

Neural correlates
of emotional face processing
in bulimia nervosa

Submitted by

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Table of Contents

Abstract	4
1 Introduction	5
2 Bulimia nervosa – background and characteristics	6
2.1 Clinical features and prevalence.....	6
2.2 Causes, contributory factors and comorbidity	7
2.3 Emotional dysregulation in eating disorders and bulimia nervosa.....	9
2.4 Summary of previous research and rationale of the study	12
3 Event-related potentials and emotional face recognition	14
3.1 Processing faces and emotional expressions	14
3.2 Electrophysiological measurements and the ERP technique.....	16
3.3 Emotional face processing stages as reflected by ERPs.....	18
3.4 Brain electrical source analysis	20
3.5 The functional neuroanatomy of emotional face processing.....	21
3.5.1 Structures for perceiving emotion from faces	23
3.5.2 Structures for the recognition of emotion in faces	25
3.6 Aim of the study	28
4 Methods	30
4.1 Subjects.....	30
4.2 Instruments	31
4.3 Stimuli and Procedure	33
4.4 EEG recording	34
4.5 ERP preprocessing and analysis	35
4.6 Brain electrical source analysis	36
5 Results	37
5.1 Sample characteristics	37
5.2 Emotional face recognition performance	38
5.3 ERPs waveform analysis	39
5.4 Spatiotemporal analysis of underlying sources	44

6 Discussion	50
6.1 Decreased emotional awareness but normal classification skills in BN	50
6.2 Differences in ERPs: Reduced N2 and elevated P3 amplitudes during emotional face processing in BN	51
6.3 Sources of neural activation during emotional face processing in BN.....	53
6.4 Summary.....	56
Reference List	58

Abstract

Objective: Empirical evidence suggests substantial deficits regarding emotion recognition in bulimia nervosa (BN). However, the nature of this impairment is subject of ongoing research. Aim of the current study was to investigate the processing of emotional faces in patients with BN.

Methods: Event-related potentials (ERPs) were recorded from 22 female patients with BN and 22 matched healthy controls while viewing neutral, happy, fearful, and angry facial expressions, and further analysed by using the brain electrical source localization method (BESA). Subjects' facial recognition performance was tested separately in a categorization task. In addition, emotion identification skills were assessed with the Toronto Alexithymia Scale (TAS) and the Eating Disorder Inventory (EDI subscale Interoceptive Awareness).

Results: BN patients reported greater difficulty in identifying their own feelings as well as in the regulation of emotional states. Although performance in the categorization task was comparable in BN and controls, the present ERP data demonstrate significant differences at the post-perceptual level of emotional face processing. While early processes of structural encoding, as indexed by the N170, were found to be intact, BN patients had a significant reduction of N2 amplitudes and showed higher P3 amplitudes in response to facial stimuli than healthy subjects. Furthermore, a source analysis in the time interval of the N2 revealed that these differences could be related to specific structures that collaborate with the emotional face processing system. In addition to core structures of face recognition, a dipole in the inferior parietal lobule was found in healthy controls as responding to fearful faces, whereas BN patients' data revealed neural activity in the parahippocampal gyrus.

Conclusion: The findings of the present study provide novel electrophysiological support for a differential processing of emotional faces in patients with BN as compared to healthy controls. Results suggest that BN patients have deficits in earlier and automatic emotion classification, which are followed by an increased allocation of attentional resources to compensate for those shortcomings. That mechanism might account for bulimics' comparable ability to classify a variety of emotional expressions on a behavioral level, but also underlines existing findings of increased difficulties in recognizing and evaluating emotions in BN.

1 Introduction

It's hard to imagine a life without emotions. We are seeking for moments of pleasure and happiness and try to avoid those that lead to sadness or pain. Emotions are what life makes worth living. The research of emotional states, their neural correlates, and their role for the regulation of social cognition and behavior have become important topics in cognitive neuroscience (Adolphs, 2003), and many studies have begun to elucidate the neural network for the processing of emotions by measuring brain responses to emotionally salient stimuli.

Although this work has already outlined a considerable framework on the regions and temporal dynamics of emotional processing, research into deficits of emotional regulation, which are found to be central features in many disorders, including bulimia nervosa, has received only little empirical attention. Several lines of evidence suggest that eating disorders are associated with substantial deficits in experiencing and regulating emotions. Controversy exists regarding whether bulimic patients have a reduced ability to recognize facial expressions of emotion, which is known to play an essential role in social communication.

Therefore, the present study aims to investigate the processing of emotional faces in patients with bulimia nervosa and in healthy control subjects by using cognitive, behavioral, and electrophysiological measures. Before presenting details of existing literature, a brief overview on clinical features in bulimia nervosa will be provided. A separate chapter will focus on the physiological and neuroanatomical background of emotional face recognition, as well as on the event-related potential and source localization techniques which were used. Following the description of method and results of the present study, experimental findings of the processing of emotional faces in bulimia nervosa will be examined and discussed.

2 Bulimia nervosa – background and characteristics

Eating disorders, most notably anorexia nervosa (AN) and bulimia nervosa (BN), are complex mental disorders that share the psychopathology of overevaluating one's own shape and weight. In general, they are defined as disturbances of eating habits or weight-control behavior, that should not be secondary to other medical disorders and that result in a significant impairment of physical or psychosocial functioning (Fairburn & Harrison, 2003). While AN is characterized by a sustained and determined pursuit of weight loss, frequent episodes of uncontrolled overeating (binge eating) are followed by efforts of compensating for the excessive intake in patients with BN.

2.1 Clinical features and prevalence

Bulimia nervosa (Greek *βούλημία*, from *βοῦς* “the ox” and *λιμός* “the hunger”) is a relatively newly recognized eating disorder that was first defined by Russell in 1979 (Russell, 1979). By evaluating themselves solely in terms of their shape and weight, BN patients mislabel issues of food, eating and self-control as being more important than any other aspect in their life. Attempts to control weight through restrictive dieting are undermined by repeated cycles of binge eating. During such “binges”, the person feels a lack of control and consumes unusual large quantities of food over a short period of time. Binge eating is followed by an inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics or other medications (purging-type), but the individual may also take corrective actions such as fasting or intense exercising (non-purging type). Patients with BN are of normal or above average body weight (Walsh & Devlin, 1998; Fairburn et al., 2003).

Among all eating disorders, BN has the highest prevalence and mostly occurs in young females aged 16-35 years. It has been found to be about 20 times more common in women than in men, appears predominantly in western societies and has a prevalence rate of 1-2%. The disorder is characterized by a chronic, sometimes episodic course and tends to be self-perpetuating. Moreover, because of the denial and shame associated with the illness, BN can often go unacknowledged so that intervention and treatment is delayed for many years (Fairburn & Harrison, 2003). Little is known about the long-term course and outcome of BN, although findings indicate that about one third of the patients who recovered from BN rapidly relapse (Keel, Dorner, Franko, Jackson, & Herzog, 2005) and many remain chronically symptomatic, with some migrating between the different categories of eating disorders (Fichter & Quadflieg, 2004).

2.2 Causes, contributory factors and comorbidity

The etiology of BN still remains unclear but social, psychological, genetic and biological factors all seem to play a role for the development of this disorder. Several contributory factors have been identified to promote eating pathology (for a review see Fairburn & Harrison, 2003). Environmental risk factors include premorbid experiences like adverse parenting, sexual abuse, family dieting or an emphasis on slimness. Other risk factors identified in bulimics are certain character traits, most prominently low self-esteem or anxiety. In addition, childhood and parental obesity, early menarche and parental alcoholism have been among the predisposition for BN. Hereditary factors may increase the risk of developing BN, as suggested from investigations about familial transmission (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). Genetic studies have examined serotonin (5-HT)-related genes as possible causes. However, as no associations have yet been clearly replicated, genes that might be involved in the development of the disorder

still have to be verified (Fairburn & Harrison, 2003). Altered serotonin neurotransmitter activity, which has been found in BN patients, seems very likely to contribute to a susceptibility to develop this disorder, because serotonin is involved in the regulation of satiety and mood. As these alterations persist even after recovery of BN, it seems plausible that they are not merely a consequence of abnormal eating regulation but might be a major factor in the development of eating disorders or associated mood disturbances (Kaye et al., 2001). Furthermore, the satiety hormone cholecystokinin (CCK), which is released insufficiently in some patients with BN, might account for a sustained abnormal eating behavior (Devlin et al., 1997).

It is generally agreed that the majority of patients with BN have a coexisting psychiatric condition, although processes that give rise to such comorbidities haven't been fully elucidated yet. Mood disorders have been found to co-occur in the presence of BN and other eating disorders in a vast number of cases (Blinder, Cumella, & Sanathara, 2006). It has been argued that bulimic pathology and depression may be reciprocally related, because each disorder increases the risk for onset of the other disorder. Depressed individuals seem to binge eat in order to distract from negative emotions and use compensatory behaviors to reduce physical discomfort and anxiety about weight gain. Conversely, feelings of shame and guilt, that result from binge eating, increase the probability for a depression (Stice, Burton, & Shaw, 2004). BN has also been associated with significant elevations in one or more anxiety disorders, with obsessive-compulsive disorder and social phobia being the most common. The onset of anxiety disorders precedes the emergence of BN in the majority of cases (Godart, Flament, Lecrubier, & Jeammet, 2000; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004), which indicates that early-onset anxiety may be one predisposing factor towards the development of BN.

2.3 Emotional dysregulation in eating disorders and bulimia nervosa

Research into the psychological processes underlying BN revealed that most bulimics have substantial difficulties in recognizing emotions and an inability to cope appropriately with emotional states. In fact, without the ability to identify the experienced emotion, choosing an effective reaction is hardly possible (Sim & Zeman, 2004). This inability, which may also be termed as “mood intolerance” (Fairburn, Cooper, & Shafran, 2003), is regarded as one of the main mechanisms that promote the eating disorder. Bulimic patients respond to negative mood, such as anger, anxiety, or depression with binge eating as a regulatory behavior (Stice, 2001). Moreover, this seems to be accompanied with a decreased awareness of the triggering mood state (Fairburn, Cooper, & Shafran, 2003). Empirical research has found a poor interoceptive awareness, i.e. difficulties in recognizing and discriminating internal states - including emotions and sensations of hunger or satiety - in adolescent girls with BN (Sim & Zeman, 2004). In addition to self-report measures, Sim and Zeman (2004) also assessed emotional awareness by using two objective measures. Their findings demonstrate that girls with BN, as compared to the depressed and community control groups, exhibited significantly longer latencies to retrieve emotional information and endorsed significantly more labels to describe emotional situations.

Studies on emotional awareness in eating disorders emphasize alexithymia as a possible mediating factor. Alexithymia refers to a cognitive-affective deficit, which is defined as a multidimensional construct with three core deficiencies: (1) difficulties in identifying feelings; (2) difficulties in describing feelings; and (3) limited imagination capacity with a concrete/ externally oriented style of thinking (Bagby, Parker, & Taylor, 1994; Taylor, Parker, Bagby, & Bourke, 1996). Several studies reported high levels of alexithymia among patients with BN (Corcos et al., 2000; Sim et al., 2004; Bydlowski et al., 2005;

Gilboa-Schechtman, Avnon, Zubery, & Jeczmien, 2006; Montebarocci et al., 2006; Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007), especially on the first two factors measuring difficulties in identifying feelings and difficulties in describing feelings (Kessler, Schwarze, Filipic, Traue, & von Wietersheim, 2006). However, several investigators have stressed a correlation between depression and alexithymia, as measured with the Toronto Alexithymia Scale (TAS) self-report questionnaire. Higher TAS scores in eating disorders have been mainly related to negative mood; after controlling for depression, TAS scores were similar in eating disorders and controls (Bydlowski et al., 2005; Montebarocci et al., 2006). Therefore, measuring alexithymia with the TAS might not be sufficient to investigate emotion processing deficits in eating disorders. By investigating a broader construct of emotional awareness, including an individual's capacity to describe not only his or her own emotional experience but also the emotional states of others, Bydlowski et al. (2005) suggested a marked impairment in emotion processing in eating disorders, which is independent of affective disorders.

Deficits in the identification of emotion in others are also indicated by several studies investigating facial emotion recognition in eating disorders. Faces are multi-dimensional stimuli conveying not only information about a person's identity, gender, or age, but also more social signals related to emotion, trustworthiness, attractiveness or intention (Vuilleumier & Pourtois, 2006). The ability to decode socially relevant information is essential to both automatic and volitional behavior (Adolphs, 2001). While some studies found no significant differences between patients with AN or BN and control subjects in their ability to recognize facial emotions (Mendlewicz, Linkowski, Bazelmans, & Philippot, 2005; Kessler et al., 2006), several other studies suggested that patients with AN show difficulties in recognizing emotions from facial expressions, as measured with

performance tests (Zonnevijlle-Bender, van Goozen, Cohen-Kettenis, van Elburg, & van Engeland, 2002; Kucharska-Pietura, Nikolaou, Masiak, & Treasure, 2004). These deficits could contribute to poor social skills found in eating disorders such as problems in communication and empathy. Electrophysiological techniques are able to reveal abnormalities in the processing of stimuli even in the absence of differences in overall behavioral performance. In a recent ERP study, Pollatos and colleagues (Pollatos, Herbert, Gramann, & Schandry, in preparation) showed that females with AN exhibited decreased P3 amplitudes in response to unpleasant facial expressions and suggested that this could be linked to a diminished cognitive processing ability of emotional faces conveying negative signals.

Two other ERP studies also revealed abnormal P3 components in eating disorders for the processing of non-face stimuli. Whereas in one study, AN subjects elicited significantly higher P3 amplitudes for body images and simple geometrical shapes (Dodin & Nandrino, 2003), in another study a prolonged P3 component was shown in an auditory two-tone discrimination task for anorexic and bulimic patients (Otagaki, Tohoda, Osada, Horiguchi, & Yamawaki, 1998). Dodin and Nandrino (2003) suggested, that these differences point to a deficit of automatic information processing that could be explained in terms of a cortical hyperarousal. According to this view, individuals with AN or BN are characterized by an controlled information processing bias, that entails an attentional overload and that results in difficulties in inhibiting irrelevant information.

Other lines of research have focused on neural disturbances in AN and BN in order to investigate eating disorders and associated emotional dysregulation. Functional imaging studies have used food and body shapes pictures or investigated subjects while eating to

trigger symptom-related neural activity. Data on BN, however, are limited and seem to differ from those on AN.

A single photon emission tomography (SPECT) study showed that perfusion of the frontal lobes increased in AN patients that ate cake (Nozoe et al., 1993). In opposite to AN, the perfusion of frontal areas decreased in BN while eating, which was demonstrated in another study (Nozoe et al., 1995). In a fMRI experiment, food pictures elicited higher activation in the anterior and lateral prefrontal cortex in AN than in controls, but lowest in BN. Both BN and AN patients recruited medial orbitofrontal and anterior cingulate cortex instead of the inferior parietal lobule and left cerebellum, which were activated in healthy controls (Uher et al., 2004).

Other findings on AN include elevated activity in prefrontal cortex, anterior cingulate, insular cortex, and amygdala while viewing high-caloric drinks (Ellison et al., 1998), in bilateral medial temporal lobe and visual association cortex in response to high-calorie foods (Gordon et al., 2001), and in amygdala as elicited by morphed images of subjects' bodies (Seeger, Braus, Ruf, Goldberger, & Schmidt, 2002).

Taken together, in a large number of eating disorder patients, an abnormal activity in frontal regions has been found in response to symptom-related stimuli such as food. As similar dysfunctions have been found in obsessive-compulsive and affective disorders, Uher et al. (2004) note the possibility of a common affect-related circuit based in the medial prefrontal cortex that is activated by disorder-specific stimuli.

2.4 Summary of previous research and rationale of the study

To summarize, the emergent picture from studies investigating emotional awareness in eating disorders indicates that patients with BN, and similarly in AN, have substantial

deficits in the processing of emotions. Many studies have shown a poor ability in recognizing and describing internal states and emotions in BN, which has been linked to alexithymia. In addition, BN patients seem to have deficits in information processing while perceiving emotional stimuli. While some work has focused on abnormalities in the processing of symptom-related stimuli such as food or body images, others have suggested difficulties in the identification of emotions in faces.

But whether patients with BN have impairments in the recognition of emotional faces is still not answered satisfactorily. Data on BN, although more prevalent than AN, is limited. Moreover, most of the research has relied solely on self-report to assess the patients' ability to identify emotions in faces. Results of these categorization tasks are not clear-cut. It is possible, that patients can show comparable performance when images are presented for a relatively long time to answer, which can be considered as artificial. Also, patients could learn to categorize shown faces by means of typical features that clearly indicate an emotion (e.g. a smile for happiness). Such a performance test then measures more cognitive than emotional recognition abilities (Kessler et al., 2006). Gilboa-Schechtman et al. (2006) suggested, that emotional processing among eating disorders should be examined more integratively with multiple measures. Taking these considerations into account, the aim of the present study was to investigate emotional face processing in BN by using self-report and behavioral measures as well as electrophysiological and source localization methods.

3 Event-related potentials and emotional face recognition

In this study, event-related potentials (ERPs) have been used to investigate emotional face processing in BN. Because of their excellent temporal resolution, ERPs can serve as an useful tool in oder to determine different stages giving rise to perceptual, cognitive, emotional and behavioral processes in human everyday living. Although lacking accurate spatial resolution, they can be used in source analysis methods to infer the location of neural activity that gave rise to particular ERPs measured. The purpose of the following sections is to provide a background on the topic of the recognition of emotions from faces as well as an overview over the ERP technique and the source localization analysis.

3.1 Processing faces and emotional expressions

The perception of faces is known to be an essential part in social interactions and one of the most developed visual processing skill in humans. Two types of information have to be extracted in order to recognize a face: First, the face must be identified as belonging to a unique individual, out of innumerable different faces and taking into account changes in viewing angle, facial expression, and appearance. The recognition of identity must be based on those features of a face, that are invariant across changes in expression. Second, a face provides a wealth of information related to social communication that have to be extracted from changeable aspects of a face (e.g. emotional expression and eye gaze) (Posamentier & Abdi, 2003; Haxby, Hoffman, & Gobbini, 2000). Including both invariant and changeable features of faces, the face perception system is suggested to engage highly specialized systems, an idea that is supported by clinical cases with selective deficiencies in face recognition. Prosopagnosics fail to identify people on the basis of their face but have an intact facial expression processing, while other patients have normal performances in the identification of faces but are impaired in the ability to recognize emotions from

faces (see e.g. Posamentier & Abdi, 2003, for a review). An influential cognitive model of face perception by Bruce and Young (1986) was the first that emphasized distinct psychological processes involved in the recognition of identity and in the recognition of facial expression (Bruce & Young, 1986). According to their model, the processing begins with the structural encoding of visual features of faces, which is followed by specialized functions that analyse different types of information that are conveyed in a face or associated from existing knowledge.

Faces provide a broad range of information that facilitate social behavior and experience, especially through the expression of emotions. Neurobiologists and psychologists have conceptualized emotions as concerted and adaptive psychophysiological processes that are triggered by certain objects or situations to prepare an organism to act effectively in certain contexts. An emotional response typically involves several components including bodily changes, conscious experience (subjective feelings), appraisal of environmental and internal information as well as behavioral aspects, e.g. facial expression (Damasio, 1999; Gorman, 2004; Schandry, 2003). Based on the work by Ekman (Ekman, 1993; Ekman, 1999), it is generally accepted that facial expressions are innate and universal, as members of different cultures classify them in the same way. Although it is debatable whether emotional expressions might form a continuum comprising a small number of dimensions (e.g. level of arousal, intensity, pleasure or aversion, etc.), or if they are to be conceptualized as discrete classes (see e.g. Adolphs, 2002), the majority of research uses six basic categories of emotions conveyed in faces: happiness, surprise, fear, anger, sadness, and disgust.

Numerous neurophysiological studies suggest a distributed neural system for the processing of identity and expression of faces. The next sections will provide a background of the methods used in this study. Then, important findings will be reviewed, that have already made significant contributions to our understanding of the timing and structures with that facial expressions are processed.

3.2 Electrophysiological measurements and the ERP technique

As compared with other brain imaging methods, such as the hemodynamic approaches fMRI and PET which indirectly measure brain activity by recording slow metabolic changes that are a consequence of neural activity, electroencephalography (EEG) is one of the electromagnetic approaches for noninvasively and directly recording the electrical activity of neuronal populations with a millisecond temporal resolution (Savoy, 2001; Gevins, 2002; Luck, 2005). The physiological basis of the EEG signal, which is recorded by electrodes placed on the scalp, originates in currents that are produced by a summation of post-synaptic potentials from a large number of neurons. In the process of neuronal signal transmission, post-synaptic potentials are changes in membrane voltage that arise when neurotransmitters bind to receptors of the postsynaptic terminal. If, for example, an excitatory neurotransmitter is released into a synapse causing ion channels to open, positive ions flow into the postsynaptic neuron. Thereby the extracellular concentration of positive ions will be reduced, leading to a net negativity on the outside of the apical dendrite region (a current “sink”). The positively charged ions flow out of the neuron at its cell body and basal dendrites, yielding a net positivity in this area (a current “source”). Together, this polar structure of positive and negative electrical charges at the neuron creates a (very small) dipole. In order to make such voltages recordable at the scalp, a whole population of neurons must be activated similarly at the same time and must be

aligned in a parallel orientation so that voltages will be summated and do not cancel each other out. Fortunately, the layered structure of the cerebral cortex with vertically oriented pyramidal cells and the synchronous activity of many neurons during information processing provides recordable signals at the level of the scalp surface.

In order to measure brain activity to certain stimuli, the event-related potential (ERP) technique is used (see e.g. Luck, 2005). ERPs are electrophysiological responses that occur before, during and after a specific physical stimulus or mental event. Such stimulus-related activity can be extracted from the continuous EEG recording. Assumed that the repeated presentation of the stimulus always elicits equivalent responses while all other unrelated brain activity occurs randomly, time-locked signal-averaging increases the signal-to-noise ratio. That way, any unrelated activity will average to zero and any stimulus-related activity will be visible in the average. In order to investigate effects in a group, grand averages (GAs) are created by averaging together the averaged waveforms of the individual subjects. Represented graphically with time (x-axis) and voltage (y-axis), the resulting ERP waveform consists of successive components, that can be described as a series of positive and negative waves. Typically, those components are named with a 'P' or 'N' (to indicate positive or negative deflection) and a number (to specify the timing of the peak). The sequence of the components reflect different stages during cognitive processes. Traditionally, ERP components have been classified according to their latency as being either "exogenous" or "endogenous". Short-latency components appear to reflect bottom-up processing in that they are sensory-specific, sensitive to the size and intensity of the stimulus, and are elicited maximally over modality-specific brain areas. By contrast, later components are not sensory-specific, depend more on the properties of the given task, and

are generally linked to post-perceptual stages that might involve top-down processes, e.g. memory, attention, or response selection.

3.3 Emotional face processing stages as reflected by ERPs

Early cortical processing of faces, like any other visual perception, begins in occipital cortices that perform basic operations on the individual features of a stimulus and on figure-ground segmentation in order to construct a structural representation of that object. In comparison to most other visual stimuli, the processing of faces requires a very fast categorization at the unique level (the individual) and rapid associative processes linking the percept with socially relevant information, e.g. the quality of the facial expression (Adolphs, 2002). Previous research has shown enhanced responses to negative emotional expressions (see Vuilleumier & Pourtous, 2006 for an overview) already from 40 to 100 ms, which appears to be generated in V1 (primary visual cortex). Emotional modulations also have been reported in the early component P1, which is largest at lateral occipital electrode sites and peaks between 100-130 ms. These early effects are supposed to display rapid but coarse perceptual routes that occur in parallel to the full structural encoding stage (Adolphs, 2002).

A substantial amount of research has focused on the N170, an ERP component assumed to reflect face-specific neural systems in the infero-temporal cortex. Whereas non-face stimuli demonstrate a smaller or absent N170, faces have shown to elicit responses peaking approximately 170 ms at occipital-temporal electrode sites (Bentin, Allison, Puce, Perez, & McCarthy, 1996). In line with the early structural encoding stages of cognitive models (Bruce & Young, 1986), many studies have found that this component is not influenced by the saliency of internal facial features, indicating that the N170 presumably provides a perceptual encoding and categorization process as a basis for subsequent expression and

recognition analysis (Eimer, 2000). However, as others also reported emotional modulations in N170 more recently (Blau, Maurer, Tottenham, & McCandliss, 2007), its exact role is still a topic of debate.

Post-perceptual processing of faces, such as recognition of its identity or expression, has been consistently reported to happen during the time windows subsequent to the N170 component, ranging in the N2 and the P3 (see Adolphs, 2002; Vuilleumier & Pourtois, 2006). The N2 (or N200), which has been shown to include several subcomponents, is thought to reflect stimulus contrast and can be observed from 200-350 ms. Its amplitude is viewed to index the degree of attention which is focused on the stimulus. Therefore, the N2 component is generally regarded as reflecting automatic and deliberate processes of stimulus evaluation, discrimination, and classification (Näätänen & Picton, 1986; Luck, 2005). Posterior ERP effects around 230-250 ms have been found to discriminate emotional from neutral faces (Krolak-Salmon, Fischer, Vighetto, & Mauguiere, 2001; Balconi & Pozzoli, 2003) and to elicit significantly higher amplitudes for threatening as compared with friendly or neutral expressions (Sato, Kochiyama, Yoshikawa, & Matsumura, 2001), thus indicating an early decoding process of emotional expressions of faces in that time window.

Differential effects of emotional versus neutral faces have been reported to occur particularly in later ERP components such as the P3 (or P300) wave. Consisting of several distinguishable, task-dependent subcomponents such as the P3a and P3b, the P3 is often found to be sustained over a prolonged time range from 300 to over 400 ms, characterized by a large positivity and recorded maximally over centro-parietal scalp-regions (Luck, 2005). The P3 is primarily associated with working memory processes as well as the allocation of attentional resources. Since its amplitude is larger when subjects devote more emphasis to a task, the P3 is regarded to reflect the amount of cognitive effort that is

needed for the evaluative categorization of meaningful stimuli (Kok, 2001). Concerning the processing of faces, a variety of studies have shown that emotional expressions elicited significantly higher P3 amplitudes than neutral expressions (Carretié & Iglesias, 1995; Krolak-Salmon et al., 2001). Such late responses may reflect more complex cognitive activity beyond the sensory-processing triggered by emotional stimuli.

3.4 Brain electrical source analysis

Source localization methods are used in order to identify the location and orientation of neural structures that elicited a particular voltage distribution on the scalp (Luck, 2005; Slotnick, 2005). Thereby, solutions of two discrete but dependent problems have to be found. A specific cortical activation, which can be described by current dipoles, produces a unique scalp voltage topography (“forward problem”). For realistic head shapes, modeled of several concentric shells with varying conductive properties (brain, skull, scalp), this precise distribution can be predicted. More difficult however is solving the “inverse problem”: For any given scalp voltage topography there exist an infinite number of possible source configurations that could produce the same scalp distribution (Helmholtz, 1853).

The brain electrical source analysis (BESA) technique (Scherg & Berg, 1996), an equivalent current dipole approach that was used in this study, assumes that the spatiotemporal scalp voltage distribution can be modeled by using a small number of current dipoles, each of which represents the summation of neural activity within a cortical area. Moreover, every dipole is supposed to be stationary with one fixed location and orientation, but varies in strength over time. After determining the minimum number of dipoles underlying a given scalp topography by a principal components analysis, a model-fitting algorithm is used to estimate those locations and orientations that yield the best fit

between the model and the data. Dipoles' positions are modified in an iterative procedure, so that they are adjusted slightly and reduce the residual variance with every iteration (Luck, 2005; Slotnick, 2004).

The recognition of emotion from facial expressions is mediated by a distributed neural system. The most prominent structures involved, which have been investigated in studies using ERPs, lesions and functional imaging techniques, are reviewed in the following section.

3.5 The functional neuroanatomy of emotional face processing

In line with the functional Bruce and Young (1986) model of emotional face analysis, emphasizing separate psychological processes for the recognition of identity and emotion, current neuro-anatomical models support a view of face recognition that involves distinct neural structures in at least two steps of processing (Adolphs, 2002; Haxby et al., 2000): The first step, in which the structural encoding of basic visual features takes place (=perception), has been associated with early processes mainly mediated by a “core system” of face perception (Haxby et al., 2000). In a second step, additional processes serve to link a perceptual representation with existing conceptual knowledge in order to derive a meaning from the face and its emotional expression (=recognition). The “extended system” (Haxby et al., 2000) consists of neural structures of other cognitive functions, e.g. attention or emotion, that collaborate with the core system and provide appropriate supplementary information for the expression and recognition analysis of faces.

Adolph's (2002) model for recognizing emotion from facial expressions, depicted in Figure 1, shows different stages from initial perception to later processes which link the percept to conceptual knowledge as well as major structures and corresponding processes involved.

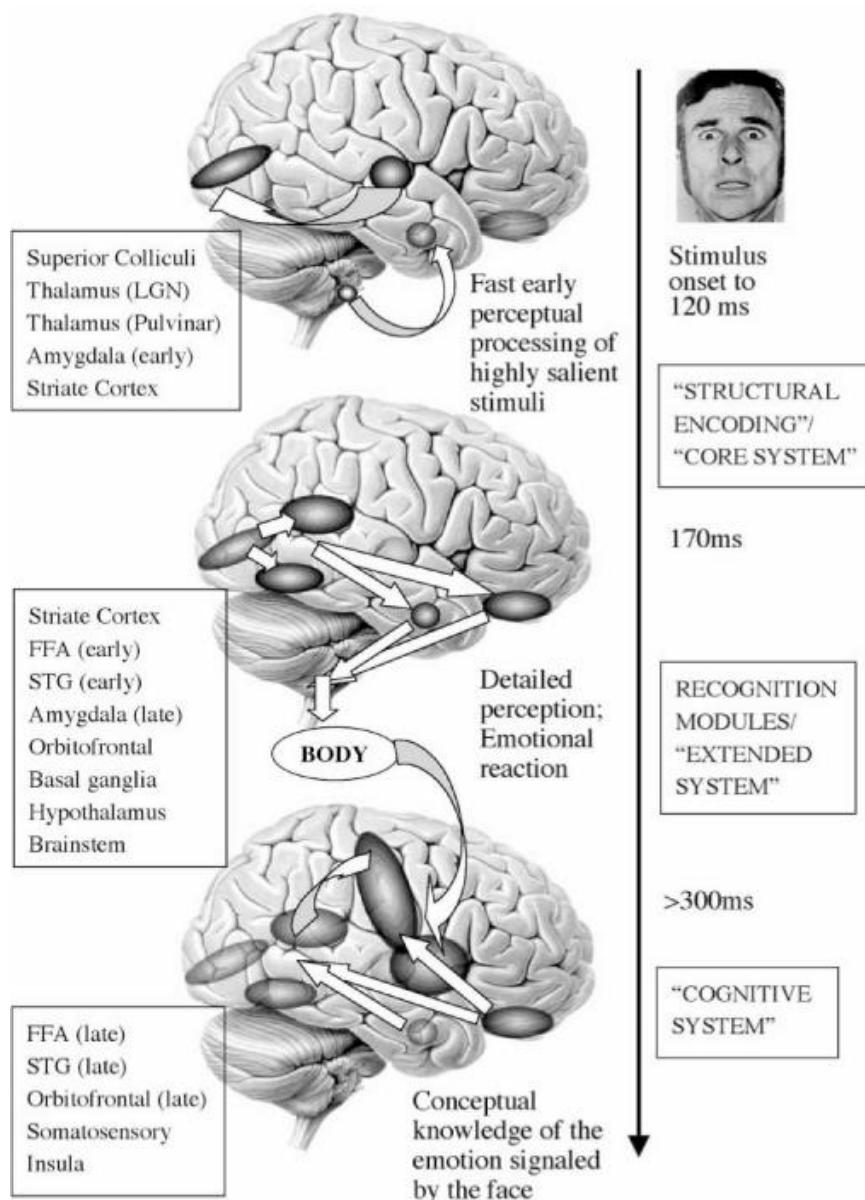


Figure 1: Adolph's (2002) model outlining the processing of emotional facial expressions as a function of time. The main structures involved are depicted on the left, corresponding timing of processes is shown on the right. Note: LGN = lateral geniculate nucleus; FFA = fusiform face area; STG = superior temporal gyrus. Source: (Adolphs, 2002).

3.5.1 Structures for perceiving emotion from faces

Following the model of Adolphs (2002), the initial processing of emotional faces involves two routes to perception: Subcortical mechanisms that bypass striate cortex include the superior colliculus, the pulvinar thalamus, and amygdala. They presumably represent structures that are specialized for the fast, coarse and automatic processing of certain highly salient stimulus features, and are assumed to function in parallel with the second route to perception, the cortical route. Early cortical processing begins in primary visual areas, which provide input for the subsequent construction of a more detailed perceptual representation in regions more anterior. Particular attention has been focused on three bilateral regions in occipito-temporal visual extrastriate cortex subsumed as the core system for face perception (Haxby et al., 2000). These regions, depicted in Figure 2, are in the lateral fusiform gyrus, the superior temporal sulcus, and the inferior occipital gyrus, and appear to be involved in different functions of face processing.

Neuroimaging studies have consistently shown that the fusiform gyrus is activated by faces, as compared with evoked responses to other common objects or non-objects, and with activity often bilaterally but more reliably found on the right (Kanwisher, McDermott, & Chun, 1997). Although termed as the “fusiform face area” (FFA), it has been revealed that this area is also activated when subjects are experts in the discrimination between nonface objects, e.g. birds or cars (Gauthier, Skudlarski, Gore, & Anderson, 2000), suggesting this area to be involved in perceptual processes for recognizing faces and other objects at the subordinate level with unique properties. Most importantly, the fusiform gyrus is viewed to be mainly involved in the processing of the structural, non-changeable, and mainly static characteristics of faces, leading to the construction of a personal identity behind a face (Haxby et al., 2000). In contrast, the region of the superior temporal sulcus (STS) seems to be more involved in the perception of changeable properties of faces. With

the processing of motion-related information, this structure contributes to the recognition of social relevant information embedded in the emotional expression and gaze direction (Haxby et al., 2000). The third structure of the core system, the inferior occipital gyrus, has been proposed to provide information about both structural and changeable features to the fusiform gyrus and the superior temporal sulcus, respectively (Haxby et al., 2000).

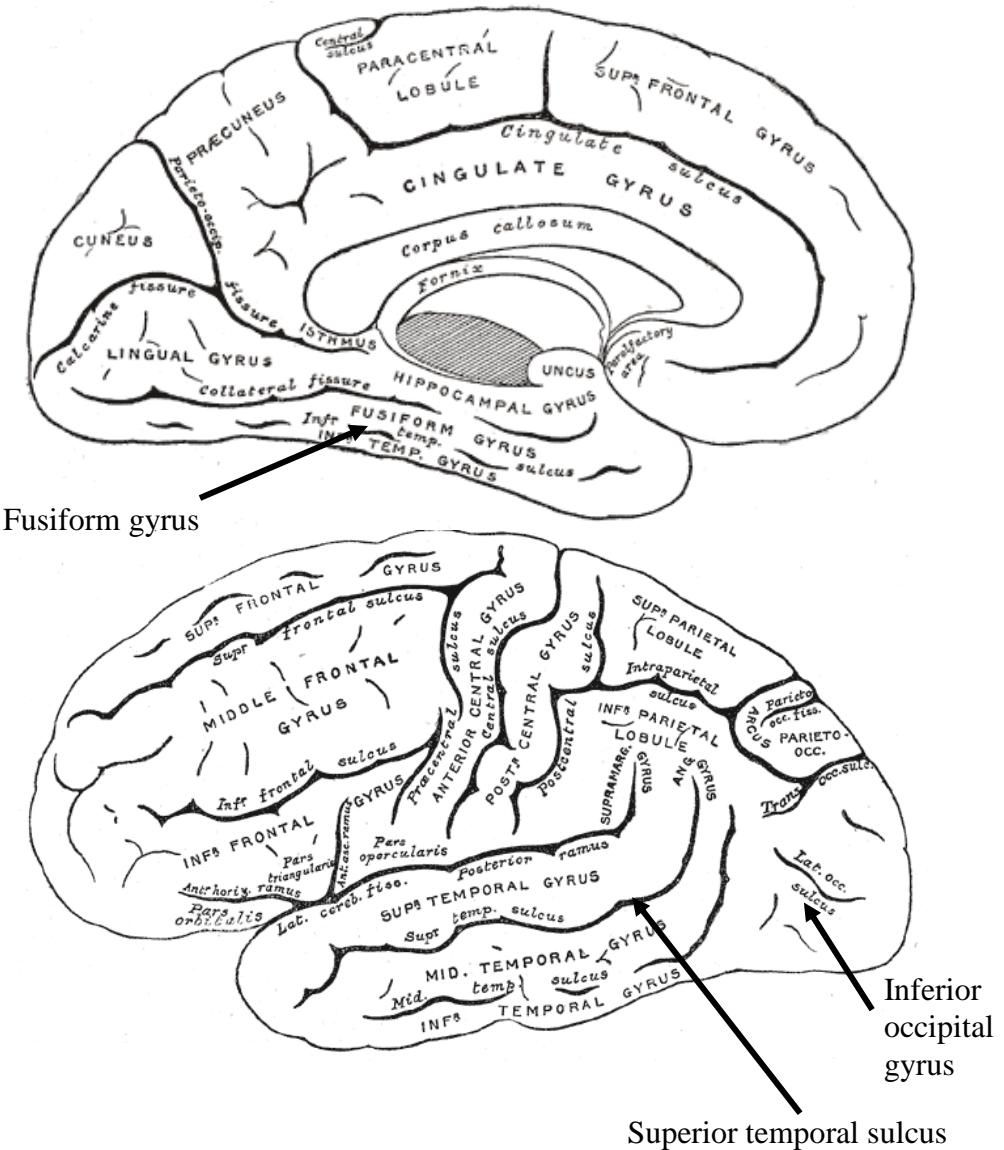


Figure 2: Core structures of face processing. The lateral fusiform gyrus, as shown on the medial surface of the left hemisphere (upper image). The superior temporal sulcus and the inferior occipital gyrus, as viewed from the lateral surface of the left cerebral hemisphere (lower image). Source: (Gray, 2000)

3.5.2 Structures for the recognition of emotion in faces

While the structural representation of a face and the perceptual information about the facial expression is encoded by processes and brain areas mentioned above, additional anatomical structures are recruited in order to link those representations with conceptional knowledge, giving meaning to faces (Adolphs, 2002). Emotional expressions in faces have been found to evoke responses in a number of different brain areas which are associated with emotion processing in general. Major structures included in this network, the amygdala, the orbito-frontal cortex, somato-sensory cortices, and basal ganglia, shall be described shortly.

Anatomically located in the medial temporal lobes, the amygdala is not a single homogenous structure but consists of several nuclei that subserve different functions and that are interconnected with multiple other brain areas. Shared in common is the amygdala's ability to modulate a large array of responses concerning attention, memory, executive functioning, and emotional reactions (including behavioral, autonomic, and endocrine changes), which depend on the emotional and social significance of the perceived stimulus (Adolphs, 1999; Adolphs, 2002). Accordingly, the amygdala has been shown to play a complex role in the processing of facial emotions, participating both in early perceptual mechanisms as well as in later processes of cortical recognition. Numerous studies, that have either examined patients with lesions in the amygdala or used functional neuroimaging in normal subjects, have provided evidence that the amygdala is an essential structure for recognizing emotions from facial expressions, particularly those that signal danger or threat such as fear, anger, disgust, or sadness (for an overview see Adolps, 2002). Subjects with damage to the amygdala have been found to show difficulties in recognizing facial emotions of negative valence (Adolphs, Tranel, Damasio, & Damasio, 1994) and to judge those faces as looking trustworthy, which are given the most

negative characteristics by normal subjects (Adolphs, Tranel, & Damasio, 1998). Functional imaging studies revealed that the amygdala is activated automatically by multiple emotional expressions of negative valence, in normal subjects especially for viewing fearful faces (Morris et al., 1996) or in psychiatric populations, e.g. subjects with a social phobia for looking at neutral faces (Birbaumer et al., 1998). Although most of the literature has focused on the preferential processing of the amygdala in response to fear-related stimuli, there are also findings that support a more general view. According to this account, the amygdala might trigger processing resources to resolve ambiguity in highly salient stimuli that may be pleasant or aversive (Whalen, 1999; Davidson & Irwin, 1999).

Another key structure in the processing of emotional faces is the orbitofrontal cortex, which is located within the frontal lobes above the orbits of the eyes. Based on extensive connections between this region and the amygdala on the one hand as well as temporal cortices on the other hand, the orbitofrontal cortex has been proposed to play a major role in modulating the processing of emotionally significant stimuli (Adolphs, 2002). Consistent with this view are findings which show that damage to the orbitofrontal cortex, predominantly on the right, could lead to impairments in recognition of emotional faces (Hornak, Rolls, & Wade, 1996). Furthermore, neuroimaging studies have shown increased activation in orbitofrontal cortex following the presentation of facial expressions, especially those of anger (Phan, Wager, Taylor, & Liberzon, 2002). While the amygdala seems to play a major role in an automatic and implicit processing of facial emotions, regions in orbitofrontal cortex are viewed to modulate those processes in a more explicit and context-depending way (Narumoto et al., 2000; Adolphs, 2002). Taken together, these two structures might participate in the process of emotional face recognition by linking the perceptual representation with existing knowledge about the emotion. As Adolphs (2002) argues, this can be accomplished via multiple connections to other brain areas: (a) to temporal and occipital visual cortices, in order to fine-tune the categorisation of the facial

expression; (b) to hippocampus and cortical regions, in order to retrieve stored representations about that emotion; (c) to different other structures, including motor areas, hypothalamus, and brainstem nuclei, that might contribute to the generation of knowledge through “mirroring” the observed emotion.

Besides amygdala and orbitofrontal cortex, somatosensory-related cortices have been found to participate in the processing of emotional meaning in faces. Lesions in right primary and secondary somatosensory areas have been found to impair facial emotion recognition, possibly by interfering with processes that represent somatic information related to that emotion (Adolphs, 2002). Similarly, functional imaging studies revealed that the insula, a visceral somatosensory cortex, was activated by various facial expressions (Phan et al., 2002). Lesion studies, neuroimaging studies, and observations made in diseases like Huntington’s disease have provided evidence for the basal ganglia, which consist of many different nuclei, as an additional structure in the neural network of facial emotion recognition (for an overview see Adolphs, 2002). A meta-analysis of functional imaging studies by Phan et al. (2002) found the basal ganglia presumably activated by the emotions of happiness and disgust. Its detailed role however remains to be specified.

In addition to the structures mentioned above, several other brain areas also might play a role in face processing. Mechanisms of selective attention might be involved, especially for facial expressions that display threat or danger (Palermo & Rhodes, 2007). Importantly, the processing is not strictly hierarchical, but also includes feedback connections (Adolphs, 2002). Figure 3 shall provide a structural overview of brain areas processing emotional faces and illustrate their main connections.

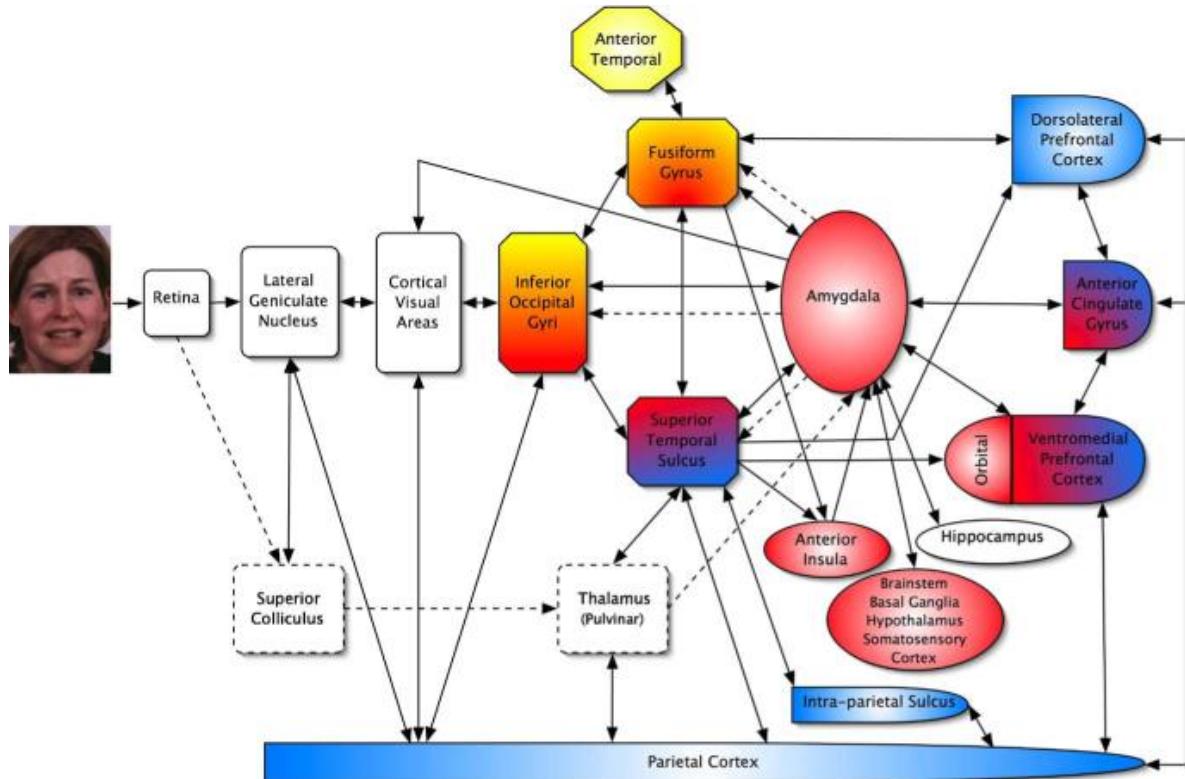


Figure 3: Structures for the processing of emotional faces. The three rectangles with beveled edges indicate the core system for face perception, areas shaded in yellow represent regions involved in the processing of identity, areas in red show regions involved in emotion analysis, and those in blue reflect the fronto-parietal cortical network involved in spatial attention. Solid lines indicate cortical pathways, dashed lines represent the subcortical route for rapid and coarse emotional expression processing. Source: (Palermo & Rhodes, 2006).

3.6 Aim of the study

Aim of the present study was to investigate emotional face processing in BN by using cognitive, behavioral, and electrophysiological measures. Based on the empirical literature regarding eating disorders and recognition of facial expressions, several hypotheses were tested. If BN is characterized by an impairment in facial emotion recognition, patients with BN would perform worse in a task in that they have to categorize faces according to emotional expressions, as compared to healthy controls.

Furthermore, if individuals with BN have difficulties in identifying emotions in faces, these deficits would be reflected in post-perceptual processes of emotional face recognition, in the time range of the ERP components N2 and P3. More specifically, if

emotional faces are processed with more cognitive demand in BN, amplitudes of N2 and P3 would be greater in BN than in control subjects. Another possibility would be that of a BN patients' diminished cognitive processing ability of faces, especially those conveying negative expressions, that would result in decreased amplitudes of N2 and P3. In contrast, earlier structural encoding processes, as indexed by the face-specific N170, are expected to be comparable to those of healthy controls.

In an exploratory analysis, brain structures that could give rise to such ERP differences in post-perceptual face processing of emotional content are investigated by using the source localization method BESA. It is hypothesized that differences in ERP responses between BN and control subjects reflect a dysfunctional activation pattern in structures related to the processing of emotional information in faces.

4 Methods

4.1 Subjects

Twenty-two patients with current bulimia nervosa (BN) were recruited from local consultation units for eating disorders (ANAD e.V., Pathways, Caritas Ambulance, Cinderella e.V., TCE Therapy Center) and paid for participation. All patients were females (mean age = 23,95 years; SD = 7,3) and met DSM-III/ IV criteria for bulimia nervosa as assessed by the Structural Clinical Interview for DSM-III Axis I Disorders (SCID, for a description see 4.2). They had been ill for an average duration of 9,13 years (SD = 7,64 years), with a first episode occurring at a mean age of 15,59 years (SD = 2,74 years). The mean Body Mass Index (BMI) was in a normal range, with a value of 20,83 kg/m² (SD = 3,48 kg/m²). Seven of the 22 patients (31,82 %) were receiving psychotropic medication including antidepressiva and pain relievers, six (27,27 %) were taking contraceptiva. Ten patients (45,5%) possibly had major depressive symptoms, nine (40,9%) a generalized anxiety disorder, eight (36,4%) showed anxiety disorder, six (27,3%) a social phobia, and four (18,2%) a specific phobia. This was indicated by a self-report questionnaire containing items from the SCID, which was administered as a screening measure to assess for possible presence of anxiety and depressive symptomatology (see 4.2). However, it is not to be equated with a full diagnosis. Given the high rates of comorbidity between mood, anxiety and eating disorders, all patients with BN were included in this study to preserve ecological validity.

Patients were compared with 22 females of similar age (mean age = 25,00 years; SD = 3,18), levels of education, and BMI (21,92 kg/m²; SD = 2,60 kg/m²), who received either course credit or were paid for participation. None of them had a past or current eating disorder. Of the 22 control subjects, one (4,55 %) was receiving an antidepressivum, two (9,09 %) were taking pain relievers regularly, and 10 (45,45 %) were taking contraceptiva.

4.2 Instruments

The current study was conducted in accordance with the Declaration of Helsinki and ethically approved by an institutional review board. Written informed consent was obtained from all patients and control subjects. After measuring height and weight, participants were asked to complete a series of self-report questionnaires (see below) and to answer questions about personal data (age, educational background, medication, ICD-10 and DSM-III/ IV criteria of bulimia nervosa as well as onset and duration of illness).

The Restrained Scale

The Restraint Scale (Herman & Polivy, 1980) is a widely used self-report measure for the assessment of dietary restraint, that includes 10 items scoring from 0 to 3 and 4 (maximum score = 35), surveying thoughts about weight and behaviors relevant to eating disorders. Higher scores indicate a higher restraint in eating behavior.

The Toronto Alexithymia scale (TAS-20)

Alexithymia was assessed with the TAS-20 (Bagby et al., 1994), which consists of 20 items loading on three factors: (1) difficulty in identifying feelings, (2) difficulty in describing feelings, and (3) externally oriented thinking. Each TAS-20 item must be rated on a five-point Likert scale from “strongly disagree” to “strongly agree”. In addition to a total score (higher scores reflect greater alexithymia), single scores for the three subscales were calculated.

A Self-Control-Scale (SCS-12)

In order to investigate individual's skill of coping with problems appropriately, 12 items were included in a questionnaire that assessed the participants' self-control. Examples for the items (some are reversed) include “I can overcome temptations very well”, “I refuse

things that are bad for me”, “It’s hard for me to abandon bad habits”. The statements are scored on a five-point Likert scale from “applies not at all” to “applies fully”.

The Eating Disorder Inventory – 2 (EDI): Subscale “Interoceptive Awareness”

The EDI is a commonly used self-report questionnaire that addresses symptoms associated with eating disorders (Garner, 1991). In this study the subscale “Interoceptive Awareness” from the EDI was used to examine the participants’ perceived ability to recognize and accurately respond to internal states, including emotions and sensations of hunger and satiety. It consists of 10 items in a six-point Likert scale that require participants to answer whether each statement applies from “always” ranging to “never”.

The State Trait Anxiety Inventory (STAI)

To quantify anxiety, the Spielberger State Trait Anxiety Index (Spielberger, Gorsuch, & Lushene, 1970) was used. The STAI questionnaire consists of 40 items on a 4-point rating scale measuring the anxiety state (Form X 1, 20 items) and anxiety disposition (Form X 2, 20 items). Minimum and maximum scores range from 20 to 80 points for each form.

The Structured Clinical Interview for Axis I DSM-III Disorders (SCID)

The Structured Clinical Interview for DSM-III (SCID) is regarded as a standard method for the detection and characterization of various Axis I disorders (Spitzer, Williams, Gibbon, & First, 1992). Administered by an interviewer with extensive experience, it is designed to yield a reliable and valid psychiatric diagnosis. Since a full diagnostic SCID interview would not have been reasonable for the scope of the current study, participants were asked to fill in a questionnaire containing the items of the SCID modules that assess Eating, Anxiety and Panic Disorders, Social and Specific Phobia, Generalised Anxiety Disorder as well as Major Depressive Disorder.

The Beck Depression Inventory (BDI)

The BDI, the most widely used self-report depression questionnaire, was administered as a measure to assess the presence of depressive symptomatology (Beck, 1978). Each of the 21 items includes four statements with ratings from 0 to 3, in which higher scores indicate an increased severity of depression.

4.3 Stimuli and Procedure

Participants were seated in a comfortable chair in a dimly lit and sound attenuated chamber, and a 19-inch computer screen was placed at a viewing distance of approximately 140 cm at the center of their field of vision. Stimuli were a set of 200 full-color photographic pictures of young, european adult faces selected from the Karolinska Directed Emotional Faces (KDEF) image battery (Lundqvist, Flykt, & Öhman, 1998), that included neutral, happy, fearful and angry facial expressions (50 different pictures of each category, half depicting male and half female faces, all in frontal view).

The EEG-experiment consisted of three experimental blocks (two blocks with 67 pictures, one block with 66 pictures). In each block, facial expressions from all categories were presented in random order, with equal probabilities, but without immediate stimulus repetition of the same person or facial expression. Each trial began with a 500-ms white fixation cross at the center of the black screen. The stimuli were presented for 1500 ms and were separated by an intertrial interval of 1500 ms. Before starting the EEG-recording, all participants read carefully through printed instructions about the experimental procedure, that informed them about the upcoming pictures of emotional faces in three blocks of about 4 minutes each. Further they were instructed to attend to the stimuli very closely, to sit quietly and to look at the center of the screen to minimize muscle and eye movement artifacts. Oral instructions and explanations were given by the experimenter in addition. No

other tasks were imposed on the subjects during the EEG experiment in order to avoid other brain processes, e.g. the preparation and execution of motor responses, that may alter the recorded electrophysiology. After each block, there was a break allowing subjects to rest for approximately 1-2 minutes.

Subsequent to the EEG experiment, participants performed a categorization task. They were shown a selection of 40 of the previously presented faces (10 of each category, randomly ordered). Again, preceded by a 500-ms fixation-cross, the stimulus was shown for 1500 ms. Participants were given 10 seconds to classify the depicted facial expression by checkmarking one of the possible categories (neutral, happy, fearful, angry) on a response form. They were instructed to respond quickly and to carry out a categorization even in the case of uncertainty. The whole experiment lasted approximately 2,5–3 hours.

4.4 EEG recording

EEG was recorded with Ag-AgCl electrodes from 62 leads over both hemispheres with DC amplifiers (bandpass: 0.01-100 Hz; SYNAMPS, NeuroScan) and digitized at a sampling rate of 1,000 Hz. Electrodes were mounted in an electrode cap (Easy Cap, Falk Minow Services) at equidistant positions. All electrodes were referenced to Cz and grounded with an electrode on the left cheek. Offline, EEG was re-referenced to linked mastoids. For the BESA analysis, data assessed with the original reference was used. Horizontal and vertical electrooculograms (EOG) were recorded from the outer canthi of both eyes (EOG_H) and from above and below the left eye (EOG_V). Electrode impedance was kept below 5 KΩ.

4.5 ERP preprocessing and analysis

The EEG was averaged off-line for epochs of 1200 ms, starting 200 ms prior to stimulus onset, and ending 1000 ms afterwards. The data was examined for EOG, muscle or other electrophysiological artifacts. Eye blink correction was conducted based on methods outlined by Gratton et al. (Gratton, Coles, & Donchin, 1983), which was implemented in the analysis software Brain Vision. Trials containing any voltage exceeding $\pm 120 \mu\text{V}$ were excluded from analysis. Average ERPs were computed separately for each subject and each of the four stimulus conditions.

To evaluate differences in ERPs response for the two groups, three components of standard ERPs elicited by faces were investigated: the N170 (140-200 ms), the N2 (190-260 ms), and P3 (270-400 ms). Respective time windows were chosen on the basis of visual inspection of the data and in accordance with earlier studies.

For further statistical analysis of the ERPs, mean amplitudes were averaged for 12 regions, determined by hemisphere (right/ left), horizontal plane (anterior/ medial/ posterior), and vertical plane (inferior/ superior), as visualized in Figure 4. The data were statistically evaluated with repeated measures ANOVAs with ‘hemisphere’ (right/ left), ‘region’ (antero-inferior/ antero-superior/ medial-inferior/ medial-superior/ postero-inferior/ postero-superior), and ‘category’ (neutral/ happy/ fearful/ angry) as within-subject factors and ‘group’ (bulimic patients/ control subjects) as between-group factors. Greenhouse-Geisser corrections were used when appropriate.

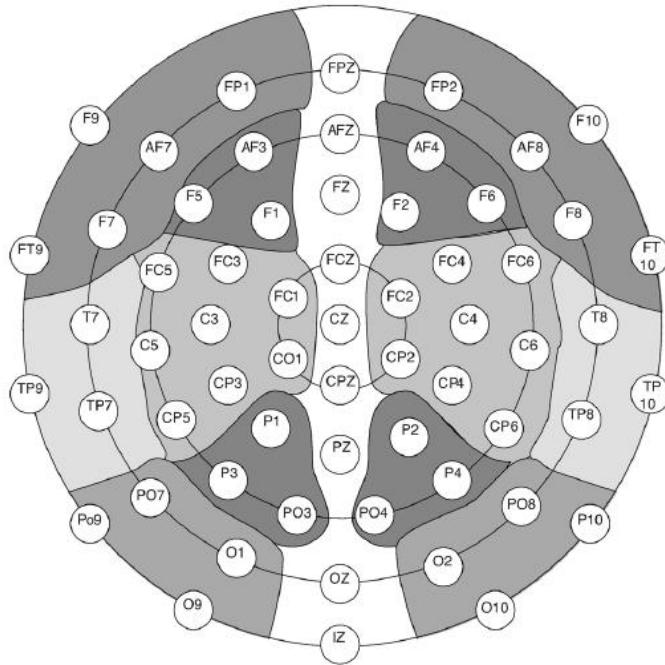


Figure 4: Layout of the electrode array. Electrodes in the shaded clusters were grouped for statistical analysis. Frontal electrodes are shown at the top of the figure.

4.6 Brain electrical source analysis

In order to determine the location and timing of neural sources that contribute to the ERP scalp recordings, a brain electrical source analysis was performed using the BESA software. Although there is no unique solution to the inverse problem – intracerebral sources cannot be uniquely calculated through given scalp fields - BESA offers algorithms that allow a spatio-temporal modelling of current dipoles over defined time intervals. The modelling process began with a principal component analysis (PCA) of the GA in the selected time interval, that showed the main waveforms contributing to the total variance. The results of the PCA gave information about the number of dipoles that should be used in the model (two dipoles for each principal component). The orientation and location of the dipoles were computed by an iterative, least-squares method, which minimizes the residual variance, a value that indicates the percentage of data that cannot be explained by the modelled dipoles, and maximizes the goodness of fit (GOF).

5 Results

5.1 Sample characteristics

One-way ANOVAs were conducted to compare participants in the BN and control groups on sociodemographic and questionnaire data (see Table 1). There were no significant group differences as a function of age or the BMI. The two groups had the same educational level, which was assessed by a scoring system for the German school system.

Table 1: Sociodemographic and questionnaire data of BN patients and controls

	BN Mean (SD)	Controls Mean (SD)	F (df=1,42)	p
Age (years)	23,95 (7,3)	25,00 (3,2)	0,38	n.s.
Educational level	3,67 (0,6)	4,09 (0,6)	3,05	n.s.
BMI	20,83 (3,5)	21,92 (2,6)	1,39	n.s.
Restrained Eating Scale	23,05 (6,2)	9,82 (5,6)	55,43	***
TAS (Identifying Feelings)	21,55 (6,0)	12,14 (3,5)	40,26	***
TAS (Describing Feelings)	15,00 (3,7)	9,59 (3,4)	25,35	***
TAS (Externally Thinking)	17,50 (4,3)	15,86 (3,3)	2,02	n.s.
TAS (Total Score)	54,05 (9,1)	37,59 (7,5)	42,63	***
SCS-12	24,05 (6,0)	28,77 (7,2)	5,60	*
EDI (Interoception)	30,32 (9,1)	48,50 (5,2)	66,45	***
STAI-State	42,59 (9,2)	35,59 (5,3)	9,51	**
STAI-Trait	55,18 (11,6)	38,55 (8,6)	29,22	***
BDI	39,52 (10,2)	25,33 (3,8)	35,51	***

Note: BN = bulimia nervosa; SD = standard deviation; BMI = body mass index; n.s. = not significant; p < .05 = *, p < .01 = **, p < .001 = ***

As expected, patients reported significantly more disturbed eating attitudes and behaviors than controls, as measured by the Restrained Eating Scale ($F(1,42) = 55,43$, $p < .001$). They also showed higher STAI state and trait anxiety ($F(1,42) = 9,51$, $p < .01$ and $F(1,42) = 29,22$, $p < .001$) and BDI depression scores ($F(1,42) = 35,51$, $p < .001$) than the controls. Moreover, patients endorsed more difficulty in the identification of bodily sensations, as addressed by the EDI subscale “Interoceptive Awareness” ($F(1,42) = 66,45$, $p < .001$), and in the appropriate regulation of emotional states, as measured by the SCS-12 ($F(1,42) = 5,6$, $p < .05$). Patients were significantly more alexithymic than the controls. Comparisons

revealed significant differences between the groups for the TAS total score ($F(1,42) = 42,63, p < .001$) and for the TAS subscales “Difficulties Identifying Emotions” ($F(1,42) = 40,26, p < .001$) and “Difficulties Describing Emotions” ($F(1,42) = 25,35, p < .001$). However, patients and controls showed comparable results for the subscale “Externally Oriented Thinking”.

5.2 Emotional face recognition performance

The participants’ performance in the emotional face categorization task is visualized in Figure 5. In order to determine group differences for the ability to discriminate between the presented emotions, a repeated-measures ANOVA was conducted. The analysis revealed a significant main effect of emotional face category ($F(3,126) = 7,50, p < .001$), which indicates that the four emotions are categorized differently. Happy and fearful faces (correctly categorized by all participants in 98,64 % and 97,50 %, respectively) were recognized more easily than angry (95,45 %) and neutral faces (93,64 %).

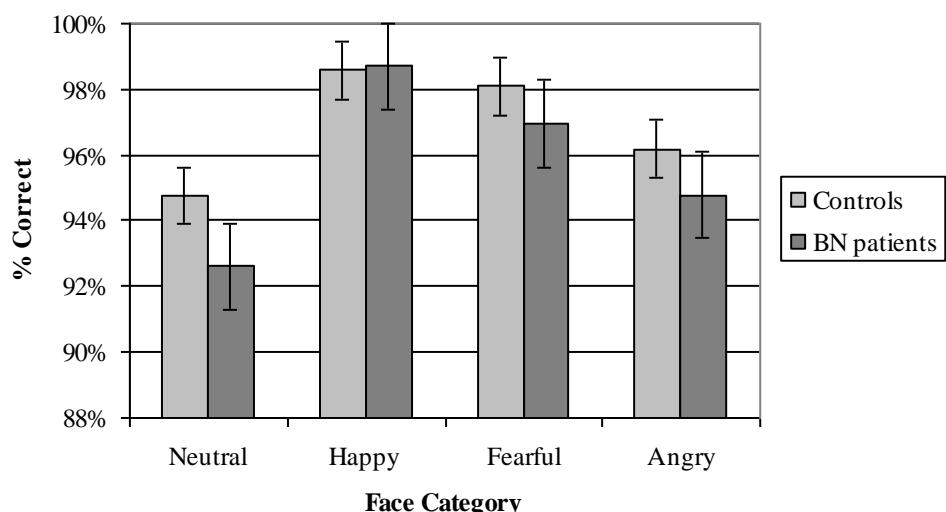


Figure 5: Recognition performance of healthy controls and BN patients. Percentages of correctly recognized emotional expressions are visualized for every category. Bars represent standard error of means.

A comparison of the recognition performance shows very small, but no significant differences among the two groups, thus indicating that patients are not impaired regarding the emotional face recognition skills on a behavioral level.

To further investigate the data, Spearman-Rho correlations between recognition performances and questionnaire scores were calculated. Analysis revealed no significant correlations between correct categorization and BDI, STAI-State, STAI-Trait, EDI (Subscale Interoceptive Awareness), SCS-12, or Restrained Eating scores. Significant negative correlations could only be observed between participants' recognition performance of neutral faces and the TAS total score ($r = .32, p < .05$) as well as the TAS subscale "Difficulty in Describing Emotions" ($r = .41, p < .01$).

5.3 ERPs waveform analysis

Figure 6 provides an overall picture of ERP morphology across the scalp for BN patients (left) and controls (right), showing the GA responses to all emotional and neutral face categories at the midline electrodes Fz, Cz, and Pz (from top to bottom). Emotional modulations of the waveforms are evident for both groups, clearly observable starting at about 150 ms post stimulus. A comparison of GAs of the groups in each emotional face category, illustrates differences particularly around 200 ms, and in the time range of 300 - 400 ms.

To evaluate differences in ERPs response for the two groups, three components of standard ERPs elicited by faces were investigated: the N170 (140-200 ms), the N2 (190-260 ms), and P3 (270-400 ms). Respective time windows were chosen on the basis of visual inspection of the data and in accordance with earlier studies; the corresponding mean amplitude was examined in detail.

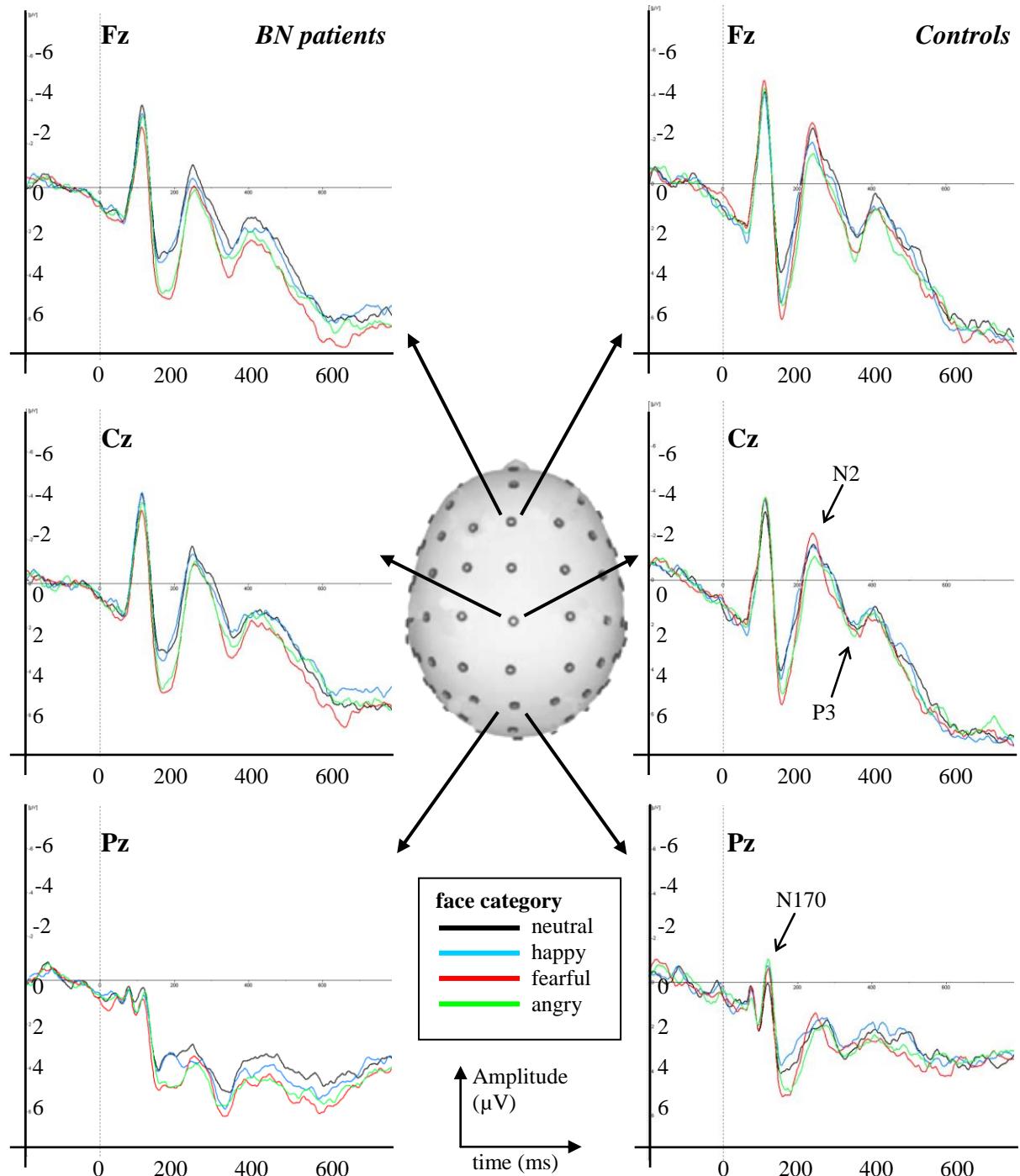


Figure 6: Overview of event-related potentials (ERPs) for bulimic patients (left) and healthy control subjects (right). Shown are grand averages (GAs) for all face categories (neutral, happy, fearful, angry) across the midline electrodes Fz, Cz, and Pz (from top to bottom). Of primary interest are the ERP components N170, N2, and P3, which are observable over central and/ or posterior sites. Note: Positive voltages down.

N170 (140-200 ms)

There was no significant mean N170 amplitude difference between the two groups. The ANOVA revealed a main effect for region ($F(5, 215) = 14.80, p < .001$) and category ($F(3,129) = 25.77, p < .001$) as well as significant interaction between those two factors region and category ($15,645) = 12.52, p < .001$), indicating a differential processing of emotional faces among both groups.

N2 (190-260 ms)

The ANOVA revealed a main effect for group ($F(1, 42) = 5.33, p < .05$), confirming that mean N2 amplitude of the bulimics ($2.08 \mu\text{V}$) significantly differed from that of the controls ($1.45 \mu\text{V}$). Moreover, a main effect for hemisphere ($F(1, 42) = 6.36, p < .05$) indicated a higher mean activity in the right hemisphere, and a main effect for region ($F(5, 210) = 26.62, p < .001$) revealed that medial-superior and postero-superior regions accounted for most of the N2 activity. In addition, a main effect for category ($F(3, 126) = 9.26, p < .001$) was found, in that responses to fearful and angry faces differed significantly from neutral and happy faces. The analysis showed a significant interaction between the factors hemisphere and region ($F(5,210) = 5.33, p < .05$) and between the factors region and category ($F(15, 630) = 6.93, p < .001$). However, a group \times category interaction did not reach statistical significance ($F(3,126) = 1.74, p = 1.67$).

P3 (270-400 ms)

ERP differences between BN patients and control subjects could also be observed in the P3 time window. This was reflected by a significant group effect ($F(1, 42) = 4.77, p < .05$), in that bulimics revealed higher mean P3 activity ($2.08 \mu\text{V}$) than controls ($1.45 \mu\text{V}$). Furthermore, the ANOVA revealed main effects for region ($F(5, 210) = 21.74, p < .001$), category ($F(3, 126) = 3.80, p < .05$), and a significant region \times category interaction ($F(15, 630) = 2.61, p < .05$), again no significant interaction between factors group and category.

To further illustrate the processing of faces in BN patients and healthy controls, the next two figures show difference waves and topographical maps of the scalp voltage distribution derived from the GAs for neutral (Figure 7) and fearful (Figure 8) expressions.

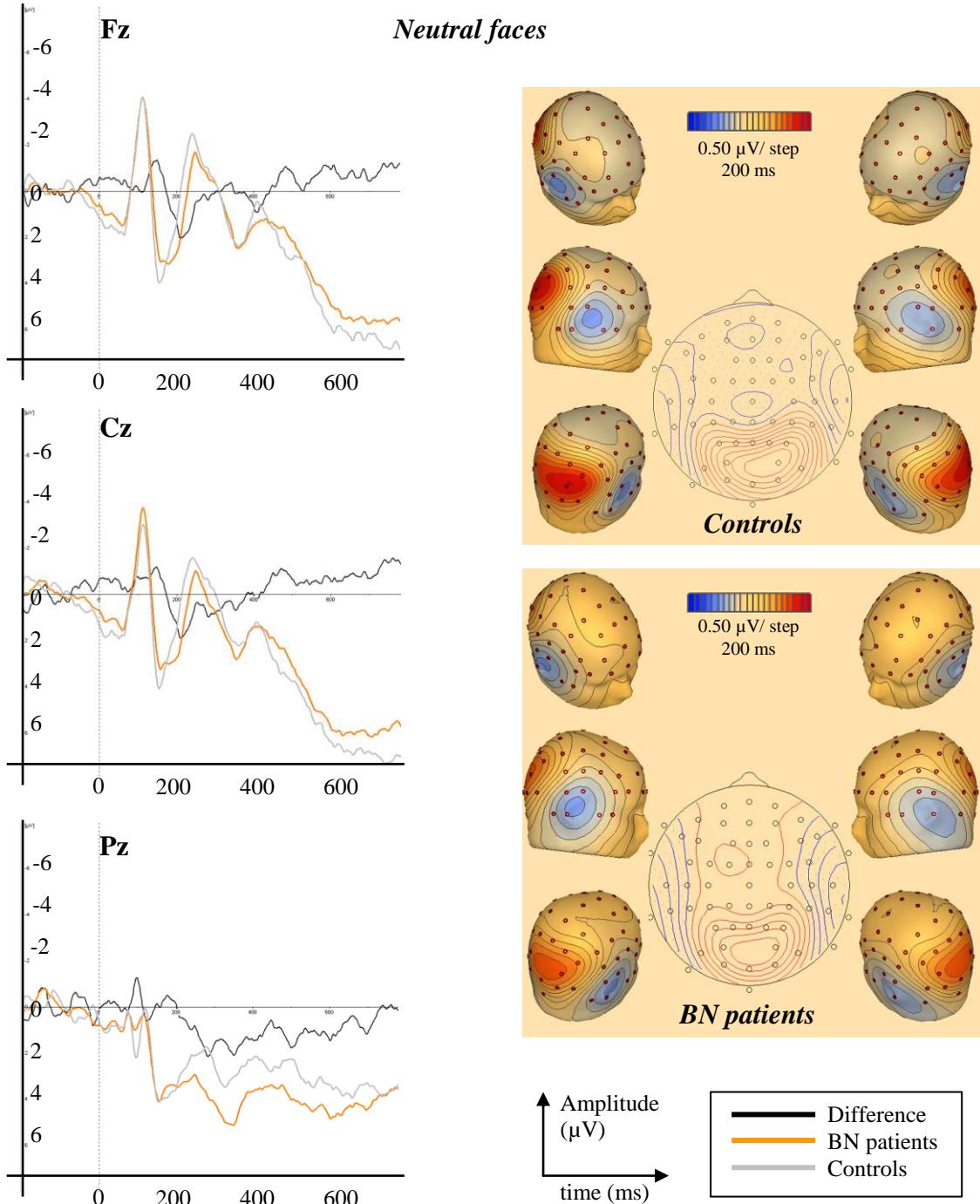


Figure 7: Neutral faces – Difference waves of grand averages (GAs) from BN patients and healthy control subjects (left). The GAs show differences at 200 ms at frontal and central electrode sites, as well as from 300 ms at posterior sites. **Topographic maps** (right) show the voltage distribution on the scalp at 200 ms. The bilateral distribution is seen for both groups. A distinct midline focus is observable in the map of BN patients.

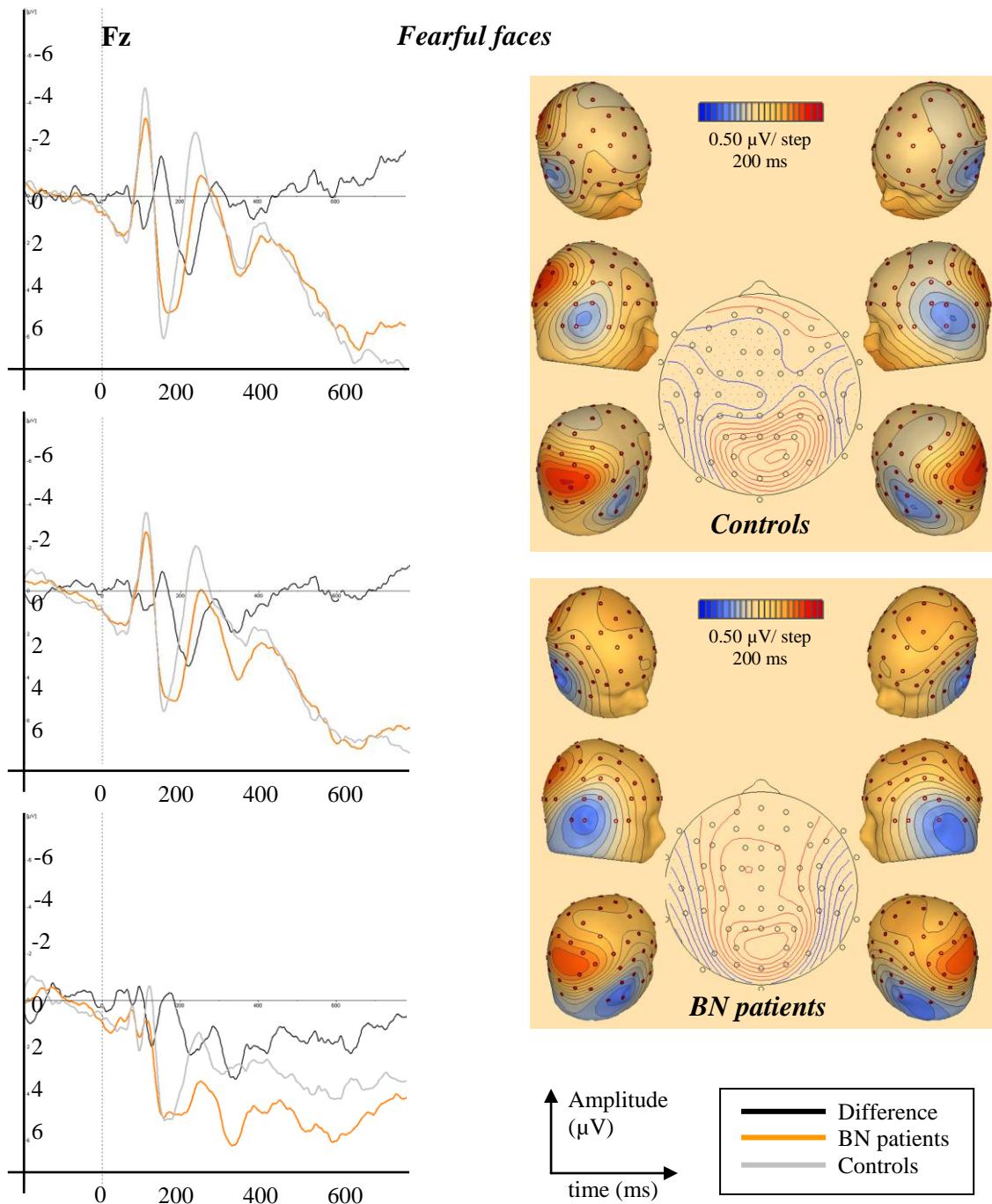


Figure 8: Fearful faces – Difference waves of GAs from BN patients and controls (left). The GAs show even more differences at 200 ms at frontal and central sites (and from 300 ms at posterior sites) as compared to those elicited by neutral faces (Figure 7). **Topographic maps** (right) of the voltage distribution at 200 ms. As for neutral faces, a bilateral distribution in both, and a central midline in BN patients is observable.

5.4 Spatiotemporal analysis of underlying sources

In order to investigate differences in emotional face processing between bulimic patients and control subjects, a spatiotemporal source analysis was carried out. To account for differences regarding category, sources for both “neutral” faces and “fearful” faces were examined in detail.

For each group and each of the two face categories, a PCA of the GAs was computed. Every PCA revealed two main waveforms contributing significantly to the total variance (cutoff criterion: explained variance less than 1%). To select a relevant time interval, reliable activation differences of the two groups and peak latencies of the principal components were considered.

Both components showed an early activation peak around 100 ms post stimulus and a later activation peak around 200 ms. In the subsequent measurement window (300-1000 ms), components’ curves increased continuously without observable peaks. Since significant ERP differences of the two groups were identified starting from 190 ms, and no peaks were present from 300 ms, the N2 time interval of 190-260 ms was chosen for the spatiotemporal source analysis in all cases.

Neutral faces - control subjects

The PCA on the GA of control subjects for neutral faces revealed two principal components (explained variances 94,8% and 4,9%). Based on this result, a model with four dipoles was developed by using an iterative, least-square method. The final model explained 93% of the total variance. Source waveforms and locations are depicted in Figure 9. Sources 1 and 2, with an activation peak in the time interval 190-260 ms, were located in the right and left middle temporal gyrus. Sources 3 and 4 were both adjusted to

fit their earlier peak activity around 130-150 ms. One was located near the left inferior occipital gyrus and the other in the right fusiform gyrus.

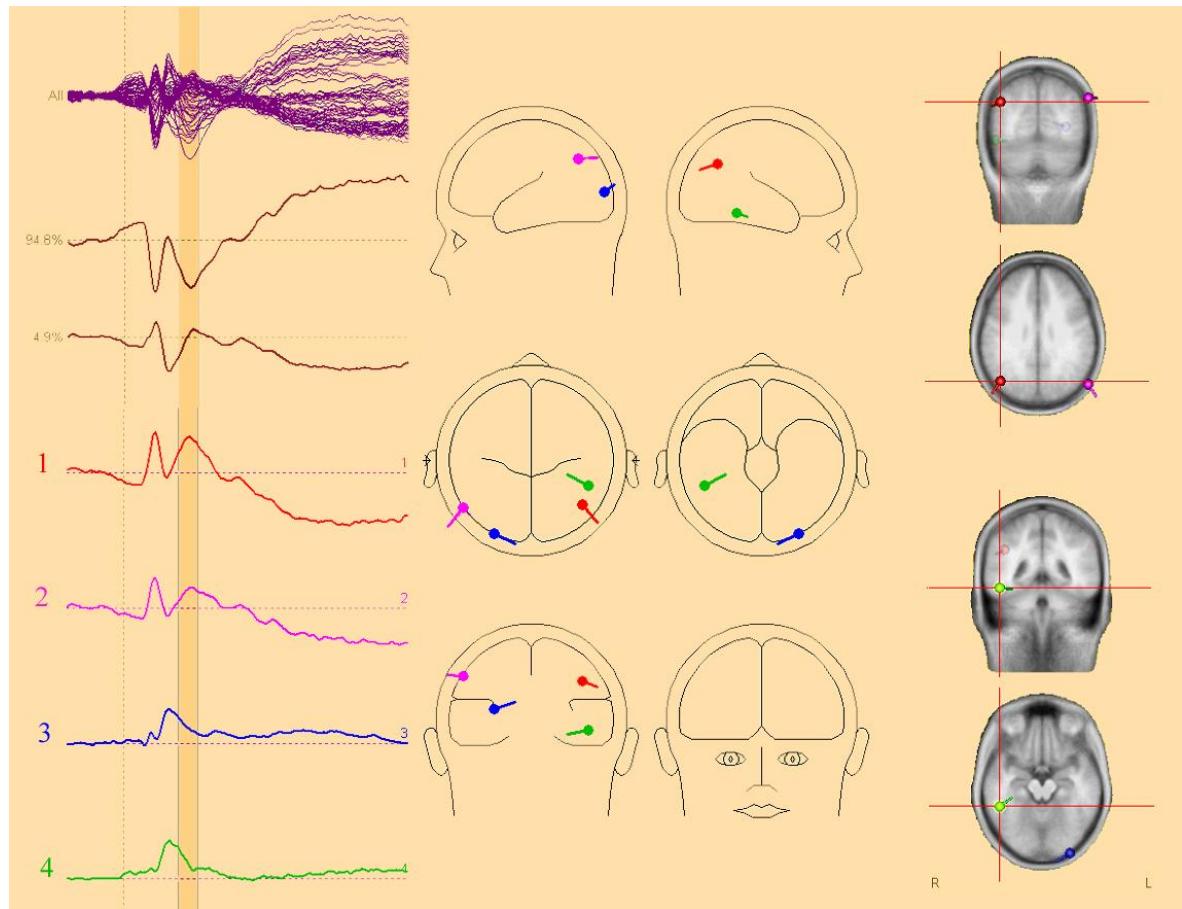


Figure 9: Brain electrical source analysis model : Neutral faces – Control subjects. The left side of the figure shows channel overplot and the two principal components. Below these, the four source waveforms are depicted. The shaded area illustrates the time window of investigation (190-260 ms). To the right, locations of the dipoles are displayed both in a head scheme and in standard MRI anatomical view. The first and second dipole is located approximately in the right and left middle temporal gyrus, whereas third and fourth dipoles are near inferior occipital gyrus and fusiform gyrus.

Neutral faces – BN patients

Similar to the results of the control subjects, a PCA on the GA of neutral faces for the bulimics revealed two principal components (explained variances of 90,6% and of 9,0%, respectively), so that four dipoles were fitted for a model (see Figure 10). With a first peak around 110 ms, activity waveforms for dipole 1 and 2 showed a second maximum in the investigated time range 190-260 ms and resembled data of the control subjects in curve

progression. Likewise, source 1 located in the right middle temporal gyrus; source 2 however was found to be located in the left middle occipital gyrus. Activity waveforms of dipoles 3 and 4, very similar to those of control subjects, both showed a single peak at 130-150 ms; therefore the third and fourth sources were fitted to that time interval in addition. Again, locations of sources 3 and 4 were found in right fusiform gyrus and left inferior occipital gyrus. This model accounted for 90,64% of the total variance.

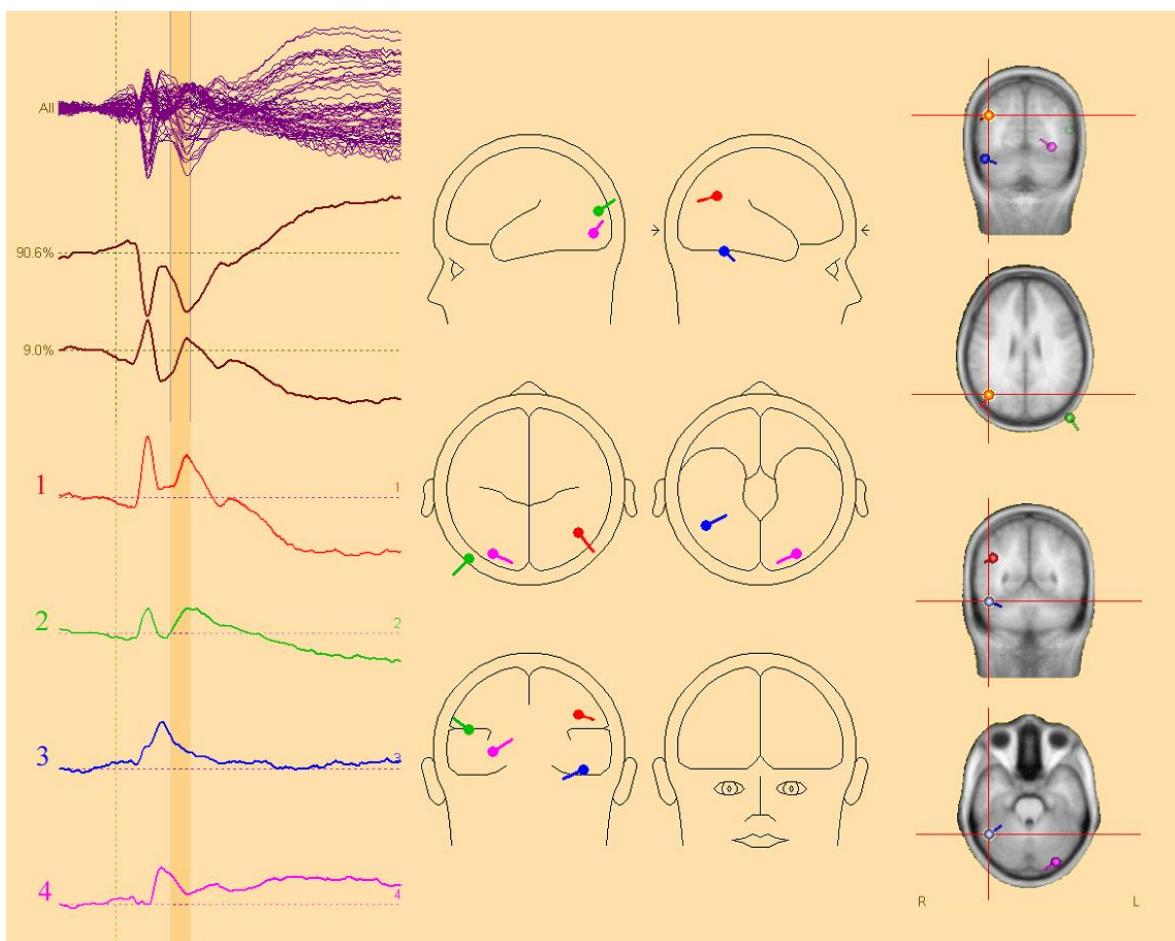


Figure 10: Brain electrical source analysis model : Neutral faces – BN patients. Channel overplot, the two principal components, as well as the four source waveforms are depicted to the left. The shaded area illustrates the time window of investigation (190-260 ms). To the right, locations of the dipoles are displayed both in a head scheme and in standard MRI anatomical view. Similar as for the control subjects, the first and second dipole was found near the right and left middle temporal gyrus. The third and fourth dipoles are again located near fusiform gyrus and inferior occipital gyrus.

Fearful faces – control subjects

With two principal components revealed by the PCA (explained variances 90,6% and 8,9%), a model with four dipoles was created for the data for control subjects' processing of fearful faces. The activity waveforms resembled those for neutral faces, so the same steps of analysis were done. In doing so, the following sources have been found: right middle temporal gyrus (source 1), left inferior parietal lobule (source 2), right fusiform gyrus (source 3), and left inferior occipital gyrus (source 4). The final model, which is depicted in Figure 11, explained 95,96% of the total variance.

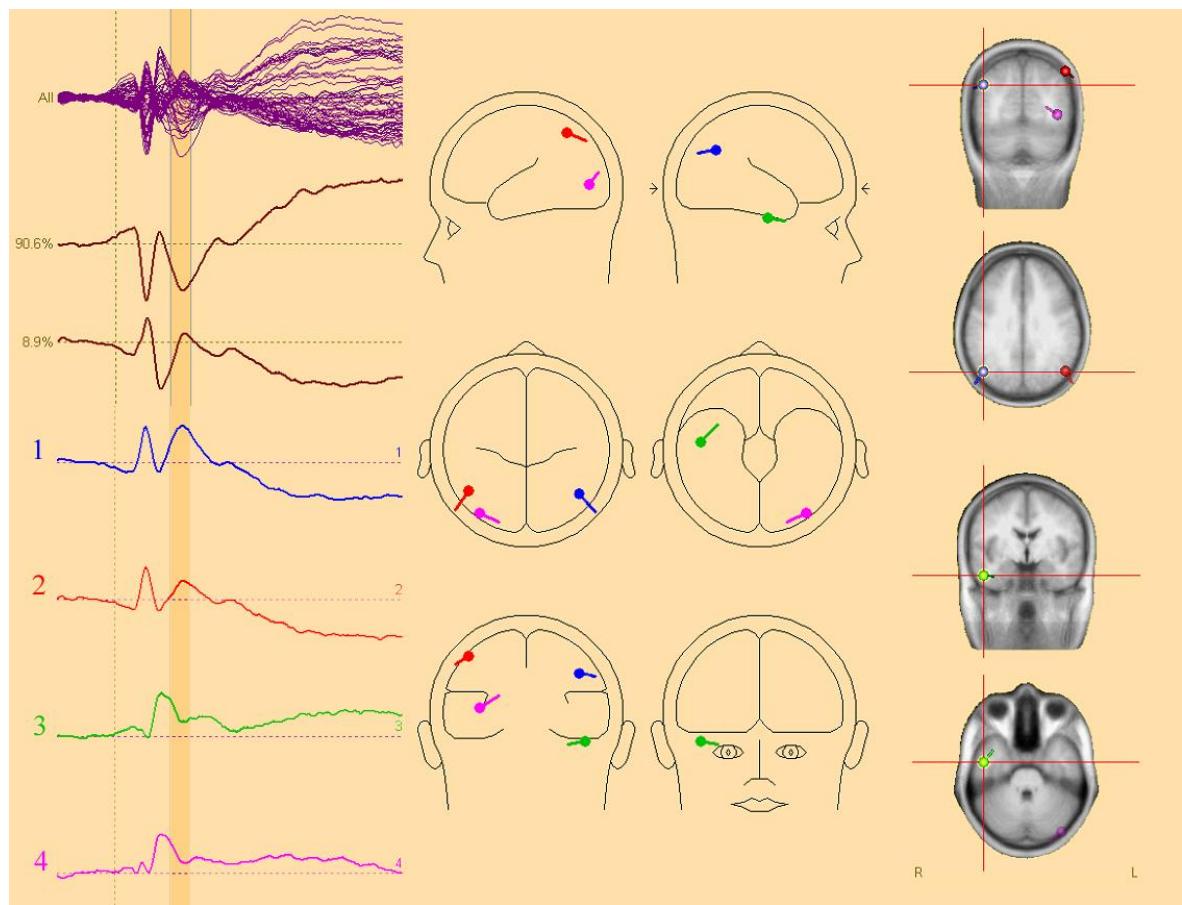


Figure 11: Brain electrical source analysis model : Fearful faces – Control Subjects. To the left, channel overplot, the two principal components, and the four source waveforms are depicted. The shaded area marks the time window of investigation (190-260 ms). To the right, locations of the dipoles are displayed both in a head scheme and in standard MRI anatomical view. The analysis revealed the first dipole to be located near the middle temporal gyrus, and the second in the inferior parietal lobule. The third and fourth dipoles are in the fusiform gyrus and inferior occipital gyrus.

Fearful faces – BN patients

The PCA on the GA of bulimics viewing fearful faces resulted in two principal components (explained variances 81,9%, and 17,7%; see Figure 12). Dipoles 1 and 3 resulted in activity waveforms with two peaks (around 190 ms and 300 ms), before increasing to a maximum activity in the late slow wave time interval. Thus, in the presence of all other sources, dipoles 1 and 3 were slightly adjusted to fit to their local maximum at 190 ms. Dipoles 2 and 4 have an early peak activity at 100 ms and a later peak at 250 ms. From 300 ms, both show a steady but weak increase in activity.

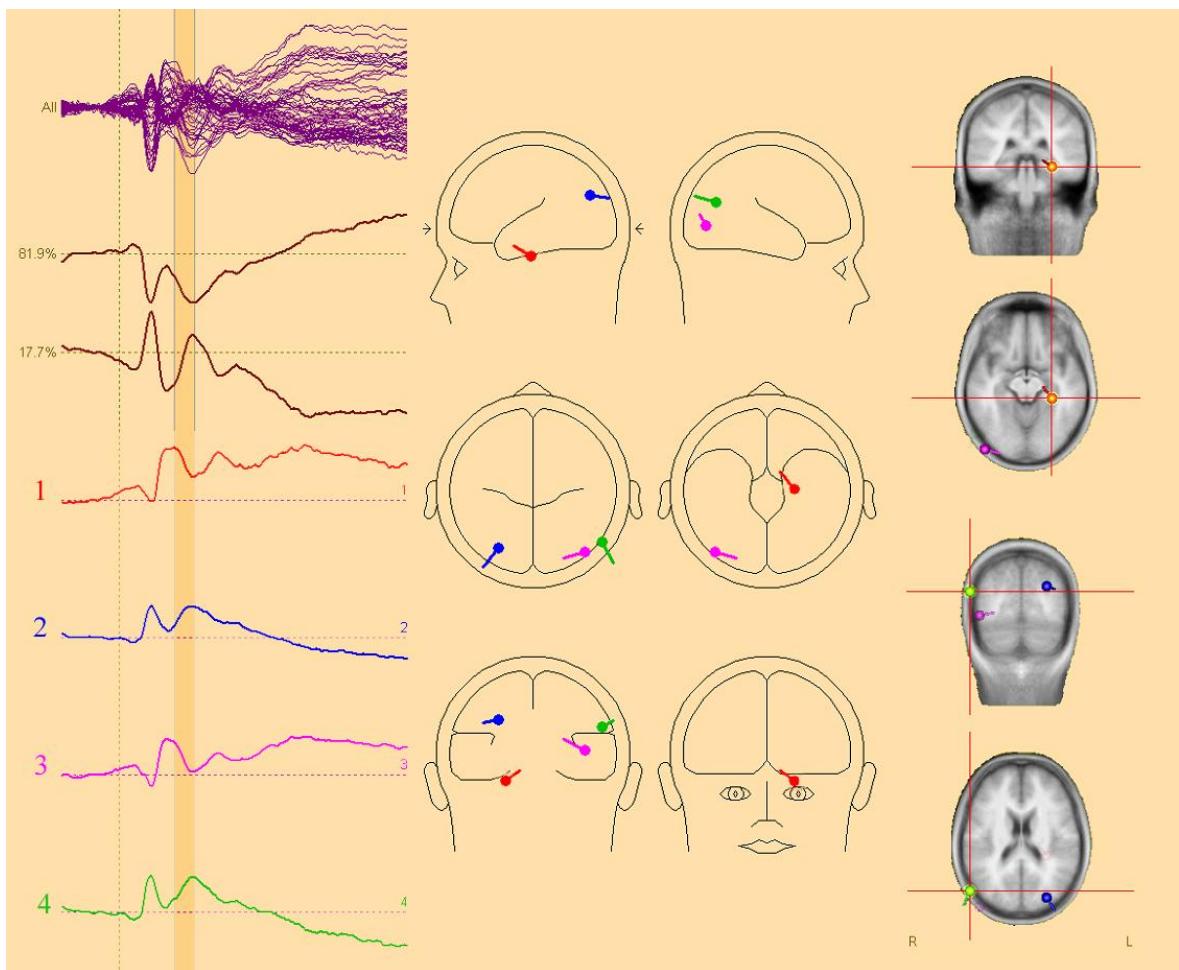


Figure 12: Brain electrical source analysis model : Fearful faces – BN patients. Channel overplot, the two principal components, as well as the four source waveforms are depicted to the left. The shaded area illustrates the time window of investigation (190-260 ms). To the right, locations of the dipoles are displayed both in a head scheme and in standard MRI anatomical view. In strong contrast to the other models, the first dipole was found in the parahippocampal gyrus. The second, third, and fourth dipoles were located in the superior occipital gyrus, the inferior occipital gyrus, and the middle temporal gyrus, respectively.

In contrast to the other models, the strongest activity was found to be in the left parahippocampal gyrus (dipole 1). The following dipoles 2 and 3 located in the left superior occipital gyrus, and the right inferior occipital gyrus, respectively. The right middle temporal gyrus was found to be the fourth dipole. This model explained 95,35% of the total variance.

To further test the validity of all the models developed above, supplementary dipoles have been added to them. None of those new dipoles could be fitted, which suggests that the models explained the data best in the investigated time window.

For an overview of the models obtained, Talairach coordinates and anatomical correlates are given in Table 2.

Table 2: Dipoles with Talairach coordinates, anatomical correlates, Brodmann areas (BA), hemisphere, peak latency and dipole strength (in the time interval 190-260 ms)

Dipole	Talairach coordinates (x,y,z)	Anatomical correlate (BA)	Hemisphere	Peak latency (ms)	Peak dipole strength (nAM)
neutral faces – control subjects					
1	43, -67, 30	middle temporal gyrus (BA 39)	right	231	40
2	-57, -71, 35	middle temporal gyrus (BA 39)	left	233	23
3	-32, -95, 2	inferior occipital gyrus (BA 18)	left	159	39
4	48, -41, -13	fusiform gyrus (BA 37)	right	159	42
neutral faces – BN patients					
1	41, -65, 27	middle temporal gyrus (BA 39)	right	248	47
2	-50, 91, 10	middle occipital gyrus (BA 19)	left	251	28
3	46, -52, -23	fusiform gyrus (BA 37)	right	162	52
4	-30, -84, -9	inferior occipital gyrus (BA 18)	left	162	41
fearful faces – control subjects					
1	44, -66, 31	middle temporal gyrus (BA 39)	right	237	41
2	-48, -65, 46	inferior parietal lobule (BA 40)	left	238	21
3	49, -5, -26	fusiform gyrus (BA 20)	right	159	47
4	-39, -83, -3	inferior occipital gyrus (BA 18)	left	162	43
fearful faces – BN patients					
1	-28, -32, -9	parahippocampal gyrus (BA 36)	left	190	59
2	-29, -79, 25	superior occipital gyrus (BA 19)	left	245	34
3	47, -90, 8	inferior occipital gyrus (BA 18)	right	190	36
4	58, -72, 19	middle temporal gyrus (BA 39)	right	250	38

6 Discussion

Albeit not undisputed, recent research suggested an impairment in the recognition of emotional faces in eating disorders. Aim of this study was to determine whether patients with BN have deficits in the processing of emotional expressions. Although performance in a categorization task was comparable in BN and control subjects, the present ERP data demonstrate significant differences at the post-perceptual level of emotional face processing. Furthermore, a source analysis revealed that these differences could be related to specific structures that collaborate with the emotional face processing system.

6.1 Decreased emotional awareness but normal classification skills in BN

In accordance with previous studies, questionnaire data showed that BN patients were characterized by deficits in emotional functioning. They reported greater difficulty in identifying their own emotional and physiological sensations as well as in the regulation of emotional states. Providing additional support for bulimics difficulty in identifying and describing emotions, BN patients were found to be significantly more alexithymic than the controls, as measured with the TAS. Although additional effects of comorbid mood and anxiety disorders haven't been disentangled yet, it can be concluded that individuals with BN have limited access to their own emotions.

Based on above findings, one could assume that these impairments also cause difficulties in representing another person's emotional experience, e.g. that conveyed in faces. Contrary to expectations, in the categorization task patients with BN showed only very small, but no significant differences from healthy controls in their ability to classify neutral, happy, fearful, and angry faces. This finding dovetails with other research on eating disorders that detects no impairments in emotional face recognition skills on a behavioral level. However, as already addressed earlier, performance tests may not be

sufficient to reveal emotion processing deficits in eating disorders, because subjects might classify basic emotional features of faces correctly but they might not comprehend the emotional or social meaning of that expression.

6.2 Differences in ERPs: Reduced N2 and elevated P3 amplitudes during emotional face processing in BN

The present ERP data provide novel evidence for differential processing of emotional faces in BN as compared to healthy controls. As expected, while the structural encoding level of facial stimuli, as indexed by the N170, was found to be intact, significant differences were observable during emotional expression processing in the subsequent time windows of N2 and P3.

Emotional and neutral faces elicited a negative deflection around 230 ms (N2), which was distributed mainly over posterior sites, in both BN and control subjects. The electrophysiological activity observed in N2 is assumed to represent specific cognitive processes for the early decoding of emotion in facial expressions. As the most prominent finding, BN subjects had a marked reduction of the mean N2 amplitude for all faces in contrast to healthy control participants. The general reduction might reflect impaired cortical activation of automatic processes subserving emotion discrimination and classification in BN. Moreover, N2 potentials were greatest for fearful faces in controls, a finding which is consistent with previous research on healthy adults, whereas bulimics' N2 peaks were lower for emotional than for neutral faces. It seems that while greater attentional resources are allocated to process highly affective stimuli such as fear in healthy participants, the degree of attention focused on facial expressions is decreased and early cortical decoding processes are not generated sufficiently in individuals with BN.

Differences in the processing of emotional faces between BN patients and controls could also be observed in the P3 component, which is regarded to reflect working memory and attentional processes. Here, as compared to healthy controls, BN subjects elicited significantly higher P3 amplitudes for all facial expressions, that are observable over P3-related centro-parietal scalp regions. This suggests that individuals with BN devote a higher amount of cognitive effort in order to evaluate and categorize facial expressions accordingly. Moreover, bulimics showed enhanced modulation for those faces conveying emotional information, which was rather weakly pronounced in healthy participants.

Taken together, the ERP differences between BN and control subjects - the general reduction of the N2 and the subsequent enhancement of P3 to emotional as compared to neutral faces - raise the possibility that difficulties in earlier and automatic emotion classification were followed by an increased allocation of attentional resources to compensate for those deficits. That mechanism may account for bulimics' comparable ability to classify a variety of emotional expressions on a behavioral level, as demonstrated in this study and other neuropsychological reports, but also underlines existing findings of substantial difficulties in recognizing and evaluating emotions in BN.

While no other study on eating disorders addressed the N2 component, two studies have investigated the effects of visual stimuli on the P3 in AN. Nevertheless, the results of the current experiment did not replicate those from the study of Pollatos and colleagues (in preparation), in which AN subjects exhibited decreased P300 amplitudes to negative emotional faces and failed to show an emotional modulation, as compared to healthy participants. Rather, the effects on P3 in this study could parallel Dodin and Nandrino's (2002) finding, in that AN patients showed significantly higher P3 amplitudes in response to body images and simple geometric shapes than control subjects. The authors suggested that this difference can be explained in terms of an increase in arousal, entailing a

heightened level of attentional resources. AN patients would therefore have deficits in automatic information processes and a bias towards an analytical controlled information processing, wherein stimuli are treated regardless of their relevance to a specific situation. Similarly, current results could be associated with this controlled information processing bias, because BN subjects also showed an enhanced P3. However, this greater allocation of attentional resources was not irrespective of stimulus type, since the P3 of BN was characterized by emotional modulations with highest amplitudes for fearful, angry and happy expressions and lowest for neutral faces. Furthermore, observed effects of the N2 in BN in this study are difficult to reconcile with this account. On the one hand, it could be stated that the general reduction of N2 relates to deficits in automatic information processing. On the other hand, this reduction would hardly be consistent with a hyperaroused state in eating disorders, unless its impact displays only in later processing stages.

As results differ strikingly, it has to be stressed that discrepancies between both studies mentioned above and the results of the current study may be largely due to methodological differences, including the selection of stimuli (body and geometrical shape images versus emotional faces). Most importantly it is unclear, if individuals with AN and BN share the same common mechanisms for processing of emotional stimuli. Although both eating disorders show deficits in the recognition of emotion, the results of this study provide evidence that BN patients show a reduction of N2, but also an enhancement in P3 during emotional face recognition.

6.3 Sources of neural activation during emotional face processing in BN

Further support for the differential processing in BN at an post-perceptual stage of emotional face recognition derives from the source analysis, which was carried out in the

time interval of the N2 component. Brain activation and underlying dipoles in BN patients versus healthy control subjects were compared for neutral and fearful faces.

Across neutral faces, both healthy controls and BN patients showed a general pattern of brain activation to faces, which is consistent with previous research (see e.g. Vuilleumier & Pourtois, 2006). The common sources identified located in the middle temporal gyrus, fusiform gyrus, and inferior occipital gyrus, whereas in BN patients the middle occipital gyrus was found additionally, instead of bilateral middle temporal gyrus dipoles in control subjects. Concerning peak activation, the structure of waveforms closely matched for sources in both groups respectively. These regions are highly consistent to face-related areas reported by fMRI and PET studies as well as by depth electrode recordings (Vuilleumier & Pourtois, 2006). Moreover, locations of the dipoles correspond approximately to the core system for face perception (lateral fusiform gyrus, superior temporal sulcus, inferior occipital gyrus) that mediates both invariant and changeable aspects (e.g. expression) of faces (Haxby et al., 2000). The data obtained suggest that individuals with BN elicit activation patterns and sources very similar to those of healthy subjects when presented with neutral faces.

The models obtained for fearful expressions show that different neural sources may be activated in patients and controls in the recognition of emotion in faces in the time range of the N2 component. Middle temporal gyrus, fusiform gyrus, and inferior occipital gyrus were again found as sources presumably mediating the visual analysis of faces in healthy controls. In addition, a dipole was located in the inferior parietal lobule, a region which is regarded to be part of a top-down attentional control system that modulates activity in extrastriate cortex (Hopfinger, Buonocore, & Mangun, 2000). Facial expressions displaying threat or danger are very likely to automatically elicit processes of visual attention (Palermo & Rhodes, 2006). The finding of involvement of greater attentional

resources is in accordance with present ERP data, indicating that fearful faces are processed more thoroughly and elicit a higher mean N2 amplitude in healthy subjects.

Activity recorded for the visual processing of fearful faces in BN patients has been found to be generated in the superior and inferior occipital gyrus as well as in the middle temporal gyrus. In addition, source analysis revealed another, and even stronger dipole activity located in the parahippocampal gyrus. This region is adjacent to the hippocampus and has been traditionally associated with learning and memory processes (Zola-Morgan & Squire, 1993). Being a part of the limbic system, functional imaging studies have revealed this area to be involved in emotional processes as well, so that besides other structures, most prominently the amygdala, activity in the parahippocampal gyrus has been found to be evoked by fear-related pictures (Phan et al., 2002). It is however worth considering that amygdala responses to fearful expressions have been suggested to generate direct modulatory influences on visual cortex and thus enhance the processing of emotional stimuli, whereas the hippocampal area has been shown not to be linked to such emotional modulation (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Interestingly, one PET study found that AN patients exhibited greater activation in bilateral parahippocampal gyri compared with control subjects, when averaged across all experimental conditions including the viewing of food and non-food images (Gordon et al., 2001). The authors suggested that this finding is similar to results in patients with psychotic disorders and may be related to the body image distortion common to AN. However, these results should be interpreted with caution. A recent study that investigated facial emotion recognition in schizophrenia by using fMRI and ERPs found no such increases in activation of the parahippocampal gyrus in patients (Johnston, Stojanov, Devir, & Schall, 2005). Furthermore, performance deficits in schizophrenia patients were associated with early stages of face processing in that study, which contrasts present results of facial expression recognition in BN. Integrating those findings highlighted above and the results of the

current study, it seems very likely that the parahippocampal gyrus is - besides other areas for the processing of visual features - part of a distributed network that is activated in eating disorders and presumably related to the decoding, but not to the modulation and enhancement of the processing of negative emotions.

6.4 Summary

In summary, the findings of the present study provide novel electrophysiological support for a differential processing of emotional faces in patients with BN as compared to healthy controls. Reviewed literature suggests a process that includes both an early stage of facial feature encoding as well as subsequent stages of expression and recognition analyses that can be assessed by scalp-recorded ERPs. Current results provide evidence for an impaired processing of emotional faces in BN that occurs at the post-perceptual level. It seems that patients with BN are characterized by deficits in earlier and more automatic classification processes, as indexed by a reduction of the N2, and deepened evaluation of the emotional content in faces afterwards, as indicated by an enhancement of the P3. This mechanism could ultimately lead to the finding of normal performance in facial emotion recognition tasks in BN on a behavioral level. Additional support for the conclusion that patients with BN have deficits in the emotional processing of faces emerges from the source analysis that was carried out in the time interval of the N2. While the models obtained suggest that individuals with BN engage sources very similar to those of the control group when presented with neutral faces, a different activation pattern can be observed for fearful faces. In addition to sources commonly found for mediating the visual analysis of facial features, a dipole in the inferior parietal lobule, indicating greater attentional resource allocation for fearful faces, was found in healthy subjects. Contrary, BN patients' data revealed neural activity in the parahippocampal gyrus, presumably processing negative

emotions but not producing direct enhancing effects on visual cortex, which could relate to the absence of an emotional modulation.

Although the current study underlines existing findings of substantial difficulties in recognizing and evaluating emotions in BN, results are exploratory and should be regarded with caution. Since the source analysis method does not provide the anatomical precision reached by functional imaging studies, there is potential for error in the localization of activation foci. This imprecision is of particular relevance to the findings of the parahippocampal gyrus, which is adjacent to other important areas such as the hippocampus or amygdala. Given that the nature of emotional dysfunction in eating disorders is a topic of more recent research with diverse results, replication of the present findings about facial emotion recognition in BN will be critical. Future studies would benefit from the joint use of cognitive, behavioral, and physiological measurements as well as from the inclusion of clinical control groups such as depression or anxiety patients to further elucidate the mechanisms underlying the deficits of emotional processing in eating disorders in general and in BN specifically. The prevalence and social significance of human emotions and their disorders ensure that the research of emotion and its role in social cognition and behavior will be an increasingly important theme in modern neuroscience.

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Declaration of autonomy

I hereby confirm that I did this work by myself and that I have used no other sources/references than those mentioned in the reference list.

Nicole Kühnpast, January 2nd, 2008