with the classic EEG frequency bands (Lopes da Silva, 2011).

From the very first reports, EEG oscillations have been studied in relation to levels of arousal and alertness (Berger, 1969). Direct stimulation of the reticular ascending system (theoretically corresponding to activation states) has been reported to strongly suppress EEG slow waves (Moruzzi & Magoun, 1949). Suppression of ongoing slow waves during activation states is typically accompanied by an increase in fast oscillations (Steriade, Amzica, & Contreras, 1996). Accordingly, in healthy adults the raw EEG during deep sleep is mainly characterized by low-frequency oscillations in the delta and theta ranges; alpha waves are prevalent during states of relaxation, while faster rhythms, such as beta and gamma, characterize active wakefulness, thus prevailing during mental or physical efforts (Kilner, Mattout, Henson, & Friston, 2005; Steriade, 2005). Delta, theta, and alpha oscillations span over relatively large cortical regions, and result from synchronous activity of large assemblies of neurons, being considered *global processing modes* (Knyazev, 2007). Accordingly, these bands have been hypothesized to subserve integration across diverse cortical sites, by synchronizing activity across widely spatially distributed neural assemblies (Nunez, 1995). Beta and gamma oscillations, or *local EEG modes*, are higher in frequency, lower in amplitude, and distributed over a more limited topographic area. Growing evidence suggests that, not only in relation to their prevalence in the raw signal, but also considering their occurrence after external stimulation, all frequency bands of the human EEG may have some functional significance. Accordingly, each frequency band has been linked to specific cognitive/behavioral processes, such as the emergence of percepts, memories, emotions, thoughts, and actions (Knyazev, 2007).

Since the different frequencies are superimposed on the raw EEG signal, a common analytical strategy to study the cognitive/affective modulation of specific frequencies is to calculate the *power spectrum* of the signal, by applying a Discrete (or Fast) Fourier Transform (D/FFT) (Buzsáki, 2006). FFT decomposes the sine waves that constitute the signal itself, then computing the *power* (frequently expressed in squared amplitude, μV^2) for each specific frequency. Commonly, power is averaged across contiguous frequencies, to obtain the *power density* (i.e., $\mu V^2/Hz$ or fT^2/Hz) within the classical EEG bands. Since theoretically to apply the FFT the signal should be stationary (same mean and variance), long EEG recordings are divided in shorter epochs. The FFT is then computed for each epoch and averaged. Importantly, this methodology increases the signal to noise ratio (SNR), due to the averaging itself (Nitschke, Miller, & Cook, 1998). Nonetheless, too short epochs can drastically decrease the frequency resolution of the FFT (calculated as 1000/epoch length in ms). Moreover, since FFT assumes infinite repetitions of the signal, the repetition of short segments can create discontinuities, which may affect the power spectrum. Therefore, the epochs are smoothed at the beginning and at the end and then partially overlapped (*windowing*).

To summarize, 1) EEG signal is oscillatory in nature, reflecting synchronous activation of ensembles of neurons; 2) EEG oscillations are often grouped in standard frequency bands, which subtend different psychological and behavioral functions with a certain degree of specificity; 3) Changes in ongoing EEG bands can be measured converting the signal from the time to the frequency domain.

2.3 From event-related potentials to event-related oscillations

2.3.1 Event-related potentials (ERPs): basic principles

The occurrence of a discrete external stimulation is reflected in transient modifications of the EEG signal. This response superimposes on the ongoing oscillations, which are usually much greater in amplitude compared to the response itself. Therefore, multiple trials related to a particular event are often averaged in the time domain, in order to extract the portion of neural activity which is temporally related to the event, namely the event-related potentials (ERPs) (Luck & Kappenman, 2011; Figure 2.4).

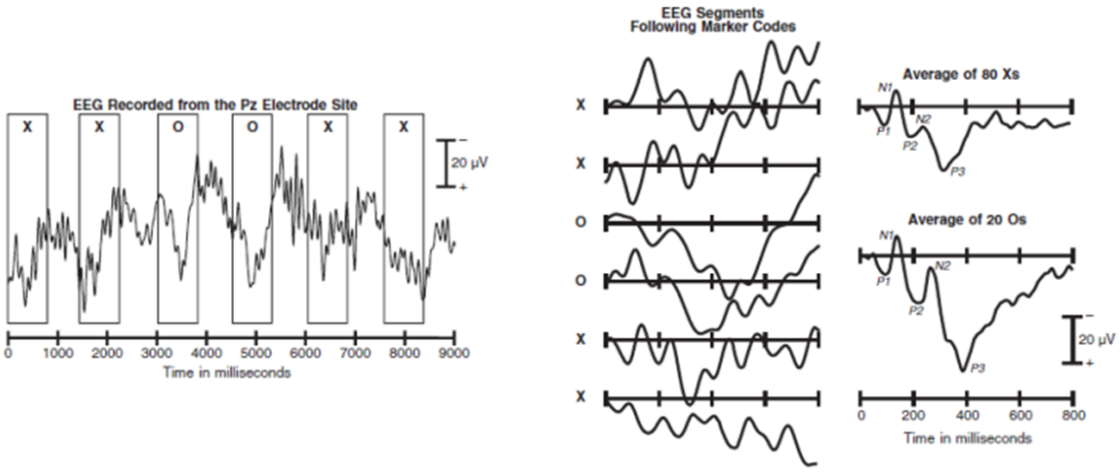

Figure 2.4 Example of ERPs from a visual odball paradigm: the subject views frequent "X" and infrequent "O" stimuli (oddball). The response to each stimulus superimposes on the ongoing signal (*left*). Averaging multiple trials allows suppressing the activity unrelated to the stimulus (such as the noise) and extracting the event-related potentials (*right*). Adapted from Luck, 2005.

Importantly, the activity which is not time and phase locked to the stimulus is cancelled out in the average. As depicted in Figure 2.4, after averaging, ERP waveforms appear as a series of negative and positive deflections in voltage, which vary in amplitude and duration over time (Keil, 2013). Specifically, ERP waveforms can be defined as "*a depiction of the changes in scalp-recorded voltage over time that reflect*

the sensory, cognitive, affective, and motor processes elicited by a stimulus" (Kappenman & Luck, 2011, p. 2). The distribution of positive and negative peaks in the ERP depends on the position of the generating dipole in the brain as well as on its orientation with respect to the scalp (Luck & Kappenman, 2011). The *amplitude* of the peak is generally interpreted as an index of the strength of the underlying process or component, while the *latency* informs on the timing of the response.

Stimulus-related potentials reflect the different stages of stimulus' processing. Accordingly, within few decades of milliseconds after stimulation, the so-called *exogenous components* appear, reflecting the information flow through the sensory pathways. After this exogenous sensorial activity, the following *endogenous ERP components* mirror the cognitive processes elicited by the stimulus (Kappenman & Luck, 2011; Luck, Woodman, & Vogel, 2000; Luck, 2005). Within 200 ms from stimulus presentation, endogenous ERPs reflect the early perceptual encoding of the stimulus. For instance, in the case of visual stimuli (see Figure 2.4), the P1 (80-130 ms, first positive deflection) and subsequent N1 (100-150 ms, first negative deflection) peaks are sensitive to the physical features of the stimulus, indexing early sensory processing within the extra-striate visual cortex. Interestingly, the amplitude of these potentials is also modulated by rapid changes in selective attention on the stimulus (Luck et al., 2000), including the allocation of motivated attention on emotional stimuli (Batty & Taylor, 2003; Foti, Hajcak, & Dien, 2009; Keil et al., 2001; Weinberg & Hajcak, 2010). Accordingly, some authors suggested that this early attentional capture is particularly pronounced for threatening stimuli compared to pleasant and neutral ones, supporting the notion of a fast threat-detection mechanism in the brain (Carretié, Hinojosa,

Martín-Loeches, Mercado, & Tapia, 2004; Carretié, Mercado, & Tapia, 2001; Delplanque, Lavoie, Hot, Silvert, & Sequeira, 2004; Hung, Smith, & Taylor, 2013; Olofsson & Polich, 2007; Smith, Cacioppo, Larsen, & Chartrand, 2003; Williams, Palmer, Liddell, Song, & Gordon, 2006). After the perceptual encoding in the first 200 ms, processing within the 200-300 ms time range reflects stimulus discrimination, conflict monitoring and initiating of response selection processes (Di Russo, Taddei, Apnile, & Spinelli, 2006; Smith, Smith, Provost, & Heathcote, 2010). After 300 ms, ERPs components are sensible to several processes such as 1) resources allocation on the task, which is related to the *cognitive salience* of the stimulus; 2) cognitive effort; 3) memory storage (Luck, 2005). As shown in Figure 2.4, the amplitude of the P3 component is larger for infrequent compared to frequent stimuli in an odball task and, more In general, the P3 increases with the cognitive salience of the stimulus. Similarly, in emotional paradigms, the P3 and the subsequent long-lasting positivity (Late Positive Potential; LPP) are modulated by motivational salience and motivated attention on the stimulus. Accordingly, starting from 200/300 ms after stimulus, ERPs positivity increases with the motivational relevance of the emotional stimuli (Amrhein, Mühlberger, Pauli, & Wiedemann, 2004; Briggs & Martin, 2009; Codispoti, Ferrari, & Bradley, 2006, 2007; Conroy & Polich, 2007; Cuthbert et al., 2000; Junghöfer, Bradley, Elbert, & Lang, 2001; Keil et al., 2002; Mini et al., 1996; Olofsson & Polich, 2007; Palomba et al., 1997; Peyk, Schupp, Elbert, & Junghöfer, 2008; Schupp et al., 2007, 1997). Summarizing, the analysis of event-related oscillations allows tracking in time the neural processing of the stimulus, from perceptual processing, to allocation of attention and memory storage.

In general, and also in research on emotional processing, different analytical strategies have been employed in the study of ERPs, such as 1) comparing the peak amplitude/latency at specific scalp sites across groups/conditions (e.g., Palomba, Angrilli, & Mini, 1997); 2) measuring the area subtended by the peak or the mean activity within a time-window (e.g., Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000); 3) comparing ERP waves using multiple t-test corrected for family-wise error (e.g., Hajcak, Dunning, & Foti, 2009) or 4) extracting the latent components underlying the wavelets using Indipendent and/or Principal Component Analysis (ICA,PCA) (e.g., Carretié, Hinojosa, Martín-Loeches, Mercado, & Tapia, 2004; Chapman & McCrary, 1995). Studies using high-density EEG recordings also analyzed the ERPs in terms of topographical distribution on the scalp (e.g., Gianotti et al., 2008), or in terms of the underlying brain sources at time-windows of interest (e.g., Styliadis, Ioannides, Bamidis, & Papadelis, 2014) (for a comprehensive review see Hajcak, Weinberg, MacNamara, & Foti, 2011).

It is important to consider that ERPs waves or peaks often result from superimposition of the simultaneous activation of multiple underlying neural sources, which possibly subtend different cognitive/affective processes (Luck, 2005). Therefore, techniques which allow isolating the underlying determinants of the signal, such as the extraction of its components using ICA or PCA, the estimation of the underlying neural sources via source localization, or the decomposition of the signal in different frequencies, contribute to disentangle the overlapping cognitive/affective processes which determine the shape of the ERP waveforms (Hajcak et al., 2011). In particular, as it will be detailed in the next paragraph, compared to other techniques, the time-

frequency decomposition of the event-related signal allows studying 1) the contribution of different EEG frequencies to the signal, which are associated with specific cognitive and affective processes; 2) both the *evoked* and the *induced* oscillations, that is the whole range of event-related activity.

2.3.2 Time-frequency decomposition of the EEG signal

As introduced in paragraph 2.2, through a FFT transformation, the raw EEG signal can be converted from the time to the frequency domain, extracting the averaged *power density* within each frequency band. Nonetheless, power analysis on long portions of the signal implies losing information about the time course of the brain activation. On the contrary, the time–frequency decomposition of brain's oscillatory activity computes the variations in time of the power at different frequencies (Herrmann, Grigutsch, & Busch, 2005). Importantly, the EEG activity related to a specific event can be represented in the time-frequency domain (Bastiaansen, Mazaheri, & Jensen, 2011). Several methods have been developed to represent the response in the frequency domain, while preserving the information about timing.

Both linear and non-linear transforms exist to compute time-frequency decomposition of the signal, but linear methods are more commonly used (Wacker & Witte, 2013). Some of these techniques, such as the short-time Fourier transform, apply FFT on short overlapping epochs after stimulus occurrence to extract the time course of the oscillatory response. Other techniques, such as the Hilbert transform, extract the power (and the instantaneous phase) of the signal, after it has been filtered at specific frequencies of interest. However, the most widely used methods are the *wavelet* transforms, and in particular the continuous Morlet wavelet. A Morlet wavelet

is obtained from the multiplication of a Gaussian curve with a specific oscillatory frequency (Figure 2.5). Convolving the obtained wavelet with the event-related signal in the time domain allows extracting signal's power changes in time. Importantly, a trade-off exists between the time and frequency resolution of this time-frequency representation. Gaussians curves with low standard deviation (Figure 2.5 A) result in short wavelets with few oscillatory cycles. Thus, they guarantee a high resolution in time, but a low resolution in the frequency domain, compared to long curves (Figure 2.5 B) (Herrmann, Rach, Vosskuhl, & Strüber, 2014).

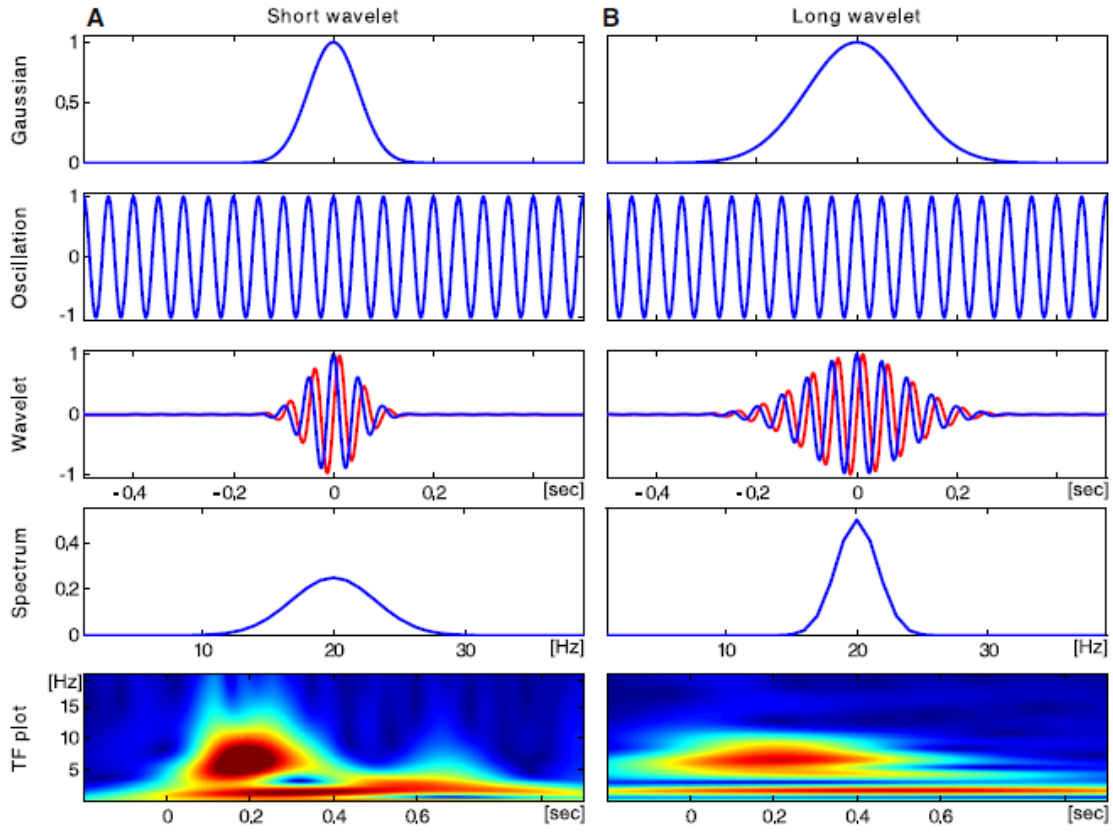

Figure 2.5 Time and frequency resolution of wavelet transforms. Two wavelets (*third row*) are generated by the multiplication of a Gaussian curve (*first row*) and an oscillatory frequency at 20 Hz (*second row*). When convoluting the wavelet with an evoked response, a time-frequency representation of the event-related changes can be obtained (*fifth row*). When a short wavelet is used (column A), the time-frequency data have a high resolution in time, but low in the frequency domain (in the example, the responses above and below 5 Hz are partially overlapping). With longer Gaussians (column B), a higher frequency resolution is achieved, at the expenses of the precision in time.

2.3.3 Evoked vs. induced activation

Event-related oscillations can be divided in two categories (Herrmann et al., 2005, Figure 2.6):

- *Evoked oscillations*, which consist in brain responses always occurring at the same latency and with the same phase compared to the stimulus. In other words, at the single trial level, the evoked oscillations are both time- and phase-locked to the stimulus. When multiple trials are averaged to compute an evoked-potential in the time domain, these oscillations sum up to constitute the ERP components (Figure 2.6; *bottom left*).
- *Induced oscillations*, which are time-locked to the stimulus, but not phase-locked. In other words, these oscillations always occur with the same timing, but their peaks are not aligned. Thus, after averaging in the time domain, induced oscillation don't sum up, disappearing from the ERP (Figure 2.6; *bottom left*).

Differently from the ERP analysis which consists in averaging single trials in the time domain, in time-frequency analysis single trials are firstly converted in the time-frequency domain, and then averaged (Figure 2.6, *right*). The fact that the single trials are transformed in the time-frequency domain before averaging allows preserving the information about induced activity. In fact, since power values are by definition positive, independently from the phase, when the average is computed both the evoked and the induced activities are preserved in the average (Figure 2.6, *bottom right)*. On the other hand, if the time-frequency decomposition is applied after averaging in the time domain, only the evoked response will appear in the spectrum.

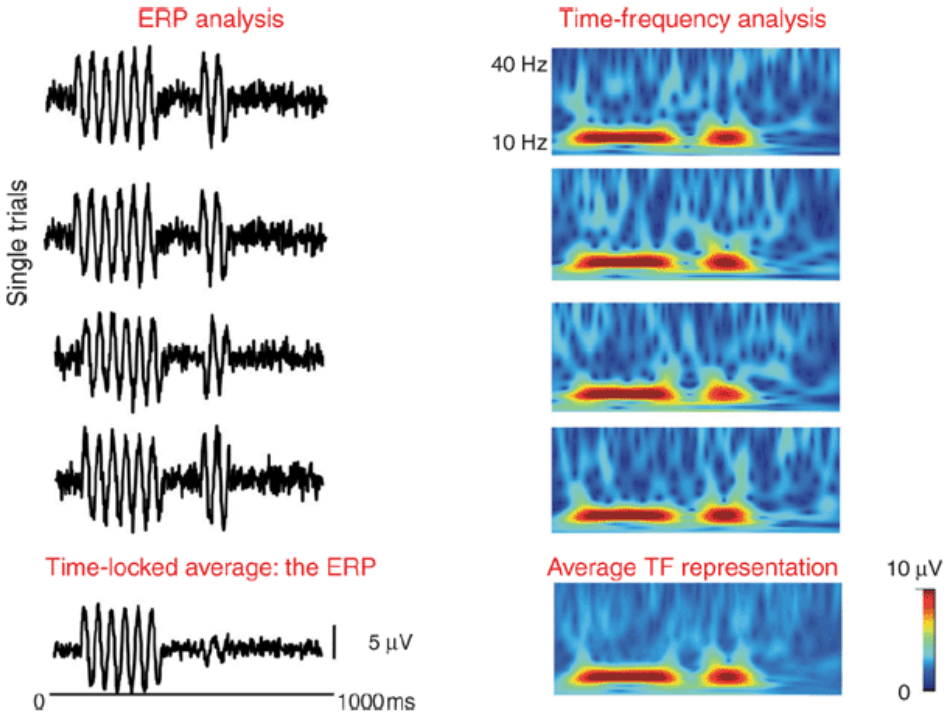

Figure 2.6 *Left*: representation of both evoked (first group of oscillations) and induced (second group) 10 Hz oscillations at the single trial level in the time domain. Note that averaging in the time domain cancels the induced oscillatory activity, due to differences in phase across trials. *Right*: representation of both evoked and induced oscillations at the single trial level in the frequency domain. When averaging amplitude (or power) values, which are always positive, both the evoked and the induced response are preserved. Adapted from Luck & Kappenman, 2011.

The combination of the evoked and induced oscillations is referred to as *total activity* or *event-related spectral perturbations* (ERSP; Herrmann et al., 2014). Often, results from time-frequency analyses are reported in terms of event-related synchronizations/desynchronizations, that is in terms of *proportion (or percentage) of changes in power in the active state compared to the baseline*; an event-related synchronization (ERS) corresponds to an *increase in power* for a specific frequency range compared to baseline, while an event-related desynchronization (ERD) corresponds to a *decrease in power*.

2.4 Affective modulation of EEG bands

Both the study of affective modulation of *ongoing EEG bands* (i.e., measured computing the power spectrum over a prolonged period of time) and of *time-frequency* responses to emotional stimuli (e.g., event-related synchronization/desynchronization) have had large diffusion in the Affective Neurosciences. The most common experimental paradigms employed for studying affective modulation of *ongoing EEG bands* in humans can be summarized into two categories: 1) passive viewing/hearing of emotional stimuli, such as emotional video clips, or long lasting emotional pictures or sounds (often from standardized stimuli sets, such as Bradley et al., 2007 and Lang, Bradley, & Cuthbert, 2008); 2) imagery of emotionally significant events and/or standardized emotional scenarios (Bradley & Lang, 2007). As it will be detailed in the next paragraph, several studies suggest that the power density within each EEG band, and especially those which are prevalent in the raw signal of awake adults (i.e., theta, alpha and beta), is specifically modulated by different affective states and/or ongoing emotional processing.

On the other hand, due to the effectiveness of visual stimuli in capturing attention in humans, the large majority of studies on *event-related modifications* of EEG bands during processing of emotional stimuli involved presentation of emotional pictures. Among this category of emotional stimuli, pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) have been extensively employed in research on emotional processing. The IAPS images have been rated by a large sample of young adults on three scales indicating valence (pleasant/unpleasant), arousal (calm/activation) and dominance (controlled/controlling) (Self Assessment

Manikin; SAM; Bradley & Lang, 1994), and therefore represent a useful standardized tool in the field. Similarly, pictures representing emotional faces, often taken from standardized sets, have been frequently presented to investigate emotional processing of socially-relevant stimuli. One of the most frequently employed standardized set of emotional faces is the Pictures of Facial Affect (POFA; Ekman & Friesen, 1976), containing 110 black/white photographs of facial expressions which have been validated in cross-cultural studies. More recently, other standardized sets for emotional faces have been developed, such as (just for exemplification purposes) the Karolinska Directed Emotional Faces (Lundqvist, Flykt, & Höman, 1998) or the The NimStim set of facial expression (Tottenham et al., 2009), which are also frequently employed. In the present paragraph the major findings on emotional modulation of both ongoing and event-related EEG bands will be reviewed, in order to characterize the functional role of the different frequencies in the study of the motivational responses to emotional stimuli.

2.4.1 Delta band

As outlined in paragraph 2.2, delta band (0.5-4 Hz) is the prevalent rhythm during deep-sleep (slow-wave sleep) in humans. Delta is also the prevalent rhythm during wakefulness in infants, and it increases in the raw signal after neurological insults. Therefore, due to its prevalence in states somehow linked to “decortication”, delta is considered an evolutionary ancient oscillatory mode, which was dominant in the brain of lower vertebrates. Although in the past delta has been considered as a mere correlate of cortical inactivation or inhibition, recently it has been proposed that delta rhythm sustains basic motivational drives, such as the needs for sleep, food, sex

and other rewards (including drug-induced ones) (Knyazev, 2010), potentially being a cortical correlate of bottom-up information about autonomic changes (Lambertz & Langhorst, 1998). The hypothesis of a relation between delta and basic motivational drives is in line with the fact that the main hubs the motivational appetitive system, such as the ventral temgmental area, the nucleus accumbens, the ventral striatum, and the medial prefrontal cortex, are involved in generating delta oscillations (Knyazev, 2007; Figure 2.7).

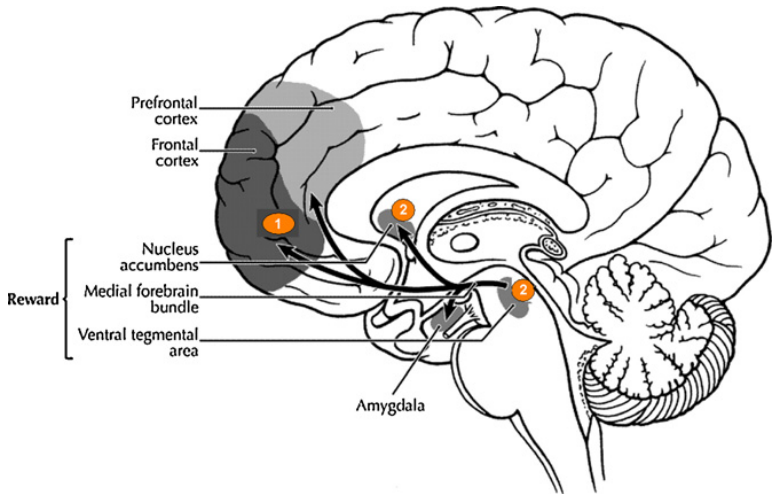

Figure 2.7 Potential sources of EEG delta activity. Orange circles show the localization of potential sources of EEG delta activity as revealed by source modeling and correlation of EEG with PET and fMRI signal in humans (1) and by direct registration of electric activity in subcortical regions of waking animals (2). Adapted from Knyazev, 2010.

Moreover, in response to cognitive tasks, event-related delta synchronization (i.e., increase in power) has been found to be one of the main underlying contributors to the P300, an ERP index of the cognitive salience of the stimulus (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992; Harper, Malone, & Bernat, 2014). Accordingly, in emotional tasks, event-related delta synchronization occurs in in response to high arousing and motivationally salient stimuli compared to low arousing stimuli, in line to

what have been observed for the P300 and the LPP components of the ERPs. In particular, Aftanas and colleagues (Aftanas, Reva, Varlamov, Pavlov, & Makhnev, 2004) presented IAPS pictures varying in valence (unpleasant, neutral and pleasant) and in arousal (low, intermediate and high). Irrespective of valence, at centro-posterior scalp sites intermediate and high-arousing pictures elicited greater delta power compared to low-arousing ones, within 1000 ms after stimulus presentation (Figure 2.8).

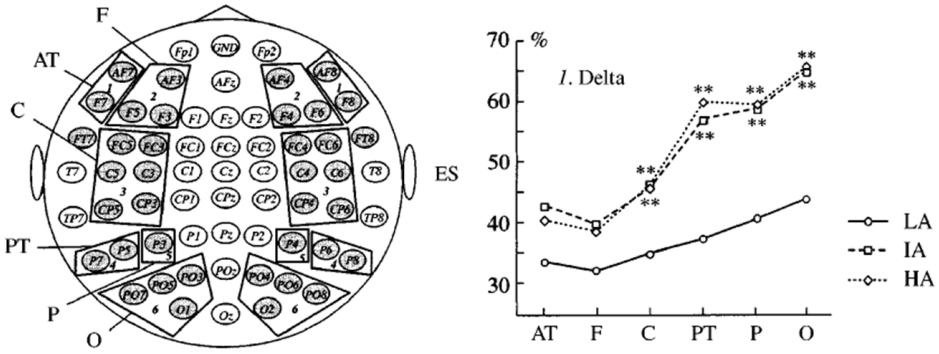

Figure 2.8 Delta synchronization at Frontal (F), Anterior Temporal (AT), Central (C), Parieto Temporal (PT), Parietal (P) and Occipital (O) scalp sites following Low Arousing (LA), Intermediate Arousing (IA) and High Arousing (HA) pictures.

It has been shown that, irrespective of valence, delta power increases across scalp sites from 500 to 1000 ms in response to high arousing IAPS pictures, and that this effect is sustained also after stimulus disappearance, from 1000 to 1500 ms (Klados et al., 2009). Greater delta band synchronization has been also reported for emotional compared to neutral faces (Balconi & Lucchiari, 2006). For instance, Knyazev and colleagues (Knyazev, Slobodskoj-Plusnin, & Bocharov, 2009) investigated explicit and implicit processing of emotional (angry and happy) and neutral faces. Both the explicit and the implicit processing of the emotional faces elicited greater synchronization in the delta (and theta) range compared to neutral faces.

2.4.2 Theta band

Lewis (2005) proposed that theta (4-8 Hz) underlies integrated and synchronous activity within limbic regions, and between the limbic system and other regions relevant for emotional processing (such as the visual and frontal regions). At least two types of theta activity are visible in the human EEG (Schacter, 1977). The first one is a broadly distributed rhythm on the scalp, positively related to states of drowsiness and inversely related to brain activation/arousal (Kilner et al., 2005). Another type of theta activity, mainly expressed on frontal medial scalp sites (*frontal theta*), emerges on a number of cognitive tasks, such as those requiring mental effort and focused attention (e.g., Başar-Eroglu et al., 1992; Gevins et al., 1997), but is also thought to have a more specific relevance for affect and emotion. High-resolution EEG and MEG studies, as well as intracranial recordings, have shown that the anterior cingulate cortex (ACC) is involved in the generation of frontal theta activity (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Gevins et al., 1997; Ishii et al., 1999; Mizuki, Kajimura, Nishikori, Imaizumi, & Yamada, 1984). Moreover, frontal theta was positively correlated with cerebral metabolism in the rostral ACC (Pizzagalli, Oakes, & Davidson, 2003; Figure 2.9).

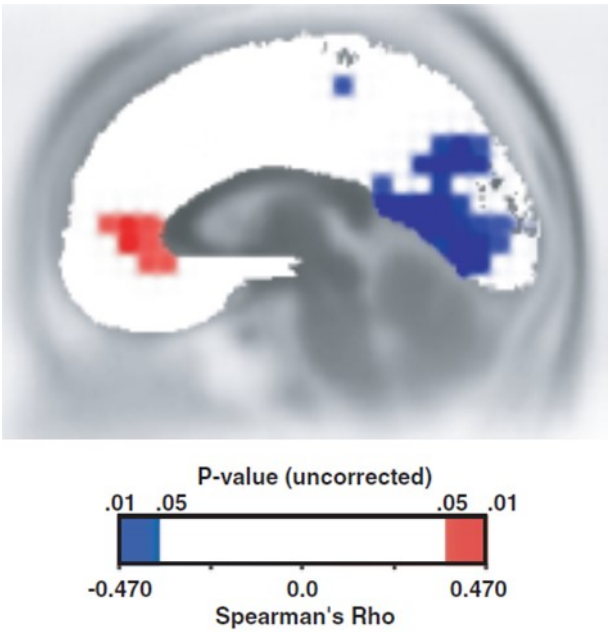

Figure 2.9 Spearman's rank correlation between current density in the theta band and glucose metabolism. In red and blue are represented significant positive and negative correlations, respectively. Adapted from Pizzagalli et al., 2003.

Consistently with the role of the rostral ACC as a key component of the emotion circuit (Bush et al., 2000; Critchley, 2003; Devinsky, Morrell, & Vogt, 1995), and in particular with its role in in reward processing (Baker & Holroyd, 2011; Hayden, Pearson, & Platt, 2009), it has been shown that *ongoing frontal theta* is associated with internalized attention and "blissful positive states" (Aftanas & Golocheikine, 2001; Inanaga, 1998; Kubota et al., 2001). In particular Aftanas and Golocheikine reported that during meditation, theta power at anterior frontal and midline frontal leads was positively correlated with subjective scores of the pleasantness of the emotional experience. In another study, Sammler and colleagues (2007; Figure 2.10) compared EEG power spectra while subjects listened to music pieces rated as pleasant vs. unpleasant. In line with previous results, particularly in the second half of the music piece, listening to pleasant music was accompanied by an increase in frontal theta

power, compared to unpleasant music (for a recent replication see Lin, Duann, Chen, & Jung, 2010). Theta power was also positively correlated with pleasantness ratings.

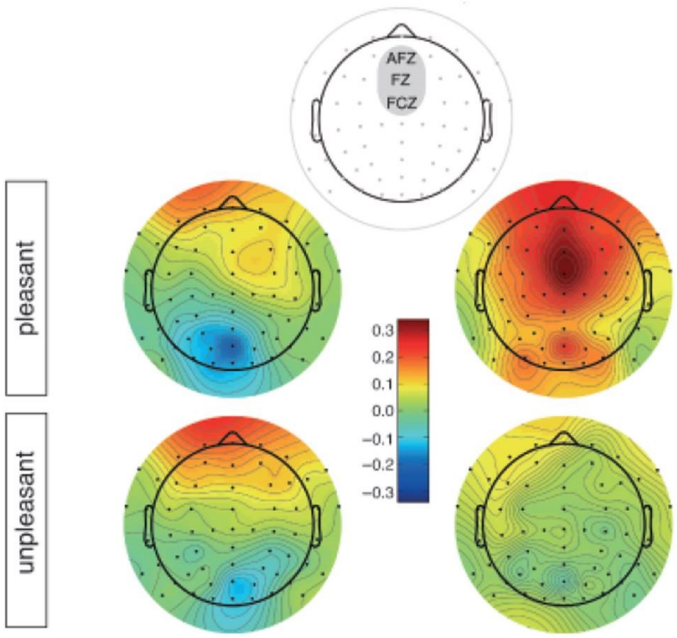

Figure 2.10 Average changes in theta power with respect to baseline during the first and second halves of pleasant and unpleasant music. In the middle mid-frontal seeds of interest selected for statistical analyses are highlighted (i.e., AFZ, FZ ad FCZ). Adapted from Sammler et al., 2007.

Recently, an increase in ongoing frontal theta emerged also during passive viewing of long-lasting (10s) pleasant compared to unpleasant pictures (Valenza et al., 2015). Accordingly, several studies have shown that theta occurrence in the ongoing signal is positively related to relief from anxiety, low neuroticism and high extraversion (Mizuki et al., 1986, 1989, 1984; Suetsugi et al., 2000).

Regarding the *event-related synchronization* of theta band in response to emotional stimuli, similarly to delta, theta band has been found to make a significant contribution to the P300 component of the ERPs. Therefore, it is not surprising that greater theta synchronization has been reported during processing of highly arousing

stimuli compared to neutral stimuli. During presentation of emotional vs neutral IAPS pictures, theta synchronization has been reported over parieto-occipital scalp site (200-500ms), especially in the right hemisphere, irrespective of valence (Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001, 2002). Other studies using IAPS (Aftanas et al., 2004; Aftanas, Savotina, Makhnev, & Reva, 2005), as well as emotional faces paradigms (González-Roldan et al., 2011), provided similar results. In particular, Knyazev et al. (2009) reported that increased theta synchronization at frontocentral scalp sites reflects heightened processing of the motivational salience of the stimulus; accordingly, frontal theta was greater in response to emotional (angry, happy) vs. neutral faces (Figure 2.11), and it was positively associated with self-reported emotional sensitivity and emotional involvement during an explicit emotion recognition task.

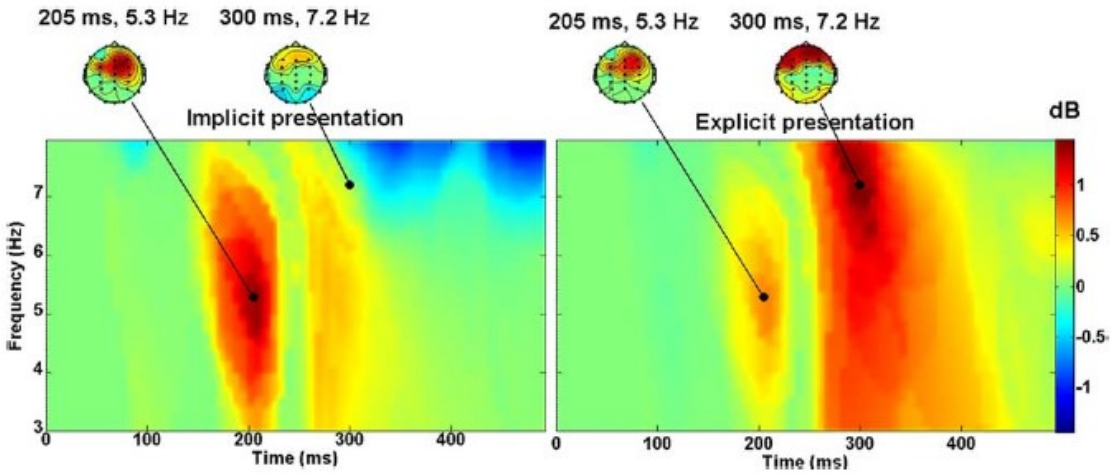

Figure 2.11 Frontocentral theta synchronization following Implicit (left panel) and explicit (right panel) presentation of emotional (angry, happy) vs. neutral faces. Red color shows synchronization and blue color desynchronization. Areas with no significant differences are set to zero and plotted in green. Adapted from Knyazev et al., 2009.

2.4.3 Alpha band

Alpha oscillations (8-13 Hz) decrease during states of emotional arousal, being prevalent during relaxed wakefulness. For instance, passive viewing of emotional film clips has been reported to reduce alpha oscillations compared to neutral videos (Aftanas et al., 1998). Nonetheless, the study of emotional modulation of both ongoing and event-related alpha band has largely focused on *frontal asymmetry in alpha power* (Güntekin & Başar, 2014). The study of alpha asymmetry at frontal sites has greatly contributed to the model of the dlPFC as a cortical correlate of *approach/avoidance* motivation, with the left frontal hemisphere being generally involved in *appetitive* behavior, and the right hemisphere being responsible for *withdrawal* from aversive stimuli (Davidson, 1988, 1998a; Dickinson & Pearce, 1977; Konorski, 1967; Lang et al., 1990, 1998; Tomarken, Davidson, Wheeler, & Doss, 1992). Since alpha power is an inverse index of cortical activity (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998; Davidson, Chapman, Chapman, & Henriques, 1990), asymmetry indices of frontal alpha power are usually calculated to evaluate the balance between left (approach) and right (withdrawal) prefrontal cortices (Allen, Coan, & Nazarian, 2004). Thus, alpha asymmetry is modulated by trait differences in the activity of the two motivational systems, which in turn drive the response to emotional stimuli. For this reason, *alpha asymmetry has been commonly considered a reliable EEG measure of affective style*, which is the balance of appetitive and aversive motivational dispositions that drives responses to emotional stimuli, dispositional mood, and vulnerability to psychopathology (Davidson et al., 2000; Davidson, 1998a, 1998b, 2004).

Accordingly, left prefrontal activity at rest, as measured by reduced alpha at left compared to right, has been related to approach motivation (Harmon-Jones & Allen, 1997, 1998; Sutton & Davidson, 1997), trait positive affect (Tomarken et al., 1992), rates of pleasantness after positive film viewing (Wheeler, Davidson, & Tomarken, 1993), reward responsiveness (De Pascalis, Varriale, & D'Antuono, 2010), dispositional optimism (De Pascalis, Cozzuto, Caprara, & Alessandri, 2013; Figure 2.12), greater emotional flexibility (Papousek, Reiser, Weber, Freudenthaler, & Schulter, 2012) and better emotional regulation (Jackson et al., 2003). On the other hand, prevalent right frontal EEG activity has been associated with withdrawal motivation (Sutton & Davidson, 1997), negative affect (Jacobs & Snyder, 1996; Schaffer, Davidson, & Saron, 1983; Tomarken et al., 1992), as well as reports of more intense negative emotions after unpleasant film viewing (Papousek et al., 2014; Wheeler et al., 1993).

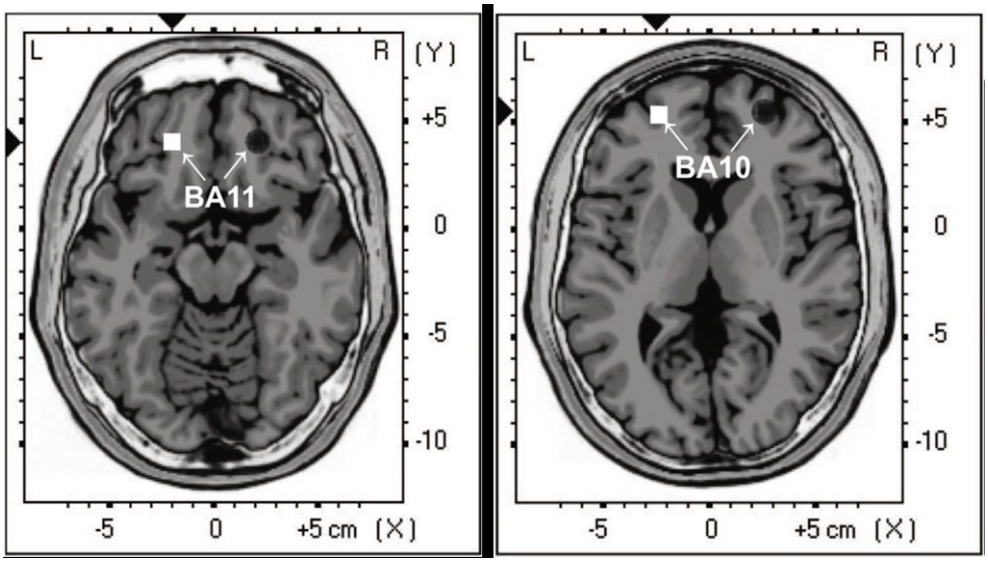

Figure 2.12 Frontal alpha asymmetry was significantly correlated with the Behavioral Activation System in the middle frontal gyrus (BA11, left panel), and with dispositional optimism in the superior frontal gyrus (BA10, right panel). White squares = left cortical regions with a relative hemispheric activation compared to the same region in the contralateral hemisphere (black circle). BA = Brodmann Area. Adapted from De Pascalis et al., 2013.

The work of Harmon-Jones and colleagues shed light on the fact that frontal alpha asymmetry, as a measure of the relative activation of the left and right dlPFC, is specifically modulated by motivational tendencies rather than affective valence (Harmon-Jones & Allen, 1997), through a series of studies on anger. Albeit being a negatively valenced emotion, anger elicits approach behaviors. Consistently with motivational model, both trait (Harmon-Jones, 2004) and state anger (Harmon-Jones & Allen, 1998; Harmon-Jones et al., 2010; Wilkowski & Meier, 2010) are associated with greater left than right activation in the prefrontal lobe, as measured with alpha asymmetry. For example, it has been shown that anger caused by social rejection is linked to an increase in left compared to right prefrontal activation (Harmon-Jones, Peterson, & Harris, 2009). Further studies demonstrated that left prefrontal activation during anger was even more pronounced when the participants were given the opportunity to approach in order to resolve the anger-producing event (Harmon-Jones et al., 2002; Harmon-Jones, Lueck, Fearn, & Harmon-Jones, 2006).

Transient emotional states have been proven to modulate alpha asymmetry as well (Coan, Allen, & Mcknight, 2006; Coan & Allen, 2003, 2004). It has been reported that left frontal activation increased during voluntary facial expressions of smiles of enjoyment (Ekman & Davidson, 1993), while it decreased voluntary facial expressions of fear (Coan, Allen, & Harmon-Jones, 2001; Stewart, Coan, Towers, & Allen, 2011). Typically, following discrete visual stimulation, power in alpha band decreases (i.e., desynchronizaiton) over parieto-occipital areas. Interestingly, alpha event-related desynchronization has been observed also at frontal scalp sites. In accordance with the *approach/avoidance model*, pleasant stimuli produced a greater ERD (i.e., power

decrease, meaning increased activity) in the frontal left scalp sites in comparison with neutral stimuli (Balconi, Brambilla, & Falbo, 2009; Balconi, Falbo, & Brambilla, 2009), while unpleasant stimuli activated more the right frontal area compared to pleasant and neutral stimuli (Balconi, Falbo, et al., 2009; Keil et al., 2001). Other EEG studies on emotional faces reported alpha desynchronization (i.e., greater neural activity) in the left frontal sites in the first 400ms for positively valenced emotions, as well as greater activation of the right hemisphere for negatively valenced emotions (Balconi & Mazza, 2010). Nonetheless, inconsistent results emerged as well. For instance, no right lateralization was found for sadness, while it was reported for both anger and surprise, in contrast with the *approach/avoidance model*. Moreover, other studies failed to find differences in alpha ERD in respect to the emotional content of the faces (Balconi & Lucchiari, 2006; Harmon-Jones, 2007), sometimes showing paradoxical alpha synchronization (Güntekin & Basar, 2007).

Emotional modulation of asymmetry in alpha band has also been studied at posterior scalp sites. Heller (1993) proposed that parietal asymmetry mainly reflects the effect of states of emotional arousal, which is thought to increase neural activation in the right hemisphere (i.e., less right alpha power). This hypothesis has been confirmed by an EEG study in which participants viewed emotional video clips (Sarlo, Buodo, Poli, & Palomba, 2005). Emotional videos elicited strong alpha suppression at parietal scalp sites compared to neutral clips, and this effect was enhanced over the right posterior locations, especially for mutilation contents. Although further research on the pattern for posterior alpha asymmetry is needed, there has been some support

for the arousal model (Aftanas, Reva, Savotina, & Makhnev, 2006; Heller, Nitschke, Etienne, & Miller, 1997; Smith, Meyers, Kline, & Bozman, 1987).

Summarizing, emotional modulation of ongoing alpha band generally supports frontal alpha asymmetry to be a measure of affective style, thus a measure of the balance between motivation to approach and withdrawal emotional stimuli, related to mood and vulnerability to psychopathology (but see Elgavish, Halpern, Dikman, & Allen, 2003; Hagemann, Naumann, Becker, Maier, & Bartussek, 1998; Heller & Nitscke, 1997; Hewig, Hagemann, Seifert, Naumann, & Bartussek, 2004; Hofmann, 2007; Reid, Duke, & Allen, 1998 for inconsistent results). Furthermore, event-related modulation of alpha asymmetry has been proved to be a useful index of motivational tendencies in response to emotional stimuli.

2.4.4 Beta band

Beta (13-30 Hz) is the prevalent rhythm in adults during wakefulness, active and arousing states, at the expenses of slow wave activity (Kilner et al., 2005; Steriade, 2005; Woodruff, Daut, Brower, & Bragg, 2011). Accordingly, it has recently been proposed that ongoing beta band signals the “status-quo” of the brain (Engel & Fries, 2010). Few studies reported emotional modulation of ongoing beta band, again prevalently focusing on brain asymmetries. Rusalova and colleagues (2003) showed that during emotional imagery of personal experiences associated with anger there was an increase in beta band in the anterior part of the left hemisphere. Consistently with this result, a similar pattern of enhanced left anterior beta activation was accounted during passive viewing of angry-eliciting emotional videos (Aftanas et al., 2006). On the other hand, asymmetries in the beta band at parietal sites have been

related to attention to emotional faces. Specifically, a study using a modified dot probe task reported that higher resting levels of beta power at right parietal sites compared to the left were associated with decreased attention (or avoidance) of emotional expressions of anger (Schutter, Putman, Hermans, & Van Honk, 2001).

Since ongoing beta is thought to reflect top-down maintenance of the present brain state, being prevalent during active wakefulness, it is not surprising that it is modulated by external or internal changes. Coherently, modifications in beta power have been reported following discrete rapid emotional stimulation (i.e., event-related oscillations). During visual processing of social-emotional stimuli, beta power typically increases (i.e., synchronization) in a first time window around 100ms, in correspondence with the evoked visual activity. After this initial synchronization, a desynchronization starting at 200/250ms after stimulus emerges, and it has been linked to increased activation of the brain areas relevant for stimulus' processing (Güntekin & Tülay, 2014; Jessen & Kotz, 2011; Wright et al., 2012). Intriguingly, both beta synchronization and subsequent desynchronization have been shown to be modulated by emotional stimuli. Initial beta synchronization following presentation of IAPS pictures has been found to be greater for unpleasant compared to pleasant stimuli across the whole scalp, and compared to neutral pictures at parieto-occipital sites (Güntekin & Başar, 2010). Recently, it has been shown that during a block-design (i.e., unpleasant, neutral and pleasant pictures presented separately), unpleasant IAPS pictures elicited greater beta synchronization compared to pleasant (at frontal sites) and neutral pictures (at occipital sites), within the 0-200ms time-window (Güntekin & Tülay, 2014; Figure 2.13).

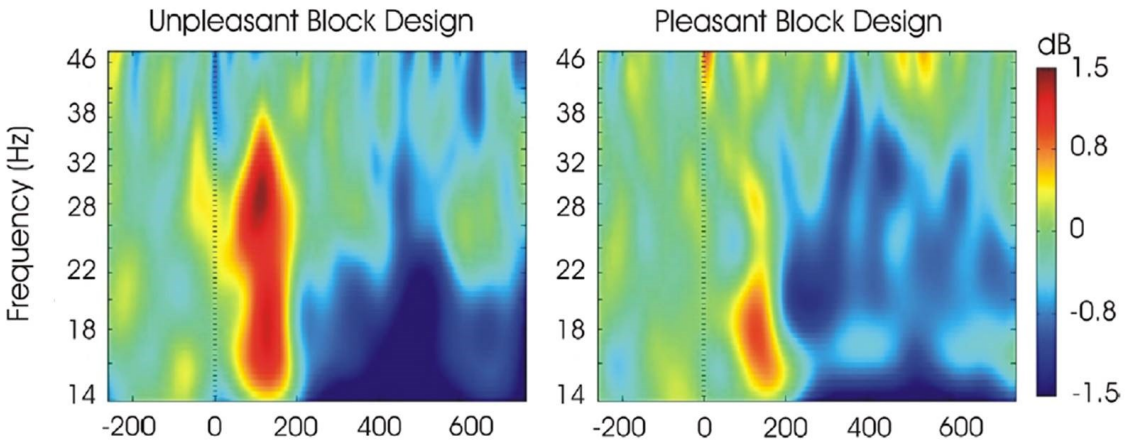

Figure 2.13 Grand average of event-related spectral oscillations at a frontal electrode (F4). The figure shows the power of beta (and gamma) oscillations expressed in decibels during block design (left: unpleasant; right: pleasant). In the first time window (0-200 ms; beta synchronization, in red), unpleasant stimulation elicited higher beta power than pleasant stimulation. Adapted from Güntekin & Tülay, 2014.

In this study, emotional modulation did not emerge in the 200-400ms time-window, in correspondence to beta desynchronization. On the contrary, other authors pointed out that desynchronization within the beta band (20-30Hz) was more pronounced (i.e., decreased power) for unpleasant compared to neutral pictures around 200ms, in the right hemisphere (Keil et al., 2001). In line with results from IAPS pictures, studies using emotional faces reported greater beta synchronization for angry compared to happy faces at left frontocentral scalp sites (Güntekin & Basar, 2007).

2.4.5 Gamma band

Gamma oscillations (30-70 Hz) are rapidly elicited following stimulation, thus their functional meaning has been tightly linked to event-related activity (Başar, 2013). Gamma has been implicated in a number of cognitive processes, such as perceptual processing, attention, memory, language and object recognition, and therefore it has been hypothesized that it signals states of activation shared by many of the abovementioned cognitive processes (Merker, 2013). As described in the “match-and-

utilization model" (Herrmann, Munk, & Engel, 2004), two temporally segregated gamma responses can be described: the *early* gamma-band response (150ms) is thought to reflect the matching of bottom-up signals with memory contents, a process which shares communalities with the "perceptual binding" (Singer & Gray, 1995). Once a stimulus has been identified and classified by comparing it with data in memory, the *late* gamma response (> 200ms) is thought to underlie the process which uses this information for coordinating behavior, redirecting attention or memory storage. Consistently, in the literature on emotional processing, gamma activation in two separate time windows has been reported. Keil and colleagues (2001) using a lateral (left/right) presentation of pleasant, neutral and unpleasant IAPS pictures, found an EEG increase in a lower gamma band (30-45 Hz) across the scalp, as early as 70-90ms, for unpleasant compared to pleasant and neutral pictures. Moreover, they described an increase in a higher gamma band (45-65 Hz) for both unpleasant and pleasant compared to neutral pictures later in time (500ms), over posterior right sites. Importantly, a recent study presenting only unpleasant and neutral pictures replicated the early and late gamma synchronization for unpleasant compared to neutral pictures, which was again more prominent at the centro-posterior regions of the scalp (Martini et al., 2012). In line with these results, intracranial recording measurements and magnetoencephalographic (MEG) studies have shown that early increases in gamma band in the amygdala are associated with detection of aversive stimuli, both during processing of IAPS pictures (Oya, Kawasaki, Howard, & Adolphs, 2002) and fearful faces (Luo et al., 2009, 2010; Luo, Holroyd, Jones, Hendler, & Blair, 2007; Sato et al., 2011). Thus, in line with the dual-route model to emotional processing (LeDoux,

2012), the authors interpreted the early activation as the automatic fast signaling of threat, and the second activation as the interaction of reentrant projection from cortical regions implicated in top-down attentional control.

2.4.6 Summary of the main findings

From the reviewed literature it emerges that:

1) High-arousing pictures elicit synchronization in slow-wave oscillations (delta and theta), reflecting heightened processing of motivationally salient stimuli, in line with the fact that delta and theta independently contribute to the P3 component of the ERPs.
2) Synchronization of *ongoing* frontal theta band reflects long-lasting processing of pleasant stimuli's emotional salience, coherently with the role of the rostral anterior cingulate cortex in the mesolimbic dopaminergic circuit associated with pleasure and reward.
3) Frontal alpha asymmetry can be considered a reliable index of affective style, mainly reflecting the respective contribute of the left and right dorsolateral prefrontal cortex in approach/withdrawal motivational tendencies. This is confirmed by event-related emotional modulation of frontal alpha asymmetry, which resulted generally consistent with the approach/withdrawal model.
4) Although there is some evidence for modulation of beta band at frontal sites to be consistent with the motivational model, the main finding for both beta and gamma bands is that they reflect fast and automatic valence discrimination during processing of transient emotional stimuli.

3 MOTIVATIONAL UNDERPINNINGS OF NEGATIVE AFFECT

3.1 Is negative affect exclusively associated with excessive withdrawal and avoidance from unpleasant stimuli?

As it has been introduced in paragraph 1.1, the appetitive and the defensive motivational systems interact in orienting responses to emotional stimuli and in influencing ongoing affect. It has been suggested that motivated attention in safe conditions is by default oriented toward appetitive stimuli in healthy individuals; nonetheless, with the proximity of a threat source, threat detection mechanisms occasionally interrupt the appetitive pattern, allocating attention toward potential danger (Cacioppo & Berntson, 1994; Frewen et al., 2008; Miller, 1959). Therefore, the defensive system commonly subserves rapid identification of threat, temporarily inhibiting appetitive behaviors (Öhman, Flykt, et al., 2001; Öhman, Lundqvist, et al., 2001). Quick identification of threat is functional to subsequently initiate action (LeDoux, 1998, 2012). Accordingly, the classic *fear response* to threatening stimuli consists in a fight-or-flight mechanism, which organizes energy mobilization in order to support action (see amygdala's projections and their effects at the cortical, hormonal, autonomic and behavioral level, detailed in paragraph 1.3.1). Nonetheless, it has been shown that specific categories of unpleasant stimuli, such as pictures of blood, mutilations and injuries, elicit a complex defensive pattern, which clearly does not facilitate action. In particular, compared to other unpleasant stimuli, passive viewing of blood-related stimuli prompts a fractioned autonomic response (i.e., compresence of increases in skin conductance and decreases in blood pressure and heart rate; Sarlo, Palomba, Buodo, Minghetti, & Stegagno, 2005), freezing-like behavioral immobilization

(Azevedo et al., 2005; Facchinetti, Imbiriba, Azevedo, Vargas, & Volchan, 2006), and heightened attentional allocation, as measured by greater cortical activation (Buodo, Sarlo, Codispoti, & Palomba, 2006; Sarlo, Buodo, et al., 2005; Schäfer, Scharmüller, Leutgeb, Köchel, & Schienle, 2010; Schupp et al., 2004), lack of startle reflex potentiation (Sarlo, Buodo, & Palomba, 2010), and longer reaction times (Buodo et al., 2002). Nonetheless, these kind of stimuli elicit strong unpleasant emotions, as they are associated with self-reports of high unpleasantness and arousal (Azevedo et al., 2005). Such a defensive response showing the compresence of prolonged attentional processing of the stimulus and behavioral immobilization supports the notion that *negative affect may arise in the absence of a clear withdrawal disposition from unpleasant stimuli*. Accordingly, under these circumstances, *the motivational systems appear to be in conflict*, resulting on one hand in increased subjective, cortical and autonomic arousal, on the other hand in a lack of action readiness and active avoidance (Cacioppo & Berntson, 1994; Miller, 1966).

Intriguingly, it has been proposed that appetitive and defensive motivational system can also be *independently activated*, other than being in a reciprocal relation, or in a conflicting one (Brown, 1942, 1948; Cacioppo & Berntson, 1994; Miller, 1959). Therefore it is conceivable that negative affect might manifest due to 1) an exaggerated activation of the defensive system, which would lead to a generalized tendency to overestimate negative information and to respond to unpleasant stimuli; 2) an hypo-activation of the appetitive system, which would determine the attenuation of the appetitive dominance in safe conditions, a reduction in approach behaviors and a diminished responses to pleasant stimuli. In the latter case, depletion of appetitive

motivation would be the underlying motivational correlate of prevalent negative affect. In the next paragraph it will be described how, also in the case of clinically relevant conditions, negative affect might not always be associated with a clear tendency to withdrawal from negative stimuli, contrary to early theories.

3.2 Motivation and action disposition in psychopathologies characterized by negative affect

Emotion-related symptoms are core features of mental disorders included in the international diagnostic systems (Kring, 2008). In particular, anxious and depressive disorders are characterized by the prevalence of negative affect and unpleasant emotionality (DSM-5 American Psychiatric Association, 2013). Early cognitive models proposed that both depressive symptoms and anxiety arise from a generalized tendency to overestimate negative information, due to a combination of trait predisposition and environmental factors (Beck & Emery, 1985; Beck, 1987). At the neural level, this has been proposed to be associated with hyper-responsivity in the limbic system, in particular the amygdala, and decreased prefrontal cognitive control (Clark & Beck, 2010). Hyper-responsivity of the defensive circuit underlying negative affect is expected to increase the individual's tendency to trigger a fight/flight response following external stimulation.

The *phobic response*, or pathological fear, is the prototypic example of motivational tendency to trigger a fight/flight response to the feared stimulus. Accordingly, the motivational theory of emotion states that phobic fear can be described as a strong disposition to withdrawal and avoid (Lang & Bradley, 2010, 2013). In line with this conceptualization, when facing the feared stimulus, individuals

with specific phobia display a clear pattern of sympathetic activation, as evident for instance in increased skin conductance and heart rate (Cuthbert et al., 2003; Globisch, Hamm, Esteves, & Ohman, 1999; Hamm, Cuthbert, Globisch, & Vaitl, 1997), potentiation of the startle reflex, and heightened behavioral avoidance (Hamm et al., 1997; Rinck & Becker, 2007). Accordingly, it has been shown that individuals with spider phobia are faster in pushing (avoid) than in pulling (approach) a lever in response to pictures of spiders, although they do not differ from controls in response to non-spider stimuli (Figure 3.1; Rinck & Becker, 2007). Overall, this psychophysiological and behavioral pattern suggests strong withdrawal disposition and activation of the defensive motivational system.

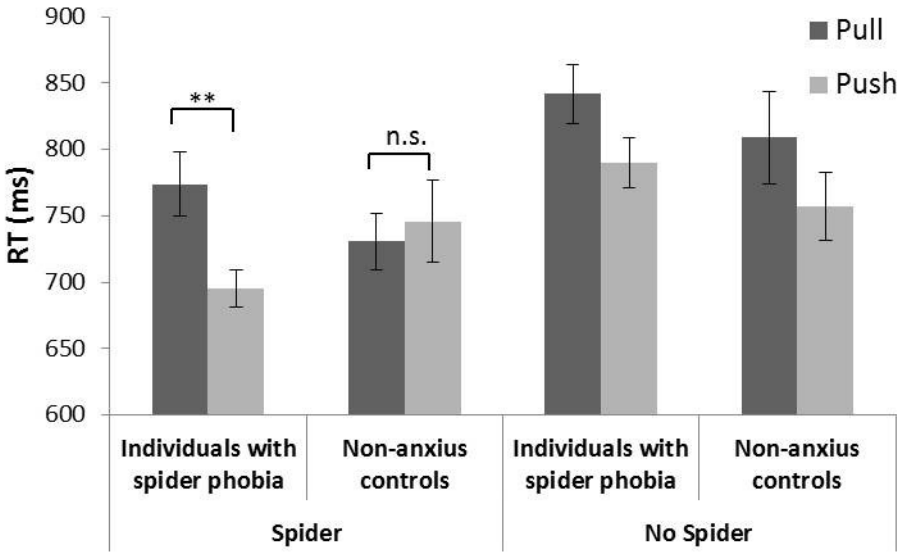

Figure 3.1 Increased behavioral avoidance in individuals with spider phobia. When facing feared stimuli ("Spider"), individuals with spider phobia, but not controls, respond faster when they are required to push a lever (avoid) compared to when they are required to pull it (approach). This pattern was not found in response to perceptually similar pictures not containing spiders. Adapted from Experiment 1 in Rinck & Becker, 2007.

Nonetheless, it is not always the case that phobia is associated with strong active withdrawal tendencies in response to feared stimuli. The blood-injection-injury

subtype of specific phobia (i.e., *blood phobia*) represents an exception in this context. Albeit being characterized by marked fear or anxiety when exposed to the phobic object (DSM-5 American Psychiatric Association, 2013), as indicated by higher unpleasantness and arousal scores compared to controls (Buodo et al., 2006), individuals with blood phobia do not show clear action disposition. Similarly to what happens in non-phobic controls when facing blood-related stimuli, but in an exacerbated way, a conflicting motivational response is produced in blood phobia. In particular, when exposed to surgery film clips, individuals with blood phobia display increased in heart rate and cardiac output, but at the same time they show a progressing fall in systolic blood pressure, compared to controls (Sarlo, Buodo, Munafò, Stegagno, & Palomba, 2008), which often leads to vasovagal syncope (Engel, 1978; Graham, Kabler, & Lunsford Jr., 1961; Hamm et al., 1997; Öst, 1992; Sarlo, Palomba, Angrilli, & Stegagno, 2002). The absence of coherent metabolic mobilization is accompanied by great allocation of attentional resources on blood-related stimuli (Buodo et al., 2006; Buodo, Sarlo, & Munafò, 2010), and by a the lack of a clear motor preparation (Sarlo et al., 2010). Overall, reduced action disposition in blood phobia seem to arise from a *motivational conflict* between motivated attention on the stimulus and defensive motivation, that is, a co-occurrence of both appetitive and defensive tendencies at the same time. In particular, this pattern does not support the presence of a clear active withdrawal disposition from the feared stimulus in blood phobia, contrary to other phobias.

In a similar way, it has been argued that *depression* may not be subtended by a straightforward increase in motivational disposition to actively withdrawal in response

to negative stimuli. On one hand, some studies support a *negative potentiation hypothesis*, which is aligned with early theories postulating that negative mood in clinical depression and in subclinical conditions (i.e., dysphoria) is actually subtended by greater withdrawal tendency and reactivity to unpleasant emotions (for a review see Bylsma, Morris, & Rottenberg, 2008). Accordingly, it has been reported that depressed individuals are characterized by greater electrodermal activity and/or startle reflex amplitude in response to unpleasant stimuli compared to healthy controls (Cook, Davis, Hawk, Spence, & Gautier, 1992; Sigmon & Nelson-Gray, 1992), but other studies failed in replicating these effects (Dichter, Tomarken, Shelton, & Sutton, 2004; Kaviani et al., 2004). On the contrary, several authors suggested that persistent and/or excessive negative mood in depression is due to *a deficit in appetitive motivation*, which reveals in loss of pleasure and anhedonia (Davidson, 2004). As stated in the introduction, lack of motivated behaviors can depend on an *independent failure* in one of the two motivational systems. Accordingly, reduction in appetitive motivation in depression has been associated to attenuated reactivity to pleasant stimuli (i.e., *the positive attenuation hypothesis*). Reduced sensitivity to pleasure and reward in depression has been indexed through diminished autonomic (Messerotti Benvenuti, Mennella, Buodo, & Palomba, 2015), facial (Berenbaum & Oltmanns, 1992; Sloan, Strauss, & Wisner, 2001) and electrocortical (Buodo, Mento, Sarlo, & Palomba, 2015) responses to pleasant stimuli, as well as reduced self-reported pleasantness compared to healthy individuals (Berenbaum & Oltmanns, 1992; Dunn, Dalgleish, Lawrence, Cusack, & Ogilvie, 2004; Sloan et al., 2001). In sum, it is an unresolved issue in the literature whether depression is better described as an

increased withdrawal tendency toward unpleasant stimuli, or as a deficit in appetitive motivation.

3.3 Aims of the research project and outline of the studies

The studies included in the present thesis aimed at investigating motivational tendencies in psychopathologies characterized by negative affect, as revealed by emotional modulation of EEG bands. It was chosen to focus on psychopathologies which potentially represent "exceptions" to common motivational disposition toward emotional stimuli. In this sense, the primary aim of the present work was to test the motivational model of emotion in clinical populations where the relationship between motivational and affective dysregulation is not straightforward. In fact, as described above, both blood phobia and dysphoria potentially represent a challenge to the model that describes negative affect uniquely as a consequence of motivational disposition to actively withdrawal from unpleasant stimuli.

In order to study whether disposition to actively withdrawal in response to the phobic stimulus is reduced in blood phobia, an emotional Go/Nogo paradigm was employed, including phobia-related and phobia-unrelated unpleasant, neutral and pleasant stimuli (Study 1). Requiring motor inhibition of consolidated responses, the emotional Go/Nogo task was perfectly suited to characterize action disposition in blood phobia when facing phobic stimuli. Accordingly, action disposition is proportional to the effort needed to inhibit a consolidated response, as it will be detailed later. Furthermore, the study of event-related oscillations in frontocentral delta, theta and in frontal alpha asymmetry in response to the task allowed measuring the neural correlates of attentional and motor processes associated to inhibition, as

well as those reflecting modulations in the approach/withdrawal tendencies. The investigation of both behavioral and EEG responses to the emotional Go/Nogo task is extremely informative in the case of blood phobia, where a conflict between motivated attention on the stimulus and withdrawal disposition seem to underlie the response to the feared stimulus.

As far as dysphoria is concerned, two studies on modulation of ongoing EEG bands during an emotional imagery paradigm including unpleasant, neutral and pleasant scripts are presented. The emotional imagery task was chosen because it requires individuals to actively imagine emotional scenes, thus being well suited to stimulate motivational tendencies. On one hand, subjective reports of valence and arousal were measured. On the other hand, both emotional modulation of frontal theta, an index of motivational salience, and frontal alpha asymmetry, an EEG correlate of approach/withdrawal motivations (see sections 2.4.2 and 2.4.3) were investigated. Therefore, in Study 2 we focused on emotional modulation of ongoing frontal theta in individuals with and without dysphoria. In Study 3, we selected a subgroup of the initial sample to investigate frontal alpha asymmetry modulation in the task. Given that the association between alpha asymmetry and depression is stronger in females compared to males (Bruder et al., 2001; Miller et al., 2002; Smit et al., 2007) and that asymmetrical alpha activity is influenced by handedness (Davidson, 1988), only right-handed females were included in Study 3. Such comprehensive investigation provided insight on whether dysphoria is associated with a deficit in pleasant emotions and appetitive motivation, or, on the other hand, shows increased

withdrawal tendencies and response to unpleasant stimuli, compared to healthy controls.

Finally, as an example of the clinical implications of the abovementioned studies, a neurofeedback of frontal alpha asymmetry training for the reduction of negative affect will be presented (Study 4). This last work will show how training healthy participants to modify their motivational dispositions, as measured by frontal alpha asymmetry, can have an impact on modulating their affectivity. Therefore, Study 4 represents a first step toward translation of findings from studies 1, 2 and 3 to clinical application. This last study highlights the importance of precisely characterizing motivational disposition underlying negative affect, in order to develop more targeted bio-behavioral interventions.

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3.4 STUDY 1: The two faces of avoidance in blood phobia: Time-frequency correlates[1]

3.4.1 Abstract

As it has been detailed above, contrary to other phobias, individuals with blood phobia do not show a clear cut withdrawal disposition from the feared stimulus. The study of response inhibition provides insights into reduced action disposition in blood phobia. Twenty individuals with and twenty without blood phobia completed an emotional Go/Nogo task including phobia-related pictures, as well as phobia-unrelated unpleasant, neutral, and pleasant stimuli. Behavioral results did not indicate a phobia-specific reduced action disposition in the phobic group. Time-frequency decomposition of event-related EEG data showed a reduction of right prefrontal activity, as indexed by an increase in alpha power (250 ms), for Nogo-Mutilation trials in the phobic group but not in controls. Moreover, theta power (300 ms) increased specifically for phobia-related pictures in individuals with, but not without, blood phobia, irrespective of Go or Nogo trial types. Passive avoidance of phobia-related stimuli subtended by the increased alpha in the right prefrontal cortex, associated with increased emotional salience indexed by theta synchronization, represents an electrophysiological correlate of the conflicting motivational response in blood phobia. Through the novel use of time-frequency decomposition in an emotional Go/Nogo task, the present study contributed to clarify the electrophysiological correlates of the overlapping motivational tendencies in blood phobia.

[1] Results from this study are reported in Mennella R., Sarlo M., Messerotti Benvenuti S., Buodo G., Mento G., Palomba, D. (under review). The two faces of avoidance: Time-frequency correlates of motivational disposition in blood phobia.

Keywords: Blood phobia; Action disposition; Go/Nogo; Time-frequency; Frontocentral theta; Frontal alpha asymmetry.

3.4.2 Introduction

Phobic fear is described as a strong disposition to withdrawal and avoidance (DSM-5 American Psychiatric Association, 2013). Accordingly, in most subtypes of specific phobias (e.g., animal or situational subtypes) exposure to phobic stimuli elicits pronounced sympathetic activation (Cuthbert et al., 2003; Globisch et al., 1999; Hamm et al., 1997), along with increased behavioral avoidance (Rinck & Becker, 2007).

Contrary to other phobias, individuals with blood phobia show a conflicting autonomic response when exposed to blood and mutilations, which often leads to vasovagal syncope (Engel, 1978; Graham et al., 1961; Hamm et al., 1997; Öst, 1992; Sarlo et al., 2008, 2002), along with a lack of a clear motor preparation when facing the feared stimulus (Sarlo et al., 2010). Nonetheless, individuals with blood phobia rate phobia-related stimuli as more unpleasant and arousing, compared to controls (Sarlo et al., 2010), similarly to individuals with other specific phobias (Hamm et al., 1997). Therefore, blood phobia seems to be characterized by a complex pattern of activation of the avoidance motivational system. In particular, the lack of clear cut active avoidance of the feared stimulus (e.g., Buodo, Sarlo, Codispoti, & Palomba, 2006; Hamm et al., 1997) suggests that action disposition is reduced in these individuals compared to controls (Sarlo et al., 2010).

It has been shown that the stronger is the readiness to act, the greater the difficulty withholding an action in a Go/Nogo paradigm (Smith, Johnstone, & Barry, 2006). Therefore, a potential way to measure action disposition is to evaluate the effort required to inhibit a planned motor response. Accordingly, in a typical Go/Nogo task, frequent Go cues require a motor response (e.g., pressing a button), whereas in

the infrequent Nogo trials subjects have to inhibit the response. Inhibition to Nogo trials is associated with increased amplitude of two components of the event-related potentials (ERPs) at frontocentral scalp sites: the Nogo N2 and the Nogo P3 (i.e., the Go/Nogo complex; Falkenstein, Hoormann, & Hohnsbein, 1999). The Nogo N2 is a negative deflection occurring 250-350 ms after stimulus onset, which have been related to conflict monitoring (Smith, Smith, Provost, & Heathcote, 2010). On the other hand, the Nogo P3 is a positive deflection occurring 300-600 ms, which is thought to reflect the inhibitory process itself (Smith, Jamadar, Provost, & Michie, 2013).

Importantly, increased action disposition typically elicited by emotional stimuli has been associated with enhanced difficulty in motor inhibition in emotional Go/Nogo paradigms, as indexed by increased amplitude of the Go/Nogo complex (Albert, López-Martín, & Carretié, 2010; Albert, López-Martín, Tapia, Montoya, & Carretié, 2012; Buodo, Sarlo, Mento, Messerotti Benvenuti, & Palomba, 2015; Messerotti Benvenuti, Sarlo, Buodo, Mento, & Palomba, 2015; Zhang & Lu, 2012). In the emotional variant of the Go/Nogo task, emotional stimuli (e.g., pictures or words) are used in place of standard emotionally neutral stimuli, thus providing a reliable measure of the emotional modulation of response inhibition (Schulz et al., 2007). Nonetheless, in some studies action disposition induced by emotional stimuli failed to elicit the expected increase in the amplitude of the Go/Nogo complex (e.g., Chiu, Holmes, & Pizzagalli, 2008).

It has been recently proposed that the ERP measures may not fully account for multiple processes that underlie response inhibition if not disaggregated in the fundamental frequencies, through time-frequency decomposition of event-related

data (e.g., Barry, 2009; Harper, Malone, & Bernat, 2014; Yamanaka & Yamamoto, 2010). For instance, it has been reported that event-related synchronization (i.e., increases in power compared to baseline) in theta and delta bands at midline frontocentral sites differentially contribute to the emergence of the traditional Go/Nogo complex in the ERPs (Harper et al., 2014). In particular, at frontocentral midline scalp sites, theta synchronization is associated with increased N2 and P3 in response to Nogo trials, thus primarily reflecting conflict monitoring prior to inhibition. On the counterpart, event-related delta oscillations contribute to the decrease in the Nogo N2 and to the increase in the Nogo P3 components, therefore more specifically reflecting motor inhibition. Moreover, there is converging evidence showing that right frontal activation, as indexed by reduced alpha activity, is implicated in both inhibitory mechanisms and withdrawal motivation (Berkman & Lieberman, 2010; Davidson, 2004; Ernst et al., 2013; Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009). Accordingly, frontal asymmetry in the alpha band has also been related to action inhibition in a Go/Nogo task. In particular, a shift toward alpha reduction at right compared to left frontal sites (i.e., increased right frontal activation) has been observed during response inhibition in Nogo trials in individuals with high personality traits of behavioral inhibition (Wacker, Chavanon, Leue, & Stemmler, 2009).

In light of these considerations, the present study investigated action disposition in blood phobia during an emotional Go/Nogo task including phobia-related pictures (i.e., mutilated bodies and injuries), as well as phobia-unrelated unpleasant, neutral, and pleasant stimuli. In particular, a time-frequency approach was adopted to study

the modulation of delta and theta activity at frontocentral midline sites, as well as alpha at right, midline and left frontal sites.

Mutilation stimuli were predicted to elicit reduced action disposition in individuals with blood phobia compared to controls (i.e., non-phobic individuals). Importantly, it has been reported that mutilation and blood-related stimuli induce also in healthy individuals a freezing-like behavioral immobilization (Azevedo et al., 2005; Facchinetti et al., 2006), along with heightened attentional allocation, as measured, for instance, by greater cortical activation for blood-related compared to other emotional stimuli (Buodo et al., 2006; Sarlo, Buodo, et al., 2005; Schäfer et al., 2010; Schupp et al., 2004). This motivational and attentional pattern of reduced action readiness was expected to be exacerbated in individuals with blood phobia compared to controls. Therefore, at the behavioral level, individuals with blood phobia were expected to show increased reaction times (RTs) in response to phobia-related stimuli compared to controls. At the neural level, it was hypothesized that individuals with blood phobia would show 1) decreased event-related delta and theta power at frontal and central midline sites, indices of less effortful response inhibition, in response to phobia-related Nogo trials compared to controls, and 2) a reduced shift toward right frontal activation for the phobia-related Nogo trials compared to controls, as indexed by increased right relative to left frontal alpha power, reflecting reduced effort in response inhibition and less pronounced withdrawal tendency. Phobia-unrelated unpleasant, neutral, and pleasant stimuli were included as control conditions, to test the specificity of the effects for mutilation stimuli.

3.4.3 Methods

Participants

Given that blood phobia is more prevalent in females (DSM-5 American Psychiatric Association, 2013), only adult right-handed females were included in the present study. In order to identify potential participants with blood phobia, the paper and pencil Italian version of Mutilation Questionnaire (MQ; Klorman, Weerts, Hastings, Melamed, & Lang, 1974) was administered to 473 students of the University of Padova. The MQ includes 30 true/false items related to personal reactions to blood, wounds, injections and medical procedures. Scores range from 0 to 30 with higher scores corresponding to more severe symptoms of fear and avoidance. Individuals with scores equal to or greater than 18 (i.e., the 85th percentile of the observed distribution) were preliminarily selected and were administered the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown, Di Nardo, & Barlow, 1994) by a trained psychologist. Individuals who met the diagnostic criteria for blood-injections-injury subtype of specific phobia, without reporting other specific phobias, were assigned to the group with blood phobia (*N* = 20; age, M = 22.5, SD = 1.6, MQ score, M = 20.5, SD = 2.2).

Participants assigned to the healthy control group (*N* = 20; age, M = 21.8, SD = 1.4, MQ score, M = 6.4, SD = 2) were selected from those who obtained a MQ score less than or equal to 10, corresponding to the median value of the obtained distribution, but greater than 3, corresponding to the fifth percentile, to exclude subjects with excessive familiarity with this type of stimuli. Controls were also administered the ADIS-IV to exclude the presence of phobic or anxiety disorders.

The two groups were matched for age and education (*ps* > .10). All the participants had no history of psychiatric or neurological disorders and were free from medications. The study was approved by the Ethics Committee of the Departments of Psychology, University of Padova (Italy). All the participants gave their written consent to participation in the study, in accordance with the Declaration of Helsinki.

The emotional Go/Nogo task

Stimuli were selected from the International Affective Picture System (Lang et al., 2008) on the basis of their content and their standardized ratings of affective arousal and valence (see Appendix 1). One-hundred and twenty digitized color pictures (650 × 850 pixel) were divided into four categories of 30 stimuli each: *Threat* (attacking humans and animals), *Mutilations* (mutilated bodies and injuries), *Neutral* (household objects, urban landscapes and neutral people) and *Pleasant* (erotic couples and sport/adventure). Emotional categories were matched for mean normative arousal ratings (Threat = 6.43; Mutilations = 6.28; Pleasant = 6.56; all *p*s > .39), which were significantly higher than for neutral pictures (Neutral = 2.95; all *p*s < .001). Negative stimuli were also balanced for mean normative valence ratings (Threat = 2.99; Mutilations = 2.18).

Each picture was presented in a pink or blue frame, that cued the participant to either press a key (Go trials) or withhold the key press response (Nogo trials). The colors of the frame indicating Go and Nogo cues were counterbalanced across participants. Nogo trials were 30% in total, as well as within each emotional condition, and were presented in a semi-random sequence (i.e., no more than two Nogo stimulus

had to be shown consecutively). Each picture was presented five times, so that for each category there were 105 Go and 45 Nogo trials. A 500-ms white central fixation cross on a black background preceded the presentation of a framed picture. In order to maximize the action tendency in the participants, thus potentiating the tendency to avoid negative stimuli, Go stimuli were terminated by key press responses (or lasted a maximum of 600 ms). Responses were collected up to 1000 ms. Nogo stimuli were displayed for a fixed duration of 600 ms. The inter-trial interval varied randomly between 500 and 800 ms. The task was presented by a Pentium IV computer on a 19-inch computer screen (at 100cm from participant's eyes), using E-prime 2.0 presentation software (Psychology Software Tools, Pittsburgh, PA, USA).

Procedure

Upon arrival at the laboratory, the participants read and signed an informed consent form and the ADIS-IV was administered. Participants who fulfilled inclusion criteria were seated in a dimly lit, sound-attenuated room and electrodes were attached. After a 10-min adaptation period, participants were given the instructions for the emotional Go/Nogo task: they were told to press a key with the right index finger as rapidly and accurately as possible in response to Go trials (e.g., blue frame), and to withhold the response for Nogo trials (e.g., pink frame), irrespective of picture content. Also, participants were invited to avoid blinking during picture presentation and maintain fixation. Ten trials with neutral pictures (7 Go and 3 Nogo) served as practice before the task.

Electrophysiological data recording end processing

Using an Electro-Cap (Electrocap, Inc.) with tin electrodes, the EEG was continuously recorded from 19 scalp sites (Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, T3, T4, T5, T6, O1, O2), according to the International 10–20 system, with a linked-mastoid reference. To control for eye movements and eye blinks, both vertical and horizontal electro-oculograms (EOGs) were recorded, using bipolar montages. The electrode pairs were placed at the supra- and sub-orbit of the right eye and at the external canthi of the eyes, respectively. All electrode impedances were kept below 5 kΩ. Electrophysiological signals were amplified with Neuroscan Synamps (El Paso, TX, USA), bandpass filtered (0.05–40 Hz), digitized at 250 Hz (16 bit AD converter, accuracy 0.033 μV/LSB) and stored on to a Pentium IV computer.

The EEG was corrected for blink artifacts using ICA as implemented in EEGlab (Delorme & Makeig, 2004), and further processing was run in Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). The EEG signal was epoched in the -1500-1500 ms interval around stimulus presentation, in order to prevent boundary effects, and only correct trials for both Go and Nogo were included. Each epoch was baseline-corrected by subtraction of the mean pre-stimulus voltage between -252 and -52 ms, and then segments containing residual artifacts exceeding 100 μV (peak-to-peak) in the selected recording channels were excluded.

To ensure that the employed task elicited the classic Go/Nogo complex, ERPs were calculated by averaging correct Go and Nogo trials in the time domain, separately for each participant and experimental condition. Grand-averages for the two groups across conditions were computed to identify the main ERPs components. As depicted

in Figure 3.2, the task was effective in eliciting larger N2 and P3 amplitudes in response to Nogo compared to Go trials, at frontocentral midline sites. Of note, complementary analyses confirmed that this effect reached statistical significance for both components (all *p*s < .001), ensuring the reliability of the Go/Nogo manipulation.

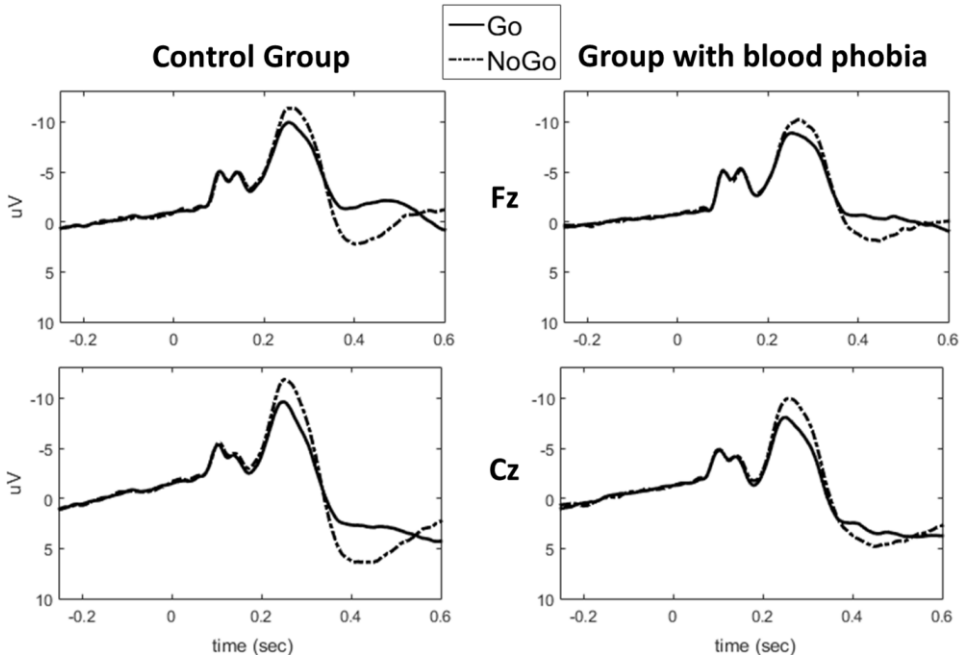

Figure 3.2 The Go/Nogo complex: grand-averages across emotional conditions of ERPs to Go and Nogo trials in the control group and in the group with blood phobia. The classic increase in N2 and P3 components to Nogo compared to Go trials emerges at frontal and central scalp sites in both groups.

With respect to the time-frequency analysis, Morlet wavelet transformation on individual trials was applied for each 1 Hz frequency bin between 1 and 30 Hz, using a mother wavelet at 1 Hz with 2 seconds time-resolution (as calculated by the Full Width at Half Maximum; FWHM). Time-frequency decompositions were then averaged for each subject and condition. The event-related synchronization/desynchronization (ERS/D) was computed as the proportion of change relative to the baseline (-252 to -52 ms) in each frequency bin at each time point. First, to verify the Go/Nogo effect on delta and theta bands reported in previous literature (Barry, 2009; Harper et al., 2014),

ERS/D grand-averages for the Go condition were subtracted from grand-averages for the Nogo condition, collapsing the emotional categories (Figure 3.3; *top*). Based on the grand-average, effects on delta and theta bands were analyzed at the discrete frequencies and at the scalp sites where the Go/Nogo effect appeared maximal (Figure 3.3; *bottom*).

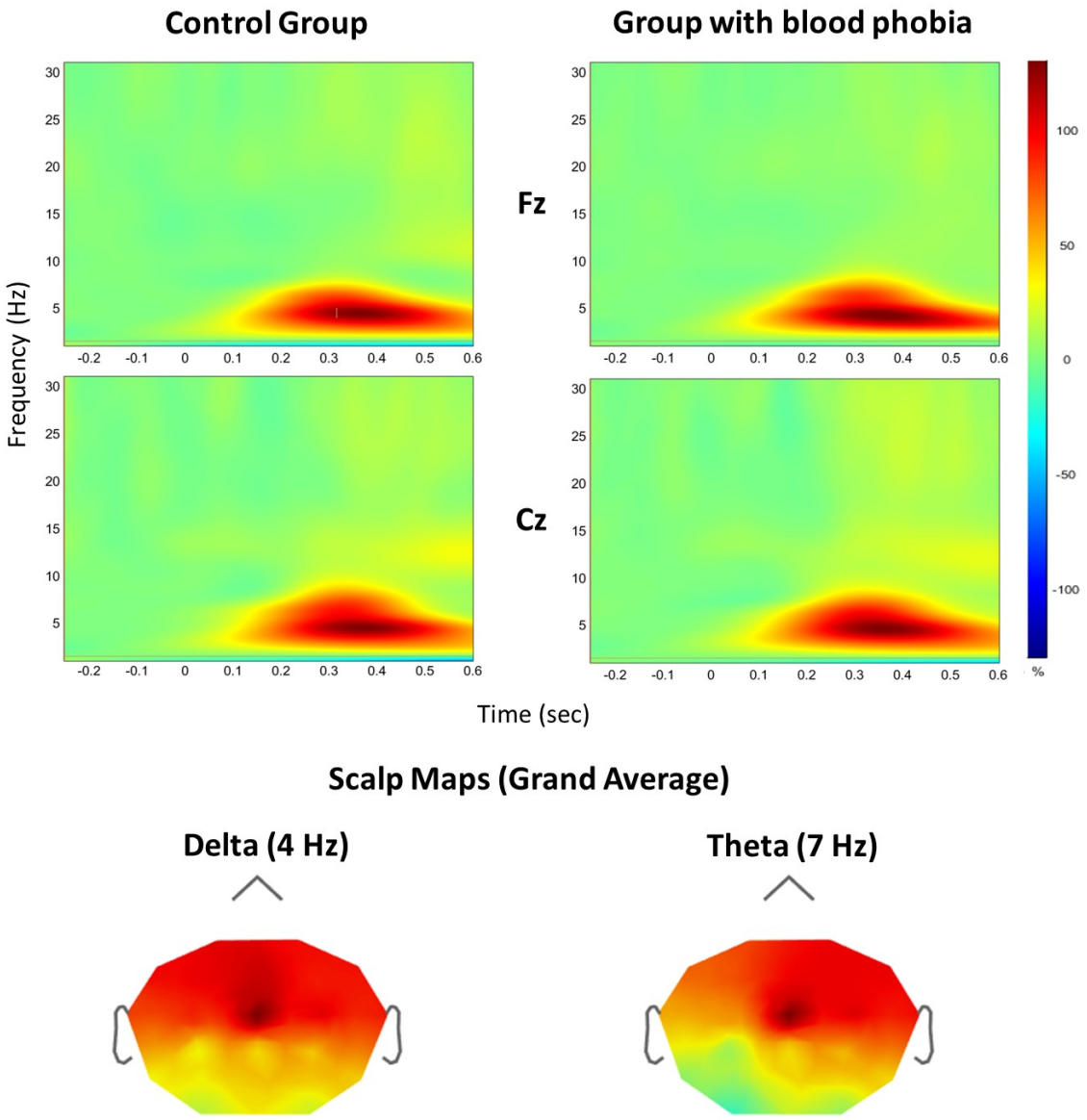

Figure 3.3 Time-frequency decomposition: grand-average ERS/ERD across emotional conditions to Go and Nogo trials (*top*) in the control group and in the group with blood phobia. Delta (4 Hz) and theta (7 Hz) power increased to Nogo compared to Go trials at frontocentral scalp sites (*bottom*).

Then, power change in time were plotted for Go and Nogo trials in each emotional condition for delta (4 Hz) and theta (7 Hz) at Fz and Cz (see Figure 3.4), in order to identify the time-windows of interest for subsequent analyses.

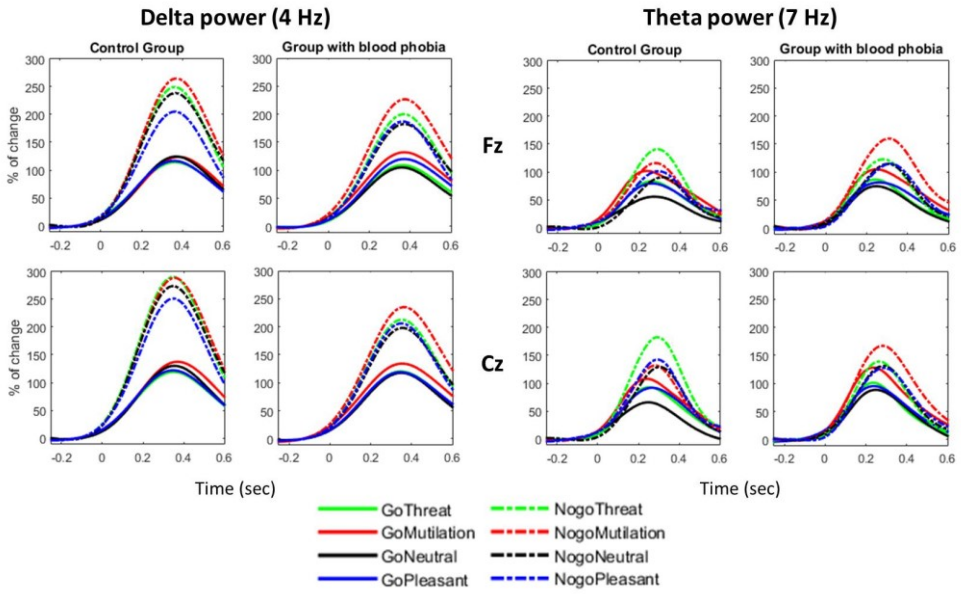

Figure 3.4 ERS/ERD for delta (4 Hz) and theta (7 Hz) power: percentage of change in time at mid-frontal (Fz) and mid-central (Cz) sites.

Based on visual inspection, response in the delta band was computed as the average ERS/D between 200 and 500ms, whereas theta band synchronization was averaged between 200 and 400 ms. As far as frontal alpha is concerned, the mid-band frequency (10 Hz) was chosen for further analysis, averaging the ERS between 100 and 300 ms (Figure 3.5).

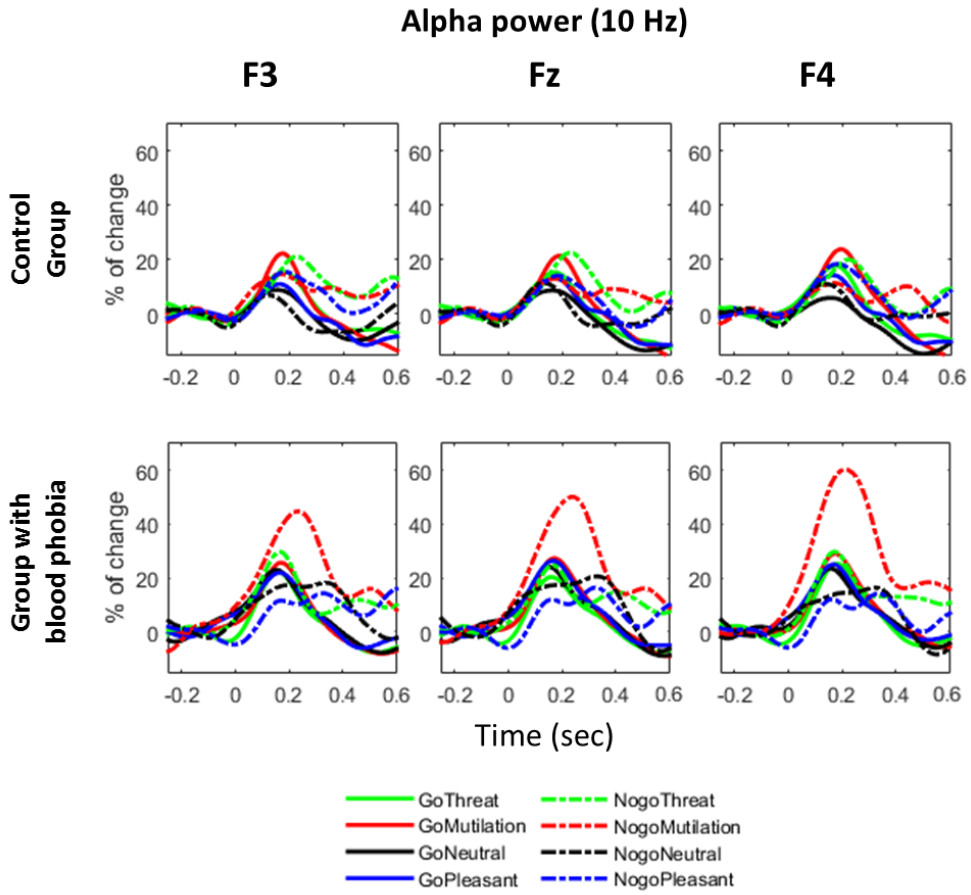

Figure 3.5 ERS/ERD for alpha (10 Hz) power: percentage of change in time at left (F3), midline (Fz) and right (F4) frontal sites.

Statistical analysis

Behavioral data

Accuracy in Go trials (i.e., percent of correct button presses) showed a ceiling effect with almost no variability among subjects. Considering all the four emotional conditions, the median accuracy in Go trials was 100%, with a minimum value of 95%. Thus, we did not perform further analyses on these scores, which clearly indicate that subjects were paying enough attention to the task. On the other hand, Nogo accuracy scores (percent of correct withholding of the response) were squared transformed prior to analysis, in order to have them normally distributed. Normality was tested

using a Kolmogorov-Smirnov test, for both squared transformed Nogo accuracy and reaction times (RTs).

Separate mixed analyses of variance (ANOVAs) on RTs in Go trials and accuracy in Nogo trials included Group (control group, group with blood phobia) as a between-subjects factor, and Category (threat, mutilation, neutral, and pleasant) as a within-subjects factor.

EEG data

To analyze modulation of frontocentral midline theta and delta, mixed ANOVAs with Group as a between-subjects factor, and Trial Type (Go, Nogo), Category and Area (frontal, central) as within-subjects factors were run separately for delta and theta bands at midline sites (Fz and Cz).

With respect to the lateralized modulation of frontal alpha band, mixed ANOVA with Group as a between-subjects factor, Trial Type, Category and Laterality (left, midline, right) as within-subjects factors was conducted at frontal sites (F3, Fz and F4), as reported in previous studies (e.g., Wacker, Chavanon, & Stemmler, 2010).

The corrected p-values for effects involving within-subjects variables with more than two levels are reported together with the Greenhouse-Geisser epsilon (ε) and the uncorrected degrees of freedom. Significant main effects and interactions ($p < .05$) were followed by Tukey HSD post hoc tests. Partial eta-squared (η_p^2) was reported as a measure of the effect size. The η_p^2 values considered to represent small, medium, and large effects are .01, .06, and .14, respectively (Cohen, 1988).

3.4.4 Results

Reaction times and accuracy

The ANOVA on RTs showed a Group main effect, $F_{(1, 38)} = 5.1$, $p = .03$, $\eta_p^2 = 0.12$, which indicated that individuals with blood phobia were overall slower to respond to Go trials compared to controls. An effect of Category also emerged, $F_{(3, 114)} = 33.9$, $p < .001$, $\varepsilon = .81$, $\eta_p^2 = 0.47$, revealing that mutilation pictures elicited slower responses compared to all the other picture contents (all *p*s < .01), and that participants responded slower to pleasant compared to threatening and neutral pictures (all *p*s < .001).

ANOVAs on Nogo accuracy scores revealed a main effect of Category, $F_{(3, 114)} = 12.0$, $p < .001$, $\varepsilon = .86$, $\eta_p^2 = 0.24$. Post-hoc comparisons revealed that accuracy was lower for mutilations compared to all the other picture contents ($p < .01$).

All other main effects or interactions did not reach statistical significance for either RTs or accuracy (all *p*s > .34). Descriptive statistics are summarized in Table 3.1.

Table 3.1 Behavioral performance: Mean (SD) Go reaction times and Nogo accuracy at the emotional Go/Nogo task for the group with blood phobia and the control group.

	Reaction Times (ms)			
	Threat	Mutilations	Neutral	Pleasant
Control group	352.7 (31.7)	369.3 (34.8)	356.3 (28.9)	362.4 (32.4)
Group with blood phobia	375.4 (35.2)	396.6 (39.9)	376.3 (36.2)	387.6 (34.6)
	Nogo Accuracy (%)			
	Threat	Mutilations	Neutral	Pleasant
Control group	92.5 (6.1)	87.1 (7.4)	90.8 (8.2)	90.2 (70)
Group with blood phobia	92.1 (4.5)	85.1 (7.8)	92.2 (5.6)	90.6 (5.9)

Note. Data are M (SD)

Delta (4 Hz)

A main effect for Trial Type emerged, $F_{(1, 38)} = 50.0$, $p < .001$, $\varepsilon = .99$, $\eta_p^2 = 0.57$, indicating that delta synchronization was greater for Nogo compared to Go trials. The main effect of Area was also significant, $F_{(1, 38)} = 4.8$, $p = .03$, $\varepsilon = .99$, $\eta_p^2 = 0.11$, indicating that delta ERS was more pronounced at Cz compared to Fz. Finally, a significant main effect of Category was obtained, $F_{(3, 114)} = 2.8$, $p = .04$, $\varepsilon = .98$, $\eta_p^2 = 0.07$. Specifically, mutilation pictures elicited greater synchronization compared to pleasant ones ($p = .04$). None of the interactions were statistically significant (all ps > .07).

Theta (7 Hz)

The Trial Type main effect, $F_{(1, 38)} = 16.6$, $p < .001$, $\varepsilon = .99$, $\eta_p^2 = 0.30$, indicated that theta synchronization was greater for Nogo compared to Go trials. Theta synchronization was also greater at Cz compared to Fz, as revealed by a main effect of Area, $F_{(1, 38)} = 4.9$, $p = .03$, $\varepsilon = .99$, $\eta_p^2 = 0.11$. Finally, a main effect of Category emerged, $F_{(3, 114)} = 7.3$, $p < .001$, $\varepsilon = .96$, $\eta_p^2 = 0.16$, further characterized by a Group × Category interaction, $F_{(3, 114)} = 3.1$, $p = .03$, $\varepsilon = .96$, $\eta_p^2 = 0.08$. Post-hoc comparisons showed that controls had more theta synchronization for threatening compared to neutral pictures ($p < .01$), whereas in the group with blood phobia mutilation pictures elicited significantly greater synchronization compared to neutral and pleasant pictures (ps < .05), and marginally significantly compared to threatening pictures ($p = .07$). None of the other interactions resulted to be statistically significant (all ps > .08).

Alpha (10 Hz)

For the alpha band, a main effect of Category emerged, $F_{(3, 114)} = 6.3$, $p < .001$, $\varepsilon = .93$, $\eta_p^2 = 0.14$, as well as a Group × Category interaction, $F_{(3, 114)} = 2.9$, $p = .04$, $\varepsilon = .93$, $\eta_p^2 = 0.07$, and a Group × Trial Type × Category interaction, $F_{(3, 114)} = 5.0$, $p < .01$, $\varepsilon = .91$, $\eta_p^2 = 0.12$. Post-hoc tests revealed that frontal alpha synchronization in individuals with blood phobia, but not controls, was greater for Nogo-mutilation compared to Go-mutilation trials, and compared to threat, neutral and pleasant Nogo trials (all *p*s < .01). The Group × Trial Type × Category × Laterality interaction also resulted to be significant, $F_{(6, 228)} = 3.0$, $p = .03$, $\varepsilon = .61$, $\eta_p^2 = 0.07$. In order to reduce the number of comparisons, the interaction with laterality was explored focusing on the Go/Nogo response to mutilation pictures. Thus, an ANOVA with Group as a between factor and Trial Type and Laterality as within factors was conducted on alpha responses to phobia-related stimuli. A significant Group × Trial Type interaction, $F_{(1, 38)} = 10.9$, $p < .01$, $\varepsilon = .65$, $\eta_p^2 = 0.22$, further characterized by a Group × Trial Type × Laterality interaction, $F_{(2, 76)} = 5.0$, $p = .02$, $\varepsilon = .65$, $\eta_p^2 = 0.12$, emerged. For mutilation contents, post-hoc comparisons confirmed that alpha synchronization was greater for Nogo compared to Go trials in the group with blood phobia, but not in controls, at each laterality (all *p*s < .001). Most importantly, in individuals with blood phobia, alpha synchronization resulted to be significantly greater at the frontal right site (F4) compared to the left site (F3) ($p < .001$), and marginally significantly to Fz ($p = .05$) (Figure 3.6).

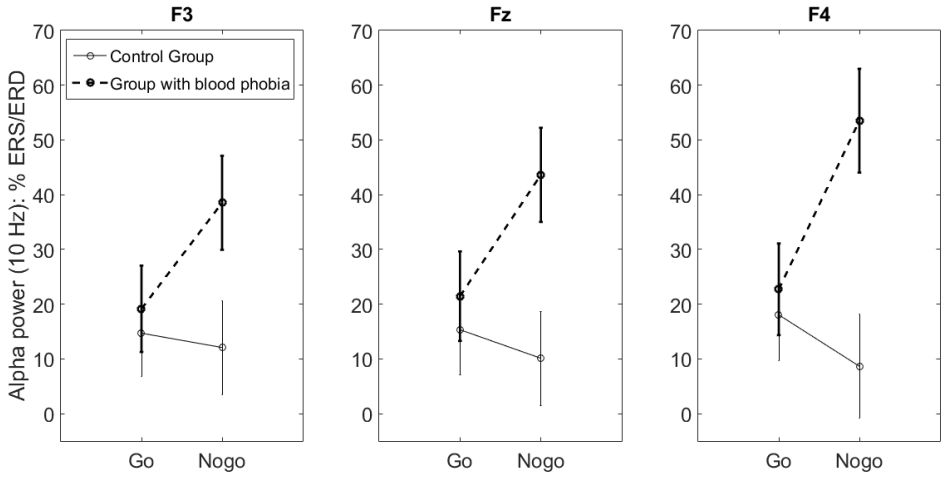

Figure 3.6 ERS/ERD in alpha power for mutilation pictures: Individuals with blood phobia showed a pronounced increase in alpha power over frontal sites to Nogo trials, which was greater at right (F4) compared to left (F3). The error bars represent the standard error of the mean.

3.4.5 Discussion

The aim of the present study was to test whether exposure to mutilation pictures was associated with a reduction in action disposition in individuals with blood phobia compared to controls. Accordingly, the motivational and attentional pattern of reduced action readiness elicited by mutilation pictures was expected to be exacerbated in individuals with blood phobia compared to controls. Therefore, at the behavioral level, RTs were hypothesized to increase in individuals with blood phobia in response to phobia-related stimuli compared to controls. At the neural level, decreased event-related delta and theta power at frontal and central midline sites, indices of less effortful response inhibition, were expected in response to phobia-related Nogo trials in individuals with blood phobia compared to controls. Moreover, increased right relative to left frontal alpha power, as an index of reduced effort in response inhibition and less pronounced withdrawal tendency, was expected in

response to phobia-related Nogo trials in individuals with blood phobia compared to controls. To our knowledge, this was the first study to use a time-frequency approach in order to investigate action disposition in the contest of an emotional Go/Nogo task.

At the behavioral level, mutilation pictures produced a parallel increase in RTs and decreased accuracy in response to Nogo trials both in healthy individuals and in those with blood phobia. Previous studies reported that, irrespective of fear levels, pictures of blood and mutilations command stronger attentional engagement compared with other emotional, high-arousing contents (Buodo et al., 2006, 2002; Sarlo, Buodo, et al., 2005). Therefore, it is likely that mutilation pictures drove participants' attention away from the Go/Nogo specific cue (i.e., colored frame), thus slowing down their responses and reducing correct encoding of the Nogo signal. Importantly, individuals with blood phobia showed reduced readiness to respond to Go trials compared to controls, as indexed by slower RTs, but this effect was not specific for mutilation pictures as it emerged across emotional categories. Previous studies suggested a mechanism of generalized hypervigilance in blood phobia in the contest of passive viewing of emotional pictures, irrespective of emotional category (Buodo, Peyk, Junghöfer, Palomba, & Rockstroh, 2007). In anxiety disorders, hypervigilance consists in the continuous scanning of the environment for potential threat, characterized by a broadening of attention and resources depletion for the ongoing task (Eysenck, 2013). In individuals with blood phobia, heightened scanning for phobia-related contents might have narrowed attentional resources on the task, thus resulting in a generalized increase in RTs.

At the neural level, modulation of delta and theta band synchronization was not consistent with the expected facilitation of the inhibition process for mutilation pictures in the phobic group compared to controls. On the one hand, both EEG bands showed greater synchronization to Nogo compared to Go trials, confirming their role in cognitive processes which subtend behavioral inhibition, in line with previous reports (Harper et al., 2014). On the other hand, this effect was not modulated as a function of group or emotion. Nonetheless, irrespective of Go/Nogo trial type, theta synchronization in controls was greater for threatening compared to neutral pictures; in contrast, it was greater for mutilation than threatening, neutral and pleasant stimuli in individuals with blood phobia. A large literature suggests that, other than reflecting conflict monitoring prior to response inhibition (Harper et al., 2014), theta synchronization in response to emotional stimuli is an index of perceived motivational salience, that is the significance of a stimulus to the individual (Güntekin & Başar, 2014; Knyazev et al., 2009; Knyazev, 2007). In particular, frontal theta is generated in the anterior cingulate cortex, which is crucial in the evaluation of stimulus salience in order to drive behavior (Bush et al., 2000; Pizzagalli, Oakes, et al., 2003). Accordingly, controls showed higher theta for threatening compared to neutral stimuli, replicating previous literature on the fast detection of threatening stimuli in healthy individuals (for a review see Carretié, Albert, López-Martín, & Tapia, 2009). In contrast, individuals with blood phobia showed a heightened perceived salience for mutilation stimuli, coherently with previous studies attesting a bias toward phobia-related pictures (Buodo et al., 2010; Sarlo, Buodo, Devigili, Munafò, & Palomba, 2011).

Results on lateralized frontal alpha were in line with predictions, with individuals with blood phobia, but not controls, showing an increase in right relative to left frontal alpha power. Alpha synchronization is negatively correlated with neural activation in the underlying structures (Scheeringa et al., 2011); therefore, this results indicated that right prefrontal cortex was hypo-activated in individuals with blood phobia in response to Nogo-mutilation trials. A vast literature exists on the specific role of the right prefrontal lobe in the inhibition of motor responses (for a recent review see Depue, Orr, Smolker, Naaz, & Banich, 2016). On this basis, it could be argued that withholding the response to mutilation compared to other trials required less inhibitory effort in the phobic group. This argumentation would support reduced action disposition in response to feared stimuli in blood phobia, as hypothesized. Nonetheless, other evidence argues against this interpretation; for instance the difference in alpha synchronization from Go to Nogo trials did not emerge in healthy controls, or in the phobic group in the other emotional conditions. This finding is incongruent with a general effect of motor inhibition on frontal alpha lateralization. Moreover, alpha power dramatically increased over all frontal sites for Nogo-mutilation trials, suggesting a pervasive, albeit more right-lateralized, inactivation of the prefrontal cortex in this specific condition in individuals with blood phobia.

The role of the prefrontal cortex in processing of emotional stimuli is coherent with the observed pattern of frontal alpha synchronization. In particular, right frontal activation (i.e., reduced alpha at right sites) has been positively associated with processing of unpleasant stimuli, withdrawal motivation and anxiety, whereas left frontal activation has been related to responses to pleasant stimuli and motivation to

approach (Davidson et al., 2000; Davidson, 2004; Harmon-Jones et al., 2010). While in the Go condition individuals with blood phobia could avoid mutilation stimuli by pressing the button (i.e., the picture disappeared at the response), this was not possible during Nogo trials, in which the stimulus lasted for the entire trial duration (i.e., 600 ms). Thus, prefrontal inactivation subtended by alpha power synchronization can be interpreted as a mechanism of passive avoidance. Accordingly, the prevalent inactivation of the right side is congruent with specific needs of diminishing anxiety and negative emotions, which are specifically subtended by the right prefrontal lobe (Shankman & Klein, 2003).

Intriguingly, the present findings are in line with previous studies which used functional magnetic resonance, reporting de-activation of ventral and dorsal parts of the prefrontal cortex in individuals with blood phobia compared to controls during passive viewing of phobia-related pictures (Hermann et al., 2007). The combination of heightened emotional salience indexed by theta synchronization and the mechanism of avoidance driven by the increased alpha in the right prefrontal cortex represents an interesting neurophysiological correlate of the conflicting motivational response to phobia-related stimuli in blood phobia. Several studies showed that individuals with blood phobia are characterized by opposite tendencies to attend and avoid the feared stimulus, as revealed both by neurophysiological (Buodo et al., 2006, 2010; Sarlo et al., 2011) and peripheral indices (Buodo et al., 2002; Engel, 1978; Graham et al., 1961; Hamm et al., 1997; Öst, 1992; Sarlo et al., 2008, 2010, 2002). Therefore, the present results argue in favor of a compresence of conflicting motivational dispositions in blood phobia, more than supporting a clear-cut reduction of action disposition, as

initially hypothesized. However, the generalized slowing down of reaction times in the phobic group might have obscured the presence of a subtle mutilation-specific reduction in action disposition. Moreover, high attentional engagement on mutilation pictures in both groups with and without blood phobia, reflected in slower reaction times for mutilation compared to other picture categories, is likely to have contributed to the reduction of group differences to the task. Future studies ought to further investigate these aspects in tasks which directly imply behavioral avoidance from the feared stimulus, as it has been previously done for other specific phobias (Rinck & Becker, 2007).

3.4.6 Conclusions

Through the novel use of time-frequency decomposition in an emotional Go/Nogo task, the present study contributed to clarify the neurophysiological correlates of the co-occurring tendencies to attend and avoid the feared stimulus in blood phobia, which represents an important clinical feature of this disorder. Moreover, studying the event-related modulation of different EEG bands helped to clarify their functional meaning in the contest of an emotional Go/Nogo task, which represents another innovative contribution to the pertaining literature. These results align with previous literature showing that blood phobia, contrary to other phobias, is not characterized by a straightforward withdrawal tendency, instead showing a co-occurrence of conflicting motivation to attend and avoid the feared stimulus.

3.5 STUDY 2: Mood-related emotional processing in dysphoria as reflected by frontal theta activity[2]

3.5.1 Abstract

It is unclear whether depressed mood is associated with decreased appetitive or increased withdrawal motivation toward pleasant and unpleasant stimuli, respectively. Several studies have examined the neural correlates of mood-related emotional processing in depression, showing a reduction of activity in the rostral anterior cingulate cortex (rACC) in response to pleasant relative to unpleasant stimuli in depressed individuals, and the opposite pattern in healthy controls. The present study aimed at examining whether frontal theta activity – an electrophysiological measure of rACC activity – could be a reliable EEG correlate of mood-related emotional processing in individuals with dysphoria. In particular, since theta rhythm generated by rACC has been interpreted as an index of motivational salience, we were interested in studying the influence of depressed mood on frontal theta associated with pleasant and unpleasant emotions. To this end, the EEG was recorded in 27 individuals with dysphoria and 29 individuals without dysphoria during an emotional imagery task, including pleasant, neutral and unpleasant scripts. Self-reported valence, arousal and vividness, and changes in frontal theta activity were measured during the task. Frontal theta activity was more reduced from baseline to the imagery of pleasant relative to unpleasant scripts in the group with dysphoria, whereas the opposite pattern was

[2] Results from this study have been published in: Messerotti Benvenuti, S., Mennella, R., Buodo, G., & Palomba, D. (2016). Frontal Theta Activity as an EEG Correlate of Mood-Related Emotional Processing in Dysphoria. *Journal of Psychopathology and Behavioral Assessment*, 1-12.

noted in the group without dysphoria. In addition, more severe depressive symptoms were correlated with greater reduction in frontal theta activity in response to pleasant, but not neutral and unpleasant, scripts. No differences between groups in subjective ratings were noted. Consistent with the key role of rACC activity in depression-related emotional dysregulation, these findings suggest that frontal theta activity may be an EEG correlate of mood-related emotional processing in dysphoria. The current study also suggests that dysphoria is more likely to be associated with abnormal processing of pleasant rather than unpleasant stimuli.

Keywords: Depression; Dysphoria; EEG; Emotion; Frontal theta activity; Mood-related emotional processing

3.5.2 Introduction

The identification of electrophysiological measures of mood-related emotional processing in dysphoria has important implications for improving our understanding of mechanisms that underlie abnormal affective and motivational tendencies characterizing depression. Several lines of evidence have shown that depression is characterized by mood-related biases which facilitate the processing of negatively-valenced information (e.g., Goeleven, De Raedt, Baert, & Koster, 2006; Jermann, Van Der Linden, Laurençon, & Schmitt, 2009; Sigmon & Nelson-Gray, 1992; for a review, see Gotlib & Joormann, 2010). By facilitating the processing of unpleasant stimuli, mood-related biases have been proposed to play a critical role in the etiology, maintenance and recurrence of depression (Clark & Beck, 2010; Kilford et al., 2015; Teasdale, 1988).

Nonetheless, there is growing evidence that depressed patients are characterized by reduced processing of pleasant relative to unpleasant verbal and pictorial stimuli and/or relative to control participants (e.g., Buodo, Mento, Sarlo, & Palomba, 2015; Nandrino, Dodin, Martin, & Henniaux, 2004; Shestyuk, Deldin, Brand, & Deveney, 2005). Based on such evidence, it has been hypothesized that in healthy individuals attention may be oriented by default toward pleasant stimuli, whereas attention to threat may take the form of a sustained background process of possible sources of danger in the environment (Frewen et al., 2008; Winer & Salem, 2016). When a significant source of danger is identified, healthy individuals are able to rapidly set their responding to danger and to interrupt the ongoing orientation towards pleasant stimuli. In this perspective, an impaired attentional orientation toward

pleasant stimuli may reflect a reduced appetitive motivation in sub-clinical and clinical depression, as evidenced by quantitative analyses of dot-probe studies (Frewen et al., 2008). These findings also lend support to the hypothesis that the inability to use positive and rewarding stimuli to regulate negative mood is one of the key mechanisms that underlie emotion dysregulation in depression (Brockmeyer, Kulessa, Hautzinger, Bents, & Backenstrass, 2015; Capecelatro, Sacchet, Hitchcock, Miller, & Britton, 2013; Gotlib & Joormann, 2010), being potentially related to core symptoms, such as loss of pleasure and anhedonia.

In addition to attentional biases, a substantial number of studies have reported mood-related biases in both emotional responding and regulation (e.g., Cook, Davis, Hawk, Spence, & Gautier, 1992; Dunn et al., 2004; Sloan et al., 2001). Such findings have been interpreted according to the negative potentiation hypothesis and the positive attenuation hypothesis. The negative potentiation hypothesis postulates that the negative mood that characterizes depression contributes to potentiate emotional responding to unpleasant stimuli. This hypothesis is consistent with studies showing that depressed individuals are characterized by greater electrodermal activity or startle reflex amplitude in response to unpleasant stimuli compared to healthy controls (e.g., Cook et al., 1992; Sigmon & Nelson-Gray, 1992). Alternatively, the positive attenuation hypothesis postulates that individuals with depression show reduced emotional reactivity to pleasant stimuli relative to neutral stimuli and/or healthy controls. Specifically, there is evidence that subjective evaluation and facial reactivity in response to pleasant, but not to unpleasant or neutral, stimuli is reduced in depressed individuals compared to healthy controls (e.g., Dunn et al., 2004; Sloan et al., 2001).

More recently, research has focused on examining the neural correlates of mood-related emotional processing in depression. Several studies investigated patterns of anterior cingulate cortex (ACC) activation in depressed patients during a variety of affective tasks, such as the emotional Stroop task and the emotional Go/Nogo task (for a review, see Pizzagalli, 2011). Specifically, a greater activation of the rostral ACC (rACC) has been consistently found in response to unpleasant stimuli in depressed patients compared to healthy controls (e.g., Dichter, Felder, & Smoski, 2009; Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Eugène, Joormann, Cooney, Atlas, & Gotlib, 2010; Mitterschiffthaler et al., 2008). Converging evidence has also reported that depressed patients show attenuated rACC activation in response to pleasant stimuli compared to healthy controls (e.g., Elliott et al., 2002; Eugène et al., 2010). Accordingly, rACC activity has been implicated as a mediator of the mood-related processing biases typically observed in depressed patients (Eugène et al., 2010).

As reported in paragraph 2.4.2, studies using high-resolution EEG and magnetoencephalographic (MEG) source modeling as well as intracranial recordings provided evidence that the human ACC is involved in the generation of frontal theta activity (e.g., Asada et al., 1999; Nishida et al., 2004). More specifically, Pizzagalli et al. (2003) have reported that frontal theta activity is associated with cerebral metabolism in rACC by means of combined positron emission tomography (PET) and EEG measurements. Contrary to the theta activity with widespread scalp distribution, that has been linked to decreased alertness and drowsy states (Schacter, 1977), theta activity with frontal midline distribution has been observed during mental effort and focused attention (e.g., Başar-Eroglu et al., 1992; Gevins et al., 1997). Consistent with

the role of rACC as a key component of the emotion circuit (Bush et al., 2000; Critchley, 2003; Devinsky et al., 1995), frontal theta activity has been also found to be implicated in emotional processing (Sammler et al., 2007) and in emotional regulation (Ertl, Hildebrandt, Ourina, Leicht, & Mulert, 2013). Specifically, Sammler et al. (2007) found a positive correlation between frontal theta activity and pleasantness of music excerpts in healthy participants: the lower the frontal theta activity, the lower the self-reported pleasantness during the listening of music excerpts. Consistent with these findings, decreases in frontal theta activity have been related to reduced processing of stimulus' motivational salience, decreased individual emotional sensitivity and emotional involvement (Knyazev et al., 2009). In particular, Knyazev et al. (2009) reported that reduced low frequency synchronization in response to emotional (angry, happy) vs. neutral faces was associated with reduced emotional sensitivity and emotional involvement during an explicit emotion recognition task.

The findings that rACC activity is implicated in depression-related emotional processing, that frontal theta activity originates from rACC, and that decreases in frontal theta activity are associated with reduced emotional involvement in healthy individuals and with anhedonia in depressed patients, raise the pertinent question of whether frontal theta activity may be an EEG correlate of mood-related emotional processing in depression. However, to our knowledge, no studies have addressed this critical issue so far.

Another unresolved issue is whether mood-related processing biases are only apparent in individuals with clinically significant depression (e.g., Elliott et al., 2002; Eugène et al., 2010), or can be reliably observed also in individuals with dysphoria, that

is, individuals who report at least two or more current depressive symptoms, at least two weeks in duration, but are not formally diagnosed with major depression, minor depression or dysthymia (Judd, Akiskal, & Paulus, 1997; Judd, Rapaport, Paulus, & Brown, 1994). Indeed, although there is evidence indicating that mood-related processing biases also characterize individuals with sub-clinical depressive symptoms at the behavioral level (Joormann, 2004; Peckham, McHugh, & Otto, 2010), it is still unclear whether changes in frontal theta activity may reflect mood-related processing biases in dysphoria at the neural level. This is surprising because mood-related emotional processing bias may serve to create the persistent negative mood and/or anhedonia that, in turn, may put a dysphoric individual at risk for a full-blown depressive episode (Beevers & Carver, 2003). This is even more surprising if one considers that individuals with dysphoria are 4.4 times more likely to develop a first-onset major depression compared to healthy controls (Horwath, 1992). Therefore, it is important to examine whether a mood-related emotional processing bias may be a psychophysiological marker associated with dysphoria, rather than being a mere correlate of clinical depression only (Pizzagalli, 2011).

The present study aimed at examining whether frontal theta activity may be an EEG correlate of mood-related emotional processing in dysphoria. To this end, we examined frontal theta activity in individuals with and without dysphoria during an emotional imagery task, including pleasant, neutral and unpleasant conditions. The rationale for the use of emotional imagery paradigm is that it activates brain regions involved in the processing of emotional stimuli, it acts as an emotional amplifier, and it has been widely used with clinical populations (Holmes & Mathews, 2010). Moreover,

it is an active task, in which individuals are requested to actively imagine emotional scenes, thus being perfectly suited to stimulate motivational tendencies. Since decreases in frontal theta activity originating from rACC have been associated with reduced processing of stimulus' motivational salience and reduced individual emotional involvement (Knyazev et al., 2009), in case mood-related emotional processing in dysphoria was subtended by reduced approach tendencies and processing of pleasant stimuli (*positive attenuation hypothesis*), it was predicted that dysphoric individuals would show a greater decrease in frontal theta activity from baseline to the imagery of pleasant relative to unpleasant stimuli compared to the group without dysphoria. On the contrary, if predictions from the *negative potentiation hypothesis* are valid, an increase in frontal theta during the imagery of unpleasant relative to pleasant stimuli was expected, compared to the group without dysphoria.

3.5.3 Methods

Participants

In order to identify potential participants with dysphoria, 224 undergraduate students completed an online version of the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996; Italian version by Ghisi, Flebus, Montano, & Sanavio, 2006). The BDI-II is a valid and reliable self-report questionnaire that evaluates the severity of depressive symptoms in the past two weeks and is composed of 21 items. Responses

are given on a four-point (0–3) Likert scale and scores range from 0 to 63, with higher scores indicating more severe depressive symptoms.

Undergraduates who scored equal to or greater than 12 on the online version of the BDI-II (*N* = 59) were preliminarily selected, given that a score of 12 has been reported as the optimal cut-off score to discriminate individuals with and without clinically significant depressive symptoms in the Italian population (Ghisi et al., 2006). In order to confirm the presence of depressive symptoms and to exclude individuals with major depression, minor depression or dysthymia, each participant scoring equal to or greater than 12 on the online version of BDI-II was administered a paper-and-pencil version of the BDI-II and the mood episode module (module A) of the Structured Clinical Interview for the DSM-IV Axis I (SCID-I; First, Spitzer, Gibbon, & Williams, 1997; Italian version by Mazzi, Morosini, De Girolamo, Lussetti, & Guaraldi, 2000) approximately one week after the initial screening. Twenty-seven participants [25 females and 2 males; age, mean (M) = 21.0, standard deviation (SD) = 1.6; BDI-II score, M = 16.3, SD = 4.4], who scored equal to or greater than 12 on both versions of the BDI-II and had at least two current depressive symptoms, at least two weeks in duration, without meeting the diagnostic criteria for major depression, minor depression or dysthymia, were assigned to the group with dysphoria. According to previous literature (see Judd et al., 1997, 1994), individuals with dysphoria were not required to endorse at least one of the key symptoms of depression (i.e., depressed mood or anhedonia). However, the majority of dysphoric patients (*N* = 21, 78%) included in the current study endorsed depressed mood and/or anhedonia. In

addition, dysphoric individuals had no psychiatric comorbidities or lifetime depressive episodes.

In order to ensure separation between groups with and without dysphoria, we selected 29 individuals without dysphoria [25 females and 4 males; age, M = 22.3, SD = 1.9; BDI-II score, M = 3.0, SD = 2.9] with both the online and the paper-and-pencil BDI-II scores ≤ 8 (i.e., the 53 percentile). The group without dysphoria had significantly lower BDI-II scores than the group with dysphoria, $F_{(1,54)} = 178.1$, $p < .001$, $\eta_p^2 = .77$.

Participants who scored between 9 and 11 either on the online or the paper-and-pencil BDI-II, or had at least one depressive symptom as evaluated by the SCID-I interview were excluded from the present study. Participants with and without dysphoria were simultaneously recruited during the same study period. All the participants were medically healthy and free of medication.

The present study was carried out with the adequate understanding and written consent of the participants, in accordance with the Declaration of Helsinki, and was approved by the local ethics committee.

Procedure

Upon arrival at the laboratory, participants received general information about the experiment, and read and signed an informed consent form. After completing the paper-and-pencil version of the BDI-II, the participants were administered the SCID-I. Then, individuals were seated on a comfortable chair in front of a computer screen, and sensors were attached. After electrode placement, each participant rested for five minutes and then performed the emotional imagery task. The EEG was continuously

recorded during the imagery task. Participants were instructed to stay still, and to keep their gaze on a central fixation cross during the EEG recordings in order to minimize eye movements.

Emotional imagery task

Six narratives, selected from the Affective Norms of English Text (ANET; Bradley & Lang, 2007; see Appendix 2) based on standardized ratings of pleasure and arousal, were translated into Italian and categorized as pleasant (i.e., erotic scenes; narrative 4670: Pleasure, M = 8.15, SD = 1.28; Arousal, M = 8.01, SD = 1.40; narrative 4400: Pleasure, M = 8.28, SD = 1.22; Arousal, M = 7.91, SD = 1.50), neutral (i.e., grocery shopping and getting ready to go out; narrative 2540: Pleasure, M = 5.54, SD = 1.19; Arousal, M = 3.38, SD = 1.75; narrative 2580: Pleasure, M = 5.55, SD = 1.17; Arousal, M = 3.60, SD = 1.98), or unpleasant (i.e., a friend involved in a car accident and fear of being chased by a stranger; narrative 3310: Pleasure, M = 1.30, SD = 1.08; Arousal, M = 8.15, SD = 1.54; narrative 6800: Pleasure, M = 2.50, SD = 1.35; Arousal, M = 7.50, SD = 1.65).

Each imagery trial consisted of three minutes of baseline and two 90-s periods of imagery in the same emotional condition. Participants were told to listen carefully while the experimenter read the first script in the first emotional (e.g., unpleasant) condition. The experimenter read the script slowly (about 20 s), in order for the participants to fully understand the script. When the experimenter completed reading the script, the participants were instructed to press a button immediately before beginning the 90-s period of imagery. Participants were instructed to stop imagining

the first script after 90 s, to provide subjective ratings of valence, arousal and vividness (see below), and immediately perform a second 90-s period of active imagery in the same emotional (e.g., unpleasant) condition. Then, the same procedure (3-min baseline period and two 90-s imagery periods) was repeated for the other two emotional conditions (e.g., pleasant and neutral). The three emotional conditions were separated by five minutes, during which the participants were told to rest. The order of presentation of the three conditions and the two 90-s narratives within each emotional condition was counterbalanced across participants.

Self-report measures

After the imagery of each script, the participants were instructed to rate the subjective pleasantness and arousal experienced during the imagined scene using a computerized version of the 9-point Self-Assessment Manikin (SAM) scale, with higher scores reflecting greater pleasantness and arousal (Bradley & Lang, 1994). Participants were also instructed to indicate on a 9-point Likert scale how vividly they imagined each scene, with higher scores reflecting greater vividness.

EEG recording and data analysis

The EEG was recorded from 32 scalp positions using an elastic cap with tin electrodes (Electro-cap International, Inc.). The EEG sites were Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T3, C3, CZ, C4, T4, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz, O2 and A2 (right mastoid), all referenced online to A1 (left mastoid). To control for eye-movements and eye-blinks, both vertical and horizontal electro-oculograms (EOGs) were recorded using a bipolar montage. The electrodes pairs were

placed at the supra- and suborbit of the right eye and at the external canthi of the eyes, respectively. All electrode impedances were kept below 5 kΩ. The signal was amplified with Neuroscan Synamps (El Paso, TX, USA), bandpass filtered online at 0.1-70 Hz, digitized at 500 Hz (16 bit AD converter, accuracy 0.034 μV/bit), and stored on to a Pentium II computer. The EEG signal was re-referenced offline to a linked mastoids montage. A regression-based correction algorithm (Scan 4.1 software) was used to correct continuous EEG data for eyeblinks. The obtained signal was segmented in epochs of 1.024 s each and EEG chunks were automatically rejected if containing artifacts greater than ±70 μV in any channel. Then, each EEG segment was visually scored for residual artifacts. For each accepted epoch, a Hamming windowing was applied and chunks were then overlapped by 50% to minimize loss of data. A Fast Fourier Transform (FFT) method was used to derive estimates of spectral power (μV^2) in 1-Hz frequency bins for each electrode site. All spectral powers obtained were averaged, and power density values (μV^2/Hz) within the theta (4-8 Hz) band were calculated for each participant at each site.

As a first step, self-report measures (valence, arousal, and vividness), and power density values in the theta band obtained for the two-90-s imagery periods within the same emotional condition were averaged. Power density values in the theta band obtained during each 3-min baseline period were also averaged separately for each emotional condition. Changes in theta activity from baseline to imagery were calculated by subtracting the averaged values obtained during the 180-s baseline from those obtained during the two 90-s imagery periods for each emotional condition.

Mixed ANOVAs, with Group (with dysphoria, without dysphoria) as a between-subjects factor, and Category (pleasant, neutral, unpleasant) as within-subjects factor, were conducted on self-reported valence, arousal, and vividness.

A mixed ANOVA, with Group (with dysphoria, without dysphoria) as a between-subjects factor, and Category (pleasant, neutral, unpleasant), Area (frontal [F3, Fz, F4], frontocentral [FC3, FCz, FC4], central [C3, Cz, C4] and centroparietal [CP3, CPz, CP4]), and Laterality (left [F3, FC3, C3, CP3], midline [Fz, FCz, Cz, CPz], right [F4, FC4, C4, CP4]) as within-subjects factors, was conducted on changes in theta activity from baseline to imagery[3]. Significant main effects and interactions ($p < .05$) were followed by Fisher's LSD post-hoc tests. Partial eta-squared (η_p^2) and Cohen's d were calculated as measures of the effect size; the Cohen's d values considered to represent small, medium, and large effects are 0.20,0.50, and 0.80, respectively (Cohen, 1988).

3.5.4 Results

Self-report measures

For valence ratings, the significant main effect of Category, $F_{(2,108)} = 359.41$, $p < .001$, $\eta^2_p = .87$, showed that the pleasant condition was rated as more pleasant than the neutral ($p < .001$, Cohen's d = 1.55) and the unpleasant ($p < .001$, Cohen's d = 4.91). In turn, the unpleasant condition was rated as less pleasant than the neutral ($p < .001$,

[3] To control for the effects of the order of presentation of the scripts on changes in theta activity from baseline to imagery, two preliminary mixed ANOVAs were conducted including also Order as a between-subjects factor. Because we did not find any significant main effect of Order or any interaction involving Order and Category, Order was not included as a between-subjects factor in final analysis.

Cohen's d = 3.63). No significant main effect for Group or interaction between Group and Category were noted (all *p*s > .35).

Similarly, the ANOVA on arousal ratings revealed a significant main effect of Category, $F_{(2,108)} = 79.84$, $p < .001$, $\eta^2_p = .60$. Arousal was higher for pleasant ($p < .001$, Cohen's d = 1.74) and unpleasant ($p < .001$, Cohen's d = 1.90) than neutral conditions, whereas no significant difference in arousal between pleasant and unpleasant conditions was noted ($p = .65$). No significant main effect for Group or interaction between Group and Category emerged (all *p*s > .08).

With respect to vividness ratings, no significant main effect for Group or Category, or interaction between Group and Category was noted (all *p*s > .06). Descriptive statistics of self-report measures are reported in Table 3.2.

Table 3.2 Ratings of each self-report measure in the group without and with dysphoria.

Self-report measures	**Group without dysphoria (*N* = 29)**			**Group with dysphoria (*N* = 27)**		
	Pleasant	**Neutral**	**Unpleasant**	**Pleasant**	**Neutral**	**Unpleasant**
Valence	8.0 (1.0)	6.1 (0.8)	2.6 (0.9)	7.6 (1.3)	6.1 (1.2)	2.6 (1.0)
Arousal	6.4 (1.6)	3.2 (1.6)	6.4 (1.7)	6.6 (1.6)	4.0 (1.7)	6.9 (1.1)
Vividness	6.7 (1.5)	7.3 (1.1)	6.6 (1.3)	7.1 (1.6)	7.3 (1.4)	7.0 (1.3)

Note. Data are M (SD).

EEG data: changes in theta activity

The mixed ANOVA on changes in theta activity yielded a significant main effect for Laterality, $F_{(2,108)} = 8.04$, $p < .001$, $\eta^2_p = .13$, showing that theta activity was larger at

midline scalp sites than lateral sites (left: $p < .001$, Cohen's d = 0.15; right: $p < .001$, Cohen's d = 0.11), whereas no significant difference between left and right sites was noted ($p = .32$). The ANOVA also revealed a significant Group × Category × Area interaction, $F_{(6,324)} = 2.17$, $p < .05$, $\eta^2_p = .04$. As shown in Figure 3.7, at frontal and frontocentral sites, the pattern of changes in theta activity from baseline to the imagery of pleasant and unpleasant scripts was significantly different between groups.

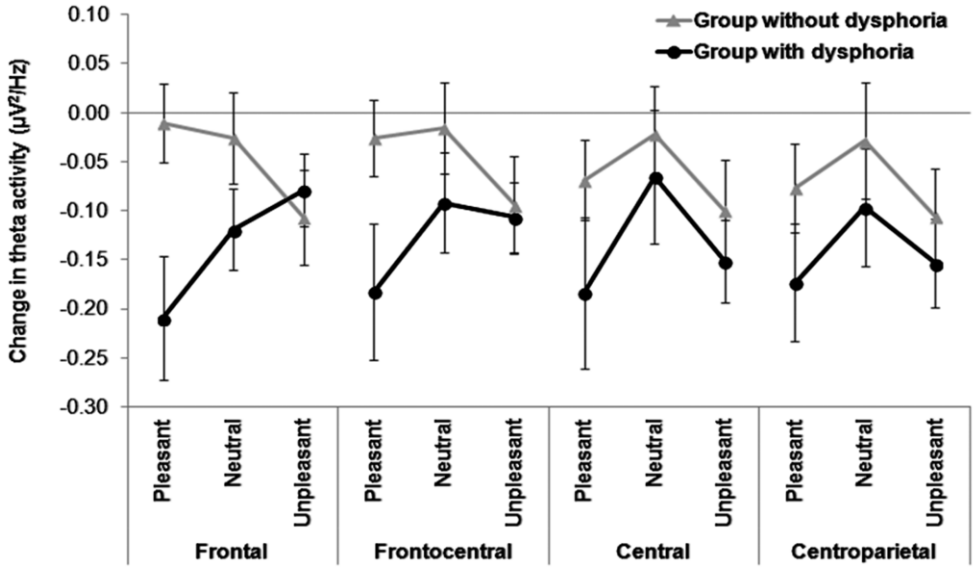

Figure 3.7 Mean (SE) changes in theta activity (μV^2/Hz) as a function of Category (pleasant, neutral, unpleasant) and Area (frontal, frontocentral, central, centroparietal) in the group with dysphoria and in the group without dysphoria.

Specifically, individuals without dysphoria were characterized by a greater decrease in theta activity from baseline to the imagery of unpleasant compared to pleasant scripts at frontal ($p < .002$, Cohen's d = 0.42) and frontocentral ($p < .02$, Cohen's d = 0.30) scalp sites. In contrast, the group with dysphoria showed the opposite pattern, that is, a greater decrease in theta activity from baseline to the imagery of pleasant relative to unpleasant scripts at frontal ($p < .001$, Cohen's d = 0.50)

and frontocentral (p < .02, Cohen's d = 0.28) sites. Moreover, it is worth noting that the difference between groups in change in theta activity from baseline to the imagery of pleasant scripts showed a medium-to-large effect size at frontal sites (Cohen's d = 0.75) and a medium effect at frontocentral sites (Cohen's d = 0.57).

At central and centroparietal sites, the groups with and without dysphoria were characterized by a greater decrease in theta activity from baseline to the imagery of pleasant (all ps ≤ .10, all Cohen's ds > 0.18) and unpleasant (all ps ≤ .05, all Cohen's ds > 0.22) vs. neutral scripts, whereas changes in theta activity did not differ between pleasant and unpleasant conditions (all ps > .26). Figure 3.8 depicts maps of change in theta activity from baseline to each emotional condition in the group with vs. without dysphoria.

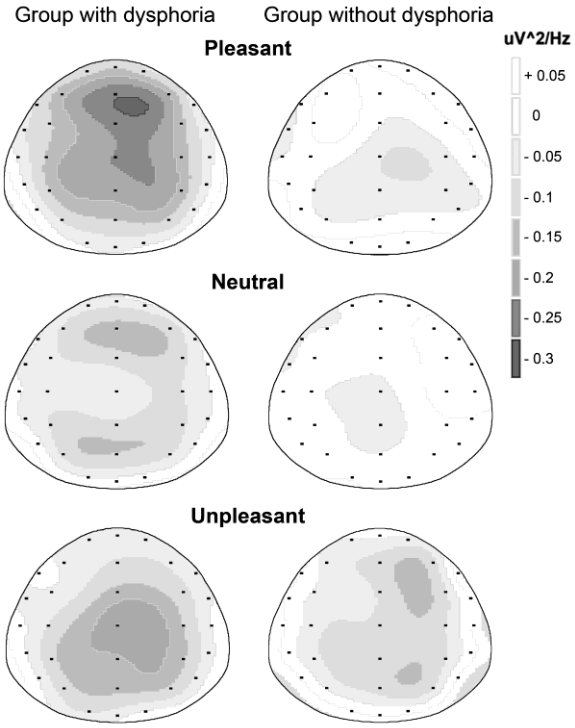

Figure 3.8 Maps of change in theta activity (µV2/Hz) from baseline to the active imagery of pleasant, neutral and unpleasant conditions in the group with dysphoria and in the group without dysphoria.

In order to test whether the interaction between the severity of depressive symptoms and the emotional category predicts change in frontal and frontocentral theta activity, we computed a linear model (ANCOVA) with Category (pleasant, neutral, unpleasant), and Area (frontal, frontocentral) as within-subjects factors, and BDI-II score (continuous variable treated as covariate) as the predictor of change in theta activity from baseline to imagery. We found a significant Category × BDI-II score interaction, $F_{(2,108)} = 3.38$, $p < .05$, $\eta^2_p = .06$, and a Category × Area × BDI-II score interaction, $F_{(2,108)} = 3.48$, $p < .04$, $\eta^2_p = .06$. A post-hoc analysis for this interaction was carried out, by calculating the single correlation between changes in frontal and frontocentral theta activity of each of the three emotional categories and BDI-II scores. An inverse correlation was noted between changes in theta activity at anterior scalp sites during the imagery of pleasant, but not neutral and unpleasant, scripts and BDI-II scores (see Table 3.3).

Table 3.3 Pearson's correlation coefficients between BDI-II scores and change in theta activity at frontal and frontocentral sites for each emotional category

		Category	
Area	**Pleasant**	**Neutral**	**Unpleasant**
Frontal	-.38**	-.14	.08
Frontocentral	-.29*	-.08	-.01

Note. **$p < .01$ *$p < .05$.

Specifically, the more severe the depressive symptoms, the greater the decrease in theta activity at frontal than frontocentral scalp sites during the pleasant imagery (Figure 3.9).

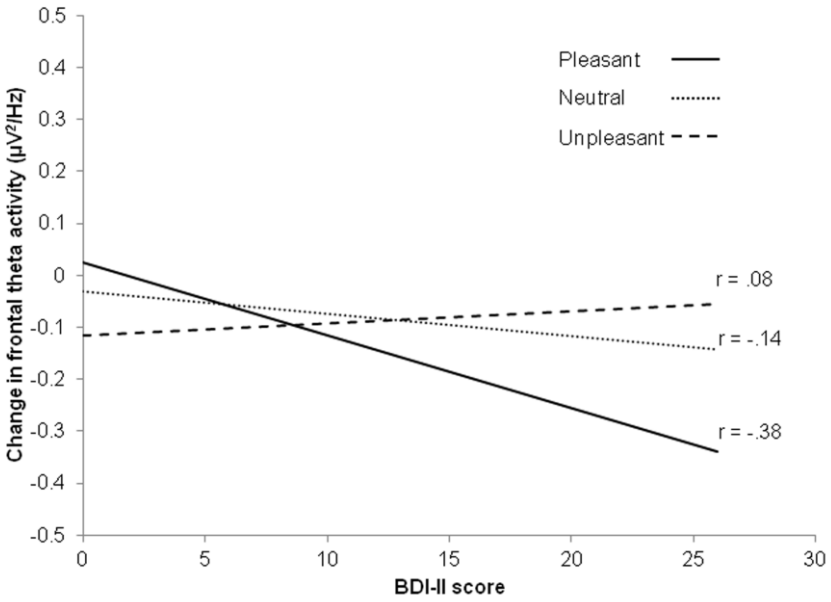

Figure 3.9 Change in frontal theta activity (μV2/Hz) from baseline to imagery as a function of emotional category and BDI-II score.

3.5.5 Discussion

The present study was designed to investigate whether frontal theta activity may be an EEG correlate of mood-related emotional processing in dysphoria. In line with the limited literature data available, the current study showed a greater decrease in frontal and frontocentral theta activity from baseline to the imagery of pleasant relative to unpleasant stimuli in dysphoric individuals, and the *opposite* pattern in healthy controls. This novel finding adds to the literature on the neural basis of mood-related processing biases in depression by showing that frontal and frontocentral theta activity could be an EEG correlate of mood-related emotional processing that characterizes dysphoric individuals (Joormann, 2004; Peckham et al., 2010). The finding that frontal theta activity reflects mood-related emotional processing is consistent with previous studies showing that the sources of this cortical rhythm are to

be located within the rACC (e.g., Nishida et al., 2004; Pizzagalli, Oakes, et al., 2003), and that rACC is involved in depression-related emotional dysregulation (e.g., Elliott et al., 2002; Eugène et al., 2010). Indeed, rACC activity has been consistently found to be increased in response to unpleasant stimuli and diminished in response to pleasant stimuli in depressed patients, whereas the opposite pattern has been observed in healthy controls (e.g., Elliott et al., 2002; Eugène et al., 2010).

Notably, we found a greater decrease in frontal and frontocentral theta activity from baseline to the imagery of pleasant scripts in the group with dysphoria relative to the group without dysphoria. In line with this finding, the severity of depressive symptoms was associated with decrease in frontal and frontocentral theta activity during the imagery of pleasant, but not neutral or unpleasant, stimuli. This is consistent with previous findings by Eugene et al. (2010), reporting an inverse correlation between the severity of depressive symptoms, as measured with BDI-II, and rACC activation for pleasant, but not neutral and unpleasant, stimuli. More importantly, these results suggest that dysphoric individuals are less sensitive to pleasant relative to unpleasant stimuli rather than the opposite pattern – that is, more sensitive to unpleasant relative to pleasant stimuli. Therefore, these results align with predictions from the *positive attenuation hypothesis*. Accordingly, a growing number of studies have recently suggested that the inability to process positive and rewarding stimuli is one of the key mechanisms that underlie emotion dysregulation in depression (Gotlib & Joormann, 2010; Joormann, 2004; Peckham et al., 2010), potentially related to core depressive symptoms, such as anhedonia, loss of pleasure and behavioral inhibition.

The suggestion that decreases in frontal theta activity may reflect reduced motivational salience of pleasant stimuli in dysphoria is also supported by the evidence that frontal theta activity is associated with emotional processing of pleasant stimuli in healthy individuals. Specifically, decreases in frontal theta activity during the processing of pleasant stimuli have been related to reduced emotional involvement in healthy individuals (Knyazev et al., 2009). Similarly, Sammler et al. (2007) reported that increases in frontal theta activity during the listening of pleasant music excerpts positively correlated with pleasantness ratings. Likewise, reduced frontal and frontocentral theta activity has been found to be associated with less positive "blissful" experience during meditation (Aftanas & Golocheikine, 2001). In line with evidence showing that greater resting rACC activity predicts better treatment response in depressed patients (e.g., Mayberg, 1997; Ritchey, Dolcos, Eddington, Strauman, & Cabezza, 2011), greater frontal theta activity within the rACC has been found to predict treatment outcome in depression (Pizzagalli et al., 2001). Because these studies examined rACC activity or frontal theta activity in resting state condition, while the current study focused on frontal theta activity during an imagery task, it is unclear whether the present findings may be associated with clinical outcome in dysphoria. Therefore, future research is warranted to examine whether changes in frontal theta activity during an emotional imagery task predicts the course of depressive symptoms in dysphoric individuals.

Notably, we found that frontal theta activity consistently decreased from baseline to the active imagery condition. This result is consistent with previous evidence suggesting that decreases in theta activity are likely to reflect an active

involvement in the emotional imagery task (Sebastiani, Simoni, Gemignani, Ghelarducci, & Santarcangelo, 2003). This finding is also in line with those of previous studies showing that rACC is a key region within the default mode network, which is referred to as a task-negative network (Broyd et al., 2009; Fox et al., 2005). While a task-positive network, including the dorsolateral prefrontal cortex, the dorsal ACC (dACC), the intraparietal sulcus and middle temporal area, becomes activated during externally-driven tasks requiring attentional and cognitive resources (Corbetta & Shulman, 2002; Sonuga-Barke & Castellanos, 2007), the default network becomes less activated during demanding cognitive tasks (Pizzagalli, 2011). This might explain why frontal theta activity, an EEG correlate of rACC activity, showed a task-induced reduction in the present study. However, given the paucity of studies examining changes in theta activity during an emotional imagery task, this hypothesis needs to be further tested.

Dysphoric and nondysphoric individuals did not differ on self-report measures of valence and arousal. This null finding diverges from those obtained by other studies (e.g., Rottenberg, Gross, & Gotlib, 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002), which reported differences between clinically depressed individuals and healthy controls with respect to self-report measures of emotional experience. An explanation for these discrepant findings may lie in the methodology used to evaluate emotional experience. The majority of previous studies reporting a significant difference between groups used a list of discrete emotions to evaluate subjective emotional experience (e.g., Rottenberg, Gross, & Gotlib, 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002). By contrast, studies, like ours, using the SAM 9-point scale to assess self-reported valence

and arousal for each script were less likely to report differences between groups at the subjective level (Allen, Trinder, & Brennan, 1999; Dichter, Tomarken, Shelton, & Sutton, 2004); but see also Sloan, Strauss, Quirk, & Sajatovic, 1997). Alternatively, it is possible that mild to moderate depressive symptoms typically reported in dysphoria may not be sufficient to elicit differences in subjective ratings of emotional experience (Mneimne, McDermut, & Powers, 2008; Sloan & Sandt, 2010).

The current findings should be interpreted in light of some limitations. First, the definition of dysphoria did not require participants to endorse at least one of the key symptoms of depression (i.e., depressed mood or anhedonia). This method for sample selection may have resulted in a heterogeneous group that may not be characterized by mood-related difficulties. It should be noted, however, that the vast majority of dysphoric patients (*N* = 21, 78%) included in the current study endorsed depressed mood and/or anhedonia. Second, we did not include behavioral measures, such as measures of attention or inhibitory control, which would have provided a more complete picture of the influence of mood-related emotional processing in dysphoria. Lastly, it is not clear whether the findings reported herein are specific for dysphoric patients or may be generalized to patients with clinically significant depression. Clearly, future research should address these issues by investigating whether frontal theta activity may reflect mood-related emotional processing in tasks requiring behavioral responses, such as the emotional Go/Nogo task, and/or in patients with major depression.

3.5.6 Conclusions

In summary, the present study showed that individuals with dysphoria are characterized by greater decrease of frontal and frontocentral theta activity in response to pleasant relative to unpleasant stimuli, while healthy controls showed the reversed pattern. The present study suggests that frontal and frontocentral theta activity may be an EEG correlate of mood-related biases in emotional processing in dysphoria. More specifically, although dysphoria is characterized by prevalent negative affect, it does not seem to be subtended by heightened withdrawal or active avoidance of unpleasant stimuli. Instead, decreases in frontal and frontocentral theta activity observed in dysphoric individuals are likely to reflect reduced processing of pleasant stimuli's motivational salience. This might as well be linked to specific symptoms of depression, such as anhedonia, loss of pleasure and behavioral apathy. Thus, the current study may contribute to a better understanding the neural correlates of motivational and emotional dysregulation that characterize dysphoria and depression.

3.6 STUDY 3: Emotional modulation of frontal alpha asymmetry in dysphoria[4]

3.6.1 Abstract

Based on the results of the previous study, showing that dysphoria is associated with reduced processing of pleasant emotions, it was investigated whether frontal alpha asymmetry, an index of the balance between approach and withdrawal motivations, would differ in individuals with dysphoria from controls. Accordingly, studies on EEG alpha band asymmetry at rest have reported that, compared to healthy controls, dysphoric and clinically depressed individuals often display relatively less left- than right-sided cortical activity at frontal scalp sites, as indicated by frontal alpha asymmetry. It has also been shown that depression-related differences in frontal alpha lateralization are more likely to emerge during emotional tasks, rather than during resting conditions. In the present study, dysphoric (*N* = 23) and nondysphoric (*N* = 24) individuals performed an emotional imagery task including pleasant, neutral, and unpleasant narratives. The group with, but not without, dysphoria showed reduced left relative to right cortical activity at frontal sites, irrespective of emotional condition. The present results provide further evidence for the presence of a stable pattern of reduced approach motivation in dysphoric individuals. Our findings are also in line with those reported in other studies suggesting that reduced approach motivation in individuals with depressive symptoms could represent an endophenotype or, at least, a risk factor for depression

[4] Results from this study have been published in: Mennella, R., Benvenuti, S. M., Buodo, G., & Palomba, D. (2015). Emotional modulation of alpha asymmetry in dysphoria: results from an emotional imagery task. *International Journal of Psychophysiology*, *97*(2), 113-119.

Keywords: depressive symptoms; dysphoria; frontal alpha asymmetry; EEG; emotion; imagery

3.6.2 Introduction

As previously mentioned, among the core symptoms of depression there are loss of interest and anhedonia. Indeed, depressed individuals are thought to have a deficit in reward seeking behaviors, and typically exhibit an affective style poorly oriented toward approach (Davidson, 1998a). A model has been proposed which states that prefrontal regions of the left and right cerebral hemispheres are involved in approach- and withdrawal-related goals, respectively (Davidson, 1988, 1998). Consistent with this model, frontal asymmetry in cortical activity, as measured with alpha asymmetry at anterior scalp sites, has been found to be related to motivational direction in healthy participants (Hewig et al., 2004). Recent studies have also reported that high levels of Reward Responsiveness (i.e., a first order factor of the Behavioral Activation System) and optimism were associated with more left relative to right cortical activity at frontal sites (De Pascalis et al., 2013, 2010). Strong support for this model comes from those studies examining frontal alpha asymmetry in individuals with depressed mood (i.e., dysphoria) or with clinically significant depression. Specifically, at frontal scalp sites, individuals with depressed mood often display a stable pattern of low cortical activity (i.e., high alpha power) in the left relative to the right side at rest (Gotlib, 1998; Schaffer et al., 1983). Consistent findings have been also observed in clinically depressed patients (Allen et al., 2004b; Baehr et al., 1998; Henriques and Davidson, 1991), and in euthymic participants with a history of depression (Henriques & Davidson, 1990; Stewart, Bismark, Towers, Coan, & Allen, 2010). Based on this evidence, frontal alpha asymmetry at rest has been interpreted as an index of affective

style, reflecting a depression-related reduced approach/appetitive motivation (Davidson, Pizzagalli, Nitschke, & Putnam, 2002).

However, some studies failed to replicate findings on resting frontal alpha asymmetry in depression (e.g., Bruder et al., 1997; Metzger et al., 2004; Stewart et al., 2014). In order to reconcile these inconsistencies, some authors suggested that resting conditions may not be ideal to detect differences in alpha asymmetry between depressed individuals and healthy controls (Coan et al., 2006; Henriques & Davidson, 1997). Specifically, it has been suggested that testing anterior alpha asymmetry, as a measure of affective style, during emotional tasks may be a more powerful approach. Indeed, emotional tasks highlight motivational differences and reduces undesirable variance associated with resting states (Coan et al., 2006; Stewart et al., 2014). Accordingly, studies examining alpha asymmetry at anterior sites in depressed individuals using emotional tasks, such as the directed facial action (DFA) task, reported reduced frontal cortical activity in the left relative to the right hemisphere compared to healthy controls, irrespective of emotional condition (Stewart et al., 2011, 2014). So far, however, no study examined depression-related frontal alpha asymmetry during an *emotional imagery* task. This is surprising given that emotional imagery has a powerful impact on eliciting emotional responses (Holmes & Mathews, 2010; Lang, 1979). Moreover, emotional imagery is an active task, in which individuals are requested to actively imagine emotional scenes, thus being perfectly suited to stimulate motivational tendencies.

In light of these considerations, the main aim of the present study was to examine patterns of frontal alpha asymmetry in dysphoria during an emotional

imagery task. Given that depression-related stable trait of reduced approach/appetitive motivation has been observed (Stewart et al., 2011), individuals with dysphoria were expected to be characterized by a relatively greater left than right alpha power at anterior scalp sites (i.e., lower left- than right-sided cortical activity) compared to controls without dysphoria, irrespective of emotional conditions.

3.6.3 Methods

Participants

Given that the association between frontal alpha asymmetry and depression is stronger in females that in males (Bruder et al., 2001; Miller et al., 2002; Smit et al., 2007) and that asymmetrical alpha activity is influenced by handedness (Davidson, 1988), only right-handed females were included in the present study. Therefore, we excluded males and left-handed individuals from the total sample described in the previous section. Twenty-three individuals who scored at least 12 both on the online and the paper-and-pencil BDI-II and had two or more depressive symptoms for at least two weeks, were included in the group with dysphoria [age, mean (M) = 21.0, standard deviation (SD) = 1.6, BDI-II score, M = 15.9, SD= 4.4].Twenty-four undergraduates who scored equal or less than 8 (corresponding to the 53th percentile) on both versions of the BDI-II and showed no depressive symptoms as defined by the SCID-I were included in the group without dysphoria [age, M = 22.2, SD = 2.0, BDI-II score, M = 2.9, SD = 2.8].

All the participants had no history of psychiatric or neurological disorders and were free from medications. Approval for this study was obtained by the Ethics Committee of the Department of General Psychology, University of Padova (Italy). All

the participants gave their written consent to participation in the study, in accordance with the Declaration of Helsinki.

Procedure and Emotional imagery task: see Method sections of Study 2.

EEG recording and data analysis

For EEG data recording and pre-processing see Method section of Study 2. For the present analyses, power density values (μV^2/Hz) within the alpha band (8-13 Hz) were calculated for each subject at each site. Power density values in the alpha band obtained from the two 90-s periods of imagery within each emotional condition were then averaged.

The asymmetry score was calculated for total alpha power by subtracting the natural log-transformed scores for each homologous left and right pair (i.e., ln[Right] - ln[Left]) in 2 scalp areas: frontal (F7 & F8, F3 & F4) and frontocentral (FT7 & FT8, FC3 & FC4) areas. Higher asymmetry scores reflect greater left relative to right cortical activity (Coan & Allen, 2004). Then, averaged asymmetry scores were calculated for each area (frontal, frontocentral) as the average of the asymmetry scores obtained from the two lateral interhemispheric electrode pairs (e.g., F3 & F4 and F7 & F8 for the frontal area; see also Schleiger et al., 2014).

A mixed analysis of variance (ANOVA), with Group (without dysphoria, with dysphoria) as a between-subjects factor, and Category (pleasant, neutral, unpleasant) and Area (frontal, frontocentral) as within-subjects factors, was performed on averaged asymmetry scores at anterior sites. In order to ensure that the results obtained for frontal asymmetry scores were specific for the alpha band, the same

ANOVAs were conducted for the asymmetry scores on theta (4-8 Hz) and beta (13-30 Hz) bands.

Self-report ratings of valence, arousal and vividness obtained for the two narratives within the same emotional condition were averaged. Mixed ANOVAs, with Group (without dysphoria, with dysphoria) as a between-subjects factor, and Category (pleasant, neutral, unpleasant) as a within-subjects factor, were conducted separately for valence, arousal and vividness ratings. Significant main effects and interactions ($p < .05$) were followed by Tukey post-hoc tests. Partial eta-squared (η_p^2) was reported as a measure of the effect size (Cohen, 1988). Whenever the sphericity assumption was violated, the Greenhouse-Geisser correction was applied. Corrected *p*-values, ε estimates and uncorrected degrees of freedom are reported.

3.6.4 Results

Self-report measures

Mixed ANOVA on valence ratings showed a significant main effect for Category, $F_{(2,90)} = 388.48$, $p < .001$, $\varepsilon = .89$, $\eta^2_p = .90$. Specifically, pleasant condition was rated as more pleasant than neutral and unpleasant ones ($p < .001$). Unpleasant condition was rated as less pleasant than neutral one ($p < .001$). No significant main effect for Group or interactions between Group and Category emerged (all $ps > .21$).

Similarly, mixed ANOVA on arousal ratings yielded a significant main effect for Category, $F_{(2,90)} = 66.98$, $p < .001$, $\varepsilon = .99$, $\eta^2_p = .60$. Post-hoc analysis revealed that arousal was higher for pleasant and unpleasant than neutral conditions ($ps < .001$), while pleasant and unpleasant conditions did not differ from each other ($p = .75$). No

significant main effect for Group or interactions between Group and Category emerged (all *ps* > .35).

Mixed ANOVA on vividness ratings showed a significant main effect for Category, $F_{(2,90)}$ = 3.15, p = .048, ε = .99, η^2_p = .07. However, post-hoc analysis revealed no significant differences among emotional conditions (all *ps* > .07). No significant main effect for Group or interactions between Group and Category emerged (all *ps* > .39). Descriptive statistics for self-report measures are reported in Table 3.4.

Table 3.4 Self-report measures for each emotion condition in the group without and with dysphoria

Self-report measures	**Group without dysphoria (*N* = 24)**			**Group with dysphoria (*N* = 23)**		
	Pleasant	**Neutral**	**Unpleasant**	**Pleasant**	**Neutral**	**Unpleasant**
Valence	8.0 (0.8)	6.2 (0.8)	2.5 (0.9)	7.6 (1.3)	5.9 (1.2)	2.6 (0.9)
Arousal	6.5 (1.6)	3.3 (1.7)	6.5 (1.7)	6.4 (1.7)	3.9 (1.7)	6.9 (1.1)
Vividness	6.7 (1.5)	7.4 (1.0)	6.5 (1.2)	6.9 (1.7)	7.3 (1.5)	7.0 (1.3)

Note. Data are M (SD).

Emotional modulation of alpha asymmetry scores in the groups with and without dysphoria

Mixed ANOVA on alpha asymmetry scores yielded a significant main effect for Group, $F_{(1,45)}$ = 5.93, p = .02, η^2_p = .12, showing that the group with dysphoria had lower alpha asymmetry scores (i.e., lower left than right cortical activity) as compared with the group without dysphoria (Figure 3.10).

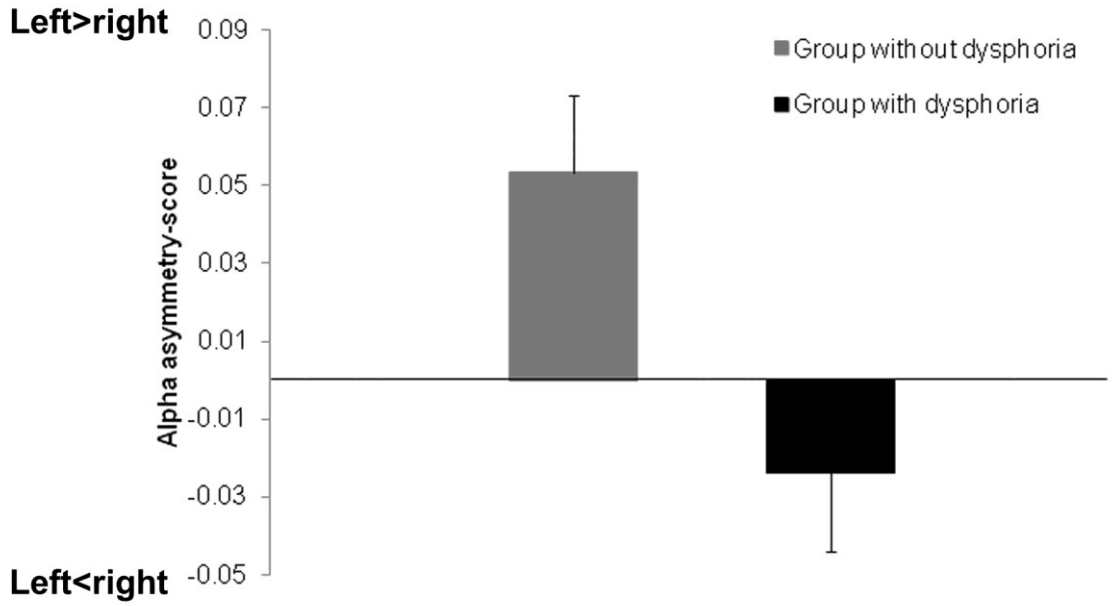

Figure 3.10 Group means of asymmetry scores at frontal and frontocentral sites. The group with dysphoria shows lower asymmetry scores (i.e., less left hemisphere activity). Bars indicate standard errors of the means.

The main effect for Area was also significant, $F_{(1,45)} = 16.27$, $p < .001$, $\eta^2_p = .27$, revealing higher alpha asymmetry scores in the frontal area than in the frontocentral area. No other significant main effects or interactions were noted (all *ps* >.17). Accordingly, an inverse correlation between BDI-II scores and mean alpha asymmetry scores at anterior scalp sites, which was calculated by averaging the alpha asymmetry scores of the three imagery conditions for each participant, was noted (r = -.29, $p = .04$). That is, the lower the left relative to right cortical activation, the more severe the depressive symptoms (Figure 3.11).

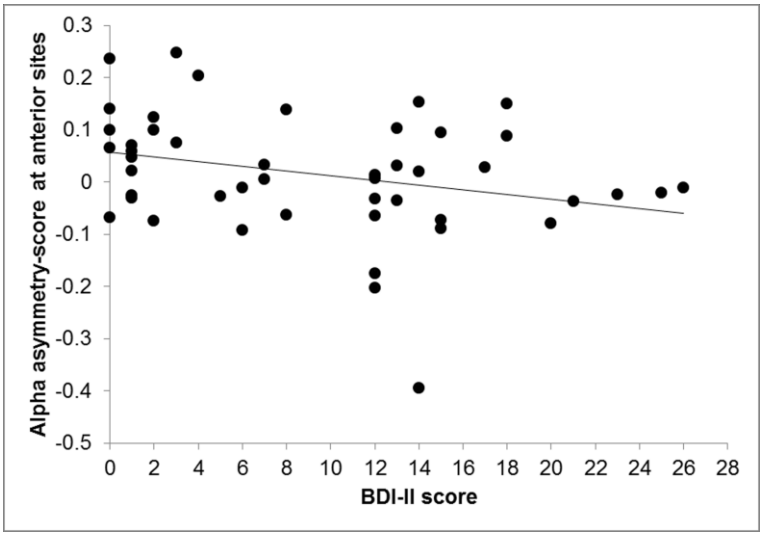

Figure 3.11 Scatterplot between the overall mean of the asymmetry scores at anterior sites (frontal, frontocentral) during the imagery task and the BDI-II score of each subject (r = -.29, p < .05).

Furthermore, although not significantly ($\chi^2_{(1)}$ = 2.55, *p* = .11), 55.5% (*N* = 13) of the participants with dysphoria were less left relative to right activated (i.e., with a negative asymmetry score), whereas 66.7% (*N* = 16) of the participants without dysphoria showed the opposite pattern.

It is important to note that neither for the anterior asymmetry scores in the theta nor for the ones in the beta band did emerge any main effect of Group, or any interaction involving Group (all *p*s > .05).

3.6.5 Discussion

The objective of the present study was to examine the influence of dysphoria on alpha asymmetry at frontal and frontocentral scalp sites in the context of an emotional imagery task. Results on subjective ratings of valence and arousal after each imagery condition revealed that the task was successful in eliciting the expected emotional responses. In line with previous studies (Mneimne et al., 2008; Sloan & Sandt, 2010),

the group with dysphoria did not differ in terms of self-reported valence and arousal from the control group. It is also worth noting that the two groups were comparable in terms of imagery task performance, as measured with self-reported vividness ratings.

With respect to anterior alpha asymmetry, the group with dysphoria showed significantly lower left cortical activity than controls across all emotional conditions, regardless of whether they were positively or negatively valenced or neutral. Consistent with recent studies on depression using emotional tasks (Stewart et al., 2011, 2014), this finding suggests a trait-like mechanism of emotional responding in dysphoric individuals. Specifically, it can be argued that individuals with dysphoria are characterized by a stable pattern of reduced approach motivation compared to controls. Our findings are also in line with those reported in other studies suggesting that reduced approach motivation in individuals with depressive symptoms could represent an endophenotype or, at least, a risk factor for depression (Coan & Allen, 2004; Davidson, 1998a). Nevertheless, the two groups did not significantly differ in terms of the number of participants who were less left relative to right activated (i.e., with negative asymmetry score). This could be due to the fact that our participants were individuals with dysphoria and not clinically depressed. However, it is noteworthy that 55.5% of the participants with dysphoria were less left relative to right activated (i.e., with negative asymmetry score), whereas 66.7% of the participants without dysphoria showed the opposite pattern (i.e., positive asymmetry score).

We found no differences in frontal alpha asymmetry scores as a function of emotional valence in both groups. Similar findings have been previously reported in the literature using visual tasks (Elgavish et al., 2003; Hagemann et al., 1998) and

emotional imagery tasks (Hofmann, 2007). It should be noted, however, that some studies employing other emotional tasks found differences in frontal alpha asymmetry scores as a function of emotional contents (Coan et al., 2001; Harmon-Jones et al., 2010; Stewart et al., 2011). Although standardized emotional imagery task may be effective for investigating trait-like motivational tendencies in dysphoria, it may not modulate this stable pattern with sufficient intensity to produce significant differences in frontal alpha asymmetry among emotional conditions.

The current findings should be also interpreted in light of some methodological limitations. First, given that the association between frontal alpha asymmetry and depression is stronger in females that in males (Bruder et al., 2001; Miller et al., 2002; Smit et al., 2007), only female undergraduates were included in the present study. However, this made it impossible to generalize the present findings to male population. Second, we did not control for menstrual cycle, which, in turn, may affect both mood and alpha asymmetry (Baehr, Rosenfeld, Miller, & Baehr, 2004). However, the purpose of the present work was to study the effect of dysphoria on alpha asymmetry during an emotional imagery task, regardless of the specific determinants of the dysphoric mood in our sample. Third, although during the emotional imagery emerged trait differences in frontal alpha asymmetry between groups with and without dysphoria, the task did not elicit significant differences in anterior cortical activations between groups as a function of the emotional conditions. This could be due to the fact that standardized narratives induce a comparable degree of emotional response between participants, which may reduce the salience of the imagined scene and the related emotional experience. Clearly, future studies are warranted to

examine how dysphoria interacts with emotions to modulate frontal alpha asymmetry during an emotional imagery task including idiographic person-specific stimuli in both female and male individuals.

3.6.6 Conclusions

In summary, the present study showed that dysphoric individuals are characterized by reduced left relative to right frontal activity irrespective of emotional condition, as revealed by frontal alpha asymmetry, suggesting that individuals with dysphoria are characterized by a trait-like feature of reduced approach motivation. Together with the results from the previous study, there is general support for negative affect in depression to arise from a reduced activity of the appetitive motivational system, which might explain general insensitivity to reward, anhedonia, loss of pleasure and decrease in approach behaviors. From the studies presented so far, the importance of the asymmetry in frontal alpha at right and left scalp sites as an index of approach and withdrawal motivational tendencies, as well as its relation with negative affect, clearly emerged. Therefore, in the last study, we will present results from a frontal alpha asymmetry neurofeedback training aimed at reducing negative affect, as a first step for the translation from basic research on affective modulation of EEG bands to clinical application.

3.7 STUDY 4: The use of a frontal alpha asymmetry neurofeedback for the reduction of negative affect[5]

3.7.1 Brief introduction to EEG biofeedback (neurofeedback)

In the previous studies, it has been highlighted that motivational dysregulation underlying negative affect is reflected by modulation of specific EEG parameters. This observation opens clinical perspectives for trainings and techniques which have the potential of directly targeting EEG frequency bands. Electric (Shiozawa et al., 2014) and magnetic stimulation (Lefaucheur et al., 2014), for instance, are increasingly adopted in the modulation of negative affect, especially in relation to pharmacologically resistant depression and anxiety. Furthermore, *neurofeedback* represents an alternative way of intervening on EEG bands, which does not require recurring to external stimulation, and have been repeatedly shown useful for the prevention and the reduction of negative affect. More in general, biofeedback is a bio-behavioral technique which aims at modifying bodily physiological activity in order to improve health and/or performance. The basic principle of the technique is to provide feedback on bodily functions which are typically out of awareness, in order to extend conscious control over them (Gilbert & Moss, 2003). Biofeedback instruments can be used to measure and feedback a wide range of physiological signals, from cardiovascular activity (e.g., blood pressure, blood flow, heart rate, and heart rate variability), skin temperature (thermal feedback), electrodermal activity (SCL biofeedback), muscle activity (EMG biofeedback), and brain activity (neurofeedback) .

[5] Results from this study are reported in Mennella R., Patron E., Palomba, D. (under review). Frontal Alpha Asymmetry Neurofeedback for the Reduction of Negative Affect and Anxiety.

Therefore, neurofeedback consists in a particular application of biofeedback in which brain activity is fed back. Several techniques capable of measuring ongoing brain activity have nowadays a neurofeedback application, such as fMRI, NIRS, MEG (for a recent review on these techniques see Thibault, Lifshitz, & Raz, 2016) and, of course, EEG. In line with the general biofeedback principles, the assumption underlying neurofeedback is that by providing real-time information on brain's activity, one can entrain, change, and regulate it (Thibault et al., 2016). Operant conditioning has been proposed as a possible mechanism of action, where the positive feedback is considered to be a reinforcement for the present bio-behavioral pattern (Miller & DiCara, 1967).

EEG neurofeedback represent a powerful clinical tool for affective regulation, since it directly retrains the electrical activity patterns in the brain. In particular, neurofeedback of ongoing bands allows feeding back changes in power at specific frequencies, thus modulating both cognitive and affective processes which they subtend. Accordingly, also due to the large availability in clinical settings, EEG neurofeedback training has been applied to many pathological conditions, such as attention deficit hyperactivity disorder, learning disability, stroke, head injury, deficits following neurosurgery, uncontrolled epilepsy, cognitive dysfunction associated with aging, depression, anxiety, obsessive-compulsive disorder, autism, or other brain-related conditions (for a review see Hammond, 2011).

3.7.2 The neurofeedback of alpha band

The studies about reconditioning and retraining brainwave patterns started between the 1960s and the 1970s (Kamiya, 2011). Most of this work began with trainings aimed at increasing alpha brainwave activity, in order to induce relaxation. In these early studies, neurofeedback was successfully employed to increase alpha power at posterior scalp locations, both using an acoustic feedback (Hart, 1968; Kamiya, 1968) and a visual one (Brown, 1970a, 1970b). Not surprisingly, due to the positive association between alpha power and relaxation, the training was readily applied to reduce anxious arousal in healthy individuals (Hardt & Kamiya, 1978; Figure 3.12).

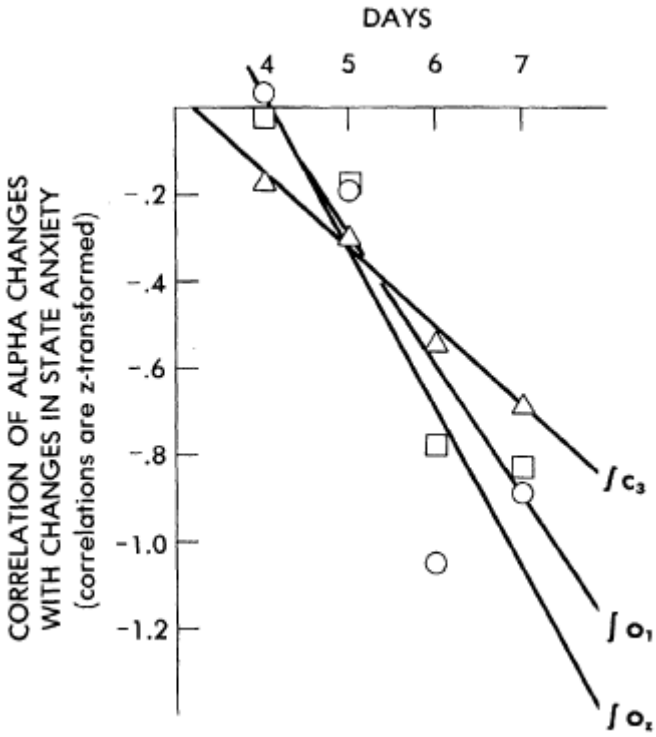

Figure 3.12 Z-transformed correlation between alpha change and state-anxiety change at different cortical sites and training times. The coefficient of determination (r2) for alpha changes at Oz, O1, and C3 was .791, .896, and .987, respectively. Adapted from Hardt & Kamiya, 1978.

In line with early results, reduction of anxious arousal through alpha (and theta) band neurofeedback has proven to be effective in increasing performance in very high level

musicians when they were performing under stressful conditions (Egner & Gruzelier, 2003). More recently, it has been reported that a single session of neurofeedback for the *reduction* of alpha band at electrode Pz induced an up-regulation of functional connectivity within the salience network in the experimental but not in the sham group, as measured after 30 minutes with fMRI (Ros et al., 2013).

Consistently with the negative association between alpha and anxious arousal, neurofeedback for the increase of alpha band has been preliminarily tested on populations with anxiety disorders. In individuals with specific phobia, neurofeedback for increasing alpha band at posterior scalp sites successfully elicited greater alpha posttreatment, as well as a reduction in anxiety scores (Garrett & Silver, 1976). In line with these results, Passini and colleagues (1977) applied 10 hours of alpha neurofeedback over three weeks on 25 anxious alcoholics compared to a matched control group. The training produced a significant increase in eyes-closed alpha power, as well a significant reduction in state and trait anxiety. Importantly, training-induced changes where almost identical after 18 months, testifying a long-term effect (Watson, Herder, & Passini, 1978). Alpha and theta band neurofeedback has also been tested on patients with posttraumatic stress disorder in two studies (Peniston & Kulkosky, 1991; Peniston, Marrinan, Deming, & Kulkosky, 1993). Overall, the training was associated with an improvement in symptomatology, reduction in hospitalization and fewer instances of recurrence of nightmares/flashbacks from follow-up assessments. Finally, case-reports supported the effectiveness of alpha neurofeedback for symptoms remission also in obsessive-compulsive disorder (for a review see Hammond, 2005).

A peculiar type of alpha neurofeedback, namely the *neurofeedback of frontal alpha asymmetry* has been proposed as a clinical tool to modulate approach/withdrawal motivation subtended by the left and right dlPFC. In the last decades, several studies supported the possibility to modulate the relative activation of the left compared to the right prefrontal cortex through the alpha asymmetry neurofeedback in healthy individuals (e.g., Allen, Harmon-Jones, & Cavender, 2001; Harmon-Jones, Harmon-Jones, Fearn, Sigelman, & Johnson, 2008; Peeters, Ronner, Bodar, van Os, & Lousberg, 2014; Quaedflieg et al., 2015).

Due to the fact that depression has been associated with an affective style poorly oriented toward approach (Davidson, 1998a, 1998b, 2004; Henriques & Davidson, 2000), frontal alpha asymmetry neurofeedback has been considered as a possible treatment for depression (Hammond & Baehr, 2009). Of note, a small number of case studies investigated the effect of alpha asymmetry neurofeedback in reducing depressive symptoms in clinically depressed patients (Choi et al., 2011). Overall the results from these works showed that several patients were able to increase the percentage of time in which right frontal activity was reduced compared to left, and that this was accompanied by an improvement in depressive symptoms (Baehr & Baehr, 1997; Baehr, Rosenfeld, & Baehr, 1997). Albeit these results were replicated (Earnest, 1999), and follow-up measurements confirmed their stability in time (Baehr, Rosenfeld, & Baehr, 2001), no controlled studies exist so far.

Interestingly, both the motivational and the valence models for frontal asymmetrical activity support the view that anxiety, other than depression, presents an altered pattern of frontal asymmetry. In particular, it has been demonstrated that

anxiety symptoms are associated with increased right compared to left frontal activity, as measured with frontal alpha asymmetry (Mathersul, Williams, Hopkinson, & Kemp, 2008). This cortical pattern has been related to heightened negative affect and withdrawal tendencies in anxiety (Shankman & Klein, 2003). Accordingly, Study 1 of the present thesis further supported that reduction in anxiety and negative emotions is associated with increased right frontal alpha power.

Surprisingly, so far not many studies assessed the effects of frontal alpha asymmetry neurofeedback on anxiety symptoms. To our knowledge, only one uncontrolled study from Kerson and colleagues (2009) applied the frontal asymmetry training to reduce anxiety in anxious adults. The authors reported that all eight individuals included in the study were able to normalize frontal alpha pattern after 8 to 32 sessions. Importantly, both state and trait anxiety scores were significantly reduced, as measured by a 6-month follow-up. Clearly more research is needed to address the question whether frontal alpha asymmetry neurofeedback is effective in the reduction of depressive and/or anxiety symptoms. Study 4 has been specifically conducted to address this question.

3.7.3 Abstract

Activity at left and right prefrontal sites underlies approach and withdrawal motivation, respectively. Neurofeedback of EEG alpha asymmetry has been proposed as a clinical tool to decrease right compared to left cortical activity. Nonetheless it is not clear whether this training targets the withdrawal or approach motivational systems, and therefore the negative or the positive affect. On this basis, the present

study employed a neurofeedback training to increase frontal alpha asymmetry (right - left), in order to evaluate discrete changes in alpha power at left and right sites, as well as in positive and negative affect, anxiety and depression. Thirty-two right-handed females were randomly assigned to receive either the neurofeedback on frontal alpha asymmetry, or an active control training (N = 16 in each group). The asymmetry group showed an increase in alpha asymmetry driven by higher alpha at right site ($p < .001$), as well as a coherent reduction in both negative affect and anxiety symptoms ($ps < .05$), from pre- to post-training. No training-specific modulation emerged for positive affect and depressive symptoms. These findings provide a strong rationale for the use of frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety in clinical settings.

Keywords: Neurofeedback; Frontal alpha asymmetry; Right prefrontal cortex; Negative affect; Anxiety; EEG.

3.7.4 Introduction

The differential activity between the right and left prefrontal lobes is thought to be associated with dispositional mood, response to emotional stimuli and vulnerability to psychopathology (i.e., the "affective style"; Coan & Allen, 2004; Davidson, 1992). In particular, right prefrontal areas drive withdrawal behaviors and mediate the experience of negative emotions, while left prefrontal areas subtend approach behaviors and positive affect (Davidson, 1988, 1998b; Harmon-Jones et al., 2010; Papousek et al., 2014, 2012).

EEG biofeedback (*neurofeedback*) has been proposed as a tool to modulate the hemispherical asymmetry in prefrontal activity, in order to regulate affect (Rosenfeld, Cha, Blair, & Gotlib, 1995). Since EEG alpha power is an inverse index of cortical activity (Cook et al., 1998; Davidson et al., 1990), the difference between alpha at right and left frontal sites (i.e., frontal alpha asymmetry) inversely reflects the activity of the right compared to the left prefrontal lobe (Allen, Coan, et al., 2004). As a preliminary step, neurofeedback studies tested whether or not it was possible to modulate frontal alpha asymmetry, as well as the effects of this modulation on reported affect. In 2001, Allen and colleagues trained two groups of healthy participants to either increase or decrease their alpha asymmetry value, computed by subtracting left (F3) from right (F4) alpha power; therefore higher scores corresponded to reduced right compared to left frontal activity. Only participants trained to decrease alpha asymmetry succeeded, and neither training modified trait affect, as measured by the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). Recently, one comprehensive study replicated Allen and colleagues' results (Quaedflieg et al., 2015). Further studies

supported the efficacy of neurofeedback for the modulation of frontal alpha asymmetry in both directions (i.e., increasing or decreasing the asymmetry value) after two (Harmon-Jones et al., 2008) or even one session (Peeters et al., 2014). Again, trait affect was not influenced by the training.

Although there is evidence for neurofeedback to be effective in modulating frontal alpha asymmetry, previous studies did not address whether observed modifications were mostly driven by changes in alpha power at right, left, or both frontal sites. Consequently, it is hard to disentangle whether the training prevalently targets the withdrawal or approach motivational system, and therefore the negative or the positive affect. From a clinical perspective, this is of particular relevance, given that similarly altered patterns of frontal alpha asymmetry have been found in different conditions characterized by affect dysregulation, such as anxiety and depression (Beaton et al., 2008; Moscovitch et al., 2011; Stewart et al., 2011, 2014). In particular, even though both anxiety and depressive symptoms have been associated with increased right compared to left prefrontal activity, in anxiety this is subtended by an excessive withdrawal motivation and negative affect (increased right frontal activation); on the other hand, in depression the asymmetry dysregulation has been related to a reduction in approach motivation and positive affect (reduced left frontal activation) (Davidson, 1998a; Shankman & Klein, 2003). For this reason, it seems crucial establishing the precise effect of frontal alpha asymmetry neurofeedback on left and right activation, in order to provide a strong rationale for its clinical application.

The present study evaluated the efficacy of frontal alpha asymmetry (F4 - F3) neurofeedback on *increasing* the alpha asymmetry index. Furthermore, it was tested whether variations in asymmetry are subtended by changes in left (F3) and/or right (F4) frontal alpha power. Finally, the effects of the training on affect were assessed using a comprehensive battery, including the PANAS, for the evaluation of both positive and negative affect, as well as measures of anxiety and depressive symptoms.

3.7.5 Methods

Participants

Thirty-two healthy and free from medication undergraduate students (M age = 23.1, SD = 1.2) from the University of Padova were enrolled. The present study included only right-handed females, given that the association between frontal alpha asymmetry and negative affect is stronger in females that in males (Bruder et al., 2001; Miller et al., 2002; Smit et al., 2007) and that asymmetrical alpha activity is influenced by handedness (Davidson, 1988). Participants were randomly assigned to receive a biofeedback training designed either to increase right (F4) relative to left (F3) frontal alpha activity (*asymmetry group*; *N* = 16), or to increase frontal (Fz) alpha activity (*active control*; *N* =16). Neurofeedback aimed at increasing alpha activity has been previously employed in order to reduce stress and anxious symptoms (Brown, 1970b; Hammond, 2005; Hardt & Kamiya, 1978), due to the positive association of alpha power with states of relaxation and low arousal. Usually, this training is carried out at posterior sites, since the alpha rhythm is predominant in the occipital and parietal regions. On the contrary, in the present study the training targeted the mid-frontal

site, to serve as a specific control condition for the frontal alpha asymmetry neurofeedback.

Both groups were comparable with respect to sociodemographic variables (Table 3.5). Participants were told that at the end of the seven sessions they would receive a monetary payment proportional to the time they had been able to produce the expected change during each training session, as indicated by a positive feedback (total payment ranged from 10 to 25 euros). The present study was carried out with the adequate understanding and written consent of the participants in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Department of General Psychology, University of Padova (Italy).

Procedure

During the first session, upon arrival at the laboratory, participants received general information about the experiment and read and signed an informed consent form. Then, individuals seated on a semi-reclined comfortable armchair in a sound dampened dimly lit recording room, where a psychophysiological assessment was carried out, including psychological questionnaires administration and electrophysiological recordings in resting conditions. After the initial session (*pre-training assessment*), participant underwent 5 sessions of neurofeedback, and one final session during which the initial assessment was repeated (*post-training assessment*), in order to evaluate the effects. The whole procedure was completed within two weeks, starting each session within the same 3-hr time window.

Psychological assessment

Participants completed the following questionnaires:

1) The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) consists of two subscales of 10 items each (i.e., negative affect, NA; and positive affect, PA). In the version of the test used for the present study, for each item, participants are asked to rate (from 1 to 5) the extent to which they have experienced a particular emotion during the present day. The two subscales reflect dispositional dimensions, with high-NA scores characterizing subjective feelings of distress and unpleasurable engagement, and high-PA scores reflecting the extent to which an individual experiences pleasurable engagement with the environment. Reliability and validity of the PANAS as a measure of positive and negative affect is high in non-clinical samples (Crawford & Henry, 2004).

2) The Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) is composed of 21 items, which the participant has to evaluate on a four-point (0–3) Likert scale. The total score ranges from 0 to 63, with higher scores corresponding to higher levels of anxiety. Reliability and validity of the BAI as a measure of anxiety symptoms are high in both community samples (Beck et al., 1988) and college populations (Creamer, Foran, & Bell, 1995).

3) The Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Italian version by Ghisi et al., 2006). The BDI-II is a valid and reliable self-report questionnaire that evaluates the severity of depressive symptoms in the past two weeks and is composed of 21 items, which the participant has to evaluate on a four-point (0–3) Likert scale. Higher BDI-II scores correspond to more severe depressive symptoms. Importantly, reliability and

validity of the BDI-II as a measure of depressive symptoms is high in both community samples (Lasa, Ayuso-Mateos, Vázquez-Barquero, Díez-Manrique, & Dowrick, 2000) and college populations (Sprinkle et al., 2002).

Electrophysiological recordings

EEG and vertical electro-oculogram (VEOG) were recorded in a standardized fashion using a computerized recording system (ProComp Infiniti, Thought Technology; Montreal, Canada). The EEG was recorded using a bipolar montage from three active scalp positions using golden electrodes. The EEG active sites were F3, Fz and F4, referenced online to Cz, consistently with previous neurofeedback studies (Allen et al., 2001). Using a bipolar montage, VEOG was recorded in order to control for eye-movements and eye-blinks. Electrodes were placed at the supra- and suborbit of the right eye.

All electrodes impedances were kept below 5 kΩ. Each physiological signal was amplified, band-pass filtered (1–100 Hz) and digitized at 2048 Hz with ProComp Infiniti Encoder.

Frontal alpha asymmetry neurofeedback

Each training session began with a 5-min baseline recording at rest with eyes open, in order to establish the baseline frontal alpha asymmetry. Mean baseline values were used to calculate the threshold for the training session, defined as mean activity + 0.85 standard deviations (Allen et al., 2001). Five 5-min biofeedback training trials followed, with a 1-min inter-trial break. Each trial was segmented in 150 2-s epochs.

Alpha power (8–13 Hz) at right (F4) and left (F3) frontal leads was extracted online using a fast Fourier transform algorithm with a Hamming window function applied to the 2-sec epoch. The difference in alpha power between right and left (F4-F3) was then computed and compared against the threshold value established during the baseline. Participants had a visual feedback consisting of a histogram reflecting the level of frontal alpha asymmetry. If the (F4-F3) alpha power difference was below the threshold the histogram was red, if the (F4-F3) alpha power difference exceeded the threshold the histogram instantly turned green. The feedback was inhibited if ocular activity exceeded ± 50 μV.

In the control condition, participants had the same visual feedback, but it reflected the changes in alpha power recorded at Fz electrode, instead of frontal alpha asymmetry. Before starting the training, participants were told that biofeedback training involved modifying the activity of their brains, and that they should try to maintain the bar green as long as they could. Participants were never told that the biofeedback was contingent on frontal alpha asymmetry and/or mid-frontal alpha.

EEG data processing

The signal was down-sampled offline at 256 Hz, and continuous EEG data correction for eyeblinks was performed through a regression-based correction algorithm (LMS regression; Gómez-Herrero, 2007). Epochs of 500 ms each were then obtained from the continuous signal and EEG chunks containing artifacts greater than ±70 μV were automatically rejected (using EEGLAB plugin Darbeliai). Each EEG segment was further inspected for residual artifacts. For each accepted epoch, a Hamming

windowing was applied and chunks were then overlapped by 50% to minimize loss of data. A Fast Fourier Transform (FFT) method was used to derive estimates of spectral power (μV^2) for each electrode site. Power density values (μV^2/Hz) were calculated averaging spectral power within the alpha band (8-13 Hz) for each participant at all sites.

Statistics

Resting frontal alpha right (F4), left (F3) and resting central (Fz) alpha measures were normalized using a natural logarithmic transformation. After transformation, data were normally distributed, as assessed with the Kolmogorov–Smirnov-test. Alpha asymmetry was calculated subtracting the natural logarithm of alpha power at F3 site from F4 (i.e., ln[F4]-ln[F3]).

Analyses of variance (ANOVAs) with Group (Asymmetry, Active control) as a between-subjects factor was used to compare the two groups in terms of age, education, resting alpha asymmetry (right (F4) and left (F3) alpha power) and central alpha (Fz).

Changes in resting frontal alpha asymmetry were evaluated running an ANOVA with Group as a between-subjects factor and Time (pre-training assessment, post-training assessment) as a within-subjects factor.

Changes in absolute alpha power at left and right sites were evaluated running an ANOVA with Group as a between-subjects factor, Time and Lateralization (F4, F3) as within-subjects factors.

An ANOVA with Group as a between-subjects factor and Time as a within-subjects factor was run to test changes in alpha power in Fz. Separate ANOVAs with Group as a between-subjects factor and Time as a within-subjects factor were conducted on each psychological measure, namely the PANAS NA and PA scores, BAI and BDI-II.

Whenever the sphericity assumption was violated, the Greenhouse-Geisser correction was applied. Corrected p-values, ε estimates and uncorrected degrees of freedom are reported. Tukey HSD test was used for post hoc analyses. Main effects and interactions were considered to be significant at $p < .05$. Partial eta-squared (η_p^2) was reported as a measure of the effect size (Cohen, 1988).

In order to evaluate the relationship between training-induced changes in frontal alpha asymmetry, alpha power at left (F3) and right (F4) sites, and subjective measures, Pearson's correlations were performed between changes in these measures (post-training minus pre-training scores). STATISTICA 6.1 software (StatSoft Inc, Tulsa, OK) was used for statistical analysis.

3.7.6 Results

Characteristics of Participants in the Asymmetry and Active control groups

ANOVAs yielded no group differences for age ($F_{(1, 30)} = 0.75$, $p = .40$, $\eta_p^2 = 0.02$), education ($F_{(1, 30)} = 0.11$, $p = 0.74$, $\eta_p^2 = 0.004$), pre-training alpha at left ($F_{(1,30)} = 0.27$, $p = .61$, $\eta_p^2 = 0.01$), central ($F_{(1, 30)} = 0.21$, $p = 0.65$, $\eta_p^2 = 0.01$) and right ($F_{(1,30)} = 0.04$, $p = .83$, $\eta_p^2 = 0.001$) electrodes (i.e., F3, Fz and F4). The descriptive statistics for each group are reported in Table 3.5.

Table 3.5 Demographics and pre-training log-transformed alpha power at frontal sites for the Asymmetry and the Active Control groups.

Variables	Asymmetry group (N = 16)	Active control group (N = 16)
Demographics		
Age	22.9 (1.2)	23.3 (1.2)
Education	17.2 (1.1)	17.2 (1.0)
Alpha power pre-training		
F3	0.69 (0.3)	0.63 (0.3)
Fz	0.45 (0.3)	0.40 (0.3)
F4	0.62 (0.3)	0.60 (0.3)

Note. Data are M (SD). F3 = left frontal site; Fz = mid-frontal site; F4 = right frontal site.

Effects of Neurofeedback on EEG Measures

From the ANOVA on frontal alpha asymmetry emerged a significant Group × Time interaction ($F_{(1, 30)} = 4.94$, $p < .05$, $\eta_p^2 = 0.14$), as depicted in Figure 3.13.

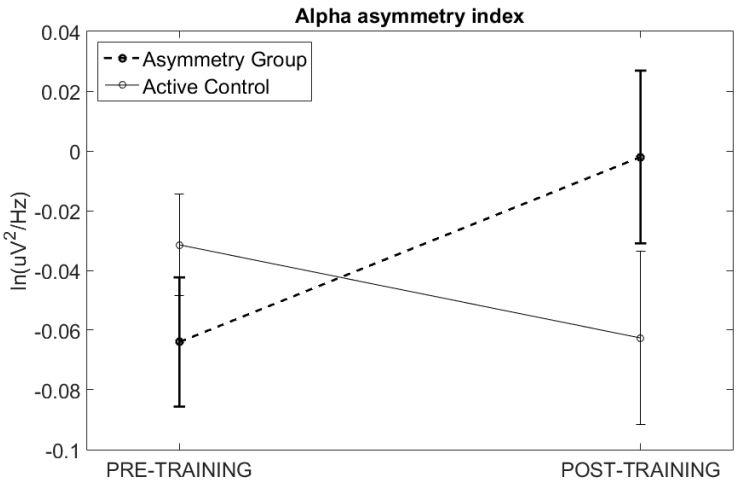

Figure 3.13 Neurofeedback modulation of alpha asymmetry: the asymmetry group, but not the active control, showed a significant increase in alpha asymmetry from pre- to post-training.

In order to further characterize this interaction, changes in alpha power at left and right sites were evaluated. The Group by Time ANOVA on right (F4) and left (F3) alpha power was run. A significant effect for Lateralization ($F_{(1, 30)} = 8.26$, $p < .01$, ε =

.99, η_p^2 = 0.22), in the context of a Group × Time × Lateralization interaction emerged ($F_{(1, 30)}$ = 4.94, p < .05, ε = .99, η_p^2 = 0.14; see Figure 3.14). Tukey post hoc showed a significant increase in alpha right (F4) power from pre- to post-training in the Asymmetry group (p < .001), whereas no significant difference in alpha right (F4) and left (F3) power from pre- to post-training was found in the active control group (p = .90). No other main effects or interactions emerged (all p's > .10). ANOVA did not show any main effect for Group and Time or Group × Time interaction on central alpha (Fz) activity (all p's > .17).

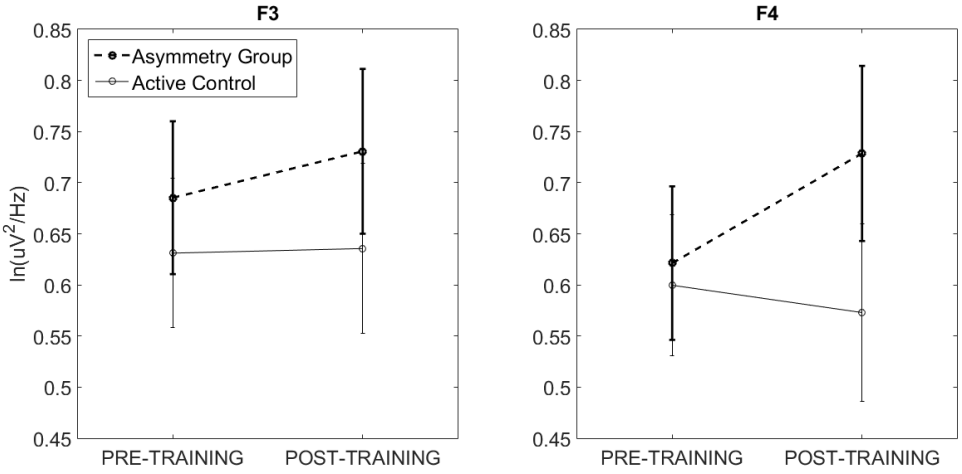

Figure 3.14 Neurofeedback modulation of left and right alpha power: the asymmetry group, but not the active control, showed a significant increase in resting alpha power at F4, but not F3, from pre- to post-training.

Effects of neurofeedback on Affect, Anxiety and Depressive symptoms

ANOVA on PANAS Negative Affect scores showed a significant main effect for Time ($F_{(1, 30)}$ = 6.78, p < .05, η_p^2 = 0.18) and a Group × Time ($F_{(1, 30)}$ = 4.13, p = .05, η_p^2 = 0.12) interaction. Tukey post-hoc comparisons revealed a significant decrease in PANAS Negative Affect scores from pre-training to post-training in the Asymmetry group (p < .05), whereas no significant difference in the NA-PANAS scores from pre- to

post-training was found in the active control group (p = .98). On the contrary, the group by time ANOVA on PANAS Positive Affect scores did not reveal a significant effect for neither Group ($F_{(1, 30)}$ = 0.43, p = .52, η_p^2 = 0.01), Time ($F_{(1, 30)}$ = 1.10, p = .30, η_p^2 = 0.04), nor Group × Time ($F_{(1, 30)}$ = 0.12, p = .73, η_p^2 = 0.004).

The Group by Time ANOVA on BAI scores yielded a significant effect of Time ($F_{(1, 30)}$ = 12.27, p < .01, η_p^2 = 0.29), further characterized by a Group × Time interaction ($F_{(1, 30)}$ = 5.51, p < .05, η_p^2 = 0.16). Tukey post hoc comparisons showed a significant decrease in BAI scores from pre-training to post-training in the Asymmetry group (p < .01), whereas no significant difference in the BAI scores from pre- to post-training was found in the Active control group (p = .85).

The Group by Time ANOVA on BDI-II scores yielded a significant effect for Time ($F_{(1, 30)}$ = 5.07, p < .05, η_p^2 = 0.14). No main effect of Group or Group × Time interaction emerged (all p's > .19). All means (SD) and statistical details are reported in Table 3.6.

Table 3.6 ANOVA on Depression, Anxiety, Positive and Negative Affect Scores from Pre- to Post-training in Asymmetry Group and Active Control.

Variables	Pre-training	Post-training	p	η_p^2
PANAS Positive Affect Score			.73	0.004
Asymmetry Group	27.56 (10.35)	29.19 (6.53)		
Active Control	29.94 (8.87)	30.75 (10.20)		
PANAS Negative Affect Score			.05	0.12
Asymmetry Group	19.25 (9.03)	14.69 (6.46)	< .01	
Active Control	18.44 (6.64)	17.88 (8.58)	.69	
BAI			< .05	0.16
Asymmetry Group	11.38 (9.56)	6.00 (5.56)	< .001	
Active Control	10.19 (9.39)	9.13 (8.00)	.42	
BDI-II			.19	0.06
Asymmetry Group	9.75 (12.38)	6.00 (7.90)		
Active Control	8.13 (7.30)	7.19 (9.59)		

Note. Data are M (SD). ANOVA = analysis of variance; PANAS = Positive and Negative Affect Schedule; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory II.

Correlational analyses

No significant correlations emerged between changes in frontal alpha asymmetry (as well as changes in left and right absolute alpha power) and changes in subjective measures from pre- to post-training (all *p*'s > .30).

3.7.7 Discussion

The present findings support the efficacy of the frontal alpha asymmetry neurofeedback in *decreasing right compared to left prefrontal activity*, in line with previous research (Harmon-Jones et al., 2008; Peeters et al., 2014). More importantly, to our knowledge, this is the first study to report that this effect is subtended by a specific *reduction in the right frontal activity from pre- to post-training*, as revealed by a significant increase in alpha power at the right, but not left, scalp site. Changes in subjective measures are in line with the neurophysiological evidences. A significant decrease in negative affect, which is thought to be subtended by the right prefrontal lobe (Jacobs & Snyder, 1996; Schaffer et al., 1983; Tomarken et al., 1992), emerged from pre- to post-training, while positive affect showed no modulation. Coherently, levels of anxiety were specifically reduced after the asymmetry neurofeedback, while no difference between groups emerged for changes in depressive symptoms.

Therefore, the present work provides a strong rationale for the use of the asymmetry training for increasing alpha activity at right prefrontal sites, in order to reduce negative affect and anxiety in clinical settings. Reduction of negative affect and anxiety could not be obtained by training the participants to increase frontal alpha power at midline (active control group). It is worth highlighting that neurofeedback to

increase alpha power has been traditionally used for the reduction of stress and anxious symptoms (Brown, 1970b; Hammond, 2005; Hardt & Kamiya, 1978), targeting the occipital and parietal sites. Since in the present study no modulation of mid-frontal alpha emerged, neurofeedback for the increase of alpha power at mid-frontal sites seems less effective compared to posterior sites.

The fact that both positive affect and depressive symptoms were unaffected by the frontal asymmetry training is mirrored by the absence of changes in left frontal activity. We hypothesized that, in order to have an impact on depression, neurofeedback ought to be focused on increasing left prefrontal activity, thus stimulating approach motivation. Interestingly, by inhibiting slow alpha and theta activity while reinforcing higher frequencies at left prefrontal sites (i.e., FP1 and F3), case report studies yielded positive results in the treatment of clinical depression (Hammond, 2000, 2005). A small number of case studies also investigated the effect of frontal alpha asymmetry in clinically depressed patients, overall showing that several patients reported an improvement in depressive symptoms (Baehr & Baehr, 1997; Baehr et al., 1997, 2001; Earnest, 1999). Nonetheless, no controlled studies exist so far, and it is unclear whether this specific asymmetry protocol modulated the left or the right prefrontal activity. Clearly, further studies are warranted to validate a specific neurofeedback protocol for the reduction of depressive symptoms.

A linear correlation between changes in frontal alpha asymmetry and changes in affective measures did not emerge. Therefore, although participants who underwent frontal alpha asymmetry training showed both a decrease in right frontal activity, and a parallel reduction in subjective measures of negative affect and anxiety, these

changes were not linearly related. Several studies supported the idea that these measures are linearly related only during the execution of emotional tasks, due to the direct involvement of the approach/avoidance motivational systems (Coan et al., 2006; Stewart et al., 2011), but that this relationship may not emerge in resting conditions (Elgavish et al., 2003; Hagemann et al., 1998; Heller & Nitscke, 1997; Hewig et al., 2004; Hofmann, 2007; Reid et al., 1998); in this respect, our results are in line with previous findings.

3.7.8 Conclusions

In summary, the present study argues in favor of the employment of frontal alpha asymmetry neurofeedback to increase right frontal alpha activity, in order to reduce negative affect and anxiety levels, laying the foundations for testing on subclinical and clinical populations. On the other hand, we suggest that future research should investigate the effects of neurofeedback training aimed at increasing left prefrontal activity on approach motivation, positive affect and depressive symptoms.

4 GENERAL DISCUSSION

4.1 A summary of the main findings

This thesis referred to a theoretical framework supporting the existence of two main motivational systems at the neural level, which underlie basic affect and responses to emotional stimuli (Davidson, 2004; Dickinson & Dearing, 1979; Lang, 2010): the *appetitive*/*approach* system, which drives approach behaviors toward pleasant stimuli and subtends positive affect, and a *defensive/avoidance* system, associated with defensive responses to threatening stimuli and unpleasant affect. The brain structures involved in the two motivational circuits have been described, with particular attention to the role of the left and right prefrontal cortex. Finally the EEG correlates of motivational tendencies elicited by emotional stimuli have been summarized.

The primary aim of the thesis was to investigate emotional processing in psychopathologies characterized by negative affect. Negative affect has been often described as an excessive tendency to withdrawal from unpleasant stimuli, which is thought to potentiate responsivity to negative stimuli. Partially in contrast with these models, we have argued that negative affect might not be always associated with a prevalence of active withdrawal tendencies. For instance, certain psychopathological conditions, such as blood phobia and dysphoria, are characterized by negative affect, although they do not seem to display heightened reactivity and action disposition in response to threatening stimuli. Since the motivational underpinnings of these two conditions potentially represent exception in the classical conceptualization of negative affect, the EEG correlates of their motivational dispositions have been

studied. In order to do so, emotional paradigms which had the characteristic of actively stimulating motivational tendencies have been employed.

As far as Study 1 is concerned, results support the presence of conflicting motivational tendencies in blood phobia when facing the feared stimulus. In particular, emotional salience of mutilation stimuli was higher for the individuals with blood phobia, as indexed by frontal theta synchronization; at the same time, mutilation pictures also induced a passive avoidance mechanism, reflected in the pronounced increase in alpha power at right compared to left frontal site. This conflicting attentional and motivational response at the EEG level is consistent with results from previous studies reporting a co-occurrence of motivational tendencies to attend and avoid feared stimuli in blood phobia (Buodo et al., 2002; Engel, 1978; Graham et al., 1961; Hamm et al., 1997; Öst, 1992; Sarlo et al., 2008). Therefore, negative affect in response to the phobic stimulus in blood phobia does not arise from a straightforward increase in withdrawal motivation and action disposition. Importantly, this reaction in blood phobia radically differs from the other subtypes of specific phobias, where a clear active withdrawal response is typically prompted.

From Study 2 and 3 emerged that, already at the subclinical level, depression is associated with an attenuated response to the emotional salience of pleasant stimuli, as indexed by the reduction of frontal theta during an emotional imagery task. Moreover, as trait-like characteristic, individuals with dysphoria also demonstrated a reduction in approach motivation, irrespective of emotional condition, as testified by a decrease in the frontal alpha asymmetry index, compared to controls (i.e., reduced left compared to right prefrontal activity). Overall, these findings support a *positive*

attenuation hypothesis for depression, suggesting that excessive negative mood is determined by attenuated reactivity to pleasant stimuli, in line with previous reports (Berenbaum & Oltmanns, 1992; Buodo, Mento, et al., 2015; Dunn et al., 2004; Sloan et al., 1997). Importantly, these findings are in line with theories describing depression as a deficit in appetitive motivation, which has been proposed to reveal in core symptoms, such as anhedonia, loss of pleasure and behavioral apathy (Davidson, 1998a, 1998b, 2004; Henriques & Davidson, 2000). On the other hand, the present results contrast with the negative potentiation hypothesis as well as with early theories of negative affect (Beck, 1987; Clark & Beck, 2010; Ferster, 1973) which proposed that dysphoria is characterized by hyperarousal and disposition to actively withdrawal from unpleasant stimuli.

Overall, these results indicate that negative affect can arise from complex patterns of interaction between the appetitive and the defensive motivational systems. Our data add to the literature a better characterization of the neural correlates of these interactive patterns in psychopathology, in the context of emotional tasks which directly stimulate motivation and action disposition. Moreover, our data offer strong support for the employment of the motivational model of emotion in the study of psychopathology. Recourse to the motivational model has several important advantages, such as the possibility of highlighting different patterns of emotional dysregulation in psychopathologies pertaining to the same nosographic category (Kring & Bachorowski, 1999). The other side of the coin is that this model allows accounting for similar emotional disturbances across disorders having markedly different symptom pictures. In this sense, this perspective strongly encourages a

transdiagnostic approach to the description and treatment of emotion-related difficulties in psychopathology. Accordingly, emotional disturbances span across the majority of psychiatric disorders included in the international classification systems, overall interfering with the achievement of emotion-related adaptive functions (Kring, 2010). Since many of these emotional disturbances can be construed as deficits motivational components of emotional processing (Kring & Bachorowski, 1999), basic research in Affective Neurosciences is important in the disclosure of the underlying neuropathological mechanisms. Discoveries in this sense have also a great potential in terms of clinical applications, especially in the context of bio-behavioral techniques such as neurofeedback.

Accordingly, in Study 4 we posed a first step toward the exploration of the clinical potential of findings emerged in studies 1, 2 and 3. In general, our first three studies supported the sensitivity of EEG bands in reflecting motivational and emotional dysregulation. For instance, in line with the pertaining literature, frontal alpha asymmetry emerged as an informative index of motivational tendencies underlying affect and emotional responses, (e.g., Allen, Coan, et al., 2004; Coan et al., 2006; Coan & Allen, 2003, 2004; Davidson, Chapman, & Chapman, 1987; Davidson et al., 2000; Davidson, 1988, 1998a, 1998b, 2004; Harmon-Jones & Allen, 1997, 1998; Harmon-Jones, 2007; Harmon-Jones et al., 2002, 2010, 2006, 2009; Harmon-Jones, 2004; Heller & Nitscke, 1997; Henriques & Davidson, 2000; Schaffer et al., 1983; Shankman & Klein, 2003; Stewart et al., 2014; Tomarken, Davidson, & Henriques, 1990; Tomarken et al., 1992; Wheeler et al., 1993). Accordingly, Study 4 investigated the effects of a frontal alpha asymmetry neurofeedback on positive and negative affect, anxiety and

depressive symptoms in healthy individuals. Participants succeeded in reducing right compared to left prefrontal activity, as indicated by a specific increase in right frontal alpha. In accordance with both the valence and the motivational models for the left and right divisions of the dlPFC, this increase in right frontal alpha power was associated with a significant reduction in negative affect and anxiety. This result, which is strongly coherent with modulation of frontal alpha in Study 1, suggests that this neurofeedback training is better suited for the treatment of subclinical and clinical anxiety, more than for depression. Accordingly, null effects on depressive scores and positive affect are in line with results emerged in Studies 2 and 3, which showed that depression more likely subtended by reduced appetitive motivation, as revealed by left-prefrontal hypo-activation. Overall, it appears that a precise description of the motivational mechanisms subtending psychological disturbances, as well as a characterization of their neural correlates, has interesting potential also for clinical applications.

4.2 Limitations of the research

The current findings should be interpreted in light of a number of limitations. First, scalp EEG indices have not been directly related to underlying neural sources in the present studies. Although a vast amount of literature supports that frontal alpha asymmetry mainly reflects the contribute of left and right dlPFC (e.g., Davidson, 2004; De Pascalis et al., 2013) and that mid-frontal theta is generated in the rACC (Asada et al., 1999; Gevins et al., 1997; Ishii et al., 1999; Mizuki et al., 1984; Pizzagalli, Oakes, et al., 2003) these results could not be replicated in the present studies, due to the low-density EEG systems used. In order to provide stronger support over the implication of

brain structures involved in the appetitive and defensive systems in the brain, high density EEG or, possibly better, MEG systems ought to be employed. In particular, MEG has been recently successfully used for frequency-specific reconstruction of cortical, and also subcortical, activation in the limbic system in response to emotional stimuli (Cornwell et al., 2008; Dunkley et al., 2014; Garolera et al., 2007; Hung et al., 2010, 2013; Leung, Ye, Wong, Taylor, & Doesburg, 2014; Luo et al., 2013, 2007; Maratos, Mogg, Bradley, Rippon, & Senior, 2009; Quraan, Moses, Hung, Mills, & Taylor, 2011; Sato, Kochiyama, Uono, Yoshikawa, & Toichi, 2016; Styliadis et al., 2014). Therefore, under the aspect of source localization of specific neural oscillation, MEG would have represented the gold standard for the present thesis. However, the use of well-defined EEG scalp indexes in this context added important information on blood phobia and dysphoria, and on the conceptualization of the motivational underpinnings of conditions characterized by negative affect. More importantly, the modulation of an easy-recordable EEG scalp index such as frontal alpha asymmetry during a neurofeedback training was effective in modifying affect in healthy individuals. Thus, this EEG training represents a ready-to-use tool for everyday clinical application, in contrast to MEG, which is still extremely expensive and largely unavailable in clinical settings.

Second, the studies reported in this thesis did not include patients with a clinical diagnosis of blood phobia nor depression. Nonetheless, as blood phobia is concerned, it is not frequent for individuals to have a formal psychiatric diagnosis. Accordingly, most individuals with blood injury phobia do not search or actively refuse medical assistance because of anxiety symptoms emerging in clinics and/or hospitals (Wani,

Ara, & Bhat, 2014). Therefore, throughout an accurate assessment based on both a self-report questionnaire (MQ) and a structured interview (ADIS-IV), we ensured participant's adherence to standard diagnostic criteria. Furthermore, it is well known that depression includes milder subclinical conditions, such as dysphoria (Judd et al., 1997, 1994). Our findings supported that, already at the subclinical level, depression is characterized by a stable pattern of reduced approach motivation and reduced processing of pleasant stimuli's motivational salience. This is in line with recent studies suggesting that reduced approach motivation may represent an endophenotype or, at least, a risk factor for major depression (Stewart et al., 2011, 2014). Importantly, studying a sub-clinical sample allowed us to exclude effects of medications on EEG results.

Finally, in the neurofeedback study, it could be argued that a significant effect of the training on depression scores did not emerge due to the fact that healthy individuals typically do not present relevant depressive symptoms. Therefore, scores might have been too low to be significantly reduced, while the training would have been effective on clinically depressed individuals. Although this hypothesis cannot be excluded, our findings on positive and negative affect argue against this interpretation. In particular, negative affect was significantly reduced in the frontal alpha asymmetry group, but not in the active controls. On the contrary, positive affect was not modified by the training. Since motivational correlates of positive affect are thought to be mainly subtended by the left-prefrontal cortex (De Pascalis et al., 2013, 2010; Harmon-Jones & Allen, 1997, 1998; Sutton & Davidson, 1997; Tomarken et al., 1992; Wheeler et al., 1993), and that depression has been related to a left-sided hypo-activation

(Davidson, 2004; Stewart et al., 2014), null findings on both measures are likely to mirror the absence of alpha modification at left-frontal sites. Similarly, the reduction in both negative affect and anxiety scores is consistent with right-sided increase in alpha power in the frontal asymmetry group.

4.3 Direction for future research

Future research ought to further investigate motivational underpinnings of psychopathologies characterized by negative affect. In the case of blood phobia, it would be informative to test action disposition through approaches which allow separating effects due to motivated attention on the stimulus from those directly ascribable to motor inhibition. Accordingly, from Study 1 it emerged that heightened attentional allocation has a consistent role in slowing down responses to mutilation stimuli in individuals with blood phobia, as well as in in healthy controls, in line with results from the literature (Buodo et al., 2006, 2002; Sarlo et al., 2010; Sarlo, Buodo, et al., 2005; Schäfer et al., 2010; Schupp et al., 2004). As it has been described in the introductive chapter, motivated attention on emotional stimuli is one of the mechanisms determining readiness to respond, in the sense that greater attention is associated with slower responses. Nonetheless, it would be interesting to dissociate whether mutilation stimuli have a direct effect on the motor readiness to withdrawal in individuals with blood phobia, other than the indirect one mediated by attention. In this sense, a possible solution could be to employ the Approch-Avoidance Task (AAT), including phobia-related stimuli. This task requires the participants to respond to picture presentation by moving a joystick, either by pushing it away from themselves (avoid) or by pulling it towards themselves (approach), based on a simple

discrimination of picture's content (e.g., whether or not it contains a certain feature). In case the attentional mechanism is the dominant one, one would expect slower responses to mutilation stimuli both in case the joystick was pulled and pushed. Otherwise, if action readiness to *withdrawal* is directly inhibited, one should observe even slower responses when the participants are required to push the joystick (avoid). As reported in the introduction, this task was effective in revealing increased withdrawal disposition in response to feared stimuli in individuals with spider phobia (Rinck & Becker, 2007). Eventually, in the context of the same task, through the use of high-density EEG systems, the activation in the motor cortices in response to mutilation stimuli could be also investigated, presumably helping to disentangle attentional from motor effects.

As far as depression and dysphoria are concerned, the present studies strongly argued in favor of a reduction in approach motivation toward pleasant stimuli as the mechanism underlying negative affect. Nonetheless, the implications on processing of unpleasant stimuli remain partially unclear. In particular, it is not well determined whether action disposition toward unpleasant stimuli is increased or decreased in depressed individuals, in the context of a tonic reduction of approach motivation. Some authors proposed that clinical depression is associated with a general insensitivity to emotional contexts, whether they are pleasant or unpleasant. In other words, depressed mood states would reduce the natural tendency of the organism to respond to external stimuli, thus biasing the organism against action (Nesse & Ellsworth, 2009; Nesse, 2000). On the contrary, the depletion of appetitive motivation could let the threat detection mechanisms subtended by the defensive motivational

system “unbalanced”. Therefore, response to sudden threatening stimuli might be stronger or faster. Such a mechanism might have been obscured in the emotional imagery paradigm, where individuals were asked to actively generate a prolonged unpleasant state. Therefore, the investigation of EEG correlates in paradigms such as the AAT, but also the emotional Go/Nogo, or other tasks requiring fast reactions or motor inhibition in response to externally presented emotional stimuli might be useful to complete this further step in understanding the complex motivational pattern underlying depression. Moreover, due to the high comorbidity between depressive and anxious symptoms, also at the subclinical level, it would be important to understand whether appetitive and defensive motivations in response to emotional stimuli in depressed individuals are influenced by the presence of anxiety.

From the methodological point of view, in line with the reported limitations, future studies ought to investigate with high resolution in frequency, in time, and in space the motivational deficits underlying negative affect and, more in general, emotion-related psychiatric disorders. Thanks to improvements in source localization, the study of EEG and MEG event-related oscillations is providing useful insights on the time course of brain responses to emotional stimuli in anxiety (Mcteague, Shumen, Wieser, Lang, & Keil, 2012), affective disorders (Domschke et al., 2016; Lee, Chen, Hsieh, Su, & Chen, 2010), posttraumatic stress disorder (Cohen et al., 2013), schizophrenia (Lee, Kim, Kim, Kim, & Im, 2010), autism (Wright et al., 2012) and personality disorders (Weber et al., 2009), among others. Importantly, in recent years, emotional disturbances started to be attributed to dysfunctional neural communication within the emotional network, more than to an impaired activation of

single brain regions (Menon, 2011). Therefore, especially thanks to the use of precise MEG brain source reconstruction, crucial information can be obtained regarding functional connectivity at different frequencies during emotional processing in psychopathology. Nonetheless, due to the novelty of these approaches, especially applied to emotional processing, only few studies have been conducted so far, for instance on schizophrenia (Popov, Rockstroh, Popova, Carolus, & Miller, 2014), autism (Leung et al., 2014), depression (Lu, Wang, Luo, Li, & Yao, 2013) and posttraumatic stress disorder (Dunkley et al., 2016). In this sense, we started several projects to investigate these aspects in psychiatric patients through the use of MEG, to take advantage of its excellent time and frequency resolution, and good spatial resolution (Cohen & Cuffin, 1987; Hari, 2011). In particular, through the collaboration with the Department of Diagnostic Imaging at the Hospital for Sick Children in Toronto we are now investigating:

- Event-related MEG responses to trauma related stimuli in soldiers with posttraumatic stress disorder (PTSD). Interest in PTSD is related to the fact that this is a disorder associated with strong anxiety and avoidance from the traumatic stimuli, thus very informative on cortical and subcortical systems implicated in withdrawal motivation. Thanks to MEG spatial resolution, the preliminary results support a hyper-responsivity of the withdrawal system both at the subcortical limbic (i.e., amygdala) and cortical paralimbic level (i.e., anterior cingulate, insula).

- Motivational deficits in adults with autism toward socially relevant stimuli, as revealed from MEG connectivity in the circuits which subserve detection of

emotional salience. Our results support *reduced* functional connectivity in these circuits during implicit emotional processing of facial expressions.

Moreover, thanks to the collaboration with the San Camillo Hospital in Venice, we started a project on the investigation of MEG correlates of dysfunctional motivational systems in neurological disease characterized by negative affect, such as multiple sclerosis. This project is aimed at clarifying the effects on affectivity and emotional responses of neurological damage, especially structural and functional disconnection within the motivational circuits. Overall, these projects will help us to move forward in the characterization of motivational underpinnings of emotional deficits, with more precise spatial information on the underlying neural circuits.

As far as frontal alpha asymmetry neurofeedback is concerned, Study 4 laid the foundations for testing on clinical anxiety. As mentioned above, only one uncontrolled study from Kerson and colleagues (2009) applied frontal asymmetry training to reduce anxiety in anxious adults, with encouraging results. We hypothesize that anxious patients would benefit from the training. Accordingly we expect frontal alpha asymmetry neurofeedback to increase alpha at right frontal sites, thus inducing a decrease in withdrawal motivation, negative affect and anxiety symptoms. As suggested in 'Limitation for the research', we cannot exclude that clinically depressed patients would benefit from the training. In particular, in depressed individuals the left-right balance in dlPFC activity is shifted toward left hypo-activation compared to right. Therefore, it is possible that in these patients the frontal alpha asymmetry training would induce an increase in left and not a decrease in right frontal activity, in contrast with the pattern observed in healthy individuals. Accordingly, several case

studies support the effectiveness of the training in reducing depressive symptoms, although they do not specify whether this is due to a change in left or right frontal activity (Baehr & Baehr, 1997; Baehr et al., 1997, 2001; Choi et al., 2011; Earnest, 1999). Therefore, the training adopted in Study 4 ought to be run on both anxiety and depressed patients, to discriminate efficacy on the two groups. Importantly, there is a strong need for a control condition such as the one employed in Study 4, since the vast majority of studies in the field are still uncontrolled (Baehr & Baehr, 1997; Baehr et al., 1997, 2001; Choi et al., 2011; Earnest, 1999; Hammond & Baehr, 2009; Hammond, 2000, 2005; Kerson et al., 2009).

Interestingly, recently EEG neurofeedback has been proven to induce changes in resting neural activity as measured with fMRI (Ros et al., 2013). In posttraumatic stress disorder, for instance, it has been reported that a single session of neurofeedback on alpha band has significant impact on resting state networks in the brain (Kluetsch et al., 2014). Moreover, fMRI and other neuroimaging techniques, such as MEG, represent promising tools to target specific brain areas with neurofeedback. In particular, recent studies showed that MEG training can be used to alter neural activity at specific neuromagnetic frequencies in target brain regions, with a time resolution up to few hundreds milliseconds (Boe, Shaun, Gionfriddo, Alicia, Kraeutner, Sarah, Tremblay, Antoine, Bardouille, 2014; Florin, Bock, & Baillet, 2014; Foldes, Weber, & Collinger, 2015; Sudre et al., 2011). Intriguingly, there is preliminary evidence for the feasibility of a neurofeedback of MEG connectivity among brain regions, which would be of extreme interest for applications in neuropsychiatric disorders (Ora et al., 2013). Nonetheless, MEG source-based neurofeedback is still a newborn technique, with

extremely high costs in terms of resources and know-how. Accordingly, it has never been tested on clinical populations so far. Therefore, EEG neurofeedback represents nowadays the simplest and ready-to-use neurofeedback training to implement in clinical settings (Florin et al., 2014).

4.4 General conclusions

Overall, findings included in this thesis represent a further step toward the characterization of motivational underpinnings underlying negative affect, as revealed by emotional modulation of EEG bands. In particular, the present results support the notion that negative affect in psychopathology is not always determined by increased avoidance disposition and responses to unpleasant stimuli. Accordingly, a specific subtype of phobia, namely blood phobia, exhibited a conflicting motivational pattern of attendance and withdrawal from the feared object, contrary to other specific phobias. Moreover, negative affect in subclinical depression resulted to be associated with a reduction in approach motivation and processing of appetitive stimuli, and not to excessive avoidance mechanisms. Overall, the results contributed to add specifications to the motivational model of emotion, presented in the introductive chapter. More importantly, these findings provided new evidence supporting the usefulness of frontal alpha asymmetry neurofeedback in decreasing right frontal activity to reduce negative affect and anxiety symptoms in healthy individuals. Taken together, these results strongly support the use of the motivational model of emotion in the study of psychopathology, to achieve a transdiagnostic characterization of emotional disturbances across clinical disorders, and to design evidence-based bio-behavioral treatments.

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Appendix 1 Emotional pictures employed in Study 1. Reference numbers from the IAPS standardized set (Lang, Bradley, & Cuthbert, 2008, and in bold from the archive of the University of Padua), and corresponding average ratings in valence and arousal.

Condition	ID	Valence	Arousal
Mutilations	**0601, 0603, 0604, 0606, 0608, 0609, 0610, 0612, 0613, 0616, 0618, 0620, 0624, 0625, 0629**, 3000, 3010, 3030, 3051, 3060, 3071, 3080, 3100, 3102, 3110, 3120, 3130, 3150, 3400, 9405	2.18 (0.57)	6.28 (0.78)
Threat	1050, 1051, 1114, 1120, 1300, 1301, 1302, 1321, 1930, 1932, 3500, 6200, 6210, 6230, 6424, 6243, 6244, 6250, 6260, 6300, 6312, 6313, 6370, 6510, 6540, 6550, 6560, 6571, 6821, 9425	2.99 (0.69)	6.43 (0.5)
Neutral	7000, 7002, 7004, 7009, 7010, 7020, 7035, 7036, 7037, 7041, 7050, 7056, 7059, 7130, 7140, 7175, 7217, 7224, 7233, 7235, 7242, 7491, 7500, 7546, 7547, 7560, 7590, 7595, 7700, 7950	4.93 (0.27)	2.95 (0.72)
Pleasant	4611, 4647, 4651, 4652, 4658, 4660, 4664, 4670, 4672, 4680, 4683, 4690, 4695, 4800, 4810, 8030, 8031, 8034, 8080, 8160, 8161, 8178, 8179, 8180, 8185, 8186, 8200, 8370, 8400, 8490	6.84 (0.61)	6.56 (3.39)

Note. Valence and arousal ratings are M (SD).

Appendix 2 Narratives from the ANET standardized set (Bradley & Lang, 2007) empoyed in Studies 2 and 3. Italian translation and normative Valence and Arousal ratings.

Condition	ID	English	Italian	Valence	Arousal
Pleasant	4670	A moan of pleasure. Your body responds slowly at first, languorously, and then with a more urgent rhythm. You feel gentle hands, a soft mouth, your back arches.	Un gemito di piacere. Il tuo corpo risponde dapprima lentamente, languidamente, poi a ritmo più urgente. Senti le mani delicate, la bocca soffice, la tua schiena s'inarca.	8.15 (1.28)	8.01 (1.40)
	4400	You shiver as your bodies brush together. You reach out. You want to touch everywhere, kiss everywhere. You hear the words, "I love you".	Hai un brivido mentre i vostri corpi si sfiorano. Allunghi le braccia. Vuoi toccare dappertutto, baciare dappertutto. Senti le parole "Ti amo".	8.28 (1.22)	7.91 (1.50)
Neutral	2540	You walk through the supermarket aisles checking things off your list as you pick each item you need off the shelves.	Cammini tra i corridoi del supermercato, spuntando le cose dalla tua lista man mano che prendi i prodotti che ti servono dagli scaffali.	5.54 (1.19)	3.38 (1.75)
	2580	You run the comb through your hair, straighten your collar, smooth out the shirt's wrinkles. Water is running in the sink. You turn it off and leave.	Ti passi il pettine tra i capelli, ti raddrizzi il colletto, lisciandoti le pieghe sulla camicia. L'acqua scorre nel lavandino. La chiudi e te ne vai .	5.55 (1.17)	3.60 (1.98)
Unpleasant	3310	You flinch, at the screech of brakes; you look up, and see the speeding car slam into your friend. Her leg is crushed, the artery torn, and blood pumps on the road.	Sobbalzi per lo stridere dei freni; alzi lo sguardo e vedi l'auto investire la tua amica a tutta velocità. La sua gamba è maciullata, l'arteria lacerata e il sangue schizza sulla strada.	1.30 1.08	8.15 1.54
	6800	It's late at night in a poorly lit parking lot. You tense, clutching the keys. Your car stands alone in the distance, when footsteps sound behind you.	È tarda sera in un parcheggio poco illuminato. Comici ad agitarti, tieni strette le chiavi. La tua automobile è isolata in lontananza, quando senti dei passi dietro di te.	2.50 (1.35)	7.50 (1.65)

Note. Valence and arousal ratings are M (SD).