Affective Stimulus Processing following Traumatic Brain Injury

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von

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DANK

Auch wenn dieser Teil der Arbeit den für mich reizvollsten Abschnitt darstellt (morgen kommt alles in den Druck...), fällt mir das Schreiben dennoch nicht wirklich leicht. Es ist eben nicht einfach, die richtigen Worte zu finden für die zahlreichen Personen, denen ich von Herzen danken möchte – dafür, zum Gelingen dieser Forschungsarbeit beigetragen zu haben, aber vor allem für die vielen aufbauenden Worte, das gemeinsame Lachen und all die kreativen Ablenkungsversuche, welche dieses „Projekt Doktorarbeit" so viel angenehmer für mich gestaltet haben. Da Dankesworte in der eigenen Sprache einfach schöner klingen, wende ich mich an dieser Stelle an die jeweiligen Personen in ihren (und auch meinen) Muttersprachen und damit gleichzeitig in den Sprachen, welche die Promotionszeit am eindrücklichsten beschreiben.

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CONTENTS

ZUSAMMENFASSUNG

Die physischen und speziell die oft langfristigen kognitiven Defizite bei Patienten mit traumatischen Hirnschädigungen wurden in der Vergangenheit vielfach untersucht und gelten zum heutigen Zeitpunkt als hinreichend erklärt. Im Gegensatz dazu besteht hinsichtlich der emotionalen Defizite, die bei Schädel-Hirn-Trauma (SHT) Patienten immer wieder vermutet wurden, ein beträchtlicher Mangel an experimenteller Forschung. Da sich die Verarbeitung affektiver Reize in den letzten Jahren als bewährtes Untersuchungsparadigma im Rahmen gegenwärtiger Emotionsforschung etabliert hat und zum zentralen Gegenstand zahlreicher diesbezüglicher Forschungsarbeiten wurde, greift auch die vorliegende Studie auf diesen experimentellen Ansatz zurück, um abnorme emotionale Reaktionen bei Patienten mit traumatischen Hirnläsionen zu untersuchen.

In einer Gruppe von SHT-Patienten und bei gesunden Kontrollprobanden wurden ereigniskorrelierte EEG-Potentiale sowie die Hautleitreaktion während der Betrachtung einer Serie standardisierter visueller Stimuli unterschiedlicher Relevanz und Valenz abgeleitet. Mit der klinischen Gruppe wurde zusätzlich ein umfassendes neuropsychologisches Screening durchgeführt, um die kognitiven Fähigkeiten der Patienten beurteilen zu können. Eine detaillierte Untersuchung der neuroradiologischen Befunde ermöglichte zudem Aussagen über die genaue Lokalisation der Hirnläsion bei jedem Patienten. Insgesamt demonstrierten die neuroanatomischen Analysen, dass die Gruppe der SHT-Patienten überwiegend Schädigungen in orbitofrontalen kortikalen Bereichen aufwies.

In einem ersten Teil der Arbeit wurden die psychophysiologischen und subjektiven Reaktionen der Patienten auf emotionale Bilder mit denen der gesunden Versuchspersonen verglichen. Insbesondere die abgeleiteten ereigniskorrelierten Potentiale (EKPs) dokumentierten signifikante Differenzen zwischen den Untersuchungsgruppen: Die generell reduzierte P3-Komponente bei den Patienten lässt auf eine weniger effiziente Verarbeitung der emotionalen Bilder schließen, welche zudem in einer deutlich schwächeren selbstwahrgenommenen Erregung (arousal) sowie einer defizitären Gedächtnisleistung für das dargebotene Bildmaterial zum Ausdruck kommt.

Die langsamen EEG-Potentiale belegen, dass die Patienten im Vergleich zu den gesunden Teilnehmern weniger erfolgreich zwischen emotional bedeutsamen Bildern und neutralen Inhalten differenzieren. Während die Kontrollgruppe nach erregenden Stimuli eine gegenüber neutralen Reizen erhöhte langsame kortikale Negativierung über okzipitalen Hirnarealen aufwies, zeigten die späten Potentiale der Patienten keine solche Modulation durch emotionale Relevanz. Als besonders beeinträchtigt bei Patienten mit frontalen Hirnschädigungen erwies sich die Verarbeitung unangenehmer Bilder, welche mit Bezug auf die langsamen positiven Potentiale (>350 ms) über frontalen Hirnregionen keine signifikanten Unterschiede zu den Reaktionen auf neutrale Reize offen legte. Widergespiegelt wurde dieses Ergebnis durch die reduzierte selbstwahrgenommene Erregung als Reaktion auf negative emotionale Reize. Dieser empirische Befund spricht für die Annahme

präfrontaler Strukturen als eine wichtigen Bestandteil des kortiko-subkortikalen Netzwerks, welches seinerseits für die Steuerung und Modulierung affektiver Reaktionen verantwortlich ist.

Der zweite Teil der Dissertation befasste sich mit dem Vergleich verschiedener Patienten-Subgruppen, welche - das spezifische Ausmaß und die Lokalisation ihrer Läsionen berücksichtigend – vorab gebildet worden waren. Dies führte zu einer Gegenüberstellung von Patienten mit ausgedehnten und solchen mit kleinen frontalen Läsionen, Patienten mit ventromedialen präfrontalen (VMPF) Läsionen und solchen ohne Schädigungen in diesem Hirnareal, und schließlich Patienten mit temporalen Läsionen und solchen ohne Schädigungen des temporalen Kortex. Der Vergleich dieser Subgruppen veranschaulicht, dass besonders umfangreiche frontale Läsionen zunächst eine eher unspezifische Beeinträchtigung neuropsychologischer und psychophysiologischer Parameter verantworten. Die deutlich reduzierte späte positive EKP-Komponente beim Betrachten der unangenehmen Bilder, welche bei Patienten mit ausgedehnter frontaler Hirnschädigung nachgewiesen wurde, verweist zudem auf ein spezifisches Defizit dieser klinischen Gruppe bei der Verarbeitung negativer emotionaler Stimuli.

Eine entsprechende Beeinträchtigung ließ sich ferner bei Patienten mit VMPF-Läsionen im Vergleich zur Gruppe ohne Verletzungen dieses Hirnareals feststellen. Zusätzlich fielen bei den ventromedial geschädigten Patienten Defizite in den frühen Phasen (160-220ms) der affektiven Bildverarbeitung auf, da hier die emotional erregenden Stimuli nicht zu der typischen frühen okzipitalen Negativierung führten.

Das Vorhandensein von Läsionen des temporalen Kortex besaß ebenfalls Konsequenzen für die Verarbeitung emotional bedeutsamer Reize. Die P3-Komponente sowie die nachfolgenden langsamen Potentiale der temporal geschädigten Patienten zeigten keine Modulierung durch die Relevanz der affektiven Stimuli.

In ihrer Bandbreite lassen diese Befunde auf ein Netzwerk neuroanatomischer Substrate schließen, welche der emotionalen Verarbeitung unterliegen und insbesondere verschiedene präfrontale, aber auch temporale kortikale Areale beinhalten. Ergebnisse der Subgruppenvergleiche wurden vor allem mit Bezug auf zeitliche Aspekte der Verarbeitung affektiver Reize und in Hinblick auf die Bedeutung spezifischer Hirnregionen für unterschiedliche Verarbeitungsphasen diskutiert.

Während die durch emotionale Bilder evozierten EEG-Potentiale in der vorliegenden Studie einen hilfreichen Parameter für abnorme emotionale Reaktionen darstellten, erwies sich die Hautleitreaktion als weitaus weniger geeignet, um Unterschiede in der Verarbeitung affektiver Reize zwischen SHT-Patienten und gesunden Kontrollen, aber auch zwischen den verschiedenen klinischen Subgruppen aufzuzeigen. So erfolgte abschließend der Versuch, einerseits mögliche Ursachen für diese diskrepanten Befunde zu nennen, um andererseits die Resultate in ihrer Bedeutung für aktuelle Theorien menschlicher Emotionen zu diskutieren.

SUMMARY

To date, physical consequences and especially the long-term cognitive deficits in patients with traumatic brain injury (TBI) are well understood, whereas systematic research on the equally important behavioral and emotional impairments is rather scarce. As affective stimulus processing is increasingly being considered an important part of contemporary theories of emotion and has therefore been extensively studied, this experimental approach was chosen for the present experiment to explore emotional alterations in brain injured patients.

In a sample of TBI patients and a group of matched healthy subjects, event-related potentials (ERPs) and skin conductance responses were recorded during viewing of a series of standardized visual stimuli differing in affective arousal and valence. In addition, the clinical group was administered a neuropsychological test battery in order to draw conclusions about the cognitive functioning in patients. Detailed analyses of the neuroradiological scans furthermore allowed for determining lesion extent and location in every patient. In summary, neuroanatomical examinations showed that TBI patients had mainly lesions in orbitofrontal brain areas.

In the first part of the thesis, psychophysiological and subjective reactions of patients to emotional pictures were compared with those of healthy controls. In particular, the ERPs revealed significant differences between the two experimental groups. The general attenuation of the P3 component in patients indicates a less efficient encoding of the visual stimuli which is also reflected by the overall reduced self-perceived arousal and the severe memory deficit for previously presented pictures.

Furthermore, the slow EEG potentials demonstrated that brain injured patients, compared to the control group, less successfully discriminate between emotionally salient pictures and neutral contents. Healthy subjects showed an enhanced late negativity over occipital areas in response to highly arousing stimuli, whereas patients' slow potentials were not modulated as a function of stimulus arousal.

A specific impairment of brain injured patients in evaluating unpleasant stimuli was revealed by the late positive potential (>350 ms) at frontal sites which did not differentiate between unpleasant and neutral pictures. This finding was further reflected by the reduced self-perceived arousal in response to negative emotional stimuli. Taken together, this evidence argues for an important involvement of prefrontal brain regions in the cortico-subcortical network associated with the elaboration of emotional stimuli and, in particular, with the modulation of affective responses to unpleasant stimulation.

In the second part of the present thesis, data of clinical subgroups with specific lesion characteristics were compared. Patients with large frontal lesions were contrasted to those with small ones, patients

with damage of the ventromedial prefrontal cortex (VMPFC) were compared to those without lesions in this specific brain area, and finally, patients with temporal lobe lesions were contrasted to those without damage to the temporal cortices. Findings from these comparisons revealed that extensive prefrontal lesions are, first of all, associated with rather unspecific alterations of psychophysiological and neuropsychological parameters. Furthermore, the reduced late positivity during viewing of unpleasant pictures found in patients with large damage in the frontal lobes points to a specific deficit in processing unpleasant stimuli related to very extensive lesions of prefrontal brain areas.

A similar impairment in processing negative emotional cues was found in patients with lesions of the VMPF who, in addition, showed deficits with respect to very early stages of affective picture processing. The 160-220 ms ERP pattern in these patients reflected less efficient visual encoding of highly arousing slides compared to patients without damage in the VMPFC.

The presence of temporal lobe lesions, as well, had important effects on the elaboration of emotionally salient stimuli. The P3 component and the subsequent slow potentials were not modulated as a function of stimulus arousal in patients with damage to the temporal cortices.

Taken together, these findings support the assumption of a network of different neuroanatomical structures which regulates elaboration of emotional cues and comprises various prefrontal cortical areas and also some parts of the temporal lobes. Evidence from the subgroups comparisons was discussed with respect to temporal aspects of affective stimulus processing and in terms of the role that specific brain structures might play for different processing stages.

Whereas EEG potentials evoked by affective pictures were found to constitute a useful indicator of impaired emotional reactions, skin conductance responses failed to reveal differences in elaboration of affective stimuli between TBI patients and healthy controls, and also between the different lesion subgroups. Possible reasons for this contradictory evidence were discussed, together with the implications they have for the assumptions of current theories of human emotion

Every neuropsychologist should have to experience a simulated brain injury for a year. I wonder how consistently well they would cope; whether they could intellectualize problems and say serenely, "I have the strategies and even though I want desperately to implement them today, I can't. Better luck next time." Would they not rail against themselves, detest their lack of function, and feel incredulous at their unpredictable performances? Could they be calm about their loss of control over thought and emotion?
CLAUDIA OSBORNE

(from: Osborne (1998) "Over my head –
A doctor's own story of head injury from the inside looking out")

1. INTRODUCTION

In her exceptional autobiographical account of the life altering experience of a Traumatic Brain Injury (TBI), Claudia Osborne describes the immediate and long-lasting effects a head injury has on cognitive skills, behavior, and personality. Together with the author, several millions of people are actually living with the consequences of TBI in industrialized countries. Although, enormous progresses have been made in recent years with regard to emergency medicine and trauma surgery, TBI still remains one of the leading causes of death and disability of young adults. Whereas physical consequences and persisting cognitive deficits have sufficiently been investigated and are well understood to date, research on the equally important behavioral and emotional impairments in brain injured patients is rather scarce.

The present thesis aims at shedding light on this neglected issue by systematically investigating responses to emotional visual stimuli in a sample of TBI patients and matched healthy controls. As affective stimulus processing has been increasingly considered an important part of contemporary theories of emotion and has therefore been well studied in healthy persons, this experimental procedure was chosen to investigate emotional alterations in brain injured patients. Furthermore, this approach allows for assessing affective elaboration on various levels: (1) central nervous processing as indicated by event related potentials, (2) autonomic activation as indexed by skin conductance response, and (3) behavioral reactions comprising subjective evaluation of emotional pictures and memory performance for affective stimuli.

A major concern of the present thesis is to give a very precise description of TBI patients in terms of their cognitive status and, in particular, their brain lesion location and extent. To accomplish this, performance of patients on a variety of neuropsychological tests is assessed, and accurate analyses of patients' radiological scans are carried out to determine lesion size and localization for each brain injured subject. This enables us to not only investigate differences between TBI patients and healthy persons, but to also compare different patient subgroups with particular lesion features. By

identifying deficits of affective processing related to damage of specific brain areas, conclusions can be drawn with respect to the particular role that these brain structures might play for the elaboration of emotion.

The following introductory part begins by providing an overview on what is known so far about cognitive, behavioral and affective consequences of traumatic brain injuries. Here, the main focus will be on studies that investigated subjects with diffuse head injury, in particular with closed head injury, as most of the patients participating in the present thesis show this particular type of brain damage. Furthermore, recent findings from studies that recorded psychophysiological measures such as event related potentials or skin conductance activity in brain injured patients will be discussed.

In the second theoretical part, some of the basic contemporary lines of thinking about the concept of emotion will be introduced by focusing on two of the currently most influential theories of emotion: (1) Peter Lang's model on emotion, and (2) the Somatic Marker Hypothesis by Antonio Damasio. In addition, a short account on neuroanatomical aspects of emotion will be given that particularly emphasizes the role of amygdala and prefrontal cortices for emotional perception and elaboration.

Finally, studies on affective visual processing in healthy subjects will be reviewed, and findings from some few clinical studies arguing for impaired emotional stimulus processing in TBI patients will be discussed.

1.1. Traumatic Brain Injury

Traumatic brain injury (TBI) is defined as an insult to the brain, not of degenerative or congenital nature, caused by an external physical force applied to the head, accompanied by some form of tissue damage to the brain. A TBI can possibly lead to temporary or permanent impairments of cognitive, physical and psychosocial functions with an associated diminished or altered state of consciousness. Traumatic brain injuries can be caused by the head hitting an object, e.g. in a road traffic accident, or by an object hitting the head, e.g. struck in sports (Label, 1997).

Two basic types of TBIs can be distinguished: open head injuries (OHI) and closed head injuries (CHI). An open head injury occurs with skull fractures or penetrating injuries which damage the integrity of the brain and the dura mater, as well as underlying tissue, vessels and cranial nerves. The first systematic studies on the consequences of traumatic brain lesions were accomplished during and after the Second World War and therefore mainly focused on penetrating head injury caused by gunshots or missile wounds (Allen, 1947, Goldstein, 1942). Brain damage resulting from open head injuries primarily consists of focal and circumscribed lesions similar to those observed

after cerebrovascular lesions (Lurija, 1947). These pioneering studies have been an important step towards a better understanding of cerebral functioning, but are no further applicable to actual issues on traumatic brain lesions related mostly to closed head injuries caused by road traffic accidents or sport injuries. Today, penetrating head injuries account for only about 10% of all head injuries (Grafman & Salazar, 1987).

During the last years, research mainly focused on closed head injuries and we now have gained a much more detailed insight into neuropathology of head trauma. The injury process is actually a cascade of events occurring at the gross anatomical and cellular levels and can be divided into several stages (Perino & Rago, 1995). First is the primary injury, which refers to the direct mechanical damage inflicted to brain tissue, with the immediate consequences including contusion, haemorrhage as well as the important effect of axonal stretching and shearing in the case of acceleration/ deceleration injuries. This damage to the brain cells and tissues is non-reversible and, therefore, not curable (Laurer, Lenzlinger, McIntosh, 2000). The main mechanism of injury is the acceleration and deceleration of the brain within the skull. This has two typical results. Damage to the brain, which is connected to the large mass of the diencephalic and telencephalic structures, may be provoked. This occurs in the most severe cases of trauma and leads to immediate loss of consciousness or even death (Jellinger, 1983). Another consequence of the acceleration/deceleration mechanism is the tearing of the long, microscopic axons comprising the white-matter tracts, the so called diffuse axonal injury (DAI). The phenomenon of DAI was described for the first time nearly 50 years ago (Strich, 1956) and is still subject to extensive research (Adams, Graham, Murray & Scott, 1982; Gennarelli, & Graham, 1998; Onaya, 2002). Although termed as “diffuse”, the pattern of axonal damage is more accurately described as multifocal, appearing throughout the deep and subcortical white matter, and is particularly common in midline structures. In mild to moderate DAI, macroscopic pathologies often remain undetected and the brains may appear normal upon radiological examination (Mittl, Grossmann, Hiehle et al., 1994). In cases with very severe DAI, the axonal pathology is accompanied by tissue tears (petaechial haemorrhages) in the white matter observable on MRI scans (see example illustrated in Fig. 1.1.1.). This level of diffuse axonal injury is usually associated with prolonged unconsciousness, high mortality and poor outcome in survivors (Gennarelli, 1993).

Secondary damages that follow the primary injury comprise edemas, hemorrhages and infections. Edema is an especially important mechanism of secondary injury, because it may cause increased intracranial pressure and lead to hydrocephalus or, by preventing sufficient blood flow, to ischemia (Levin, Benton & Grossman, 1982).

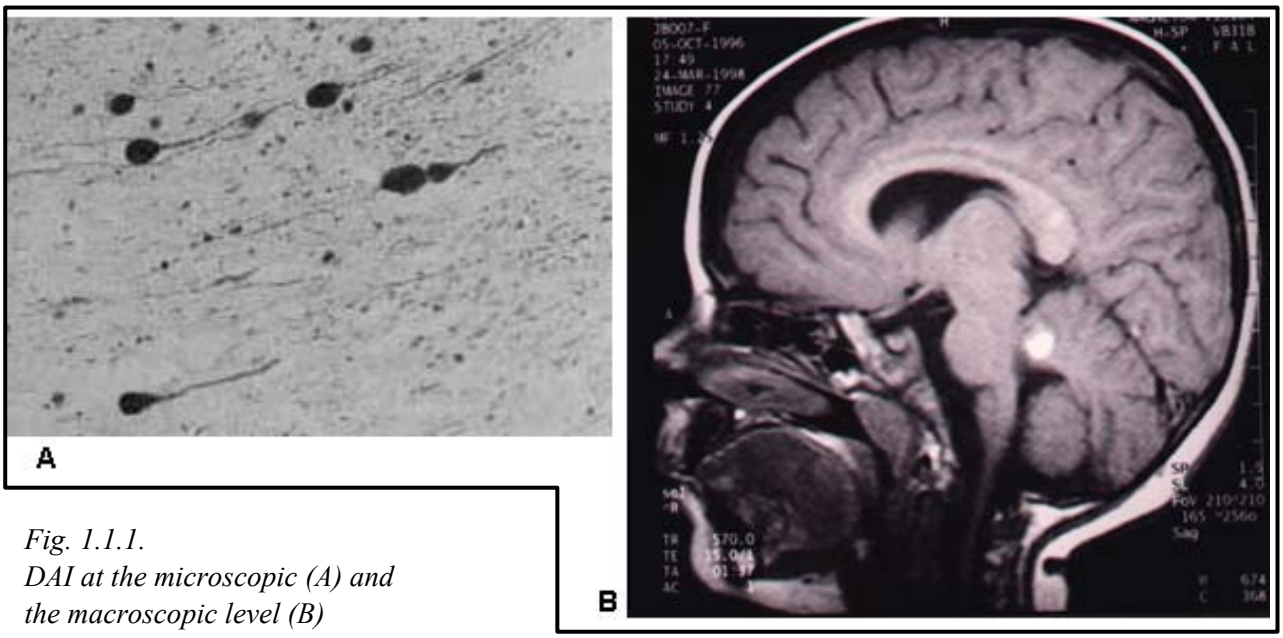

Fig. 1.1.1.
DAI at the microscopic (A) and the macroscopic level (B)

A) Axonal bulbs are shown, indicating the characteristic discrete region of swelling at the terminal stump of disconnected axons. (from Smith & Meaney, 2000)

B) Midsagital T 1 weighted image shows hyperintense lesions associated with subacute type of haemorrhages (hemorrhagic type of DAI) within the corpus callosum, central lobule and superior vermis . (from Uzan, Tureci, Tanriover et al.,1999)

When head injuries involve a significant amount of acceleration/deceleration, for instance in motor-vehicle accidents, also focal lesions can be detected that usually affect frontal and temporal portions of the brain (Adams, Graham, Scott et al., 1980). Levin and co-workers (1987) used Magnetic Resonance Imaging (MRI) to determine the neuroanatomic distribution of focal hyperintensities in patients with closed head injury and found that frontal areas are the most common location of focal lesions. The high probability of these areas to be damaged relies on the structural anatomy of the brain with temporal and inferior frontal lobes resting against a rough portion of the skull. In addition to the direct force of the impact, the rebound of the brain on the opposite side of the skull (the so-called contrecoup injury) also can produce substantial damage (Gurdjian, 1975).

One of the most important visible consequences of a traumatic brain injury is the alteration of consciousness, in severe cases represented by a comatose state. Because the depth and the length of coma have been shown to predict long-term outcome, especially with regard to neuropsychological performance (Jennett & Teasdale, 1981), the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), a measure of alterations of consciousness, often is used as an index of severity of traumatic brain lesions. Another essential tool for classification of head trauma is Post Traumatic Amnesia (PTA), a temporary inability to encode and retain new information, which often is a consequence of

significant concussions of the brain. Like GCS, length of PTA has been shown to predict severity of injury (Bond, 1990; Wilson et al., 1993).

Considering that in industrialized countries, traumatic brain injury constitutes one of the major causes of mortality among the population of adolescents and young adults (Kraus, 1993), it is important to account for some epidemiologic facts on TBI. Generally, the incidence of head trauma is approximately 200 cases per 100,000 population (Kraus & McArthur, 1996). Figure 1.1.2. illustrates a statistic on annual basis in the United Stated showing that 1.5 million annually sustain a TBI and that the incidence of TBI is extremely higher compared to other leading injuries or diseases. Again with regard to the United States, it was found, that 50.000 people annually die as a result of TIB and that currently 5.3 million Americans are living with a disability as a result of a TBI (Center for Disease Control, 2001).

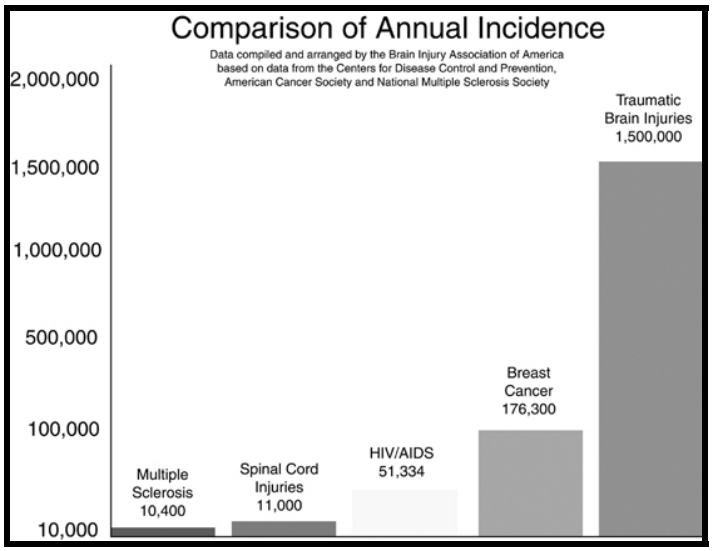

Fig. 1.1.2.
Annual incidence of TBI in the USA compared to some other injuries/ diseases.

(from: Brain Injury Association of America http://www.biausa.org/images/ what.is.brain.injury/Factsstats)

Unfortunately, for European country no detailed systematic data are available for recent years, so we make use of epidemiologic data furnished by the European Brain Injury Society in 1992 (Briani, Mazzucchi, Lombardi et al., 1992). With respect to the type of incidents causing brain trauma, data revealed an extremely high frequency of traffic accidents amounting to 82.5% of all TBIs. Injuries at work are responsible for 5.7 of traumatic brain lesions whereas sport accidents account only for 3% of cases. In addition, epidemiologic data showed a much higher incidence of TBI in men (75%) compared to women (only 24.8%). The age group of adolescent and young adults (16 to 30 years) is at particular risk for sustaining a TBI, as we can see from the example of Italy, where TBI is the major cause of death among the 15-25 years old (Lombardi & Brianti, 1995).

1.1.1. Cognitive functioning following TBI

During the last years, an extensive number of studies have been accomplished that examined neuropsychological deficits following traumatic brain lesions (see Capruso & Levin,1992; Sherer, Novack, Sander et al., 2002, for a review). Cognitive impairments are usually the most disabling sequelae of head injuries. The earliest stage of recovery from moderate to severe closed head injury is a period of post-traumatic amnesia that typically includes memory loss of events preceding and surrounding the injury and memory loss of events occurring since the injury. Following resolution of PTA, deficits may be present in a number of cognitive domains, depending to some extent on severity and dynamics of lesions but also on specific psychosocial factors or medical complications (Trexler & Sullivan, 1995). Brooks, Campsie and colleagues (1987) showed that cognitive deficits, together with behavioral consequences, are much more predominant in patients with TBI than physical insufficiencies. In addition, lasting cognitive problems constitute a more important source of stress for the patient's family than difficulties related to physical constraints (McKinlay, Brooks & Bond, 1981). Attention, memory and the so-called "executive functions" (Lezak, 1982) constitute the most commonly impaired functions, especially in the case of patients with closed head injury (Capruso & Levin, 1992). The following section summarizes important findings related to frequent neuropsychological deficits after traumatic brain lesions by putting emphasis on those cognitive tasks that are also part of the present investigation.

A variety of follow-up studies covering periods from 3 months to 7 years post-injury (Oddy, Coughlan, Tyerman & Jenkins, 1985; Van Zomeren & Van den Burg, 1985) have shown that poor concentration and general slowness are amongst the most common problems reported by severely head-injured patients or their relatives. Numerous neuropsychological studies have confirmed that attention deficits may result from traumatic brain injuries (Brouwer, Ponds et al., 1989; Ponsford & Kinsella, 1992, Spikman, Van Zomeren & Deelman, 1996). In addition, those studies indicate that deficits differentially impair attentional processes. While patients were able to maintain their attention over a longer period of time ("sustained attention") and did not produce a noticeably high amount of errors or inaccuracies, processing speed was significantly impaired. An interesting study was conducted by Ponsford and Kinsella (1992) who presented closed head injury patients with a series of task that focused on different aspects of attention. Results provided no evidence for impaired focused attention and sustained attention, but ample evidence for the presence of a deficit in speed of information processing. Where possible, head injured subjects tended to sacrifice speed to maintain accuracy. In addition, there was evidence that increasing task complexity resulted in a more substantial difference between performance of patients and healthy subjects' outcome. This

effect of growing task complexity becomes especially evident when patients are required to perform two tasks simultaneously. A reduced ability to divide attention appears to characterize patients with mild traumatic brain injury (e.g. Stablum, Mogentale and Umiltà, 1996) as well as patients with severe injury (e.g. Azouvi, Jokic, Van Der Linden et al., 1996). Summarizing present studies on attention in patients with TBI, we can conclude that head injury seems to cause an impaired capacity of information processing resulting in a slowed speed of performance. This deficit particularly tends to appear when patients are presented with complex or dual tasks that overextend their available elaboration capacities.

Memory impairments are an additional common consequence of traumatic brain injury. During the acute phase, most of the patients suffer post-traumatic amnesia, whose recovery mainly depends on the severity of the lesion. The difficulty in storing new information (anterograde amnesia) has been investigated in both clinical (e.g. Russell, 1971) and neuropsychological studies (for a review, see Levin, 1989). In addition, there is evidence for the presence of retrograde amnesia in patients with closed head injury. A study by Carlesimo, Sabbadini, Bombardi et al. (1998) revealed that the deficits involve both autobiographical and public events memories as well as early acquired basic and cultural knowledge. Also in the long run, memory deficits continue to constitute a significant burden and are reported by the majority of head injured patients even two year after acquisition of the trauma (Van Zomeren & Van den Burg, 1985). Levin, Goldstein, High and colleagues (1988) showed that one fourth of the participating head injured patients manifested defective memory on both auditory and pictorial measures even though their general intellectual functioning resulted in the normal range. An interesting work by Hall and Bornstein (1991) examined serial-position effects on a contextual memory task (paragraph recall) in patients with closed head injury. They found that although patients showed the expected primacy and recency effects, their overall immediate recall was significantly impaired.

A huge amount of research on cognitive consequences of head injury has focused on the so-called “executive functions”. According to Lezak (1982), executive functioning concerns the general ability to engage in independent, purposeful, self-directive and self-serving behavior. This includes the capacity to formulate new plans of action and to select, schedule and monitor appropriate sequences of action. Executive functions are considered to be higher level functions which control the more basic cognitive functions; they are decisive for whether and how an individual makes use of his or her knowledge and skills (Lezak, 1982). Several studies have linked executive functioning to the (pre)frontal cortex (Shallice & Burgess, 1991; Stuss, 1992; Stuss & Benson 1984) showing

that patients with frontal lesions are not able to adequately plan and regulate their behavior. As we mentioned before, although TBI is generally conceived to be a more diffuse injury including the fronto-temporal areas, additional focal lesions are frequently found in the frontal cortical regions. Interestingly it has been reported that head-injured patients themselves complain about difficulties with planning and organizing their activities in daily life situations (Hinkeldey & Corrigan, 1990). This finding, together with the fact that after traumatic brain injuries, lesions often can be localized in the frontal cortex, has led to the assumption that executive functioning may be impaired in patients with traumatic brain lesions. In fact, several authors used the term "frontal syndrome" to describe the typical pattern of cognitive deficits in patients who sustained a TBI (Grant and Alves, 1987; Oddy, Coughlan et al, 1985; Rommel, Widdig, Mehrtens et al., 1999).

To investigate the assumed dysexecutive deficit, a variety of studies have been carried out that made use of neuropsychological tests supposed to assess executive functions, such as the Wisconsin Card Sorting Test (Berg, 1948), the Tower of London (Shallice, 1982) and tests of verbal fluency (Benton, 1968). Head injured patients resulted to be impaired with respect to spontaneous production of words (Lannoo, Colardyn et al., 2001; Levin, Goldstein et al., 1991) and furthermore showed an elevated number of perseverative responses during card sorting (Levin, Goldstein et al.,1991, Stablum, Umiltà, Mogentale et al., 2000). Also planning capacities and problem solving, as revealed by performance on the Tower of London task, appeared to be affected as a consequence of traumatic brain injury (Ponsford & Kinsella, 1992).

To explore the specific contribution of frontal lesions to the dysexecutive problems of head injured patients, some authors compared test performance of patients with and without frontal lobe lesions or differentiated between distinct lesion localization within the frontal lobe. Crow (1992) used variables from a verbal fluency task, rule-breaking errors and number of words produced, to suggest localization within the frontal lobes, the orbitobasal and convexity regions, respectively. He found that the orbitally lesioned individuals produced higher levels of disinhibited responding on the test than did non-orbitally lesioned subjects. With respect to verbal fluency, Levin (1991) could show a higher percentage of perseverative errors in the group with frontal lesions as compared to closed head injured patients with no frontal damage. In addition, a study by Burgess and Shallice (1996) revealed impaired response initiation (longer latencies) and impaired response suppression (higher percentage of unwanted responses) in subjects with frontal lesions compared to either individuals with extrafrontal or no lesions.

Results of experimental investigations using head injured patients with verified lesion in different locations, however, are not always this univocal. Levin (1991) examined performance of head-injured patients on the Wisconsin Card Sorting Test and the Tower of London and could not find

differences between patients with frontal lesions and the non-frontal group on these measures of executive functioning. A similar result was described by Spikman and Van Zomeren (2000) who also studied the assumed executive deficits in brain-injured patients with and without frontal damage. A possible explanation to these ambiguous findings of the present literature could be that lesions in traumatic brain injuries cannot always be localized with exactness. Because the majority of patients have a diffuse injury, small lesions can be expected anywhere in the brain and therefore also in the frontal regions of those patients who have no demonstrated focal lesion on CT or MRI.
Another methodological issue that could generally account for problems in assessing executive deficits in head injured patients concerns the neuropsychological tests aiming to tap those functions. In recent years questions have been raised that affect the reliability of traditional measures of executive functioning. In fact, studies assessing patients with traumatic brain injury using the Tower of London (Cockburn, 1995) or the Stroop test (Trexler & Zappala, 1988) did not demonstrate differences with healthy controls. Although these tests may be novel and nonroutine to the participant, they can not be said to be unstructured, since they are rich in cues provided by the examiner. These are important factors that may confound the examination of executive functions. As Stuss (1987) mentioned, it is relatively easy "to become the frontal lobes" of a patient or research participant by providing too much external structure. Spikman, Deelan and van Zomeren (2000) made a substantial contribution to this discussion by presenting head injured patients with a series of unstructured tests tapping executive functioning. They came to the conclusion that dysexecutive problems become particularly evident in tasks that are very similar to daily life situations and that demand from patients to generate strategies by themselves without being provided with any external cue or structure.

Discussing cognitive impairments in TBI patients, one has to consider not only neuropsychological test performance but also cognitive difficulties as reported by patients themselves. Given the very frequent finding, that head injured patients show impaired insight and awareness concerning their functional status (Prigatano, 1991), the relationship between these self –reports and actually present deficits should be taken into account. Several studies with closed-head injury have typically shown low correlations between self-reported competency and actual performance, presumably because of these individuals' limited insight regarding their acquired cognitive limitations (Prigatano, Altman & O'Brien, 1990; Gass, Russell & Hamilton, 1990). This problem seems to be more common in patients with severe brain injury, who tend to report more favorably about their cognitive status than do their less seriously injured counterparts (Mateer, Sohlberg & Crinean, 1987). The degree of insight about cognitive deficits is considered to play an important role for daily living and the

rehabilitation process (Gass & Apple, 1997). Inaccurate and exaggeratedly optimistic self-appraisal can lead to poor decision-making based on unrealistic expectations, eventuating in repeated failure and devastation. In addition, patients who are aware of their deficits are more apt to be concerned about their cognitive status and to take advantage of rehabilitation opportunities.

1.1.2. Behavioral, affective and personality changes following TBI

Personality changes and behavioral disturbances have always been of crucial research interest when studying consequences of traumatic brain lesions. One of the probably most cited case studies of psychological and neurological literature is the nineteenth-century landmark patient Phineas Gage (Harlow, 1848; 1868), who sustained a severe open brain injury at work, caused by an iron bar passing through his head. Astonishingly, Phineas Gage, in some respect, was able to fully recover. He did not show any physical impairment and appeared to be as intelligent as before the accident, not presenting deficits of speech, new learning or general memory. On the other hand, profound changes in his personality became evident. Gage became irreverent and childish; he lost his respect for social conventions and offended people around him with his rude and vulgar behavior. Once a very efficient and capable worker, he now seemed to have lost his sense of responsibility. Like his friends and relatives put it, “Gage was no longer Gage!” (Harlow, 1868). Gage’s physician, John Harlow, correlated the cognitive and behavioral changes of his patient with a presumed area of focal damage in the frontal region. More than a century later, Damasio and co-workers (1994) made an extraordinary neuroanthropological effort to reconstitute the accident and determine the probable lesion location. Measuring Gage’s skull and using modern neuroimaging techniques, they came to the conclusion that the damage involved both right and left prefrontal cortices. At present, a lot of evidence confirms the assumption that parts of the prefrontal cortex play a key role for the elaboration of emotion and the control of social behavior. (Anderson, Bechara, Damasio et al., 1999; Damasio, 1994). That reason, together with the fact that TBI usually includes a more or less diffuse brain damage to frontal areas, makes brain injuries so interesting for the study of behavioral and affective alterations. Unfortunately, although a long line of research has been accomplished, there is still a lack of systematic and well-controlled studies in this field.

Early investigations were based on interviews and clinical observations (Goldstein, 1952) and made use of questionnaires that were administered to patients and their relatives. Later studies employed sophisticated factorial analyses of data trying to individualize essential components of emotional and motivational responses of head injured patients (Hinkeldey and Corrigan, 1990). In addition, the use of standardized personality inventories, such as the Minnesota Multiphasic Personality Inventory (MMPI; Fordyce, Roveche and Prigatano, 1983), became more common. All these

methodologies, however, tend more to describe but not to explain mechanisms that are responsible for modifications of the personality after TBI.

At a behavioral level, an important distinction is drawn by Lishman (1973, 1987), who differentiates between personality changes due to direct, as opposed to indirect effects of the brain injury. The former are a direct result of disturbances of neural tissue, whereas the latter are more varied, due to effects such as the individual's reactions and responses to impairments, environmental factors, premorbid personality and mental constitution and so forth. A series of authors have interviewed brain injured patients and their relatives and found evidence for long-lasting emotional and personality alterations. Lezak (1987) could demonstrate that 30-40 % of the interrogated patients with TBI showed emotional deficits comprising social isolation, depressive mood, lack of affect control and loss of initiative. An interesting long-term study was conducted by Thompson (1984), who collected information on 40 patients with severe blunt head injuries over a period of 10-15 years after trauma. Her work revealed that deficits related to emotional lability remained rather stable over time, whereas symptoms, such as sleep disturbances, irritability and loss of spontaneity tended to slightly deteriorate from 2 years post-trauma to 10-15 years. Symptoms that showed the most evident deterioration over the years were loss of interest and social isolation. Oddy (1985) interviewed relatives of patients with closed head injury and found that even after 7-8 years following the trauma, in 40% of the investigated cases, patients were described as "childish" and "not aware of their difficulties". The high importance of behavioral consequences of TBI was evidenced by Kreutzer and co-workers (1994). They could demonstrate that the amount of stress experienced by the families was significantly related to the extent of behavioral deficits of the brain injured patient and did not correlate as much with severity of trauma or neuropsychological performance. The most cited behavioral and personality alterations as a consequence of traumatic brain lesions are the following (for a review, see Prigatano, 1995):

- Irritability, agitation and loss of control
- Affective instability, frequent and rapid mood changes
- Aspontaneity and loss of interest towards the environment
- Tendencies towards depression and anxiety
- Enhanced perception of stress
- Unawareness of deficits and refusal to admit difficulties

Following traumatic brain lesions, disturbances of behavior and affect can be so severe, that patients are diagnosed with a psychiatric disorder. The most frequently found diagnoses in head injured

individuals are Major Depression and anxiety disorders and, to a lesser extent, psychotic syndromes (for a review, see van Reekum, Cohen & Wong, 2000).

Depression is the most cited psychiatric disturbance, with prevalence rates of about 26% in clinical samples at initial assessment (Fann, Katon, Uomoto et al., 1995) and 18% to 31% six months after injury (Satz, Forney, Zaucha et al., 1998). An interesting study was conducted by Holsinger and colleagues (2002), who investigated the lifetime rate of depressive illness 50 years after closed head injury. They interviewed World War II veterans who sustained a head trauma during their military services (n = 520) and veterans without head injuries (n=1198). The authors found an increased lifetime prevalence of major depression in the head injured group (18.5%) compared to those with no head trauma (13.4%). Also the rate of current major depression was higher in those veterans who had sustained a head injury during the war. In addition, the life time risk of depression was found to increase with severity of head injury. Since the data did not reveal differences in rates of depression between veterans who received head injuries in combat and those who did not, the authors excluded posttraumatic stress disorder as a possible explanation to the findings. Other studies demonstrated that the presence of a depressive disorder influences the rehabilitation process in head injured patients. Depressive patients resulted to be more impaired with regard to emotional functioning, mental health and general health perceptions. Interestingly, depressive patients also tended to rate their injuries as more severe and their cognitive status as worse, despite the lack of significant differences in objective measures, when compared to head injured patients without depression (Fann, Katon, Uomoto et al., 1995). With respect to possible predictors for the development of mood disorder following TBI, evidence from clinical studies suggests that poor premorbid level of functioning and past history of psychiatric illness are major risk factors for depression (Fedoroff, Starkstein, Forrester et al., 1992).

Anxiety disorders and psychotic symptoms are less well studied in patients with TBI. Prevalence rates revealed by different studies do not provide a clear cut picture. Frequency of anxiety disorders ranges from 11% to 70%, whereas the prevalence of a schizophrenia-like psychosis is described with frequencies from 0.7 % to 9.8 % (Rao, Lyketsos, 2000). Different variants of anxiety disorders are seen including post-traumatic stress disorder, generalized anxiety disorder and panic disorder. As expressed by Lewis & Rosenberg (1990), TBI patients often experience generalized “free-floating” anxiety associated with persistent worry, tension and fearfulness.

1.1.3. Psychophysiological responses in TBI-Patients

In this section, findings of previous studies on psychophysiological responses in patients with traumatic brain injuries will be discussed. Since the present thesis investigates psychophysiological

measures of affective stimulus processing in those patients, we have to first find out if deficits of other types of information processing could be established as a consequence of head injury. This will enable us to later discuss results of the present study in terms of their specificity for processing of affective contents only. The presentation of previous findings will focus on event related potentials (ERPs) and skin conductance as they constitute the kind of psychophysiological parameters that were used in our investigation.

EEG studies, so far, have been centered on patients with closed head injuries, mainly because behavioral studies have indicated that slow reaction time and slow information processing speed are among the most consistently observed deficits after this type of brain damage. ERP studies of head injury, starting with Curry (1980), were considered helpful in distinguishing attentive processing stages because they give a temporally continuous record of cerebral processing. Most studies employed the oddball paradigm to examine differences in ERP parameters between healthy subjects and head injured groups with varying degrees of severity and tested at varying times after the trauma (for a review, see Campbell and de Lugt, 1995; Potter et al., 2001). The majority of investigations have concentrated on N2/P3 measured to the target stimulus. Evidence regarding differences in the amplitude of the N2 deflection is mixed. Enhanced N2 after severe head injury was reported by Rugg, Cowan, Nagy et al. (1988) and by Campbell and de Lugt (1995). Rugg et al. (1988) argued that their N2 findings indicated that early stages of processing were impaired in head injured patients; the patients required more time, and had to expend more effort to categorize the target and non-target tones. The authors interpreted their data in terms of Van Zomeren's "coping hypothesis" (Van Zomeren, Brouwer, Deelman, 1984). This proposes that head injured patients compensate for their slower information processing by the expenditure of additional processing resources; in the case of the study of Rugg et al. (1988), these additional resources were reflected in the enhancement of N2. On the other hand, visual N2 has been found as reduced in amplitude in patients with closed head injury (Heinze, Munte, Gobiet et al., 1992). As the task, in this case, involved a conjunction of stimulus characteristics along two visual dimensions, the increased complexity may have been significant for the particular modulation of N2.

More consistent results have been found with respect to later stages of information processing, namely the P3 component. P3 amplitude has been interpreted as manifestation of processes related to the updating of contextual models in working memory (Donchin & Coles, 1988), and the allocation of attentional resources to stimulus evaluation. Dual task studies have shown that as the perceptual demands of a secondary task increase, the P3 evoked by targets in the primary task decreases in amplitude. This indicates that P3 amplitude is a measure of limited-capacity attentional resources (for a review, see Näätänen, 1992). During sustained attention tasks, e.g. the oddball

paradigm, correct detection of an infrequent target stimulus generates a P3 (P3b) maximal at centroparietal sites. Delivery of an unexpected deviant stimulus with no particular task significance but novel enough to attract attention also generates a P3 (P3a). The P3a is maximal at frontocentral scalp sites and is generated from 20-50 ms earlier than the P3b. According to Knight (1991), the P3b indexes voluntary phasic attention, whereas the novelty P3a reflects involuntary automatic attention to potentially significant environmental events. The most common finding of studies that investigated the P3 components in head injured patient with a variety of experimental designs is a decrease in P3b amplitude and a prolonged P3b latency (Curry, 1980; Pratap-Chand, Sinniah & Salem, 1988, Rugg et al, 1988). These findings support the view that attention speed and resources are impaired in patients with traumatic brain injury. With respect to the earlier P3 component (P3a), some studies have revealed that this component is enhanced in brain injured patients compared to healthy controls. Increased amplitude to unexpected deviant stimuli has been demonstrated by Kaipio and co-workers (Kaipio, Cheour, Öhmann et al., 2000; Kaipio, Alho, Winkler, Escera et al., 1999), who examined ERPs to auditory stimuli in closed head injured patients. The larger P3a amplitude shown by the patient group was interpreted as being related to an enhanced involuntary switching of attention to acoustic changes indicating an increased distractibility in head injured patients. Evidence on the P3a component in brain injured patients is, however, not so univocal. In his review, Knight (1991) described several studies reporting a reduced P3a in patients with brain lesions, especially in those with damage of the temporal-parietal junction and prefrontal lesions. This led the author to the proposition that the prefrontal cortex is a component of a network involved in the detection and rapid encoding of significant environmental events, and that this brain area is particularly critical for involuntary access to this encoding system.

Two interesting studies were accomplished by Solbakk and colleagues who compared ERPs and performance (reaction time, accuracy) of patients with mild head injury with no post-injury pathology observed by CT or MRI and patients with proven lesions to the frontal lobe. Using that approach, the authors attempted to investigate the claim that cognitive symptoms in mild head injury are due to a mild type of fronto-temporal injury. In the first study (Solbakk, Reinvang, Nielsen & Sundet, 1999), a dichotic listening task was applied to analyze mechanisms of selective attention whereas in a later investigation (Solbakk, Reinvang & Nielsen, 2000), a three-stimulus oddball paradigm was used to study sustained attention, and more specifically effects of interference. Interestingly, the studies showed that performance of patients with mild head injury on both the oddball paradigm and the dichotic listening task was significantly poorer compared to patients with frontal lesions and healthy controls. ERP amplitudes to deviant stimuli were attenuated in patients with mild head injury, suggesting limited availability or expenditure of

resources needed for adequate task performance. The authors concluded from their findings that focal frontal injury and closed head injury without verified lesions do not produce equivalent processing deficits. When studying consequences of mild head injury, however, it is important to note that in some cases, minor structural changes pass undetected, although patients are described as "with no pathological evidence". In fact, it has been suggested that diffuse axonal injury is the central neuropathological mechanism of mild brain trauma (e.g. Dixon, Taft & Hayes, 1993). As long as no further information on possible structural brain alterations is provided, one cannot determine the causal mechanism responsible for the demonstrated restriction of attentional resources in patients with mild head trauma.

Several of the above presented studies on ERPs in head injured patients have some important drawbacks that could also be a likely source of the contradictory findings. First, there are large variations in severity and in acuteness of injury in published studies which makes it difficult to compare the different results. Another important factor is that most investigations include a relatively small number of patients, so that effect sizes of similar magnitude may come out as significant or non-significant because of varying group size or intra-group variability. In addition, the composition of the clinical group with respect to lesion size and localization is of extreme importance, since modulation of specific ERP components may be sensitive to some and not other loci of lesion. In this regard, the main problem is the very poor documentation of neuropathological findings in patients who participate in the experiments. Some studies do not reveal any information on lesion characteristics of their TBI group (e.g. Rugg, Pickles, Potter et al., 1993), while other published studies are limited to presenting short excerpts of neuroradiological reports that grossly describe the type of lesions (e.g. Kaipio et al., 1999). This lack of clarity definitely compromises the reliability of resulting conclusions as well as the generalizability of findings.

Consequences of traumatic brain injury for autonomic reactivity, as revealed by studies on skin conductance (SC), are another important issue when considering psychophysiological measures in head injured patients. In contrast to research on ERPs, only very few studies have been published that recorded skin conductance in a group of patients with diffuse traumatic brain injury or closed head injury. Most of the research has focused on patients with focal lesions, not necessarily caused by head trauma, such as lesions of the frontal lobes or damage to the amygdala (Adolphs, Tranel, Hamann et al., 1999; Zahn, Grafman & Tranel, 1999). We will consider the important contribution of those investigations in later chapters, when neuroanatomic correlates of skin conductance and the effect of different types of lesions on affective processing will be discussed.

Peripheral indicators of autonomic nervous system activity are frequently investigated as markers of changes in activation in response to task requirements. For that reason, a common approach is to assess electrodermal responses while subjects are performing specific cognitive tasks. Lehrer et al. (1989) recorded several psychophysiological variables, including skin conductance, during rest periods and various neuropsychological tests in closed head injury patients. The study revealed that patients, compared to healthy subjects, had smaller increments in skin conductance response (SCR) frequency during the tasks versus the rest baseline. The authors did also control for anxiety variables and could not find significant between-groups differences for state or trait anxiety. Taken together, these results were interpreted in terms of a pattern of poor physiological modulation for task performance in patients with closed head injuries. Lehrer's findings have been replicated in a more recent study by Zahn & Mirsky (1999) who, in addition to the smaller rest-to-task increment in SCR frequency also found a reduced SCR amplitude and longer SCR latencies in head injured patients compared to the control group. In their investigation, Zahn & Mirsky presented their subjects with two similar experiments, divided by a temporal interval of approximately one week. Since group differences in the second experiment even reached better significance levels, the confirmed deficits in electrodermal activation could not be consequences merely of a novel situation. As a possible explanation to the more explicit group differences in the second test session, the authors suggested an enhanced intersession habituation in the head injured group. Andersson and Finset (1997) investigated how autonomic reactivity is related to different neurological diagnoses. They recorded skin conductance level and SCR frequency in patients with traumatic brain injury, cerebrovascular insults and hypoxic brain damages during a rest period and two problem-solving stress conditions (cognitive tasks). Autonomic stress reactivity was significantly reduced in all patients compared to controls, but did not differ between clinical groups. This may indicate that stress hyporeactivity as a consequence of brain damage remains quite unaffected by lesion etiology.

In concluding this literature review of previous research on consequences of traumatic brain injury, it is important to take into account a recurrent drawback that concerns large parts of the published studies. Patients diagnosed with traumatic brain injury constitute a group with a considerable variety of cognitive and behavioral symptoms and, what is even more important, with an important diversity of brain lesions. One cannot draw reasonable conclusions on behavioral, cognitive or psychophysiological impairments in those patients without having detailed information on size and location of their brain damage. As mentioned above, lesion characteristics are often described in a very neglectful way, for instance by presenting radiological reports or by shortly summarizing

neuroradiological findings. In several cases information on lesion type, location and size is not provided at all. In the present thesis, instead, one major aim was the precise localization of lesions in our group of brain injured subjects that would allow for determining lesion size and location in each single patient. To accomplish that, CT- and MRI-scans of patients were analyzed using a standard lesion mapping procedure developed by Damasio & Damasio (1989; see 2.2. for further explanations). Doing so later enables us to draw conclusions on neuropsychological and behavioral consequences of specific lesion features.

1.2. Emotion: theoretical issues and neuroanatomical aspects

More than a century ago, Williams James (1884) posed his famous question: "Do we run from the bear because we are afraid, or are we afraid because we run?" He was of the opinion that we are afraid because we run, suggesting that emotions arise as a consequence of altered bodily and physiological states. Discussed and criticized by innumerable articles, the so-called James-Lange theory (James, 1894) has enduring influence on current ideas about the generation of emotions. In fact, the psychological debate over emotion has mainly focused on the question of what gives rise to the subjective states of awareness that we call emotional experience. A particular problem is constituted by the definition of the phenomenon called emotion, its conceptualization and its operationalization. A large part of the disagreement between different theories of emotion can be subscribed to different definitions of what represents an emotion. In modern research, emotion is considered as a hypothetical construct that consists of three equally important parts in the emotional structure called emotional reaction triad. The three parts are feeling, physiology and expression. There is no such thing as cause of effect. Rather, feeling, physiology and expression are parts of a whole (Frijda, 1986). Applying this understanding of emotions provides an important advantage for research. Whereas emotion cannot be observed as such, physiology and expression constitute operationalizable characteristics, and also feelings can be examined by means of verbal expression by the "feeler".

In recent years, emotional processes have been extensively studied, particularly benefiting from the development of new technical instruments and methodological approaches. Caccioppo and Gardner (1999) appositely stated "recent research on emotions is almost as vast and diverse as emotional life itself". As a consequence to the numerous empirical findings, several theories of human emotional behavior have arisen. It would go beyond the scope of this thesis to present an exhaustive discussion on the various theoretical approaches to emotion which have been successfully reviewed by Borod, 2000 and Cacioppo & Gardner, 1999. Instead, I will focus on two of those contemporary emotion theories that are particularly relevant for the question examined in the present investigation. This is on the one hand the model proposed by Lang and co-workers, because it has important implications for the psychophysiological study of emotions, and on the other hand the work by Damasio and colleagues, since it provides particular insight into emotional alterations in brain lesioned patients.

1.2.1. Emotions as action dispositions – Lang's model on emotion

Lang and co-workers have proposed a very influential model of human emotion which in particular addresses questions that refer to psychophysiological aspects of emotional perception of external

stimuli. Published in its first form in 1979, Lang's model was termed "Bio-Informational Theory of Emotional Imagery". Since then, it has aroused a large body of research in the field of psychophysiology. Emotions are considered as "*action dispositions*" (Lang, 1995) that are subject to underlying motivational parameters. Two basic motivational systems exist in the brain - *appetitive* and *defensive* - and each can vary in terms of activation or arousal (Lang, Bradley & Cuthbert, 1998). Consequently, emotions are organized within a two-dimensional space consisting of the *valence dimension* and the *arousal dimension*. The bipolar dimension affective valence indexes the quality of emotion and goes from attraction and pleasure to aversion and displeasure. Arousal is not viewed as having a separate substrate; rather, it represents the degree of activation of either the appetitive or defensive or both motivational systems. With respect to behavioral outcome, the appetitive system is prototypically expressed by approach, whereas activation of the aversive system is related to behavioral escape and avoidance. Lang (1998) suggests responses in three different reactive systems serving as indices of emotional expression: (a) expressive and evaluative language, (b) physiological changes mediated by the somatic and autonomic systems, and (c) behavioral reactions such as tendency of avoidance or performance deficits.

However, one cannot reduce this theory to a simple correlation between the emotional state of a person in terms of valence and arousal and the resulting response pattern. The two basic motive systems determine the general behavioral tendency, referred to as "strategy", but the specific patterns of affective responding are "tactical", in that they adjust to the particular situational context and the specific requirements (Lang, 1994). This notion has important implications for empirical research where subjects are often confronted with a situation designed to evoke a particular affect (e.g. anger or fear). To control for individual "tactical" response patterns, constant experimental procedures should be employed together with standardized and reliable stimulus material. Only such an empirical approach allows for revealing the emotion's underlying strategic framework of appetite and avoidance (Lang, et al., 1998).

For this purpose, Lang and co-workers have developed the International Affective Picture System (IAPS; CSEA, 1999), a set of calibrated photographic slides which includes normative ratings of pleasure and arousal associated with each picture. Currently, the IAPS contains 720 pictures, which have been employed by an extended body of researchers worldwide in important cognitive, psychophysiological and biobehavioral studies. More recently, the International Affective Digitized Sounds (IADS; Bradley et al., 1998a), a similar stimulus set for acoustic stimuli, as well as verbal materials (Affective Norms for English Words – ANEW; Bradley et al., 1998b) have been developed. In addition, Lang and colleagues have published a subjective rating instrument, the Self-Assessment Manikin (SAM; Bradley & Lang, 1994), which allows for assessing the self-

perceived emotional experience of participants in a given experimental setting. As the present investigation, too, makes use of the IAPS and the self-assessment scale, both tools will be further explained in a later chapter (see 2.4.1.).

To date, a large amount of studies that investigated physiologic reactions during picture viewing by use of this standardized stimulus material has revealed important evidence for the existence and the specific characteristics of the proposed defensive and appetitive motivational systems as well as for the influence of the arousal dimension. With respect to defensive motivation, Bradley et al. (2001) suggest that defensive responding to unpleasant pictures is organized sequentially, reflecting the degree to which pictures evoke defensive system activation (arousal intensity). This assumption adopts some findings from animal behavior theorists who have proposed that reflex reactivity is sequentially structured depending on the proximity of threat, e.g. at different stages of predator imminence (Blanchard & Blanchard, 1989; Fanselow, 1994). On the basis of physiological reactions evoked by aversive visual stimuli in humans, Lang et al. (1997) propose a "cascade of reflex responses" which is, to some extent, analogous to the reaction patterns found in animals.

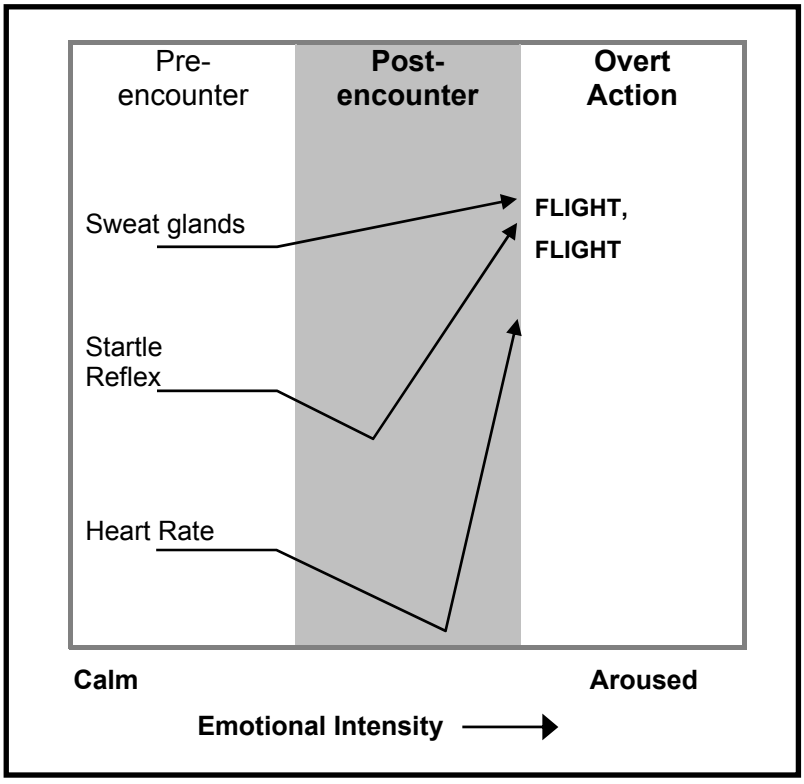

Fig.1.2.1.1.
Defense cascade model

(adapted from Bradley et al., 2001)

Figure 1.2.1.1. illustrates a schematic diagram of the defense cascade model, where the post-encounter stage reflects physiological responses visible in humans during picture viewing.

Of course, looking at picture in a laboratory setting does not correspond to real life events, thus making overt emotional actions barely possible. Nevertheless, the varying degrees of symbolic threat provided by aversive slides are sufficient for causing a specific activation of defensive

motivation, whereby different reflex systems change at a different level of motivational engagement. A slight increase of electrodermal activity, cardiac deceleration and a relative inhibition of the startle reflex are the physiological changes that typically are prompted by detection and processing of a moderate aversive cue. Together, they reflect an orienting response, where attentional resources are directed towards the stimulus and perceptual processing is facilitated. When the aversive activation is more pronounced (higher arousal), however, these reaction patterns change to a more active state signaled by greater electrodermal activity, potentiation of the startle reflex and cardiac acceleration (see Lang, Bradley and Cuthbert, 1998 for an overview). Activation of the appetitive motivational system, such as when viewing pleasant pictures, is also associated with specific alterations of physiological parameters that are more pronounced in correlation with perceived arousal. Typical reactions that can be assessed in this regard are heart rate acceleration and increase of skin conductance activity (Lang et al., 1998). Further findings regarding psychophysiological responses to presentation of emotional pictures will be presented in a later chapter, when we discuss the processing of affective visual stimuli in detail (see 1.3.).

Another important aspect of Lang's accounts is that the activation of one of the valence subsystems is not only associated with particular physiologic alterations, but it also has an important modulatory effect on other processing operations in the brain. This means that association and action programs that are linked to the currently engaged motivational system have a higher probability to be activated compared to representations that are related to the non-active valence subsystem. Thus, an aversively motivated organism should reply with an enhanced aversive/defensive response to an additional aversive stimulus, whereas reactions to a contemporaneously occurring pleasant stimulus should be reduced or even absent (Lang et al., 1998). The supposition of this "emotional priming" has been extensively tested in empirical studies employing the so-called "startle reflex paradigm". This experimental approach typically presents subjects with pictures of different valence (pleasant and unpleasant) and various degrees of arousal to pre-activate a certain emotional state. During picture viewing, a loud acoustic probe is presented that triggers a wholebody startle response, which can be assessed by measuring the Eyeblink EMG at the orbicularis oculi muscle. The most common finding of studies that have made use of the startle response paradigm is that during viewing of unpleasant slides, the amplitude of the startle eyeblink reflex is augmented (Bradley, Cuthbert & Lang, 1990; Lang, Bradley & Cuthbert, 1990). Instead, while viewing pleasant pictures, the startle response is inhibited. These results clearly support the "emotional priming model" by showing that the congruence between being in an aversive affective state and the aversive tone causes an enhancement of the startle reflex, whereas

the incongruence between being in an appetitive state and the aversive stimulus causes a reduction of the defensive response, namely the startle reflex.

Lang and co-workers have also addressed the question of how emotions are mentally represented by proposing that emotion information is coded in memory in the form of *propositional networks*. Lang (1984; 1994) maintains that these networks exist as schemas in long-term memory being entirely activated when any component stimulus is encountered. Three primary information categories are included in a network: 1) *stimulus propositions* containing information critical to recognition of the external stimulus and to the context in which it occurs, 2) *response propositions* representing every type of response made in this context (i.e., verbal statements, overt act, visceral and somatic indices of physiological arousal), and 3) *meaning propositions* that define the significances of stimuli and reactions and contain information on stimulus/behavior contingencies. The stimulus propositions provide the initial input; the implications of these stimuli are then altered by the meaning propositions present in the network. Components of propositional networks can be learned through direct experience, through instruction and through modelling, for example by watching others responding to certain stimuli or situations.

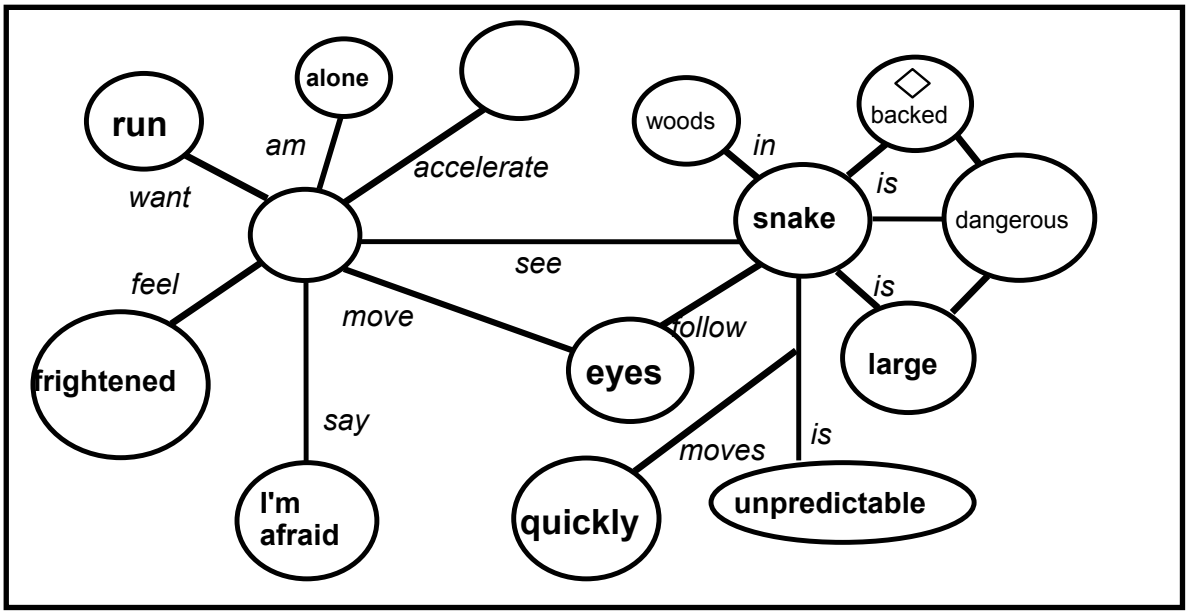

Fig. 1.2.1.2. Propositional network modelling a snake phobia (adapted from Lang, 1994)

Lang's proposal that emotions are represented by these networks has important clinical implications, in particular when discussing the cognitive basis and the assessment and treatment of anxiety disorders (Lang & Cuthbert, 1984; Lang, Davis & Ohman, 2000). It is assumed, that differences among anxiety disorders can be interpreted in terms of the degree of cognitive organization. For instance, a phobic network, as illustrated in Figure 1.2.1.2., is thought to be

characterized by numerous propositional components showing a strong coherence, that make it relatively easy to activate the network.

Different neural structures that monitor and evoke physiological reactions and behavior responses to emotional stimuli are supposed to be engaged in the appetitive and defensive motive system. They are thought to be organized in widespread neurophysiological networks that involve cortical and subcortical components. Whereas the neural basis of the aversive system is well understood, mainly because of findings from animal research, results for appetitive motivation are less clear und the number of published studies is still relatively small. Neural structures underlying the aversive system will be discussed later in the framework of the neuroanatomical aspects of emotion. A particular focus will be on the amygdala, which is considered by Lang (1998) and several other authors to be a key structure in the defensive motivational system.

1.2.2. The somatic marker hypothesis - Damasio's model on emotion

One of the most influential theoretical accounts of human emotions is presented by Damasio and co-workers (see Damasio, 1994; 1998) who derived their model in particular from the observation of patients with damage to specific areas of the prefrontal cortex (Damasio, 1995). Two important aspects of Damasio's theory is the categorization of "emotion" in terms of "primary" and "secondary" emotions and the clear distinction from the expression "feeling". The term emotion is used to "*designate a collection of responses triggered from parts of the brain to the body, and from parts of the brain to other parts of the brain, using both neural and hormonal routes. The end result of such responses is an emotional state, defined by changes within the body-proper, e.g…"* (Damasio, 1998*). Primary emotions* are the basic, innate emotions that usually come first to mind whenever the term is evoked. Examples of these easily identifiable emotions are fear, anger, surprise, sadness and happiness. Circumstances that cause primary emotions as well as patterns of behaviors that define them have been found to be consistent across species and culture. By taking into account findings from animal research as well as functional imaging studies in humans, Damasio states that primary emotions depend on limbic system circuitry, specifically the involvement of the amygdala and the anterior cingulate. While the neural mechanism of primary emotions cannot fully explain the wide range of emotional behavior, they are, however, regarded as the basic mechanism of higher order emotions (Damasio, 1994), the so-called "secondary emotions".

Secondary emotions are dependent on primary emotion. That means they can only appear if one has fully functional primary emotions. Examples are: sympathy, guilt, pride, jealousy, admiration. As Damasio puts it, "*secondary emotions occur once we begin experiencing feelings and forming*

systematic connections between categories of objects and situations, on the one hand, and primary emotions, on the other."(Damasio, 1994, p.134). The network that supports the process of secondary emotions is broader and includes apart from the limbic system also the somatosensory cortices as well as prefrontal cortical areas, in particular the ventromedial and the orbitofrontal cortex. The differential involvement of brain areas in primary and secondary emotions becomes evident from cognitive impairments exhibited by patients with differing neurological damage (Damasio, 1994). In individuals with prefrontal lesions, the ability to experience primary emotions usually remains intact, whereas secondary emotions cannot be generated. Patients with damage to the limbic system including the amygdala and the anterior cingulate gyrus are void of both primary and secondary emotions and, as a result of their damage, they are obviously blunted in their affect. This comparison between individuals with only prefrontal damage to those with only lesions of the limbic system seems to provide strong evidence suggesting that secondary emotions are dependent on primary emotions.

So far, we have briefly discussed Damasio's hierarchical theory of emotions; however, the hierarchy does not end with secondary emotions, but includes also "*feelings*" which are located right on top of the hierarchy. Emotions precede feelings, and feelings are dependent upon primary and secondary emotions. Damasio defines a "feeling" as a complex mental state that results from the emotional state and includes *"(a) the representation of the changes that have just occurred in the body-proper and are being signaled to body-representing structures in the central nervous system… and it also includes (b) a number of alterations in cognitive processing that are caused by signals secondary to brain-to-brain responses, for instance, signals from neurotransmitter nuclei towards varied sites in telencephalon*." (Damasio, 1998). Thus, feelings constitute mental representations of physiological changes that characterize and are consequent upon processing emotion-eliciting objects or states. Whereas perception of emotional events leads to rapid, automatic and stereotyped emotional responses, feelings mediate long-term modulatory behavioral influences.

Damasio proposes the prefrontal cortex, in particular the ventromedial prefrontal cortex (VMPFC) as the responsible structure for learning the association between specific classes of emotional stimuli or social situations on the one hand, and the type of emotional state usually associated with that class of stimuli or situation in prior individual experience. The VMPFC receives input from both sensory cortices and has bidirectional connections with limbic structures, mainly the amygdala, the hippocampus and the anterior cingulate cortex. Furthermore, the ventromedial areas of the frontal cortices project toward central autonomic control structures thereby exerting physiological

influence on visceral control. The broad interconnectivity of the VMPFC mainly contributes to the fact, that this cortical area plays the determinant role in linking a new event or a situation to a specific somatic state.

In the brain, the somatic state results from emotional input from the body eliciting an activity pattern in the somatosensory cortex. Every time a similar situation occurs, the ventromedial cortices, which earlier had established an association between the type of situation and the type of somatic state, trigger the reactivation of the somatosensory pattern that encoded the relevant somatic state. This reactivation can occur in one of two ways: The first way is through a "body loop", meaning that the soma changes in reaction to activation by the prefrontal cortex, and the resulting changes are sent to somatosensory cortices. The second possible path is via an "as if" loop in which the reactivation signals are transmitted directly to the somatosensory cortex (i.e. they bypass the body), which then takes on the appropriate pattern. This definition of the apposite somatosensory pattern to the situation can be either conscious or unconscious, independently from what kind of loop has been activated (Damasio, 1995).

The reactivation of relevant somatic states that marks a currently experienced event as “good” or “bad” is implied when using the term “*somatic marker*”. Damasio defines a somatic marker as “*a special instance of feelings generated from secondary emotions. Those emotions and feelings have been connected, by learning, to predicted future outcomes of certain scenarios*” (Damasio, 1994, p. 174). When a negative somatic marker is linked to an image of a future outcome it sounds an alarm. When a positive marker is associated with the outcome image, it becomes an indicator of incentive. Damasio concludes that somatic markers increase the accuracy and efficiency of the decision process and their absence degrades decision performance. However, it is important to note that somatic markers do not deliberate decisions for us; rather, they assist the decision making process by highlighting the most feasible options and eliminating the least feasible options from subsequent consideration. Damasio and co-workers tested the somatic marker hypothesis by an innovative study (Bechara, Damasio, Damasio & Anderson, 1994) that provides support to the notion that human cognition is guided by affective processes. In Bechara’s experiment, known as the Iowa Gambling Card Test, healthy subjects and brain lesioned patients gambled by selecting cards from any of four desks. Turning each card resulted in a gain or a loss of a sum of money, as revealed on the back of the card when it was turned. Normal subjects quickly learned to avoid disadvantageous desks with attractive large payoffs but also possible large losses, whereas patients with damage to the prefrontal areas were not able to learn this gainful strategy and continued to select cards from the disadvantageous desks ending up with losing great amounts of money. While performing the task electrodermal activity was recorded. Upon turning over a card, both groups

displayed a transient increase in electrodermal activity, thus an autonomic response to rewards and penalties. Over time, these changes became anticipatory for healthy subjects; that is, when choosing a card from a dangerous desk, their skin conductance response would clearly increase. For patients with lesions of the prefrontal cortex, electrodermal activity remained unaltered when facing a presumably disadvantageous decision. This shows that they failed to exhibit any proper anticipatory responses with respect to their behavior as well as their autonomic activity. Subsequently, other studies adopting the Gambling Card Task have continually replicated these initial findings (Bechara, Tranel & Damasio, 1996; 2000). Recently, Bechara et al. (1999) have examined the role of bilateral amygdala damage in comparison to frontal lobe damage on the gambling task. They found that performance of patients with bilateral lesions of the amygdala was even worse than that of frontal lobe patients. In addition, individuals with amygdala damage showed neither transitory nor anticipatory enhancement of electrodermal activity. The authors concluded that these patients were devoid of primary emotions, secondary emotions and somatic markers. While frontal lobe patients became frustrated with their bad performance on the gambling task as a result of their primary emotions being intact, bilateral amygdala patients did not exhibit any form of emotional reaction on this task.

Damasio and colleagues have amassed considerable evidence over the past years that support their view on human emotions. An important contribution of their theoretical accounts certainly consists in the explanation on how brain and body interact in producing emotions and feelings by postulating a bi-directional connection between central and peripherical processes. However, an aspect that remains unclear concerns the idea that, after the initial somatic input is linked with a specific type of situation, phenomena such as “gut feelings” can arise through a closed circuit within the brain, in other words, in the absence of input from or output to the body. The experimental work of Damasio, so far, has mainly focused on the path whereby the “body loop”, activated by the prefrontal cortex, reactivates a pattern of activity in the somatosensory cortex. It would be important, to also have experimental evidence for the functionality of the so-called “as if loop” showing that reactivation of an emotional state is in fact possible by completely bypassing the body.

Taking together Lang’s and Damasio’s theories on emotion, both models agree in suggesting that learning processes play a key role for responses to emotional stimuli and social situations. In addition, both authors postulate a network organization of the emotion underlying brain structures. Investigating affective processing in a group of patients with cortical lesions, the present thesis aims

at contributing to the discussion of specific brain areas that might be important for the evaluation of emotional stimuli.

1.2.3. Neuroanatomical correlates of emotion: the role of prefrontal cortex and amygdala

Although many neurobehavioral theorists propose different concepts on emotion, the majority of them converge on the idea that there exist two basic systems that underlie approach and withdrawal-related emotion and motivation, or positive and negative affect (Davidson & Irwing, 1999; Cacioppo & Gardner, 1999). Furthermore, there is common agreement on the assumption of partially different neural circuitries underlying the two emotion systems. A variety of evidence indicates that particular areas of the human prefrontal cortex, as well as the amygdala, play a central role in the recognition, evaluation and response to emotional salient stimuli. In the following, findings from animal research, lesion studies and recent investigation employing neuroimaging tools will be summarized that support the critical involvement of prefrontal structures and the amygdala (illustrated in figure 1.2.3.1.) in emotion.

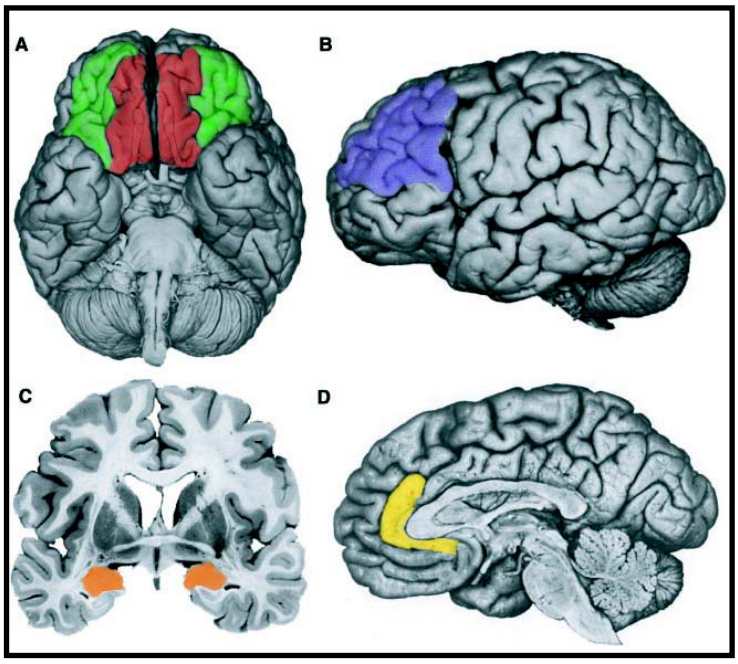

Fig. 1.2.3.1.
Key structures of the emotion underlying brain circuitry:.
(A) Orbito-prefrontal cortex in green, ventromedial prefrontal cortex in red.
(B)Dorsolateral prefrontal cortex
(C)Amygdala
(D)Anterior cingulate cortex

Adapted from Davidson, Putnam & Larson, 2000.

Prefrontal cortex

On the basis of cytoarchitectonic and functional considerations, the Prefrontal Cortex (PFC) is commonly subdivided into different areas: The dorsolateral, the ventromedial, the orbitofrontal sector and the anterior cingulum. Each of these substructures has been linked to some extent to emotion regulation.

Important evidence comes from investigations using classical aversive conditioning to study the neural substrates of the acquisition and extinction of emotional learning. A commonly observed impairment after orbitofrontal lesions in primates is the inability to extinguish or reverse associations that have been established to reinforcing events (Baylis & Gaffan, 1991; Rolls, 1996). For instance, although initial learning often emerges without difficulty, primates fail to adapt their behavior when reinforcement no longer occurs in extinction, or contingencies are changed in reversal training. The hypothesis that orbitofrontal cortices are involved in correcting responses to stimuli previously associated with reinforcement has been further confirmed by recordings from single neurons in monkeys' brains (Thorpe, Rolls & Madison, 1983). Findings from this study have led Rolls (1990) to propose that the orbitofrontal cortex is part of a mechanism that evaluates whether a reward is expected and generates a mismatch if reward is not obtained when it is expected. As a consequence, he assumed that the orbitofrontal cortex is involved in emotional responses especially in situations that include frustration. In serving such a function, the direct interconnections between the orbitofrontal cortex and the basolateral amygdala appear to be of particular importance (Kolb, 1984; Schoenbaum et al., 1998). Damage to the orbitofrontal section of the PFC has shown to provoke behavioral disturbances in monkeys (Rolls, 1996) including a decreased aggression towards humans and threatening stimuli and a reduced tendency to display the typical preference ranking for different foods. In humans, euphoria, irresponsibility, lack of affect and lack of concern for the present and the future can follow lesions of the orbitofrontal cortex. These behavioral deficits are assumed to be associated to a dysfunction in altering behavior appropriately in response to changes in reinforcement contingencies (Rolls, 1990). Furthermore, some recent evidence argues for a connection between orbitofrontal cortex and affective and fear related disorders, showing altered brain activity during pathological depression and induced sadness (Mayberg, Liotti, Brannan et al., 1999), and during provocation of fear-related symptoms (Tillfors, Furmark, Marteinsdottir et al., 2001).

The ventromedial part of the PFC, as revealed by experiments with rodents (Coutureau, Dix & Killcross, 2000) seems to play an important role for the modulation of instrumental choice behavior in response to conditioned punishment. Again, the close connection of this cortical area with the basolateral amygdala is assumed to represent a functional link between incentive value and instrumental contingencies (Cardinal, Parkinson, Hall & Everitt, 2002). In humans, a frequent finding after ventromedial prefrontal lesions is that patients can accurately describe task contingencies, but this knowledge is not sufficient to guide behavior. For example, Rolls et al. (1994) report that such patients could verbally describe how task contingencies had changed during either extinction or reversal procedures, but nonetheless were not able to alter their behavior

appropriately in a simple visual discrimination task. Comparable findings emerged from the studies of Bechara and co-workers, that have been described in a previous section (see 1.2.2.). In a complex gambling task, patients with ventral prefrontal damage continued to choose from the desks that they correctly identified as disadvantegeous. Thus, the ventromedial PFC seems to be involved in the anticipation of future positive or negative consequences of actions. In this regard, a recent functional neuroimaging study has noted ventromedial PFC activation in reponse to tasks in which choices had to be made under specified situations (Elliott, Friston & Dolan, 2000).

Support for an involvement of the anterior cingulate cortex (ACC) in emotion mainly comes from studies on consequences of brain damage to this particular cortical area (Bechara et. al, 1994; 2000; Hadland, Rushworth, Gaffan & Passingham, 2002). However, caution is advised when interpreting findings of studies on brain lesioned patients with respect to functions of the ACC. Only rarely do lesions exclusively comprise this specific cortical area; in most cases, patients also tend to have damage to the orbitofrontal cortex which could be responsible for the observable emotional consequences. Findings from animal research largely support an involvement of the ACC in social behavior. Recent reviews have reported evidence from older literature on primates that cingulate lesions lead to social disturbances (Van Hoesen, Morecraft & Vogt, 1993), for example social isolation. Hadland et al. (2002) have found that cingulate lesions in macaque apes were associated with decreases in social interactions and time spent in proximity with other individuals. In humans, lesions of the ACC have produced a variety of symptoms, including apathy, inattention, autonomic dysregulation and emotional instability (Devinsky, Morrell, Vogt, 1995). Imaging studies have revealed that the human ACC responds to emotionally significant stimuli. For example, cocaine addicts show activation in response to cocaine-associated cues; this activation is furthermore correlated with the intensity of cocaine craving (Childress, Mozley, McElgin et al., 1999; Garavan, Pankiewicz, Bloom et al., 2000). In addition, there is strong evidence that the ACC is implicated in the pathology of depression in humans. Depressives show increased blood flow per unit volume in the ACC (Drevets, 2000). If healthy subjects are requested to think sad thoughts, metabolic activity in this region augments (Mayberg, Liotti, Brannan et al., 1999). Taking together these findings, Mayberg has suggested that hyperactivity of the ACC is a primary factor in sadness and depression.

Although there is no doubt to date that prefrontal cortices play a crucial role for the regulation of emotion, studies drawing clear conclusions about the different functional roles of the various prefrontal sectors are still lacking. In particular, open questions remain concerning the involvement of the dorsolateral prefrontal cortex in emotion. In this regard, Davidson and Irwin (1999) suggest, on the basis of their review on animal and human research, that the ventromedial PFC is most likely

involved in the representation of basic affective states in the absence of immediately present incentives, while the dorsolateral PFC is probably more involved in the representation of a goal state toward which these basic affective states are directed.

Several studies investigating functional frontal asymmetries (see Davidson, 2002, for a review) have shown important differences between left- and right-hemispherical prefrontal cortices. Early evidence comes from a series of clinical studies on patients with unilateral brain damage that assessed a greater incidence of depressive symptoms following left-sided cortical lesions compared to patients having homologous lesions in the right hemisphere (for a review, see Robinson & Downhill, 1995). Because dorsolateral PFC was affected in the majority of cases, this cortical area was proposed to contribute to certain features of positive affect, and to increase, when damaged, the probability of depressive symptomatology (Davidson, 2002). Numerous findings from electrophysiological and neuroimaging studies support the view of an anterior cerebral asymmetry related to emotion and affective style. Electrophysiological measures of regional activation in healthy subjects exposed to affective stimuli found an increased left anterior activation during positive affect and increased right-sided anterior activation during negative affect (Davidson, Ekman, Saron et al., 1990; Davidson, 1995). Furthermore, studies employing PET to measure regional glucose metabolism reported a right-sided increase in metabolic rate in anterior orbital, inferior and superior frontal gyri during viewing of pleasant pictures. While presented with threatening objects or situations, subject showed a pattern of predominantly left-sided frontal metabolic increases. Findings with respect to laterality of affective processing are however, not always so univocal. Borod and colleagues (Borod, Kent, Koff et al., 1988; Borod, 1992) who investigated, in particular, the perception of facial affect have repeatedly demonstrated a dominance of the right hemisphere in the perception of emotions, regardless of the valence of the emotional stimuli. To date, there are two main speculations regarding hemispheric specialization for emotion:
1) *Valence hypothesis*, which, in his newer version, is stated by Davidson (Davidson, Gray, LeDoux et al., 1994). He assumes that approach-related processing is associated with left frontal cortices whereas anterior right cortices are responsible for withdrawal-related processing, and
2) *Right hemisphere hypothesis,* which proposes a general right-hemisphere dominance for emotional expression and perception, regardless of valence (Borod, 1992).
Since both assumptions find some support in the existing literature, it is hardly possible to make a clear statement on which hypothesis may be the most reliable.

Amygdala

Since the 1930s, when Kluver and Bucy (1937; 1939) described a syndrome that developed in rhesus monkeys following bilateral lesions of the amygdala and sourrounding temporal lobe structures, the role of the amygdala in emotional behavior has been of crucial research interest. The Klüver-Bucy syndrome in these monkeys included behavioral abnormalities, such as strinking tameness, emotional unresponsiveness, "psychic blindness" (an inability to recognize familiar objects), hypersexuality and hyperorality. Later studies that focused on specific ablation of the amygdala in monkeys (Weiskrantz, 1956) would reveal similar behavioral consequences. More recently, investigations with humans have shown that damage to the amygdala may lead to an increase in the threshold of emotional perception and expression (Aggelton, 1992) and deficits in the perception of facial expression (Adolphs, Tranel, Damasio, Damasio, 1994).

Neuroanatomically, the amygdala consists of several subnuclei that can be further divided into subregions. A number of different schemes have been adopted to label amygdal areas, suggesting, however, four nuclei to be particularly implicated in the control of emotional processes (LeDoux, 2000). These nuclei are the lateral (AL), the basal (B), the accessory basal (AB) and the central (CE) nuclei. Figure 1.2.3.2. illustrates these structers and the connections between them.

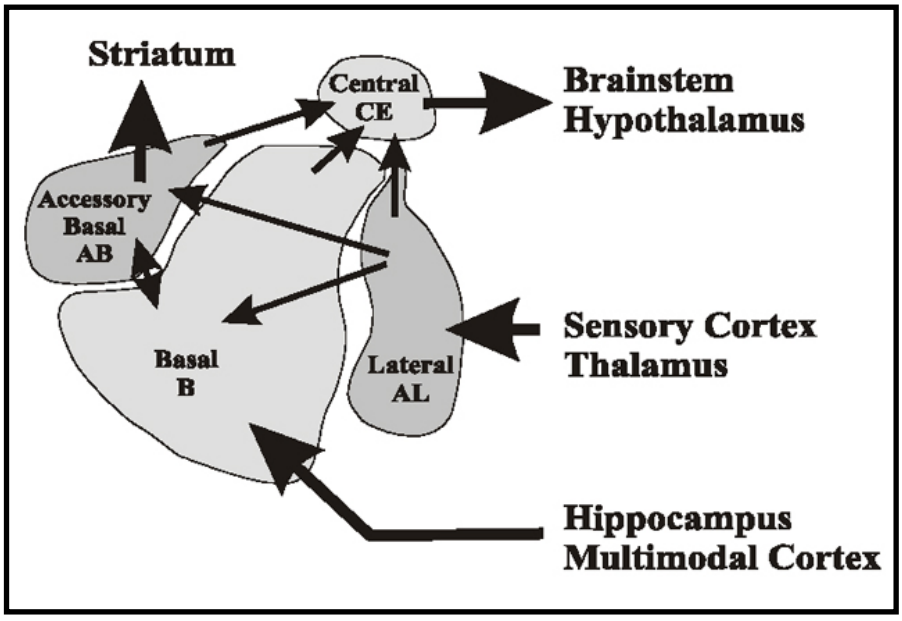

Fig. 1.2.3.2. Simplified diagram of the amygdala's intrinsic connections

(from: Fellous, Armony & LeDoux, 2002)

In a series of landmark studies that employed fear conditioning and the fear-potentiated startle in rodents, LeDoux and colleagues have demonstrated the key role of the amygdala in affective processes. They repeatedly found that lesions of different amygdaloid nuclei disrupt both the acquisition and expression of conditional fear. Results of these experiments were also used to explain details of the fear circuitry in the brain (for a review, see LeDoux, 1995; LeDoux & Phelps, 2000).

Two main input pathways for processing a sensory stimulus have been proposed (see figure 1.2.3.3. for a schematic illustration of the neurol pathways involved in auditory fear conditioning):
(1) *a rapid, shorter, subcortical route*, where sensory information goes from the thalamus directly to the amygdala and rapidly triggers fear in response to simple cues, and
(2) *a slow, longer cortical route*, where sensory information goes from the thalamus to the cortex and hippocampus and is then projected to the amygdala, taking longer to trigger fear in response to more complex stimulus objects.
The cortical route is supposed to be able to inhibit a fear response triggered by the subcortical route and to provide greater sensory discrimination. Interestingly, research from LeDoux and colleagues revealed that lesions in the auditory cortex of rats do not interfere with the conditioned response to the sound, implying that the more direct, subcortical route is sufficient to evoke behavioral fear responses. LeDoux (e.g. 1989, 1994) argues that the subcortical pathway processes information very quickly due to the fact that it involves very few neural links, but only provides rather sketchy and global information about the stimulus. In contrast, signals processed through the cortical pathways provide more detailed information but require more processing time, given that these pathways involve several neural links between the thalamus and the amygdala. Although up to now, LeDoux has mainly focused on the investigation of the auditory modality, the established principles of emotional learning are supposed to be applicable to other modalities as well.

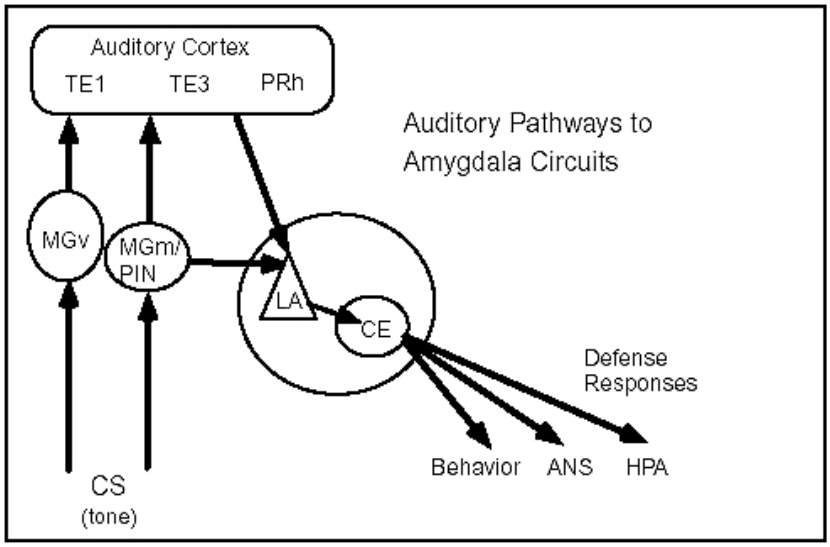

Fig. 1.2.3.3.
Neural pathways involved in fear conditioning
LA: Lateral Amygdala; CE: Central Amygdala; ANS: Autonomic nervous system ; HPA: Hypothalamus-pituitary axis; TE1: Primary auditory cortex; MGv: Medial geniculate body – ventral part; MGm: Medial geniculate body – medial division
(from LeDoux, 2000)

Over the past several years, studies have confirmed the role of the amygdala in human fear. Stimulating the amygdala causes feelings of fear (Halgren, 1992). Damage of areas of the temporal lobe including the amygdala cause impaired fear conditioning in humans (LaBar, LeDoux, Spencer & Phelps, 1995). Furthermore, studies employing functional magnetic resonance have shown increases in amygdala activity during fear conditioning (LaBar, Gatenby, Gore et al., 1998). A growing corpus of evidence is provided by investigations on recognition of negative emotions in humans. Adolphs and co-workers have repeatedly demonstrated that recognition of facial signs of fear is impaired in patients with bilateral amygdala damage (Adolphs, Tranel, Damasio & Damasio, 1994; Adolphs, Damasio, Tranel & Damsio, 1996). Activation of the amygdala has been detected when anxiety-disordered patients have been exposed to their specific anxiety-provoking stimuli. For example, when social phobics were presented with neutral faces, they showed activation of the amygdala comparable to that observed in healthy controls in response to aversive stimuli (Birbaumer, Grodd, Diedrich et al., 1998).

Recent studies have addressed the question whether the two subcortical pathways identified by LeDoux in the rat brain are equally important in human emotional experiences. Morris and colleagues (Morris, Ohman & Dolan, 1999) correlated the activity of the amygdala during fear viewing with the activity in other regions of the brain and reported the strongest relations with subcortical rather than cortical areas. In an inventive experiment, Whalen and co-workers (Whalen, Rauch, Etcoff et al., 1998) used fMRI during the presentation of backwardly masked facial expression to determine whether amygdala activation might be demonstrated in humans in the absence of explicit knowledge. They demonstrated isolated amygdala activity during presentation of negative facial expressions. Taken together, these data emphasize the importance of the direct thalamo-amygdala pathway in the human brain and support the amygdala's implication in the non-conscious monitoring of emotional stimuli.

Whereas, to date, there is no doubt on the role of the amygdala for the recognition of negative, unpleasant stimuli and fear conditioning, there is less experimental evidence that the amygdala may also be important for the processing of positive emotions. However, recent findings from both animal and human studies indicate that the supposition of the amygdala being involved in elaboration of only unpleasant stimuli might be too restrictive. In fact, studies with non-human primates have revealed that lesions to the amygdala produce severe impairments of various measures of stimulus-reward learning (for a recent review, see Baxter & Murray, 2002). With respect to humans, investigations employing fMRI repeatedly reported activation of the amygdala during viewing of sexual arousing material (e.g. Karama, Lecours, Leroux et al., 2002).

Furthermore, studies where anticipation of monetary reward was related to greater amygdala activation indicate that this brain structure might also be involved in the expectation of reward outcomes (Knutson, Fong, Adams et al., 2001). In this regard, important contributions come from research on drug craving. The amount of cocaine craving was found to correlate with amygdala activity, whereas lesions of the amygdala abolish the ability of drug related cues to trigger drug seeking behavior (Zald, 2003). Taken together, these results indicate that the amygdala is involved in the elaboration of positive or pleasant stimuli that have particularly arousing or motivating features. Consistent with this idea is the fact that also the perceptual intensity of stimuli has been shown to be related to amygdala activation. Since aversive stimulation employed in experiments is often characterized by a higher perceptual intensity compared to pleasant stimuli in similar investigations, further research should address the question whether these visual-perceptual characteristics can affect the amygdala.

Trying to relate current theoretical approaches to emotion with the findings regarding neuroanatomical correlates of emotions, we can say that prefrontal areas and the amygdala seem to be crucial elements of a network employed in emotion elaboration. Although up to now, research has mainly focused on aversive emotions, more recent finding suggest a general role of both brain structures in emotion, independently from the valence dimension. The amygdala is supposed to mediate unconscious low-level core affective processes that are triggered automatically and prepare the organism for specific behavior tendencies (e.g. fight/flight). Instead, prefrontal structures are thought to mediate conscious experience of emotions by monitoring lower level processes and, if necessary, by inhibiting or redirecting these subcortically triggered behavior patterns. In fact, one of the most important functions of the PFC is assumed to be its involvment in the anticipation of future emotional outcome and in decision making.

As could be seen so far, animal research and lesion studies in humans have mainly focused on the role of amygdala and prefrontal structures in emotion. However, this is not all. With the advances in functional neuroimaging, a growing number of studies have employed techniques as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to map brain regions associated with the processing of visual affective stimuli. Since these investigations have provided evidence for the involvement of additional areas in emotion elaboration and because visual processing of emotional stimuli is a highly relevant issue for the present thesis, I will shortly present recent findings of this research domain. In doing so, the particular focus will be on studies that employed emotional slides (not faces), for example pictures from the International Affective Picture

System (IAPS, Center for the Study of Emotion and Attention, 1999) or comparable stimulus material.

In line with the prior discussed literature, functional neuroimaging during picture viewing revealed an enhancement in amygdala activity in response to emotional salient stimuli compared to neutral slides. Whereas in most studies this activity was not linked to emotional valence, but followed both the presentation of pleasant as well as unpleasant slides (Hamann, Ely, Hoffman & Kilts, 2002), some few investigations reported greater amygdala activity during perception of unpleasant stimuli compared to pleasant pictures (Lane, Reiman, Bradley et al., 1997). However, the increase in amygdala activity appears to be more consistently influenced by the arousal factor. A relation between amygdala activation and the level of self-experienced emotional arousal as well as with later memory performance for the affective pictures has been demonstrated (Hamann, Ely, Grafton & Kilts, 1999). Also prefrontal areas, for example the orbitofrontal cortex, have repeatedly shown to be involved in affective picture processing. It remains unclear, however, whether pleasant and unpleasant stimulation is associated with activation of different cortical regions or whether there is a similar prefrontal substrate involved in processing of both valence types. Some authors reported that a wide range of emotional stimulus material (films, pleasant and unpleasant pictures, disgusting stimuli) all provoked activity in the orbitofrontal area (Lane, Reiman, Ahern et al., 1997; Reiman, Lane, Ahern et al., 1997), thus suggesting a general role of the orbitofrontal cortices in emotional processing. Instead, Northoff et al. (2000) found dissimilar extents of activity in medial orbitofrontal and ventral lateral orbitofrontal cortex during negative and positive emotional processing. Unpleasant stimuli were correlated with activation in orbitofrontal cortex and a decrease of activity in lateral prefrontal cortex, whereas pleasant stimulation provoked the exact opposite activity pattern. Similar evidence comes from PET studies reporting that sad and happy transient states affected different brain regions in divergent directions (George, Ketter, Parekh, Horwitz et al., 1995). The present thesis might shed some light on this unanswered question by investigating the consequences of differently localized brain lesions on elaboration of pleasant and unpleasant stimuli.

A very interesting finding that has contributed much to the discussion on brain regions involved in affective picture processing was reported first by Lane (Lane, Reiman, Bradley et al., 1997) and, afterwards, more accurately investigated by Lang and coworkers (Lang, Bradley, Fitzsimmons et al., 1998). Their fMRI-studies revealed that both pleasant and unpleasant pictures prompted significantly more activity in the visual cortices than neutral pictures. More precisely, cortical structures involved were the left and right occipital gyrus, the right fusiform gyrus and the right

inferior and superior parietal lobules. Furthermore, Lang's investigation showed that there were no significant differences in eye movement as a function of picture content indicating that the greater occipital activation in response to emotional slides cannot be attributable to an eye-scanning artefact.

Unfortunately, data from neuroimaging studies are not able to provide further clarification with respect to hemispherical specialization for different emotions or valence systems. Most of the investigations published so far could not find any important differences in right/left activation between negative and positive emotional processing. Consequently, decisive support for either the valence hypothesis or the right hemisphere hypothesis is still lacking. However, the number of experiments that employed techniques as fMRI or PET is still limited – further investigation of functional brain asymmetries in emotions should constitute a special challenge for research in this field.

One further limitation of neuroimaging studies that has already emerged when discussing human lesion data refers to the contribution of prefrontal cortical structures to emotion elaboration. Although to date, there is a vast amount of literature on this topic, conclusions about the specific roles of different subsections of the PFC in emotion still are confounding. This is partly due to the fact that a coherent terminology is lacking. In fact, when reviewing studies that report prefrontal brain activity in response to emotional pictures it becomes observable that different authors referring to the same studies use diverse terms to describe the investigated prefrontal structure (e.g. "medial prefrontal cortex" versus "orbitofrontal cortex" or simply "prefrontal areas"). In addition, there is a general lack of research papers that deal with the specific role of the various subsections of the PFC in emotion; often, the PFC is considered as a whole. With respect to lesion studies, there are only a very restrictive number of investigations that report well localized lesions that comprise only one specific area of the prefrontal cortices. In this regard, the present thesis may provide some more clarification by comparing emotional processing in patients with distinct frontal brain lesions.

1.3. Processing of affective visual stimuli

In the previous chapter, we have already discussed neuroanatomical structures involved in affective picture processing. In this regard, modern neuroimaging techniques offering a high spatial resolution like fMRI or PET constitute the most promising experimental approach. I will begin the following section with presenting findings from experiments that investigated the processing of emotional pictures by measuring event-related potentials (ERPs). Due to their high temporal resolution, ERPs provide important timing information about brain processes and, thus, are ideally suited to study emotional information processing. The discussion of ERP findings will only include those investigations that used IAPS pictures as stimulus material. Evidence resulting from studies employing other visual stimuli, for example emotional films or emotional facial expressions, will not be considered here since they are less well comparable to the results of the present thesis. In the second part, recent studies of autonomic responses to affective pictures will be briefly reviewed.

1.3.1. Evidence from studies of visual evoked potentials

Most of the studies investigating ERPs associated with pictures taken from the IAPS have converged in showing an enhanced P300 deflection in response to emotionally salient (i.e. pleasant or unpleasant) compared to neutral and calm slides (Cuthbert, Schupp, Bradley et al., 2000; Keil, Bradley, Hauk et al., 2002; Keil, Müller, Gruber et al., 2001; Palomba, Angrilli & Mini, 1997; Schupp, Cuthbert, Bradley et al., 2000). This finding has been interpreted with the assumption of two basic motivational circuits in the brain (Lang, Bradley & Cuthbert, 1997) that are responsible for a greater allocation of attentional resources to motivationally relevant and arousing stimuli. In this regard, an interesting contribution comes from Palomba and co-workers (1997) who reported a significant correlation between P300 peak amplitude at Pz and the total number of correctly remembered IAPS pictures. The authors drew the conclusion that the P300 reflects stimulus encoding and that consequently, emotionally relevant stimuli (pleasant and unpleasant pictures) are subject to a deeper cognitive processing compared to neutral contents. This effect previously has been termed “Dm” (Difference based on later memory performance, Paller, Kutas, Mayed et al., 1987). In fact, it has been shown that emotional slides resulted in better memory performance as compared to neutral ones (Bradley, Greenwald, Petry et al., 1992; Palomba et al., 1997).

As confirmed by several studies, the response to emotional pictures is not only characterized by an amplified P300 but also by a sustained later positivity that can last for several seconds. This positive wave typically starts in the time range from 400-700 ms after stimulus onset and reaches its maximum around 1s. Cuthbert et al, (2000) showed that greater positivity for emotional (pleasant

and unpleasant) pictures compared to neutral slides was sustained even until the fifth second of picture processing. Interestingly, the late differentiation between emotionally arousing and calm pictures can be observed during very long picture presentation periods of 6s (Cuthbert et al., 2000) as well as in response to slides that are projected with a shorter duration (Schupp et al., 2000). A factor that was shown to influence the amplitude of the late positive potentials is the self-perceived arousal. Both Cuthbert et al. and Schupp et al. reported that affective pictures of high emotional arousal elicited larger late positive deflections than less arousing affective slides. This finding, again, confirms the idea that emotional stimuli regarded as especially significant and intense are selected by the brain for sustained attentive processing as indexed by the large positive slow wave of the ERP. An important question can be raised of whether the P300 and the subsequent frontal slow wave have to be seen as dissociated processes or rather reflecting two phases of a continuous perceptual process. In this regard, Diedrich, Naumann, Maier et al. (1997) found that P300 yielded its highest amplitude at parietal sites whereas the slow positive wave reached its highest amplitude at frontal sites. Furthermore, the time course of the two ERP components was quite different: Whereas the centro-parietal P300 decreased shortly after reaching its maximum, the frontal slow wave started only about 450 ms after stimulus onset and persisted for more than a second. Thus, both temporal and spatial properties of P300 and the frontal slow wave indicated that the two components may reflect different aspects of information processing. Diedrich and colleagues suggested that the frontal positivity may be considered here as a prerequisite for motor inhibition. As behavior responses are commonly seen as one important part of the emotional response, the idea of a motor inhibition following the presentation of intense emotional stimuli would make sense. The late frontal positivity would, therefore, index an inhibition of emotional behavior which is not situationally adequate to guarantee a coherent behaviour (Diedrich et al., 1997).

However, findings from other studies were not concordant with these considerations. Both Cuthbert et al. (2000) and Schupp et al. (2000) reported that the P300 and the subsequent positive slow wave during emotional picture processing showed a similar distribution on the scalp surface with increasing amplitudes from frontal to parietal sites. These results seem to support the idea that the late positive potential depends on the same neural generator that mediates the P300 ERP component. Given the very small number of studies that have investigated slow potentials in response to affective pictures the discussion outlined so far, remains open. An advantageous experimental approach that could bring further clarification to the problem should involve the use of more electrodes or should employ distinct experimental manipulations that selectively influence either the parietal or the frontal late activity.

Only recently, a few ERP studies have revealed that the discrimination between emotionally salient and neutral pictures already happens during a very early stage of visual processing. Keil et al. (2001) reported a voltage enhancement in the N1 time window (at around 150 ms following stimulus onset) for arousing compared to neutral IAPS slides. In a subsequent study, the same author (2002) reported a sustained early negative shift selectively for pleasant pictures. With respect to the distribution of the scalp surface, the effect was most pronounced at parietal and posterior electrode sites. Similar early ERP differences between arousing and calm pictures were obtained when presenting pictures very rapidly (Junghöfer, Bradley, Elbert et al., 2002). This latter study revealed a N260 component at posterior electrode clusters in response to picture presentation that was significantly larger for highly arousing slides compared to moderately arousing stimuli. A source analysis located the main neural sources for this early discrimination in primary and secondary visual cortices. Furthermore, control analyses were accomplished to test if ERP differences were related to perceptual features of the different picture categories. The results showed that emotion discrimination of IAPS pictures is not affected by formal visual stimulus characteristics as color, brightness, spatial frequency and complexity. Taken together, these recent findings argue for an important involvement of the visual cortex in a very quick discrimination of emotional visual stimuli. The investigation by Junghöfer et al. (2002) where pictures were presented with a rate of up to 5 Hz raises the interesting question, whether this early categorization in emotional salient and neutral pictures happens before one becomes aware of it. A challenge to future studies employing this experimental approach could be to clarify, if a high-speed presentation of pictures is sufficient to evoke affective states or if it constitutes only an initial stimulus categorization limited to the sensory system.

With respect to lateralization of ERP responses to affective pictures, findings are not numerous enough to draw a final conclusion. However, some of the above mentioned studies have reported more reactivity to emotionally arousing stimuli over the right hemisphere (Junghöfer et al., 2002; Keil et al. 2001; 2002) and therefore may support a stronger involvement of this hemisphere in emotion processing.

1.3.2. Evidence from studies of autonomic responses

In investigating autonomic responses to emotional pictures taken from the IAPS, most studies have focused on heart rate and electrodermal activity. A typical finding that has been confirmed by several authors is that emotionally salient pictures provoke a larger skin conductance response (SCR) than neutral slides (Bradley et al., 2001; Codispoti, Bradley & Lang, 2001; Cuthbert, Bradley & Lang, 1996). With respect to differences between the two valence categories, results are not so

univocal. Some studies reported a more substantial increase in the magnitude of the SCR after looking at unpleasant slides compared to pleasant ones (Bradley et al., 2001), whereas there are also results showing a larger SCR in response to pleasant pictures (Cuthbert et al., 2000). However, nearly all studies agree in reporting a positive relation between the arousal level of the presented pictures and the evoked SCR. Furthermore, Cuthbert et al. (2000) could demonstrate that the late positive potential was especially enhanced for pictures provoking a heightened skin conductance response. Taken together, this may indicate that electrodermal activity changes are not systematically subject to the distinct valence systems but rather strongly influenced by the degree of activation of the motivational system.

Heart rate, too, was found to be closely related to stimulus arousal. Studies have converged in showing that viewing of arousing pleasant and unpleasant pictures produces a sustained cardiac deceleration which is not observable in response to neutral slides (Bradley et al., 2001; Palomba et al., 1997). An additional interesting finding of the latter investigation was that the extent of heart rate deceleration was positively related to the amplitude of the ERP slow wave. With respect to pleasant pictures, there is evidence that only highly arousing slides with erotic contents lead to a sustained heart rate deceleration, whereas in response to positive pictures of nature or adventure cardiac changes are only modest (Bradley, 2001). These findings, particularly those referring to unpleasant stimuli, often are interpreted by reference to Lang's defensive cascade model which implies that enhanced heart rate deceleration stands for continued attention to an aversive relevant stimulus and consequently indicates a moderate activation of the defensive motive system. Evidence related to pleasant pictures suggests a similar mechanism for the approach system, as well, whereby it seems that a rather strong stimulation is necessary before greater sympathetic activity, associated with an elevated motivation, is initiated.

Two interesting studies have addressed the question of whether cardiac and skin conductance responses to emotional stimuli are influenced by specific task manipulations such as a shortened stimulus presentation time (Codispoti et al., 2001) or repetitive exposure to the same affective valence (Bradley, Cuthbert & Lang, 1996). The former investigation showed that skin conductance responses to emotional pictures presented only for 500 ms were very similar to the effects obtained in earlier studies where stimuli usually were presented for 6s. Instead, heart rate results dramatically differed from studies employing a longer presentation time; the typical initial deceleration after emotional pictures was only minimal here and did not significantly differ between arousing and calm slides. Bradley et al. (1996) presented affective slides in continuous series of the same valence with long interstimulus intervals and could show that SCR revealed the typical reaction pattern with

differences between arousing and calm slides remaining stable over the whole block. Heart rate deceleration, instead, was visible only during the perception of arousing pictures, whereas shortly after picture offset the level quickly returned to baseline. Taken together, these findings suggest that electrodermal activity changes are very stable and resistant to experimental variations, whereas cardiac alterations seem to be particularly controlled by task requirements.

1.4. Processing of affective visual stimuli after brain lesions

To date, only very few studies have been published that measured physiological parameters in brain lesioned patients while looking at emotional pictures. Moreover, to my knowledge, no study exists, that investigated reactions to affective visual stimuli in a representative group of patients with diffuse lesions comparable to those provoked by a closed head injury. Instead, most clinical experiments in this research field were accomplished with rather small samples of patients or even with one single case with well-defined brain damage provoked by vascular lesions or surgical resections of cerebral tumors. Typically, studies focus on lesions of those brain areas that are supposed to play an important role for emotion elaboration, in particular the prefrontal cortices and medial temporal structures including the amygdala.

A substantial number of experiments on brain lesioned patients has been realized by the group of Damasio, Adolphs and co-workers who, however, did not concentrate on physiological indices of picture processing but rather on the recognition of emotional facial expressions (Adolphs & Tranel, 2003; Adolphs, Damasio, Tranel & Damasio, 1996). Their studies provided considerable evidence for the human's amygdala role in the recognition of social clues from faces. In fact, patients with bilateral amygdala damage are impaired in recognizing basic facial expressions, especially when presented with negatively valenced emotions like fear, anger and sadness (Adolphs, Tranel et al., 1994; 1999). Furthermore, recent investigations could demonstrate that patients with unilateral or bilateral amygdala lesions had noticeable deficits in judging social facial expressions like guilt or admiration (Adolphs, Tranel, 2002). This finding was interpreted by the authors as evidence that the amygdala's role traditionally related to the perception of basic emotions appears to extend to the recognition of stimuli with more complex social significance. Interestingly, this seems to be true only for facial expressions but not for the recognition of emotions from other social and contextual cues present in complex scenes. In this regard, Adolphs & Tranel (2003) came to the astonishing result that patients with bilateral amygdala damage showed more accuracy in recognizing emotions from social scenes when faces were erased than with faces present.

With respect to psychophysiological correlates of picture processing in patients with amygdala lesions, only single case studies have been published so far. Both Tranel and Damasio (1989) and

Tranel and Hyman (1990) described single clinical cases with well-defined bilateral amygdala damage and reported that skin conductance responses to emotional stimuli in the two patients did not differ from the skin conductance pattern found in healthy controls. A different result was obtained by Kubota, Sato, Murai et al. (2000) who investigated electrodermal activity (EDA) in response to masked (unseen) visual stimuli from the IAPS in subjects that had previously undergone unilateral temporal lobectomies. The authors observed reduced EDA responses to masked negative pictures when stimuli were presented to the lesioned hemisphere. This finding was interpreted in terms of the critical role that medial temporal structures, including the amygdala, seem to play for the neural substrates for autonomic, unconscious processing of negative emotion. Accordingly, Angrilli, Mauri, Palomba et al. (1996) who studied a subject with a localized lesion of the right amygdala reported that their patient failed to show the typical startle reflex potentiation induced by an aversive emotive background (unpleasant pictures). However, the patients' affective rating of the previously presented pictures successfully differed between unpleasant and calm slides. This dissociation was seen as a further indication that, whereas startle modulation through affective stimuli seems to be mediated by the amygdala, subjective evaluation of emotional material rather appears to be under the control of cortical structures.

In an insightful study conducted by Tranel and Damasio (1994), electrodermal activity was measured during presentation of highly arousing unpleasant pictures in a numerous group of patients with well localized lesions in various areas of the cerebral hemispheres. Lesion loci associated with attenuated skin conductance responses to affective slides were the ventromedial frontal region, the anterior cingulate gyrus and the right inferior parietal region. Interestingly, the results showed that damage to the ventromedial prefrontal cortices alone was not sufficient to produce SCR impairment. Only combined with anterior cingulate lesions it provoked substantial deficits of skin conductance responses to aversive pictures. The importance of the anterior cingulate gyrus in mediating EDA in the context of emotionally salient stimuli was further emphasized in a study by Zahn, Grafman and Tranel (1999). Here, patients with right and bilateral lesions in the cingulate gyrus showed reduced skin conductance responses to pleasant as well as unpleasant pictures taken from the IAPS.

Angrilli and co-workers measured cognitive performance and several physiological indices of affective picture processing in a TBI patient with a lesion in the right prefrontal cortex (orbitofrontal and ventromedial prefrontal areas). Although the patient showed no significant impairment on various neuropsychological tasks, his responses to emotional pictures were evidently deficient. He had attenuated skin conductance responses to arousing slides and his corrugator

muscle activity did not show the typical enhancement during projection of unpleasant pictures (Angrilli, Palomba, Cantagallo, Maietti & Stegagno, 1999). These results were interpreted in terms of Damasio's "somatic marker" hypothesis by stating that the patient had a deficit in retrieving past emotional experience which consequently led to an impaired physiological activation appropriate to the affective stimuli.

The above outlined studies revealed first important insights into consequences of different types of brain lesions for the elaboration of affective pictures. In line with what we know from animal research and neuroimaging studies, brain regions that seem to be primarily involved in emotional pictures processing are the amygdala and various parts of the prefrontal cortices. In fact, patients with lesions to these areas are most pronouncedly impaired in recognizing affective states from faces and in showing adequate physiological responses to arousing visual stimuli. However, so far no study has investigated ERP correlates of affective processing in a representative sample of patients with well localized brain lesions. Thus, the present thesis mainly aims at examining consequences of a TBI for the elaboration of standardized emotional pictures that vary with respect to arousal and valence. The accurate lesion mapping method adopted here, further allows for investigating the relationship between damage to specific cortical areas and impairments of affective processing, therefore providing important evidence for the assumption of these brain structures as neuroanatomical correlates of emotion.

1.5. Affective stimulus elaboration in patients with traumatic brain injury: Aims and Hypotheses

As has been outlined before, the few studies done so far with TBI patients suggest that traumatic brain lesions do not only provoke long-lasting cognitive impairments but also behavioral and emotional deficits. Furthermore, evidence from human functional neuroimaging studies together with findings from animal research propose prefrontal cortical areas as playing a decisive role within the network that modulates elaboration of emotional content.

In a first part, the present thesis examined various parameters of affective picture processing in a sample of TBI patients with predominantly prefrontal lesions and in a group of healthy subjects. On the background of prior outlined literature, the general hypothesis was that TBI patients show an impaired processing of emotionally salient stimuli. This should lead to a decreased discrimination between emotional/arousing and neutral pictures and should be mirrored by both arousal-dependent psychophysiological parameters and behavioral data.

The following predictions were tested in the first part of the present thesis:

- ERPs of TBI patients in response to affective pictures differ from those shown by healthy subjects in that they are not clearly modulated as a function of emotional arousal. In this regard, ERP differences between healthy participants and brain damaged patients are particularly evident for highly arousing (pleasant and unpleasant) stimuli compared to neutral pictures.
- Skin conductance responses of TBI patients do not show the typical amplitude enhancement during viewing of highly arousing pictures. Compared to healthy subjects, patients' SCR is primarily attenuated for unpleasant and pleasant stimuli.
- Subjective ratings of emotional arousal and valence differ between TBI patients and healthy subjects. In this regard, brain-lesioned patients show a reduction of self-experienced arousal that particularly refers to emotionally salient stimuli.
- Patients with TBI are generally impaired on recall of previously presented pictures. It will be further clarified, whether patients show an overall reduced memory performance or whether their deficit is dependent on affective picture content.

In addition, the following experimental questions were examined:

- Are the measured ERP-abnormalities of TBI patients only arousal modulated or influenced by emotional valence, as well? By determining if patients with predominantly prefrontal lesions are selectively impaired in elaborating one specific valence category, we can draw conclusions with respect to whether processing of unpleasant compared to pleasant stimuli underlies the same neuroanatomical substrates.
- Are the measured ERP-abnormalities of TBI patients linked to specific temporal stages of visual affective processing? One hypothesis states that already at an early stage, the impairment in elaboration of emotional arousing stimuli is apparent in frontal lesioned patients. The alternative hypothesis postulates that early discrimination of emotional stimuli at cortical level is driven by subcortical-limbic intact structures, and therefore early components would show a normal pattern. Instead, late stages of emotional elaboration which are related to reverberating activity at cortical level would be impaired.

In the second part, the present thesis investigated the influence of lesion extent and location on a number of parameters of emotional elaboration by comparing patients subgroups with different lesion locations. More precisely, we did compare patients with and without ventromedial prefrontal lesions, patients with large and with small lesions of the prefrontal cortex, and, at last, patients with and without temporal lobe lesions. As previously discussed, the present literature suggests that all

lesion criteria above listed are, to a certain extent, involved in elaboration of emotions. Therefore, the basic hypotheses were as follows:

- Patients with ventromedial prefrontal lesions are more impaired in elaboration of affective visual stimuli compared to patients without lesions to this cortical area.
- Patients with temporal lobe lesions are more impaired in affective stimulus processing compared to patients without damage to the temporal cortical areas.

With respect to the comparison of patients with large and with small frontal lobe lesions, no specific effect of lesion extent on elaboration of emotionally arousing stimuli was hypothesized. Instead, a rather general deterioration of affective responses as well as cognitive capacities was assumed to be associated with increasing extent of frontal brain damage.

Due to the current lack of studies investigating psychophysiological and behavioral responses to standardized affective stimuli in brain injured patients with well localized lesions, it was not possible to make more specific predictions. However, by determining the impact of lesions of specific brain areas on various parameters of emotional elaboration we particularly aimed at localizing the neuroanatomical substrates involved in cortical processing of affective pictures and investigating whether these substrates may differ, for instance, from those underlying the modulation of autonomic responses.

Since nearly all patients had bilateral brain damage, a division into subgroups with predominantly right and left hemispheric brain damage was not possible. Therefore, the present investigation cannot explore consequences of lesion lateralization for affective stimulus processing and from this, draw conclusions concerning the hemispheric specialization for emotional elaboration.

2. METHODS

2.1. Participants

23 patients with moderate to severe head injury and 23 healthy controls participated in this study. All patients were former inpatients of the neurological rehabilitation program of the "S. Bortolo" hospital in Vicenza, Italy and were selected for the study with the help of the leading neurologist. The comparison group consisted of students at the University of Padova and non- students recruited through local postings who received a small financial bonus (€ 26) for taking part in the experiment. All participants had normal or corrected-to-normal vision and no history of substance abuse or psychiatric disease. Control subjects had no history of neurological disorder. As indicated by Table 2.1.1, the two groups were matched by age, gender and handedness.

Table 2.1.1
Demographic data for controls and patients (means and SD)

	MEAN AGE (YEARS	**GENDER**	**HANDEDNESS**	**MEAN EDUCATION (YEARS)**
Patients (n= 23)	26,2 (+/- 6))	4 female 19 male	22 right handed 1 left handed	10 (+/- 2,5)
Controls (n =23)	25,7 (+/-4,6)	5 female 18 male	21 right handed 2 left handed	11,7 (+/- 2,2)

Head injury patients

Patients with moderate to severe head injury suitable for the study were recommended to the experimenter on the basis of the impression that a patient might be willing and able to cooperate and to perform the tasks. Important inclusion criteria regarding the rehabilitation status were the absence of significant motor and language impairments and a good recovery of basic cognitive functions (orientation and perception).

Individual anamnestic and clinical data for this group are summarized in Table 2.1.2. The average temporal interval between the traumatic accident and the day of the study is 36 months (range from 6 to 78 months). The average coma duration across patients is 17 days (range from 2 to 60 days). Applying the subdivision proposed by Bond (1987) which judges the severity of coma by its duration, we obtain three different categories for the head injury patients: four cases with moderate

coma (one to seven days), 16 cases with severe coma (eight to 30 days) and three cases with very severe coma (more than 30 days).

Table 2.1.2
Individual anamnestic and clinical characteristics of patients [a]

	Age	Gender	Handedness	Education (years)	Nature of injury	Time since injury (months)	Coma duration (days)
P01	35	m	right	13	Bike RTA	9	30
P02	27	m	right	8	Car RTA	22	20
P03	22	f	right	13	Car RTA	38	17
P04	31	f	right	13	Car RTA	43	14
P05	20	m	right	8	Motorbike RTA	55	15
P06	35	m	right	8	Motorbike RTA	78	50
P07	24	f	right	10	Car RTA	37	7
P08	20	m	left	13	Motorbike RTA	37	7
P09	27	m	right	8	Car RTA	18	12
P10	22	m	right	8	Motorbike RTA	66	16
P11	26	m	right	13	Pedestrian RTA	6 ½	11
P12	21	m	right	13	Car RTA	33	15
P13	20	m	right	8	Car RTA	37	11
P14	29	m	right	8	Car RTA	67	29
P15	19	m	right	8	Car RTA	9	60
P16	19	m	right	8	Accident at work	38	13
P17	24	m	right	8	Car RTA	36	13
P18	24	m	right	8	Car RTA	15	2
P19	26	m	right	13	Motorbike RTA	73	11
P20	33	m	right	13	Motorbike RTA	63	20
P21	33	m	right	8	Accident at work	6	8
P22	25	f	right	13	Car RTA	21	15
P23	41	m	right	8	Car RTA	16	2

[a] RTA: road traffic accident

2.2. Neuroanatomical analyses

For each patient except one, we were able to obtain CT or MRI scans which were essential to determine extent and location of traumatic brain lesions. Neuroanatomical analyses of these scans were conducted according to the standard method developed by Damasio & Damasio (1989). Lesions of various types were included in the analyses. Size of lesions was not specified a priori. Both focal and circumscribed damaged areas, as well as large or diffuse lesions were included. Also regarding lesion location there was no a priori limit; patients with both lesions in the left and right hemisphere took part in the study. The lesion mapping method proposed by Damasio and Damasio is very helpful when – as it was the case with our patients – brain images are not available in digital format, thereby rendering computer programs capable of automatically localizing damaged brain tissue not applicable. The Damasio group developed a set of standard brain templates that serve as a virtual road map of the localization of cortical lesions making it possible to chart lesions visible on CT or MRI images on the appropriate standard template. Figure 2.2.1. illustrates a patient's CT cut and the specific lesion charted on the appropriate templates at every level at which it occurs. Lesions of every patient that were visible on CT or MRI scans were first plotted on horizontal template brain slices and subsequently transferred to lateral templates of each cortical hemisphere (see Fig. 2.2.2.). Finally, as illustrated in Figure 2.2.3., lesions of all patients were collectively plotted on a single standard template with different degrees of lesion-overlap between individuals marked by different colors.

To determine the lesion volume for each patient, we estimated the extent of lesioned brain tissue by counting the number of marked pixels on the respective horizontal template (see Appendix A for an overview of single horizontal templates with marked lesions for each patient). Subsequently, the percentage of damaged brain tissue was determined. This calculation was accomplished separately for each hemisphere and afterwards for the whole brain. Results of neuroanatomical analyses are listed in Table 2.2.1..

Table 2.2.1. Mean lesion size (indications for each hemisphere and for the whole brain)

	Volume of lesions in the left hemisphere (as percentage of brain tissue in the left hemisphere)	**Volume of lesions in the right hemisphere** (as percentage of brain tissue in the right hemisphere)	**Volume of lesions in the whole brain** (as percentage of overall brain tissue)
Patients' mean (n=22)	3.56 %	2.28 %	2.95 %
Range	0.35 % - 12.37 %	0 – 9.16 %	0.23 % - 9.45 %

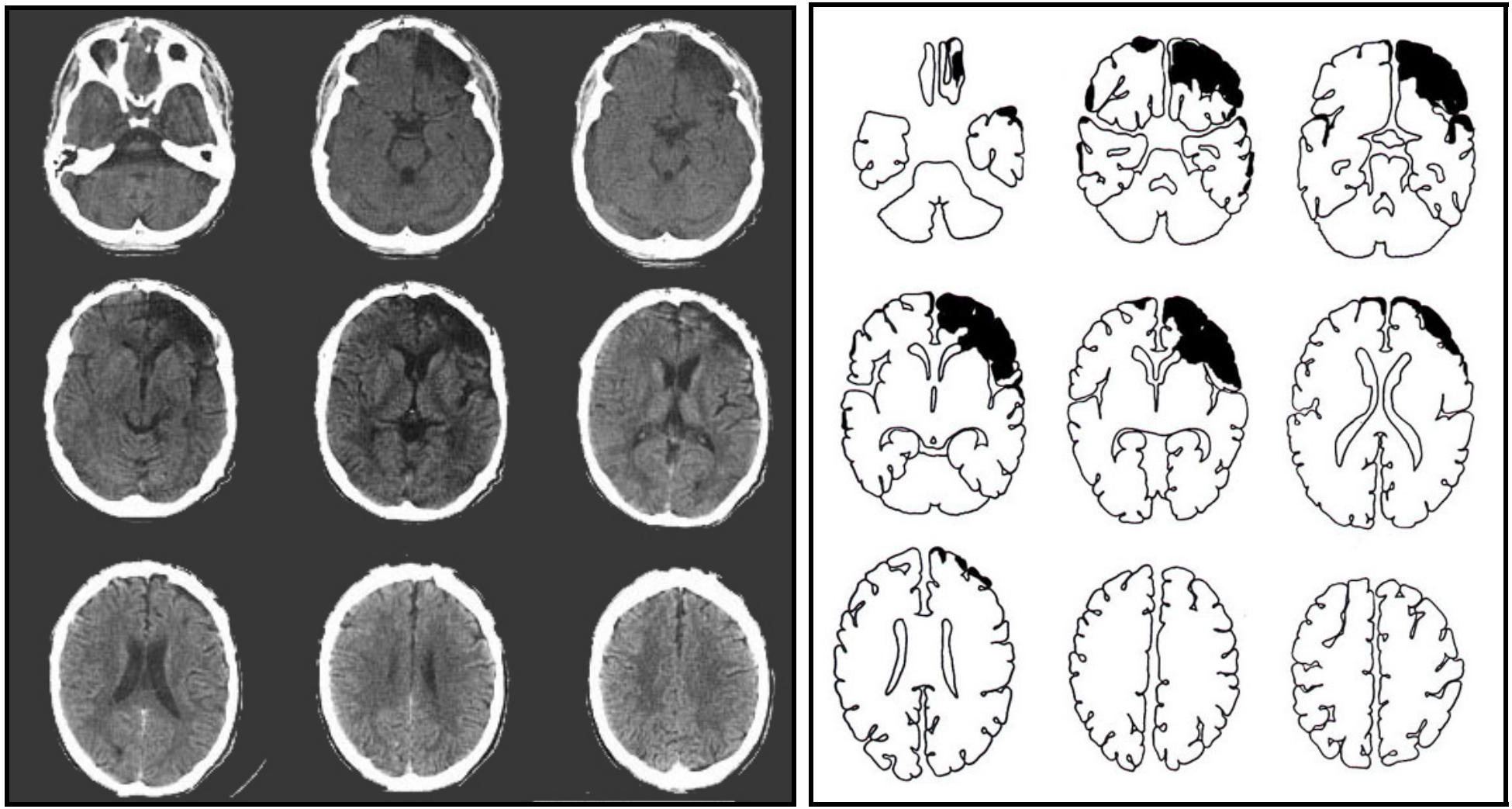

Fig.2.2.1 Selection of Patient's CT cuts (left) and the correspondent standard templates with charted lesions (right)

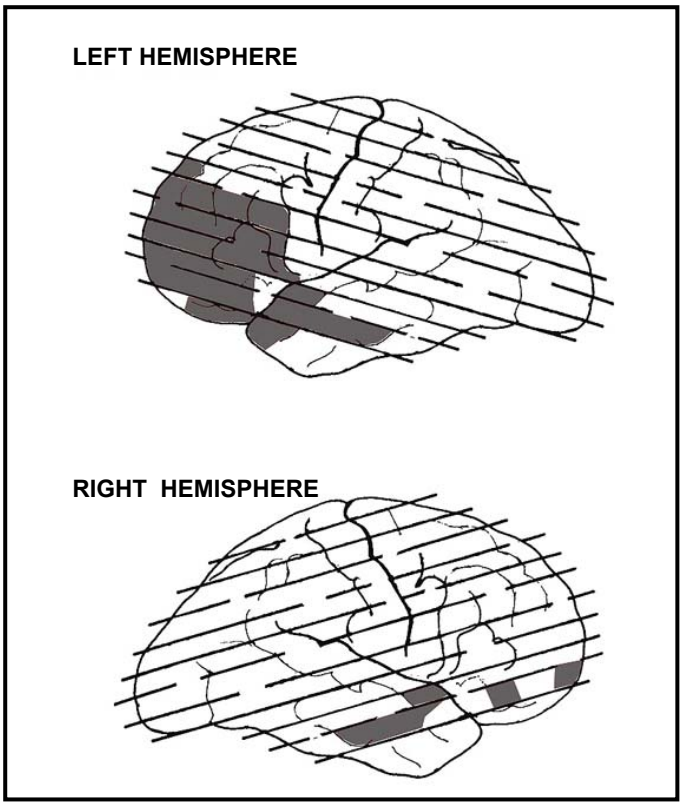

Fig.2.2.2.
Standard lateral template with charted lesions (same patient as above)

Note:
For a better illustration of overall lesion volume, lesions of deeper cortical layers are also mapped on the lateral surface

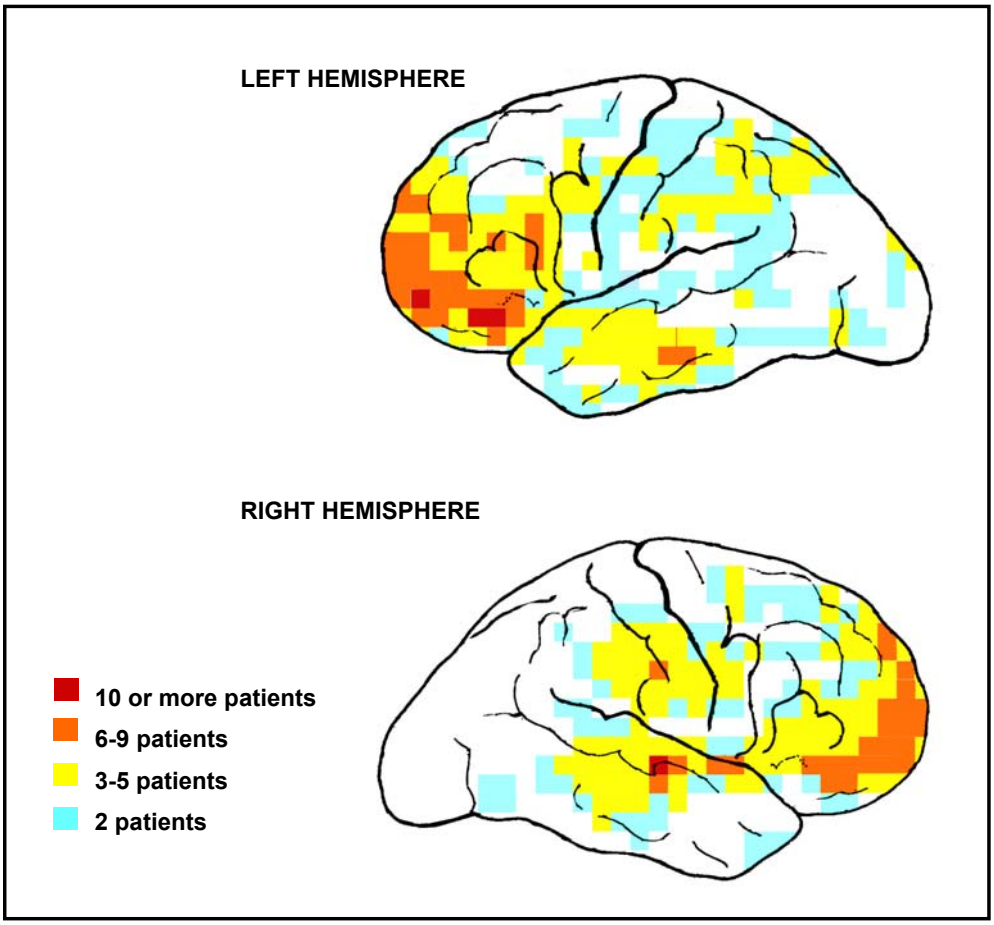

Fig.2.2.3 Overlap diagram showing superimposed lesions of 22 patients (different colors refer to the number of individuals presenting a lesion in the same quadrant)

Summarizing the findings from the neuroanatomical analyses, we can make the following statements to describe the lesion characteristics of the patient group:

- Only three patients sustained an open head trauma, whereas the vast majority (20 cases out of 23) suffered a closed head injury,
- For every patient brain damage was visible on CT or MRI scans, even though lesion extent showed substantial variations between patients,
- Mean volume of lesions in the left hemisphere was evidently larger compared to average brain damage to the right hemisphere,
- As illustrated in Figure 2.2.4., in most cases lesions were bilateral (e.g. patients with large lesions in the right hemisphere tended to present substantial damage to the left hemisphere, as well),
- With respect to the left hemisphere, the highest concentration of lesions was found in the anterior orbitofrontal cortex (Brodman area 10, 11) and in the prefrontal areas (46)
- With regard to the right hemisphere, again the orbitofrontal and the prefrontal cortex were most frequently damaged. In addition, an evident lesion overlap was revealed around the superior and middle temporal gyri (Brodman areas 21,22),
- In all but one patients, head injury led to damage to parts of the frontal lobes
- Lesions of the amygdala could not be determined; in patients with temporal lobe lesions, brain damage was mostly restricted to cortical areas
- In no case, a lesion of the anterior cingulate gyrus (Brodman area 24) could be identified

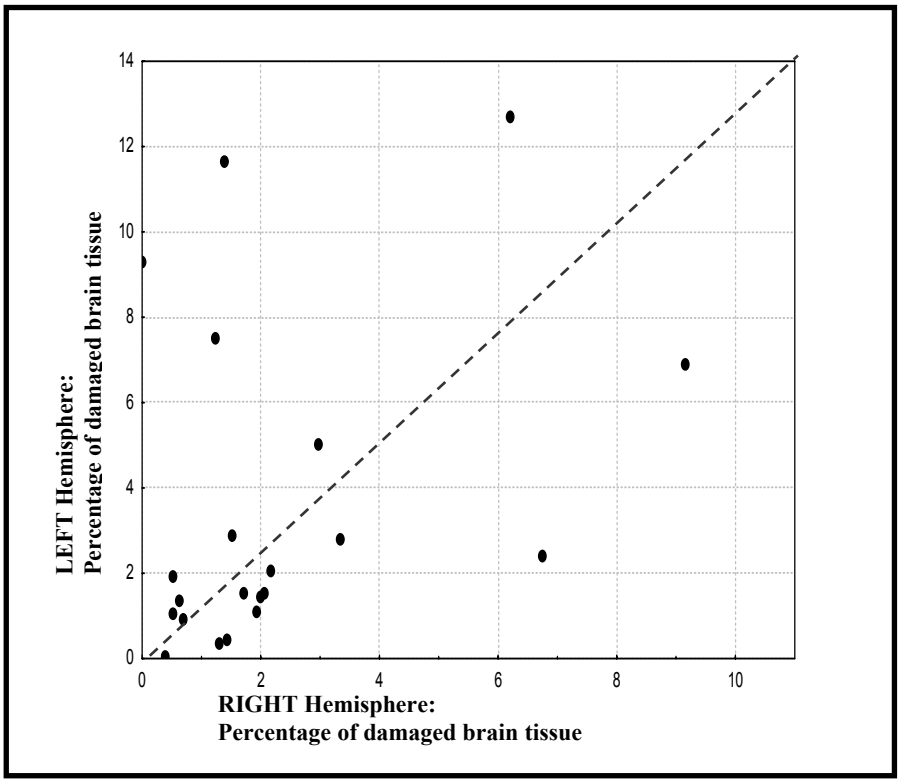

Fig. 2.2.4. Scatterplot depicting individual lesion volume percentage of right and left-hemispherical damaged brain tissue; (n=22 patients)

The lesion analysis technique adopted in the present investigation allowed us to better visualize the location of lesions on universal templates and to further compare approximate lesion location and extent from different patients. As we will see in a later chapter, results of the accomplished lesion analyses were additionally employed to divide patients into different subgroups on the basis of their individual lesion characteristics (see chapter 5). It is important to note, however, that this method has its limits. The person drawing the lesion on the template needs to find the corresponding location on the clinical scan and manually define the lesion, which is often difficult because the template and the scan are viewed at different orientations and scales. Therefore, the translation from the location of lesion to a generic brain template is subject to rather individual decisions (e.g. by focusing on different landmarks) which consequently make exact replication of lesion mapping results difficult. In addition, the final presentation of lesions from several patients on a standard brain is somewhat simplified, as it hides any unique variations found in the original lesion of the patient's brain (e.g. shift in the location of brain structures due to edema). For these reasons, results of such a lesion analysis method cannot be interpreted in terms of an exact definition of individual lesion location and extent. It constitutes, however, a useful tool for describing the approximate lesion characteristics of brain damaged persons and for drawing comparisons between patients with distinct lesion features. When presented with head injured patients for whom brain images are not available in digital format, the manual method proposed by Damasio& Damasio certainly is still the most appropriate approach to the localization of brain damage.

2.3. Neuropsychological assessment

In a separate session of approximately two and a half hours patients were administered a neuropsychological battery which consisted of a variety of cognitive tasks mainly focusing on those functions that are supposed to be particularly impaired in closed head injury patients (i.e. attention, memory and executive functions).

The neuropsychological assessment had been accomplished only with patients and not with control subjects, since the he intention was not a statistical comparison between the two groups. The main objective of this extra session was to determine the actual level of cognitive performance for each patient.

During the initial part of the examination, the *Mini-Mental State Examination (MMSE*; Folstein et. al, 1975) was administered together with a few other non standardized short screenings for language

comprehension, language expression, perception, orientation and motor skills with the purpose of assuring that no patient showed substantial deficits in one of these fundamental cognitive domains. The MMSE is a common standardized screening test for cognitive impairment. It was first described by Folstein in 1975 as a "practical method for grading the cognitive state". The screening tool was intended to assist psychiatric residents in the cognitive part of the mental status exam but was never meant to be used for diagnosis of dementia. The advantages of the MMSE consists in its brevity (5-10 minutes to administer) and in the fact that it represents a useful tool in the initial global assessment of many domains including: orientation to time and place (10 points), repetition and recall of 3 words (3 +3 points), attention and calculation (5 points), language (8 points) and visual construction (1 point). Scores from 25-30 indicate unimpaired performance.

Subsequent to the MMSE a few short non standardized tasks were administered to patients:

- Reading of non-words
- Description of a complex scene to investigate spontaneous speech
- Comprehension task consisting of 6 sets with 4 depicted objects each. Patients had to indicate the particular item requested by the experimenter.
- Naming of unusual views (silhouettes of objects, e.g. a bicycle)
- Naming of 8 different colors
- Association figure – color
- Repetition of short sentences
- Comprehension of complex orders

The initial examination of basic cognitive functions was followed by the application of a variety of standardized neuropsychological tests which are presented in the following section together with cognitive functions they were supposed to assess.

Non-verbal Intelligence

Raven Standard Progressive Matrices (SPM, Raven, 1965) were used to assess subjects' non-verbal intelligence. The test was designed to measure a person's ability to form perceptual relations and to reason by analogy independent of language and formal schooling. The Standard Progressive Matrices consist of 60 items grouped into five sets (A-E), each set containing 12 items. Each item includes a pattern problem with one part removed with six to eight pictured inserts to choose from, one of which contains the correct pattern. Each set involves different logical principles for finding the missing piece to complete a pattern, and within a set, items become increasingly difficult. The

SPM is an untimed test and requires about 40 minutes. The number of correctly completed figures serves as an index of performance.

Premorbid intelligence level:

The *TIB* (Test di Intelligenza breve; Sartori, Colombo, Vallare et al., 1995), an Italian version of the National Adult Reading Test (NART; Nelson, 1982), allows estimating the IQ based on a simple and rapid reading test. Apart from its use as a quick method of estimating the actual intelligence level, the TIB is also employed because of its important capability of resistance to cognitive deterioration. The test depends on the particular characteristic of the Italian language that lexical stress on multisyllabic words is not determined by rule, but must be learned. There is a dominant stress pattern, with the main accent falling on the penultimate syllable, and there are two less frequent patterns with the main accent falling on the antepenultimate syllable or on the last syllable. Because of the predominance of words with main stress on the penultimate syllable, this has been labeled the "regular" form, whereas the less frequent form is labeled "irregular". The regularity of the stress form has an effect on pronunciation latencies and errors in normal adults (Colombo, 1992).

The TIB consists of 34 low frequency words mostly with an irregular stress pattern and of 20 high frequency words added to control for the reading proficiency of common words. Only reading of low frequency words determines the final TIB test score. The validation studies on a healthy population (Colombo, Sartori and Brivio, 2000; Sartori, Colombo, Vallare et al., 1995) have shown a significant correlation between the TIB and each of the three Intelligence Quotients provided by performance on the WAIS scales (Wechsler, 1981). On the contrary, in studies with Alzheimer patients and brain injured subjects, the TIB IQ was significantly higher than the WAIS IQ (Sartori et al., 1995), suggesting that the former estimated the premorbid intellectual level while the latter estimated the present level of cognitive functioning. Thus, we used the TIB with patients in our study as a tool to estimate the IQ previous to the traumatic brain injury.

On the TIB, subjects were asked to read aloud each of the 52 words carefully. The experimenter recorded each error (separately for stress and mispronunciation errors) relative to the irregular word list.

Semantic memory:

Semantic long-term memory was examined using the Italian test "*breve racconto*" (Novelli, Papagno, Capitani et al., 1986), which consists of a short story formed by 28 logical elements. The story is read to the subject by the experimenter and immediately after the subject is requested to tell

the story again citing every detail he can remember. It is not necessary to repeat the whole passage word by word but to mention as many logical elements as possible. Subsequent to the first recall, the story is read again by the experimenter and the subject is told that he has to retell the story again later. A period of about 10 m follows filled with an interposed test that should be quite different from the memory test, in order to avoid interferences. In our study we filled this short distractive period by administering patients the TIB and the Attentive Matrices. The patient is then requested to retell the story again as he or she remembers it. No additional questions are asked when the patient does not remember all of the story elements. The test score is determined by calculating the mean of the number of correctly repeated elements during both recall periods with scores ranging from 0 to 28 (perfect performance).

Incidental memory:

To assess incidental memory performance we used the short Italian tool *"Lista animali"*. The experimenter reads a list of 20 animals to the patient, each of the items followed by the question "Tell me, what is the typical color of this animal!". At the end of this apparent color-naming task, the patient is asked to recall as many of the former mentioned animals as possible without necessarily repeating them in the same order. "Lista animali" is a rather simple incidental memory task, which is mainly used with brain damaged patients to determine pathological deficiencies of incidental memory performance. Certainly, this test is not appropriate for evaluating memory functioning in healthy subjects.

Auditory immediate recall:

The *Digits Forwards* taken from the *WAIS-Digit Span Subtest* (Wechsler, 1981) was employed to evaluate auditory immediate recall. Freedom from distractibility is thought to be another cognitive component related to this test. On this task, the examiner reads a number of digits at one-second intervals, which the subject has to repeat back to the examiner in the same order. The size of digit sequences increases progressively from two to nine digits, with two different trials for each sequence. The test is concluded when the subject fails both trials of a particular digit span. The highest number of digits correctly recalled by the subject serves as an index of performance.

Attention, Cognitive Switching:

The *Attentive Matrices,* adapted from the Visual Search and Attention Test (VSAT, Trenerry, Crosson, DeBoe & Williman, 1990), were used to assess attention and visual search capacities. The test consists of three visual cancellation tasks (see Fig. 2.3.1.) that require the subject to cross out

numbers that are identical to the target. In the first task only one number has to be identified, whereas in tasks two and three, respectively, two and three types of numbers have to be cancelled. Since the time limit to complete one template (45 s) remains the same for each of the three parts, the level of difficulty increases with ongoing performance. Test score is determined by the number of overall correctly marked items with scores ranging from 0 to 60.

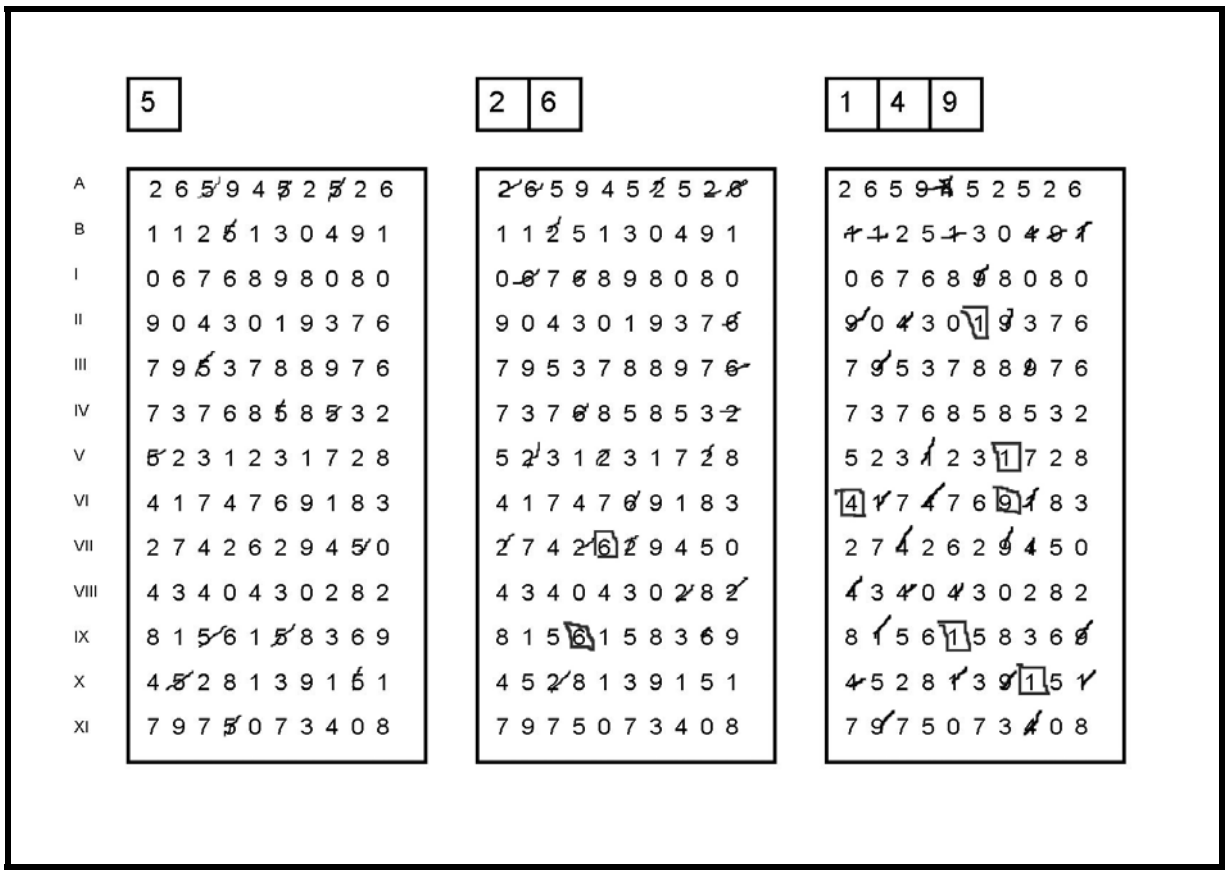

Fig. 2.3.1 "Attentive Matrices": Example of a completed (cancelled digits) and corrected (encircled digits) test form (reduced in size)

The *Trail Making Test* was originally designed as part of the Army Individual Test Battery (1944) and is now included in several general and specific-purpose neuropsychological test batteries (e.g. Halsstead-Reitan Battery, Reitan & Wolfson, 1993). The test comprises of two parts: Trial Making Part A (TMT-A) and Part B (TMT-B). TMT-A involves drawing a line connecting consecutive numbers from 1 to 25, which are distributed over an A4 page. In TMT-B, the subject is required to draw lines between the numbers one to thirteen and the letters "A" to "L" (in our case, using the Italian alphabet, between "A" to "N"), alternating between numbers and letters (eg, 1-A, 2-B, etc). During performance the examiner points out errors as they occur, and error-correction influences the time to complete a trial, which is recorded and determines the final test score. TMT-A is a test of graphomotor speed, attention and sequencing. Since TMT-B requires the switching from one

category (numbers) to another (letters), the task is assumed to test, beside attention and sequencing, also mental flexibility.

“Executive Functions” (problem solving, cognitive flexibility and cognitive fluency):
Three tests that are supposed to be sensitive to executive functioning were included in the neuropsychological test session: the Wisconsin Card Sorting Test (Berg, 1948; Heaton, 1993), the Tower of London (Shallice, 1982) and a test of verbal fluency (Novelli, Laiacona, Papagno et al., 1986).
The *Wisconsin Card Sorting Task* was developed in 1948 (Berg) to assess "abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies." Subjects are required to match 128 cards with different coloured shapes to 4 key cards presented by the experimenter without being given any rule for matching cards. The participant must decide how to sort the cards, and is given a “yes” or “no” feedback from the experimenter that should enable the subject to determine which matching principle to use. Rules change during the test and the subject is required to switch from the former sorting strategy to a new one in order to get a positive feedback. The number of correctly completed categories, the number of necessary trials, the number of perseverative responses (failure to switch from one sorting principle to the next) and unspecified errors were measured.

The *Tower of London task* was originally designed by Shallice (1982) to investigate planning impairments in patients with frontal lobe lesions. It consists of a flat board on which three pegs of differing heights are spaced and hold three wooden balls (red, blue and green). The subject is presented with a standard start arrangement of balls (see Fig. 2.3.2.) and with a goal position to achieve with a specified number of moves. In our experiment, the goal state was depicted on A4 sized cards, with coloured pictures to represent pegs and corresponding balls.
The subject is told to transform the starting state into the goal position in a predetermined number of moves while following three rules: Each ball can only be moved from one peg to another, only a specified number of balls could be placed on each peg at a time and only one ball should be moved at a time. Participants are reminded of the rules when they are broken and asked to restart their solving on that problem. The test includes 12 subproblems ranging in difficulty from two to five moves. Final test score was determined by the number of problems solved without errors in less than 60 seconds, where three points were given for executions that took less than 15 seconds, two points for problem solutions within 30 seconds and one point for problems solved within 60 seconds.

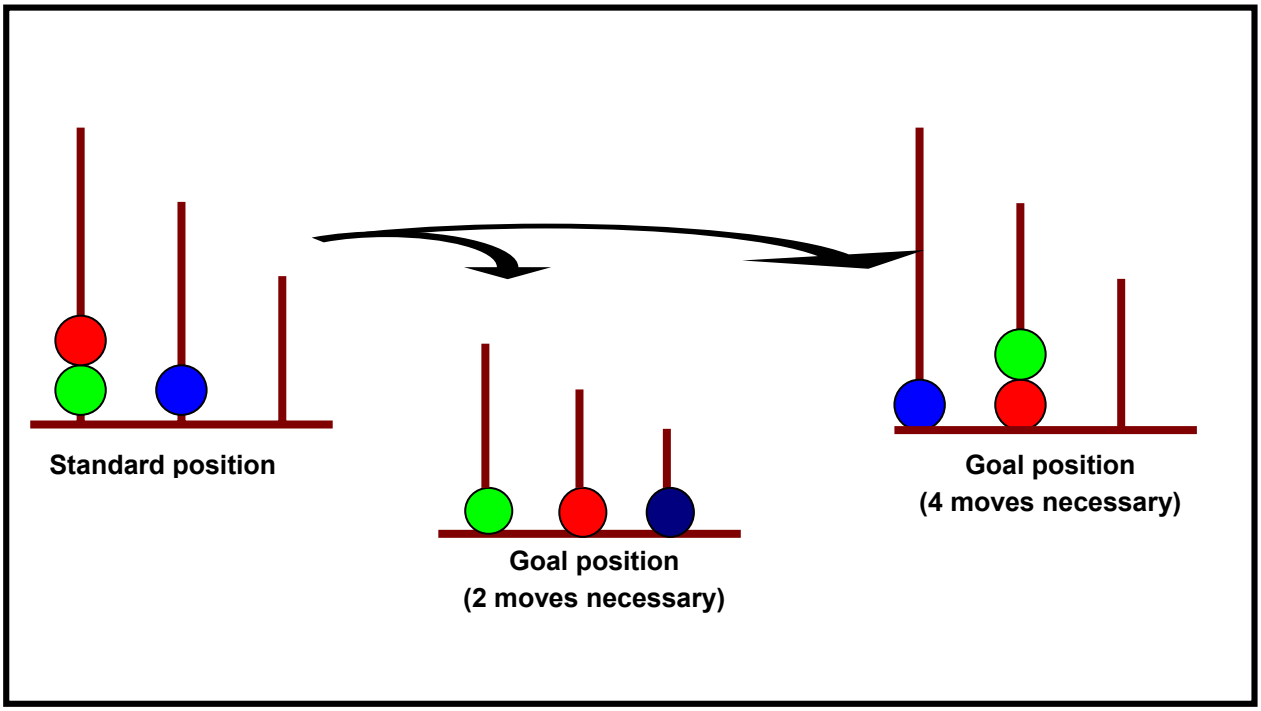

Fig. 2.3.2. Tower of London test (Shallice, 1982): Standard position and two subproblems

To assess cognitive fluency, the *Italian verbal fluency* task (test di fluenza verbale) developed by Novelli et al. (1986) was used, which includes spontaneous production related to phonemic and semantic categories. For the phonemic verbal fluency task the subject is asked to produce as many words as possible beginning with the letters “F”, “P” and “L” in three separate trials. One minute is allowed for each trial. Subjects are instructed not to give proper names or different words derived from the same root (e.g. different tenses of a verb or diminutive names). Letter cues are administered in a fixed order. The final score was deduced from the sum of the number of correctly produced words for each trial. For the semantic verbal fluency task the participant is asked to produce, again in three separate trials, as many words as possible belonging to the semantic categories “car brands”, “fruits” and “animals”. Task administration and scoring is the same as for phonemic categories.

2.4. Experimental design

The present experiment was composed by the following four parts: electrophysiological recordings (ERPs and SCR) to investigate the elaboration of affective visual stimuli, an immediate free recall task for prior presented emotional material, a self evaluation of the participants' affective reaction to the stimuli, and answering a personality questionnaire.

2.4.1. Stimulus material

IAPS – pictures

Seventy-five colored pictures were selected from the International Affective Picture System (IAPS, Centre for the Study of Emotion and Attention, 1999) with three categories differing in affective valence: Twenty-five pictures depicted pleasant events (e.g. erotic couples, sports, etc.), twenty-five pictures showed neutral events (e.g. household objects, buildings, etc.) and another twenty-five pictures depicted unpleasant scenes (mutilated bodies, dangerous animals, attack scenes etc.).

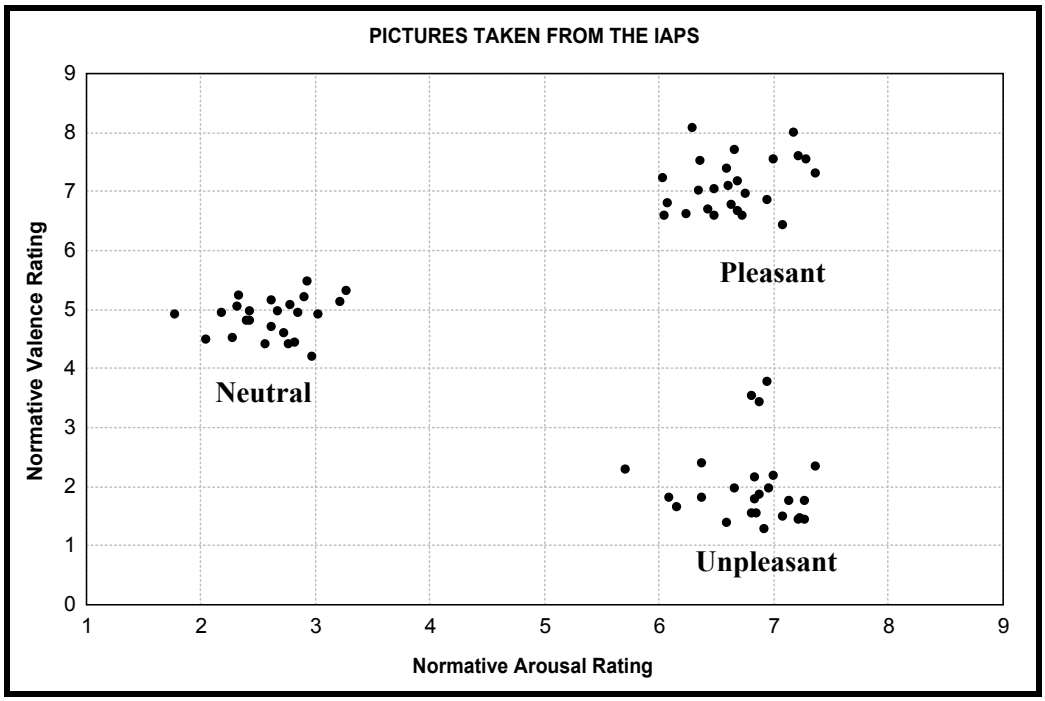

Fig.2.4.1 Normative affective values for pictures used in the present experiment

As shown in Figure 2.4.1., the three content groups were selected such that there was no overlap in IAPS normative affective valence ratings, i.e. the three stimulus categories were distinct and representative of affect type. Mean normative valence (rated on a nine-point scale with high values indicating pleasantness) was 7,14 for pleasant pictures, 4,87 for neutral pictures and 2,02 for unpleasant pictures. All neutral pictures had lower standard emotional arousal ratings (mean: 2,72) than the pleasant (mean: 6,63) and the unpleasant (mean: 6,79) pictures. (See Appendix B for IAPS slide numbers and normative arousal/ valence ratings for individual pictures.). Two orders of picture presentation were created with the constraint that no more than three stimuli of the same category were shown consecutively. Subjects were randomly assigned to one of the two sequences.

SAM (Self Assessment Manikin)

For the measurement of subjective emotional responses to the affective stimuli a paper and pencil version of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994) was used. The SAM consists of three rating dimensions, valence, arousal and dominance. Every dimension is illustrated as a nonverbal scale ranging from 1 to 9 with higher values representing more positive valence (pleasure), higher arousal and more feelings of dominance. In the present experiment only the scales of valence and arousal were used. The SAM is supposed to be a useful instrument when determining the subjective experience of emotion associated with processing affective stimuli (Bradley & Lang, 1994) and since it has also been successfully employed with clinical populations and children we regard it as an adequate and comprehensible instrument to use with brain damaged patients.

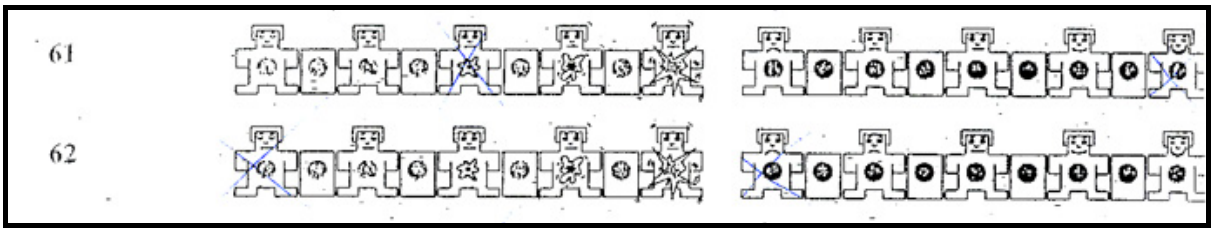

Fig. 2.4.2 SAM-Example (Arousal-rating on the left, Pleasure-rating on the right)

MPQ –BF (Multidimensional Personality Questionnaire – Brief Form)

To test personality differences between patients and healthy controls, all participants were administered the Multidimensional Personality Questionnaire - Brief Form (MPQ-BF; Patrick, Curtin, & Tellegen, 2002), which is a 155 item version of Tellegen's (1982) MPQ. The abbreviated higher order dimensions from the MPQ-BF correlate highly (r = .92 to .98) with the full version scales from Tellegen's (1982) original instrument (Patrick et al., 2002). The MBQ-BF is a measure of "normal" personality characteristics that consists of 11 primary scales with high internal-consistency reliabilities (alphas in the MTR range from .77 to .88) and cohere in a three-factor, higher order structure comprising orthogonal dimensions labeled positive emotionality, negative emotionality and constraint. Positive emotionality is indicated primarily by subscales "Well-Being", "Social Potency", "Social Closeness", "Achievement" and "Absorption", whereas negative emotionality is indicated mainly by "Stress Reaction", "Alienation" and "Aggression". Individuals scoring high on negative emotionality have a low threshold for the experience of negative emotions such as fear, anxiety and anger whereas individuals scoring high on positive emotionality have a low threshold for the experience of positive emotions and tend to view life as an essentially pleasurable experience. The third dimension constraint is represented for the most part by subscales

"Control", "Harm Avoidance" and "Traditionalism". Individuals scoring high on this factor tend to act in a cautious and restrained manner, avoid thrills, and endorse and conform to social norms. Items of the "Unlikely Virtues"- scale control for participants' tendency to give socially desirable responses.

2.4.2. Procedure

After arrival at the laboratory, aim and methodology of the study were explained, afterwards participants read and signed an informed consent form and answered a few questions about demographical data. Patients were asked a few additional questions regarding the nature of the traumatic incident and some clinical aspects. Next, the MPQ was explained to the participants and they were required to fill in the questionnaire.

Participants were then seated in a comfortable chair in a small sound-attenuated room and electrodes were attached. Prior to running the EEG experiment, two short calibration runs, necessary for later correction of eye movement artifacts, were accomplished. Following with their eyes a colored spot presented on the computer screen, subjects had to perform 20 horizontal (10 to the left and 10 to the right of the screen) and 20 vertical (10 up and 10 down) eye movements during each calibration run.

Next, participants where told that a series of pictures would be presented and that they should attend to each picture the entire time it appeared on the screen. They were also instructed to maintain gaze on the centre of the screen during the short periods between slide presentations and to avoid excessive exploratory eye movements and blinks while pictures were presented. All slides were shown on a 17 inch monitor (Samsung Sync Master 4Plus), approximately 80 cm in front of the subjects eyes. The picture size of 32 x 24 cm was equivalent to a vision angle of 22° horizontally and 17° vertically. Each picture was shown for 4 s with an interstimulus interval randomly varying between eight and ten seconds. Before starting the experimental session, participants were presented with eight low-arousal slides serving as practice trials.

Following psychophysiological recordings, subjects were given an incidental free-recall test, in which they were instructed to write down, in any order, a word or short sentence describing each of the prior presented pictures they were able to remember. Participants were told to provide a clear description so that the recalled slide could be identified by the experimenter. 10 minutes were given as free-recall period.

The last part of the experimental session consisted in a second presentation of the 75 different pictures, and this time subjects were asked to rate every picture on two categories, affective valence and arousal, using the self-assessment manikin. Since participants had to rate each picture in the

short time period between slide appearances on screen, the interstimulus interval between trials was longer than during the psychophysiological session, varying between 10-12 s.

2.4.3. Electrophysiological recordings

ERP- recordings:

The electroencephalogram (EEG) was recorded with a DC-amplifier (MES, Munich) from 19 positions using an electrode cap (Fz, Cz, Pz, Fp1, C3, F3, F7, T3, T5, P3, O1, Fp2, C4, F4, F8, T4, T6, P4, O2). Additional Ag/AgCl electrodes were placed on the mastoids and on Nz. The vertex (recording site Cz) was chosen as reference. Vertical and horizontal electro-oculogram (EOG) were recorded with two electrodes placed about 1 cm horizontally to the eyes on the left and right outer canthi and two electrodes about 1 cm below eyes. Electrode impedances were kept below 8 kOhm. Data were recorded continuously, sampled at 250 Hz with filter settings DC (Highpass) to 70 (Lowpass) and stored for offline analysis.

Skin conductance –recordings:

Skin conductance activity was measured from Ag/AgCl electrodes (10 mm diameter) placed on the thenar and hypothenar eminence of the right palm with 0.05 M NaCl isotonic gel. Skin conductance responses were sampled at 250 Hz and stored on a computer by means of a 0.5 V constant voltage skin conductance coupler. Resolution was set to 2000 pts/uSiemens.

2.5. Data reduction and analyses

EEG data

Offline analyses with EEG data were made using Konstanz Format (EEG and Psychophysiology Data Analysis Programs, Berg, P., 1999) and programs written with *National Instruments LabView* software (NI, Austin, Texas, USA). Data were first corrected for slow DC shifts by polynomial correction over the whole recording. Epochs starting 200 ms before stimulus presentation and ending 6 s after were determined; data of each epoch being referred to a pre-stimulus baseline of 150 ms. Data were transformed to average reference and filtered between 0 and 12 Hz.

Epochs were corrected for eye movement and blink artifacts following a technique of Berg and Scherg (1994) that allows using also the electrodes around the eyes as EEG electrodes. This method takes into account the assumption that the measured potential at an electrode is the linear sum of contributions (source components) from brain and eye sources and determines independently source vectors for eye and brain activity. Together with the temporal information (i.e. amplitude at each

electrode as a function of time) of each vector a source component is defined. For eye movements these source components are estimated on the basis of empirical data taken from the individual eye movement calibration trials performed prior to the experimental session. Eye correction is then accomplished by subtracting from artifact contaminated data the source components of the EOG, but at the same time specifying the contribution of brain source components and leaving those unaltered. As a result of the MSEC method the EOG electrodes can be analyzed as EEG electrodes in the artifact-free corrected data. Other conventional artifact correction methods consisting of estimating a transmission coefficient with regression methods and subtracting the estimated potion of the EOG from the EEG have the disadvantage that also some proportion of the EEG is subtracted and therefore the EEG topography might be changed. Being able to use also data from EOG electrodes which could provide important information on orbitofrontal brain activity for further analyses was of a great significance for the present study, mainly because of two reasons: First, orbitofrontal areas are supposed to play an important role in the elaboration of visual affective stimuli and second, nearly each of the brain injured participants had lesions involving frontal areas and therefore it was essential to use an ocular artifact correction which does not affect frontal brain activity. After eye artifact correction each trial was visually inspected and excluded, if there were remaining artifacts of any kind (muscle potentials, large drifts etc.).

Skin conductance response

Skin conductance was analyzed offline using a program written in LABVIEW. Mean and maximum change scores, deviated from a 1s pre-picture baseline, were determined for epochs lasting from 1s to 5s post-stimulus-onset and represented the measure of electrodermal activity elicited by each stimulus.

General statistical analyses

Statistical analyses were accomplished using STATISTICA (Statsoft, Inc., 2001) and StatView 5.0 (SAS Institute Inc.). Individual statistical designs for different data types are reported in the following section separately for each parameter. All significant main effects (Alpha= 0.05) were followed by post hoc tests (Newman-Keuls) to identify specific differences. Degrees of freedom were adjusted by means of Greenhouse-Geisser method (Greenhouse & Geisser, 1959) where appropriate. Results are presented by reporting uncorrected *F* values together with the Greenhouse-Geisser epsilon and corrected *p* values.

3. TBI PATIENTS - NEUROPSYCHOLOGICAL PERFORMANCE AND PERSONALITY PROFILE

3.1. Neuropsychological functioning in TBI patients

Neuropsychological data from 22 patients were included into statistical analysis. Due to health problems at the time of the examination, one patient could not participate in the neuropsychological test session. Patients' result in the Mini-Mental State Examination (MMSE) and those obtained in the non standardized short screenings are listed in Table 3.1.1.. Only raw data are summarized, as no normative data are available for these tests that have been employed with the purpose of assuring that patients had no substantial deficits of fundamental cognitive domains as comprehension, perception and orientation.

Tab. 3.1.1. Overview on patients' performance on MMSE and non-standardized short screenings

MMSE	Mean score = 27.5 (range 25-30)
Reading of non-words	All patients (n= 23) scored 5 out of 5
Spontaneous speech	21 patients presented fluent speech, two subjects were slightly inhibited
Comprehension task	21 patients scored 6 out of 6, two patients scored 5 out of 6
Naming of unusual views	21 patients scored 3 out of 3 one patient scored 2 out of 3
Color naming	20 patients scored 8 out of 8, two patients scored 7 out of 8
Association figure-color	18 patients scored 3 out of 3, two patients scored 2/3, another two scored 1/3
Repetition of short sentences	Eight patients scored 3 out of 3, eight patients scored 2/3, another six scored 1/3.
Comprehension of complex orders	4 patients correctly responded to all orders, 10 subjects scored 7 out of 8, five patients scored 6/8 and another three scored 5/8

Statistical analyses on patients' performance on standardized neuropsychological tests were accomplished by transforming all raw scores into z values using the appropriate normative data presented in the specific literature. The relationship between coma duration, time elapsed since injury and cognitive performance was assessed using Pearson correlation coefficients. Figure 3.1.1. shows the average performance of patients in the specific cognitive tasks. Generally, a test result that diverges more than one standard deviation from the norm is considered to be abnormal whereas a difference of more than two standard deviations is regarded as a pathological outcome.

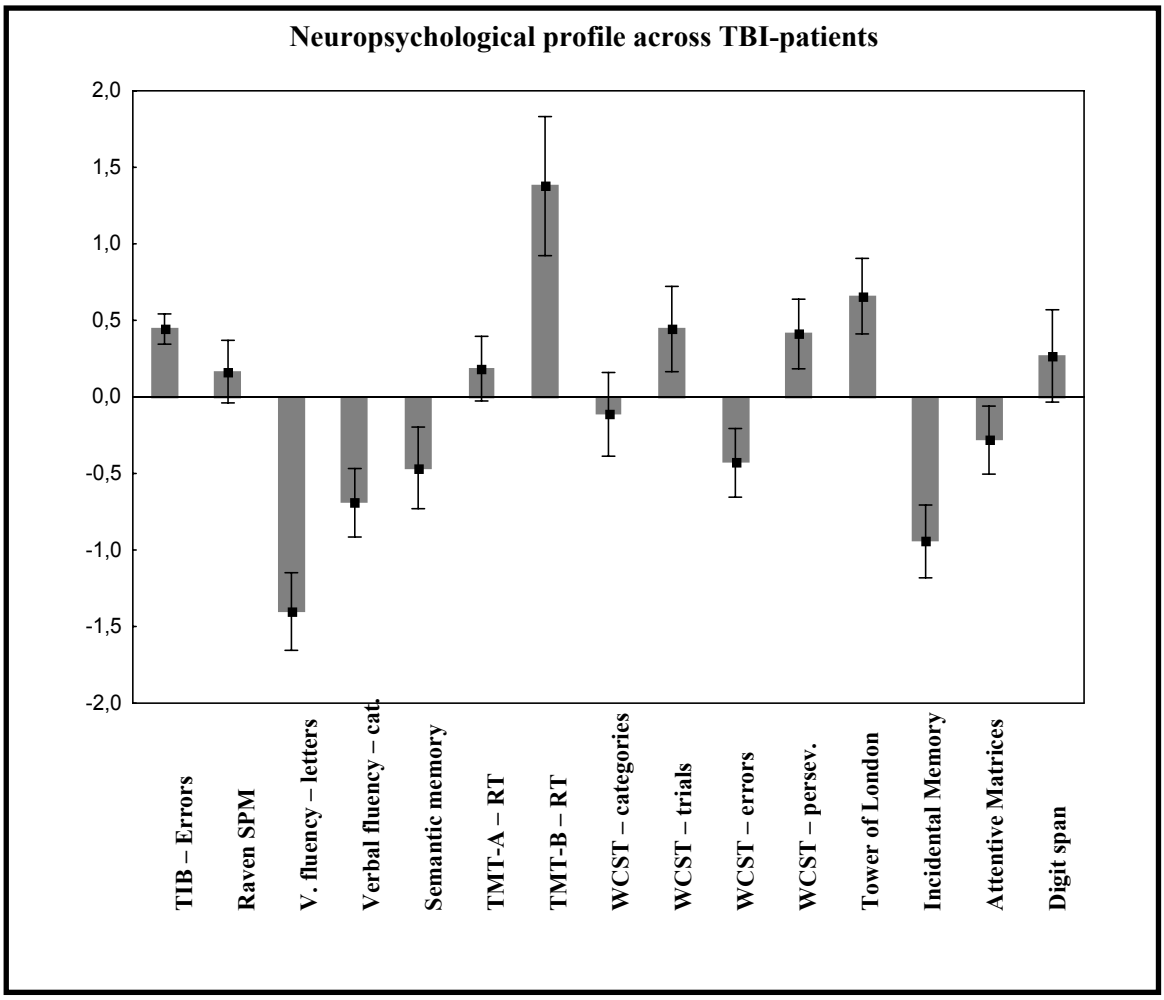

Fig.3.1.1. Neuropsychological profile of brain injured patients test results are z-transformed for comparability of patients with standard populations described in the respective test norms (Means +/- standard error).
Note: Lower z-scores do not necessarily indicate worse performance; in case of reaction time tasks, e.g. TMT, higher z-scores reflect worse performance than the normal population.

Looking at patients' profile in Fig. 3.1.1. we can determine two tasks in which patients' group mean differs more than one standard deviation from the given norms: Verbal fluency for letters (z-mean: -1.40) and Trial-Making Test Part B (z-mean: 1.38). Patients were impaired in spontaneous production of words beginning with a predetermined letter and in solving a graphomotor speed task which required them to switch between two cognitive sets. The incidental memory performance of patients resulted slightly below the critical border of one standard deviation with a group mean of z= -0.94. No other neuropsychological task revealed differences between brain injured patients and normal populations. Although inspection into scatterplots of the various neuropsychological variables showed some individual test scores falling out of the normal range (mean +/- 1 SD), the average group result of patients for those tests did not distinctly differ from standard scores.

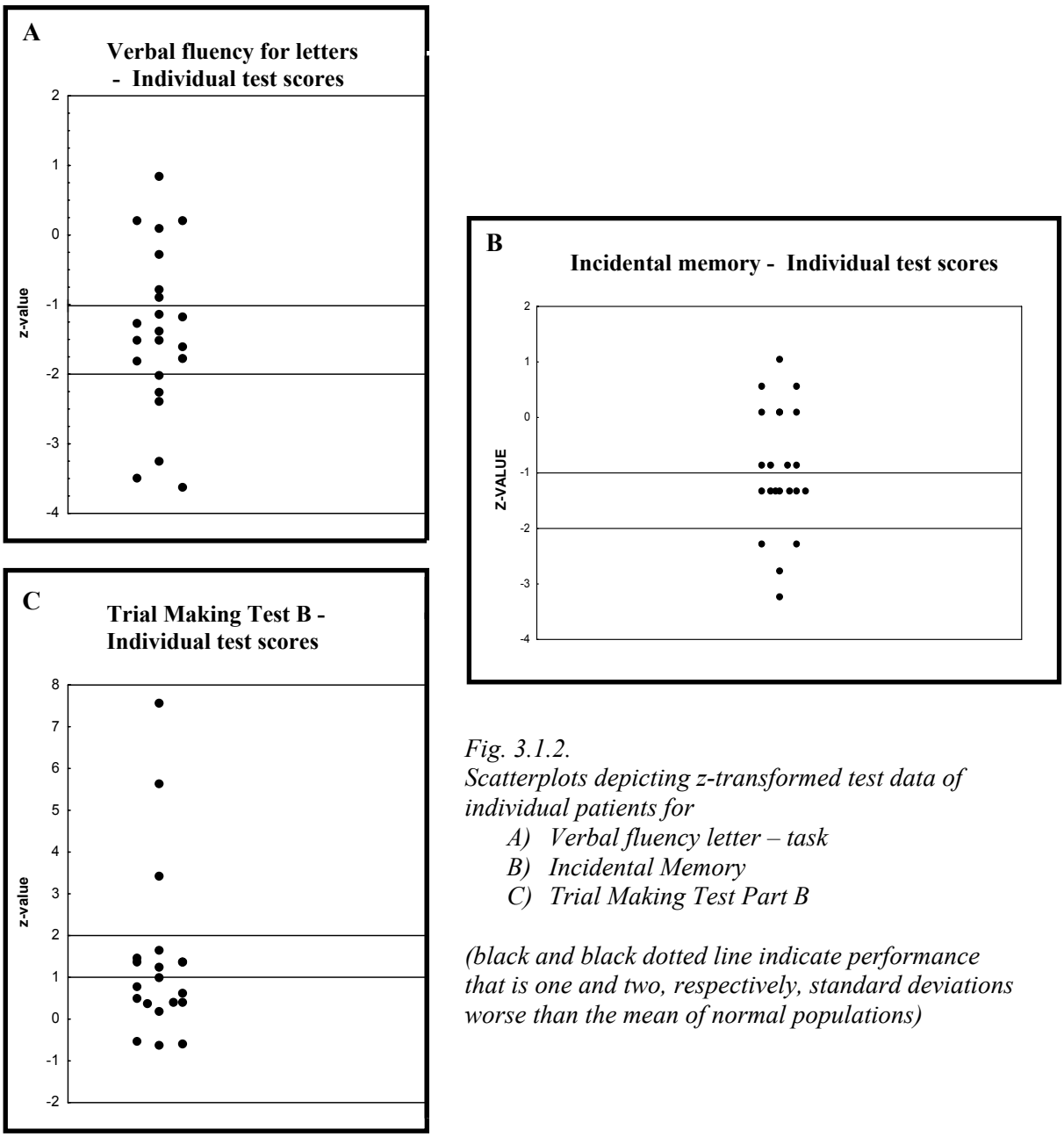

Fig. 3.1.2.
Scatterplots depicting z-transformed test data of individual patients for

A) Verbal fluency letter – task
B) Incidental Memory
C) Trial Making Test Part B

(black and black dotted line indicate performance that is one and two, respectively, standard deviations worse than the mean of normal populations)

Relationship of demographic-clinical variables and neuropsychological performance:

Pearson correlation coefficients were used to explore the relationship between age, coma duration, time elapsed since acquisition of brain injury and total lesion size and cognitive performance in patients. The correlation pattern is summarized in table 3.1.2. reporting only significant results or trends of significance.

Table 3.1.2 . Significant correlations between age, clinical variables and neuropsychological performance (trends are written in italic)

	Age	**Coma duration**	**Time elapsed since injury**
Digit span	*r = -.43 (p<.052)*	r = -.47 (p< .05)	
Verbal fluency letters		r = -.48 (p< .05)	
TMT – B (solving time)		r = .55 (p< .05)	
Incidental Memory		r = -.50 (p< .05)	
WCST – completed categories			*r = .41 (p< .07)*
WCST – nonperseverative errors			r = -.49 (p< .05)
Attentive Matrices			*r = .40 (p< .06)*

It is important to note that total size of traumatic brain lesion did not correlate with any measure of cognitive performance. In addition, no relationship between coma duration and overall lesion extent could be found.

Discussion

The neuropsychological examination consisted of several short screenings including the MMSE aiming at globally testing the intactness of essential cognitive abilities such as language comprehension, language expression, perception, orientation, and motor skills. In addition, a number of neuropsychological tests comprising Raven's SPM, WCST, Tower of London, TMT parts A and B, verbal fluency and other standardized tasks were employed to accurately investigate different cognitive domains such as nonverbal intelligence, memory, attention, problem solving, and executive functioning.

Mean group score on the MMSE was high with 27.5 with all patients achieving 25 or more points. Taken together with the patients' good performance on the basic short screening, this indicates that fundamental cognitive domains were not impaired in TBI patients. This was to be expected since one important inclusion criteria for participation in the experiment was a good recovery of basic cognitive functions as well as the absence of significant language or motor impairments. Evidence for the intactness of patients' basic cognitive abilities is important for the discussion of findings from other parts of the examination. For example, eventual deficits in more specific and complex neuropsychological tasks cannot be interpreted as deriving from comprehension problems or perceptual deficits.

The extensive evaluation with standardized neuropsychological tests revealed that on most tasks, patients' z-scores laid within the normal distribution of one standard deviation, meaning that in these cases, patients' performance did not significantly deviate from test scores of a comparable

healthy population. The only two tests where patients yielded evidently worse results compared to the normal population were the TMT, part B, and the phonemic verbal fluency task. A slight deficit became visible for the incidental memory task.
The three neurocognitive measures showed a significant correlation with the factor coma duration, with TMT-B being negatively correlated, whereas word fluency and incidental memory were positively correlated to coma length. A further negative relationship with coma duration could be found for the digit span task that, in addition, was inversely related to age. Another factor resulting slightly associated with neuropsychological performance was the time elapsed since acquisition of head injury which showed a negative correlation with the number of errors on the WCST and, to a minor extent, was positively related to the number of successfully completed categories on the same task.

Taken together, the neuropsychological profile obtained for TBI patients emphasizes that despite the extensive brain damage present in most subjects, the majority of their cognitive abilities have remained unimpaired or, considering that the average time elapsed since acquisition of head trauma was 36 months, have recovered very well. Patients' nonverbal intelligence was normal and did not differ from the premorbid intelligence score. Furthermore, no deficits were found for memory measures as "digit span" and "semantic memory" and for the performance on the attention tasks TMT A and the Attentive Matrices. Both the verbal fluency task and TMT-B where patients showed evident impairments aimed at investigating executive functioning by measuring cognitive fluency and mental flexibility, respectively. The poor spontaneous production of words in brain injured patients has previously been confirmed by several other studies (Lannoo, Colardyn et al., 2001; Levin, Goldstein et al., 1991). Also the prolonged practice time on the TMT-B has repeatedly been found in TBI patients and patients with frontal lobe injury (Spikman et al., 2000; Stuss et al., 1989). The fact that in the present examination, patients' performance on both TMT part A and the Attentive Matrices resulted unimpaired argues against the presence of a general information processing deficit or poor visual search skills. Instead, the problem of TBI patients to quickly switch between two cognitive sets points at a specific problem of attentional control necessary for distributing attentional resources to two simultaneous tasks. Since the processing of one cognitive set (letters) requires a momentary suppression of the other set (numbers), deficient attentional switching in TBI patients could be due to a lack of inhibition (Arbuthnott & Frank, 2000).
Those neuropsychological aspects that were impaired in brain injured patients were all associated with length of coma. Patients with longer coma duration had a reduced processing speed on TMT-B, produced fewer words in the phonemic verbal fluency task and performed worse on the incidental recall test. Taken together with the finding that these impairments were neither

influenced by lesion extent nor by the time elapsed since acquisition of brain trauma, this suggests that length of coma may be primarily indicative of cognitive deficits following TBI. This conclusion is in line with a number of studies that found coma duration to be one of the most reliable predictors of neurobehavioral outcome after TBI, especially when measured by return to work criteria (Cattelani, Tanzi, Lombardi & Mazzucchi, 2002; Stambrook, Moore, Peters et al., 1990).

Typically, TBI and, in particular, lesions of the prefrontal cortex have been linked to substantial impairments of executive functions. It is rather surprising that patients performed well on most measures of executive functioning given that the area of greatest lesion overlap was found in prefrontal areas. In particular the intact performance on the WCST and the Tower of London, both of which were designed to test executive functions as abstract reasoning, cognitive flexibility, and planning abilities, represents a rather atypical outcome. A possible reason for this could be that greatest lesion overlap was in the anterior orbitofrontal cortices (Brodman areas 10, 11), whereas less patients presented damage to the dorsolateral prefrontal cortices. In addition, none of the patients had a lesion of the anterior cingulate gyrus (Brodman area 24). However, several studies have linked performance on the WCST and the Tower of London to dorsolateral prefrontal and anterior cingulate cortices. Milner (1963) found that dorsolateral frontal brain damage was associated with a poor performance on the WCST, whereas inferior and orbital frontal lesions did not cause such impairment. Weinberger, Berman and Zec (1986) could confirm this notion in a physiological study by determining a relative increase of activity in prefrontal dorsolateral areas during execution of the WCST. With respect to the Tower of London task, recent PET and MRI studies (Dagher, Owen, Boecker & Brooks, 1999; Lazeron, Rombouts, Machielsen et al., 2000) revealed that dorsolateral prefrontal areas and the anterior cingulate gyrus were particularly activated during task performance. In view of these findings, it can be assumed that in the present study, the unimpaired performance of TBI patients on the WCST and the Tower of London task is due to the fact that in most cases, brain damage did neither comprise the dorsolateral prefrontal cortex nor the anterior cingulate gyrus thus leaving intact the patients' problem solving and planning abilities.

Apart from these considerations, an important general methodological aspect has to be taken into account when discussing results of tests that aim at investigating executive functions. As we have discussed earlier, in recent years questions have increasingly been raised with respect to the reliability of traditional measures of executive functioning. In this regard, there is growing evidence that neuropsychological tests, such as the Tower of London, may be too structured and too rich of external cues, thus resulting in inadequate investigation of executive functions (Stuss, 1987). A

promising approach to this problem seems to be the application of tasks that are non-routine, very similar to daily life situations and that do not provide any external cue (Spikman et al., 2000).

No significant correlations between age and any of the neuropsychological test result could be found, although a statistical trend ($p < .52$) was visible for the relationship between the digit span task and age of patients indicating that an increase of age was associated with a deterioration of immediate memory performance. Since patients constituted a rather young group with a mean age of 26 years and only one subject being older than 35, the finding that age did not have any decisive influence on cognitive performance was expected. However, it has been suggested that TBI sustained earlier in life may aggravate the effect of "normal" cognitive aging thus leading to an accelerated decline in cognitive functioning (Klein, Houx, Jolles, 1996). Perhaps the poor performance of older patients in the digit span test could be interpreted as an indicator of an abnormally early process of age related cognitive deterioration. Of course, this provisional conclusion has to be further explored in studies that optimally should investigate large clinical samples of TBI patients covering an extensive age range.

In summary, results of the neuropsychological examination suggest that most cognitive functions are within the normal range. The severity of injury, emphasized by the extended mean coma duration of patients, together with the fact that on average, an extended period has elapsed since acquisition of the head injury, indicates good recovery of cognitive functions in most patients. Evident impairments were only observed in spontaneous production of words and cognitive switching, suggesting a long-lasting deficit of mental flexibility in TBI patients. Patients' intact performance on measures of executive functioning supports the assumption advanced by recent functional imaging studies that anterior orbitofrontal areas might not play a key role in cognitive functions such as problem solving and planning abilities.

The overall heterogeneity of neuropsychological data as illustrated, for instance, by scatterplots (Figure 3.2.), points to the fact that cognitive impairments caused by a diffuse TBI can be very various compared to the neurobehavioral damage provoked by focal lesions. In this regard, it is important to keep in mind that, although neuroanatomical analyses have resulted in the identification of predominantly lesioned brain areas in our patient group, a TBI may, as well, imply diffuse brain damage that often remains undetected upon neuroradiological assessment. Therefore, when examining TBI patients to study the effects of visually identified lesions, results have to be interpreted with some caution. What may appear to be an effect of a focal lesion may be no more than the focal lesion interacting with the more diffuse damage. An aspect of our study which confirms this consideration is the finding that the extent of brain lesion is not associated to cognitive

performance of patients, whereas the length of coma was found to correlate with neuropsychological impairments, thus representing a much better index of severity of injury and a good predictor of later cognitive consequences, as well. Nevertheless, the question of whether it is possible to successfully differentiate TBI patients on the basis of their lesion extent and location will be addressed in a later part of the present thesis.

3.2. Personality characteristics

Differences between patients and healthy subjects on MPQ-subscales were analyzed with two-tailed t-tests for independent populations. Results on the MPQ were available for 21 patients and 23 controls. Table 3.2.1. summarizes t-test outcomes for each subscale. Patients and healthy subjects differed with respect to "wellbeing" and "traditionalism" with patients obtaining higher scores than controls. Furthermore, patients were more likely to report certain virtues that only doubtfully comply with the truth.

MPQ- SUBSCALE	Mean Patients	Mean Controls	t-value	p
WELLBEING	**7,62**	**6**	**2,16**	**p< 0,05**
SOCIAL POTENCY	4,65	5,43	-0,97	0,34
ACHIEVEMENT	6,17	5,78	0,51	0,62
SOCIAL CLOSENESS	7,2	8,04	-0,89	0,38
STRESS REACTION	5,65	6,57	-0,95	0,35
ALIENATION	3,54	2,78	0,82	0,42
AGGRESSIVENESS	2,81	3,91	-1,53	0,13
CONTROL	7,75	6,87	0,90	0,37
HARM AVOIDANCE	9,68	8,04	1,45	0,15
TRADITIONALISM	**8,57**	**6,04**	**3,03**	**p < 0,005**
ABSORPTION	6,02	7,22	-1,28	0,21
UNLIKE VIRTUES	**5,18**	**2,35**	**4,97**	**p < 0,0001**

Tab. 3.2.1. Means, t- and p-values for each participant group and MPQ subscale (significant differences are printed in bold)

Patient's data were z-transformed using mean and standard deviation of controls' results distribution. Fig. 3.2.1. depicts patients' scoring on each MPQ-subscale as deviation from outcomes of healthy subjects.

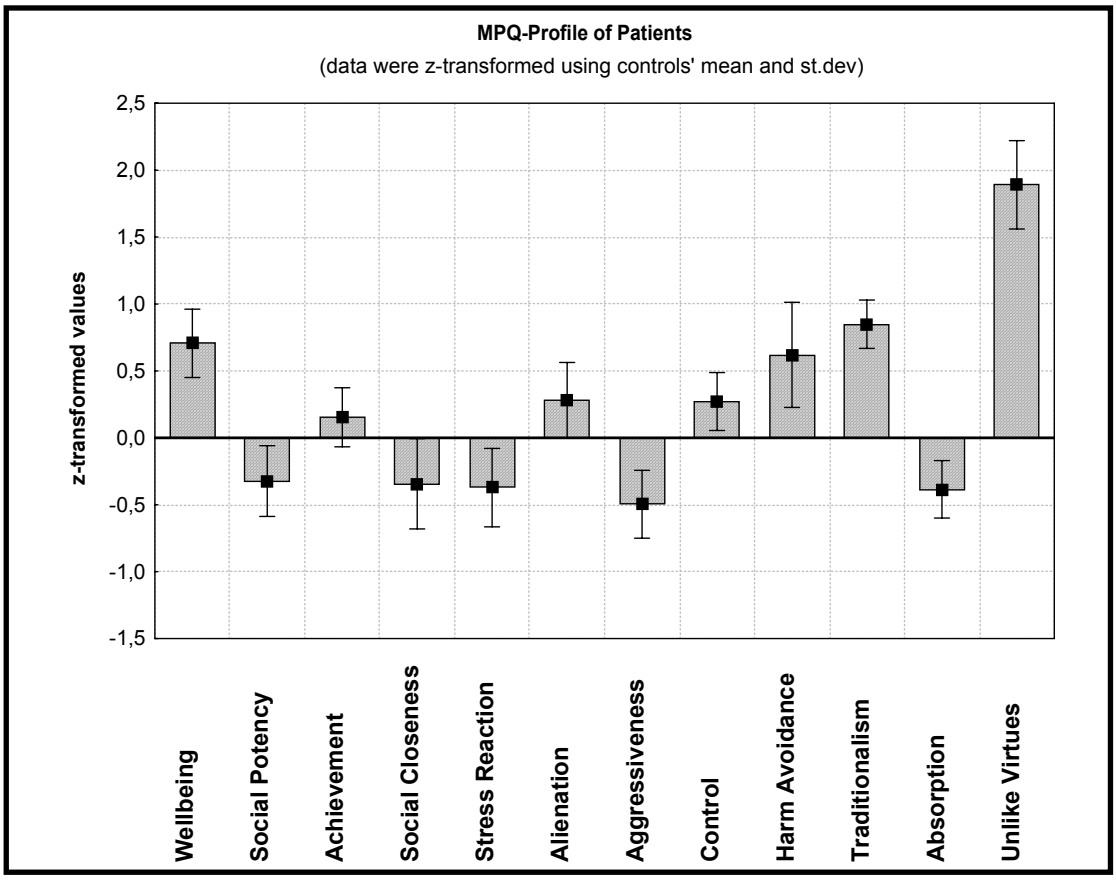

Fig. 3.2.1: MPQ scores of patients (test results were z-transformed for comparability between patients; means and standard errors are shown)

Discussion

The MPQ-BF was administered to participants in order to receive an impression about personality profiles of TBI patients and healthy controls. As of this writing, the MPQ-BF has never been used with brain injured patients, therefore no comparable data are available. Studies which made use of the Minnesota Multiphasic Personality Inventory (MMPI) to investigate personality changes and behavioral disturbances in patients with head injury repeatedly reported higher levels of emotional and somatic distress in this clinical group (Cattelani, Gugliotta, Maraviat & Mazzucchi, 1996; Leininger, Kreutzer & Hill, 1991). Because the MMPI is a tool specifically developed for psychiatric populations, concerns have arisen about its suitability for studying neurological patients. For example Gainotti pointed out that there is "*no reason to believe that emotional and personality changes resulting from damage to a specific brain structure (or from brain lesions in general) must correspond to the psychiatric diagnostic criteria*" (Gainotti, 1993, p.260). Based on this consideration, the MPQ-BF that was designed to measure "normal" personality characteristics, was regarded here as a more appropriate instrument.

The resulting MPQ-BF profile for brain injured patients did not confirm the higher emotional distress level reported by several earlier studies. On most MPQ subscales, scoring did not differ

between TBI patients and healthy controls. Noticeably higher scores of brain injured patients were only found for the "Wellbeing", "Traditionalism" and "Unlikely Virtues" scales. The elevated score on the latter scale indicates a tendency of TBI patients to appear socially desirable by attributing virtues on themselves that they do not possess. This propensity to present oneself in a particularly positive manner is connected with the again elevated score of patients on the "Wellbeing" subscale that measures the disposition to feel good about oneself and to have an optimistic attitude towards the future. These findings are in line with a series of studies reporting unawareness of deficits and the refusal to admit difficulties in brain injured patients (Gass, Russell & Hamilton, 1990; Prigatano, 1995). The exaggerated self-appraisal seems to be strongly related to injury severity, as patients with severe brain injury tend to report most favorably about their cognitive status (Mateer, Sohlberg & Crinean, 1987). Investigations using other personality questionnaires have shown that the perceived level of emotional distress and related affective disturbances, are similarly influenced by injury severity. In fact, Hoffman and co-workers (1999) and Leininger and colleagues (1992) found that less seriously injured patients demonstrated pronounced profile elevations on various MMPI-subscales indicating abnormal emotional alteration, whereas patients with a more severe injury had normal scores. A comparable result was recently reported by Golden & Golden (2003) who subdivided head injury patients according to length of consciousness and, subsequently, investigated MMPI-2 personality profiles for each subgroup. They came to two conclusions that are of particular importance for the discussion of MPQ findings in the present study: First, coma duration was a strong predictor of personality changes after brain injury. Second, from mild to moderate-severe head injury, there was a general increase in personality dysfunctions, whereas the most severe group consistently showed the least pathological scores suggesting a repetitive pattern of denial. In the present investigation, the clinical group mostly consisted of patients with a severe TBI, as indicated by the mean coma duration of 17 days and the fact that in only two patients, coma length was less than one week. Therefore, the overall high injury severity may account for patients' exaggerated reports of well-being and positive personal attributes. In light of these considerations, the elevated score of patients on the "traditionalism" subscale can be interpreted as a further indication of their tendency to present themselves in a socially desirable way by endorsing high moral standards and supporting traditional and religious values.

In summary, both the neuropsychological and the MPQ-profiles of TBI patients show that most of their cognitive functions and personality characteristics do not deviate from the norm. In particular the intact performance on perception and attention tasks leads to the assumption that a major impact of neuropsychological deficits on the elaboration of affective picture can be excluded.

4. ELABORATION OF AFFECTIVE PICTURES - COMPARISON BETWEEN BRAIN INJURED PATIENTS AND HEALTHY SUBJECTS

4.1. Event related Potentials

Time windows and electrode clusters for statistical analysis of ERP data were chosen on the basis of prior assumptions about visual processing of emotional stimuli and by means of visual inspection into grand mean waveforms. Given our hypothesis of an early differential involvement of visual cortex for different emotional contents, the examination of the first time windows focused on scalp voltages at posterior sites. As event-related peaks, especially N1 and N2 were not identifiable (see Grand Means in Figure 4.1.2. and 4.1.3.), temporal area measures seemed to be more appropriate for these waveforms. For the early potentials mean voltages were assessed in two time windows, 160-220 ms and 220-280 ms. These data were submitted to repeated measures analysis of variance (ANOVA) including group (TBI-patients, healthy subjects) as the between factor. Repeated measurement factors were picture content (3 levels: pleasant, neutral, unpleasant), hemisphere (2 levels: left, right) and recording site (2 levels: parietal: P3, P4; occipital: O1,O2).

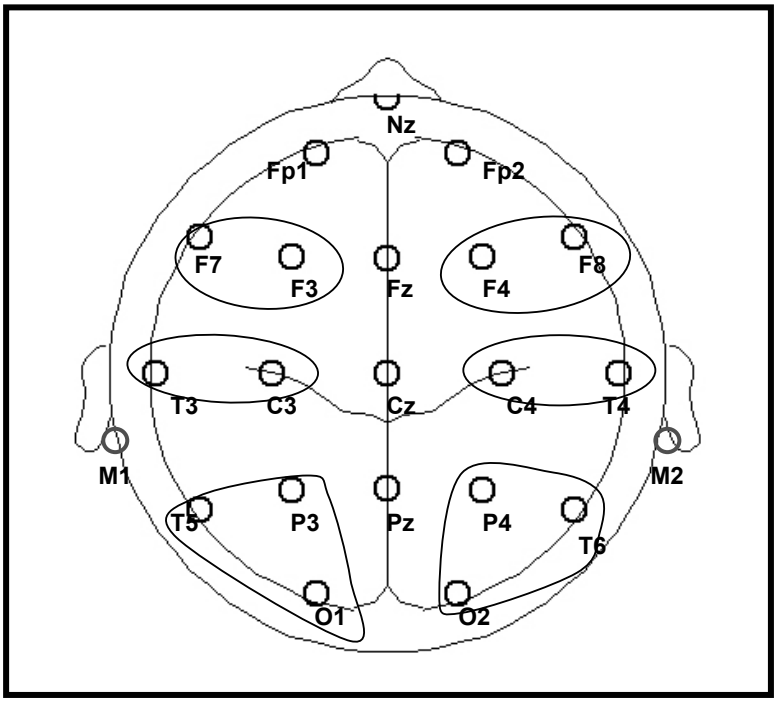

Fig. 4.1.1. Layout of the electrode array (Ve1, Ve2, Ho1 and Ho2 are not shown here). Encircled sites: channel clusters used for ANOVAs on late potentials

The positive going deflection around 300 ms, particularly visible at parietal and central sites, (see Figure 4.1.3.) was analyzed by means of two time windows: an early P300 window (280-350 ms) and a later P300 window (350-420). The ANOVA of the P300 related time intervals included a factor "recording site" with three levels: frontal (F3, F4), central (C3, C4) and parietal (P3, P4).

For the analysis of late potentials and the slow wave, mean amplitudes were computed for six time windows comprising a temporal interval from 450 ms up to 4 s after stimulus onset: 450-550ms,

550-650 ms, 650-1000 ms, 1-2 s, 2-3 s, 3-4 s. As shown in Figure 4.1.1., hemisphere-symmetrical clusters were formed around frontal, temporal and parieto-occipital recording sites. Mean voltages obtained in the relevant time windows were subject to a repeated measurements ANOVA consisting of the between factor group and the repeated measurement factors picture category (pleasant, neutral, unpleasant) hemisphere (left, right) and site (frontal, temporal, parieto-occipital).

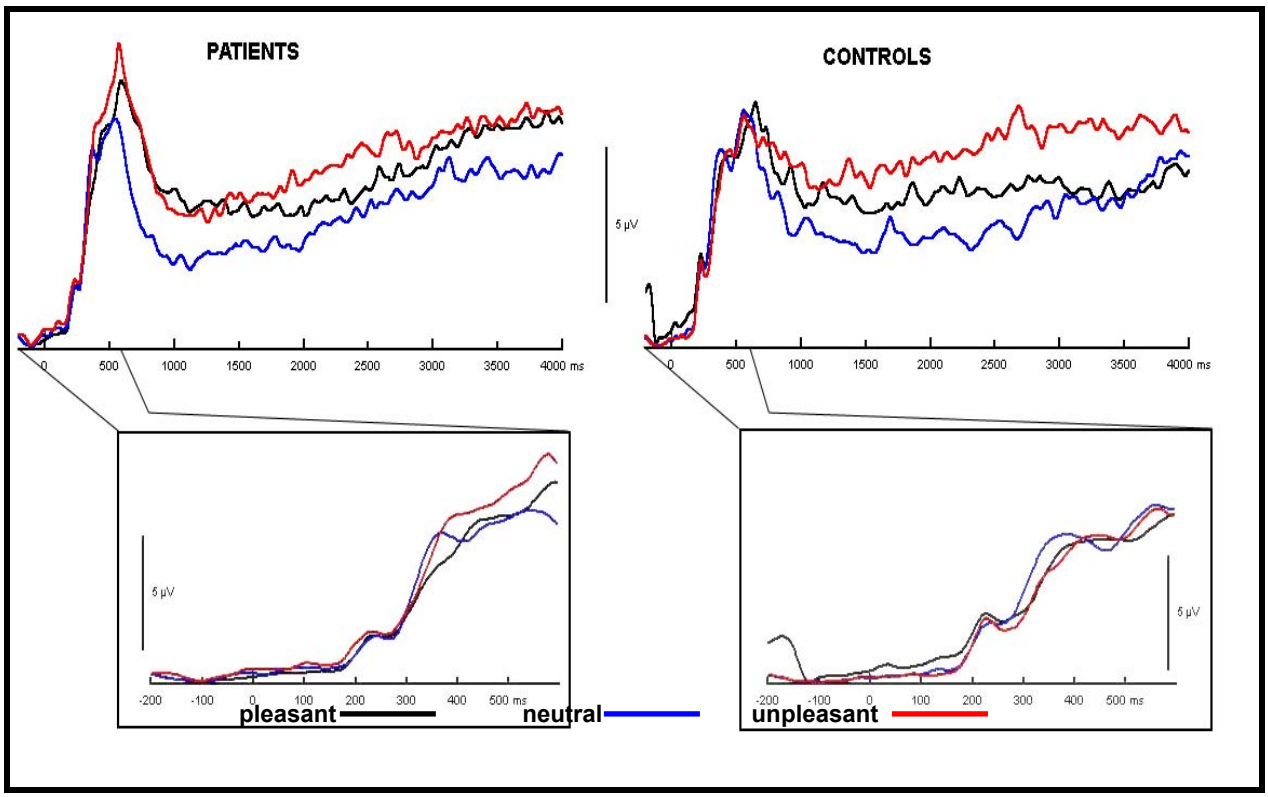

Fig. 4.1.2. Global field power obtained at 26 recording sites separately shown for patients and controls (ERP waveform for the whole 4s and underneath an excerpt of global activity of the first 600 ms)

The global field power curve, i.e., averaged electrical activity over all channels, trials and subjects, is shown in Figure 4.1.2., separately for each of the two participant groups. ERP traces at single electrodes corresponding to 26 sites of the international 10/20 system are shown in Figure 4.1.3. EEG data from one control subjects and one patient were contaminated with too many artefacts and thus had to be excluded from further analyses.

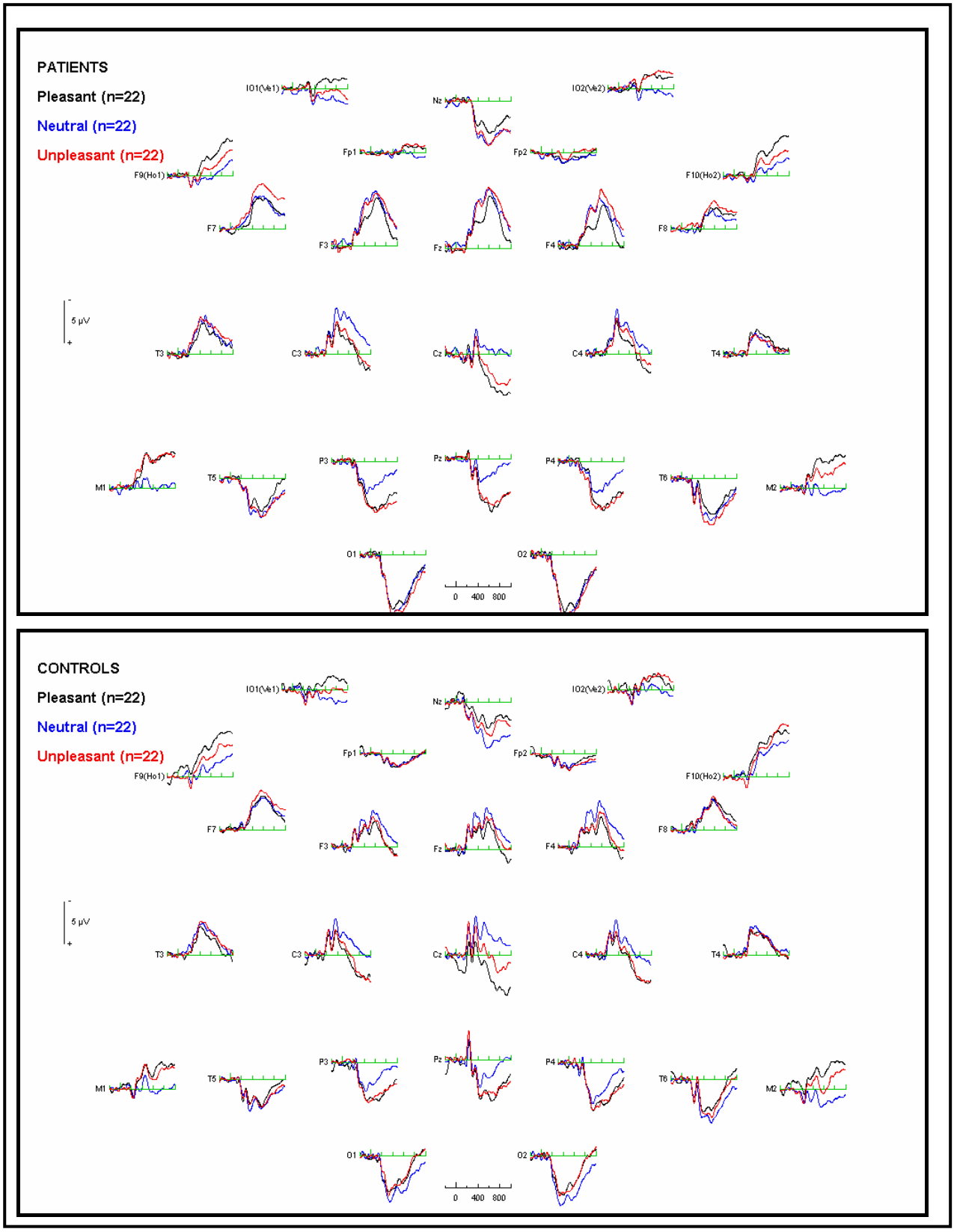

Fig. 4.1.3. Grand mean event related potentials (-200 to 1s) for each subject group at all electrodes corresponding to sites of the International 10/20 system. Note: Positive is down.

Early components

Mean voltage in the 160-220 ms time window did not show an overall effect of emotional content, but resulted in a Picture Category x Group effect (F(2.84)= 3.48, p< .05, Σ= .98). For healthy subjects, the expected posterior negative shift[1] after arousing pictures was visible only during viewing of unpleasant stimuli, whereas patients showed a negative deflection only in response to pleasant pictures. In post hoc analyses (Newman-Keuls test) simple differences did not reach statistical significance.

The 220-280 ms time window exhibited a Category x Site effect (F(2.84)= 3.61, p< .05, Σ= .96). Occipital sites showed a significant negative shift[1] for pleasant (post hoc: p< .05) and unpleasant (p< .01) content compared to neutral slides, whereas at parietal sites there was no discrimination between emotionally arousing and neutral pictures. The significant three way interaction Category x Hemisphere x Site (Figure 4.1.4.) revealed that differences at posterior sites related to picture content were more prominent in the right hemisphere.

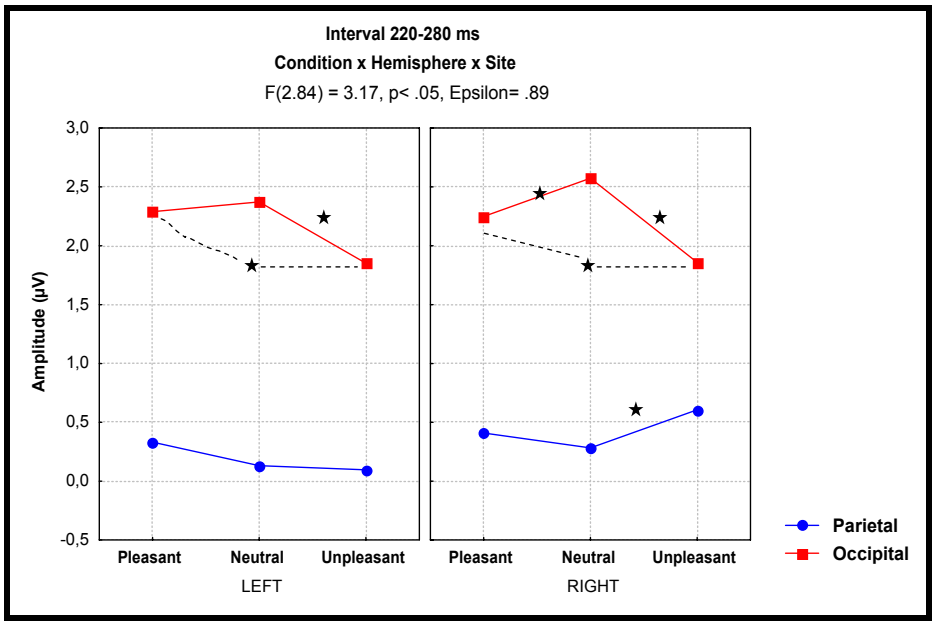

Fig. 4.1.4. Left- and right-hemispheric posterior sites: mean amplitudes in response to different emotional picture content (indicates statistically significant (p< .05) post-hoc comparisons between categories at each site)*

Post-hoc tests demonstrated that right-hemisphere occipital sites discriminated between emotional (pleasant and unpleasant) and neutral pictures whereas in the left hemisphere ERP amplitudes for

[1] The terms "negative shift", "negative deflection" and "negativity" as well as "positive shift", "positive deflection" and "positivity" do not necessarily indicate negative or positive amplitudes, but rather refer to a relative statement (e.g. a negative shift after unpleasant pictures compared to neutral contents)

pleasant pictures did not differ from those to neutral stimuli. In addition, there was an effect of valence on amplitudes at occipital sites in both hemispheres with pleasant slides producing a minor relative negativity compared to unpleasant pictures (post hoc: $p < .01$). The only significant difference at parietal sites could be found in the right hemisphere, where unpleasant pictures were associated with a greater positivity compared to neutral slides (post hoc: $p < .05$).

P300 windows

In both the early (280-350 ms) and the late (350-420 ms) P300 time windows pronounced main effects of picture category were found (early window: $F(2.84) = 15.5$, $p < .0001$, $\Sigma = .95$; Late window: $F(2.84) = 18.69$, $p < .0001$, $\Sigma = .90$). Across all selected scalp areas, P300 amplitude was significantly larger in response to affective pictures (pleasant and unpleasant) than during viewing of neutral slides (post hoc-difference: $p < .001$). A main effect of Site revealed that parietal sites contributed most to the overall positivity in both the early P300 ($F(2.84) = 69.76$, $p < .0001$, $\Sigma = .64$) and the late P300 window ($F(2.84) = 100.28$, $p < .0001$, $\Sigma = .69$). In addition, Picture Category x Site interactions resulted for both the early P300 ($F(4.17) = 3.19$, $p < .05$, $\Sigma = .56$) and the later P300 window ($F(4.17) = 4.24$, $p < .01$, $\Sigma = .56$) which showed that effects of picture content differed between electrode sites (see Table 4.1.1. for an overview on mean voltages). In the early 280-350 ms window, frontal and central sites showed a pronounced amplitude enhancement for pleasant and unpleasant, compared to neutral content (post hoc: $p < .001$), whereas activity at parietal sites did not discriminate between picture categories. In the late P300 window, additional differences related to emotional content became evident with pleasant pictures yielding higher amplitudes than unpleasant slides at frontal sites ($p < .01$). At parietal areas, an enhanced positivity for unpleasant slides compared to neutral stimuli ($p < .01$) could be observed in this later time interval.

Tab. 4.1.1. Mean Voltages (μV; and SE) in the two P300 windows, at 3 sites, for pleasant, unpleasant and neutral picture content

	Pleasant	**Neutral**	**Unpleasant**
Early P300 (280-350 ms)			
Frontal	-1.51 (0.35)	-2.67 (0.38)	-1.81 (0.30)
Central	-1.68 (0.34)	-2.71 (0.40)	-1.70 (0.34)
Parietal	1.74 (0.33)	1.65 (0.36)	2.18 (0.38)
Late P300 (350-420 ms)			
Frontal	-2.15 (0.42)	-3.78 (0.39)	-2.99 (0.49)
Central	-2.39 (0.42)	-3.73 (0.46)	-2.64 (0.48)
Parietal	3.04 (0.43)	2.60 (0.44)	3.52 (0.46)

Differences between subject groups resulted for the late P300 time window (350-420 ms). Figure 4.1.5. shows groups' mean amplitudes at each of the three analyzed sites for single slide categories.

Whereas at frontal and central sites, healthy subjects presented enhanced positivity during viewing of arousing slides, patients amplitudes showed a less clear cut response pattern. At frontal regions, patient did not exhibit the voltage amplitude enhancement for unpleasant slides, which did not statistically differ from neutral contents. Response to pleasant pictures, instead, was associated with a very pronounced positivity compared to both neutral and unpleasant slides (post hoc: $p < .01$). At central sites, patients showed overall reduced P300 amplitudes, exhibiting however a similar response pattern compared to controls' voltage means for each picture category.

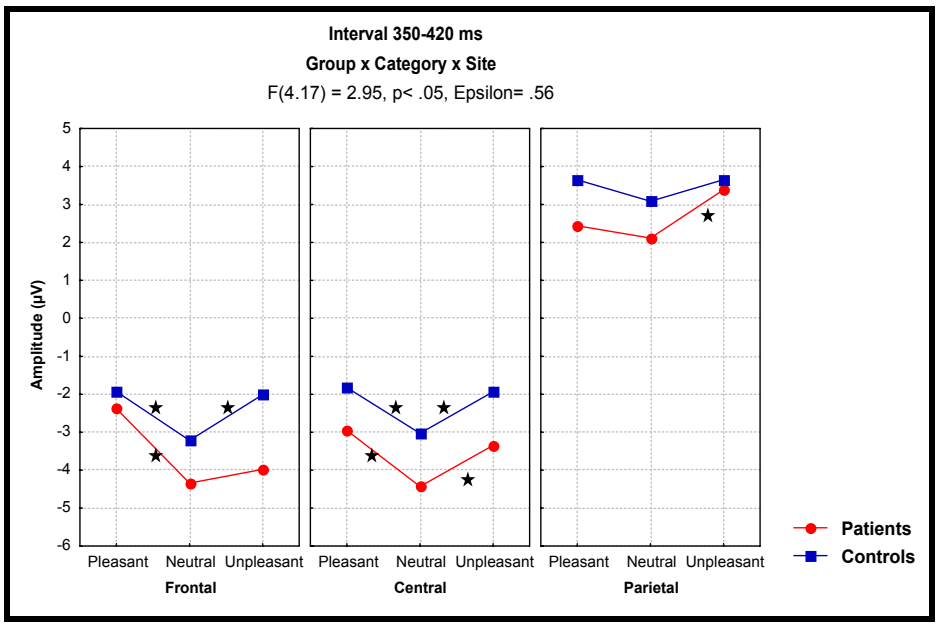

Fig. 4.1.5. Late P300 window: mean amplitudes of patients and controls at 3 sites for pleasant, unpleasant and neutral pictures (indicate statistically significant differences between categories within each group)*

At parietal areas, fewer differences between emotional contents became evident with only patients showing enhanced mean amplitude in response to unpleasant pictures compared to neutral slides ($p < .01$).

Groups further interacted with factors Hemisphere and Site ($F(2.84) = 4.4$, $p < .05$, $\Sigma = .67$) indicating that, in the right hemisphere, patients showed lower amplitudes compared to controls at all sites ($p < .05$), whereas in the left hemisphere groups differed only at frontal sites with patients' late P300 amplitude being markedly reduced compared to controls' response ($p < .01$).

Late potentials and slow wave

Time interval 450 ms - 1s

Separate ANOVAs on time windows 450-550ms, 550-650ms and 650-1000 ms resulted in a consistent main effect of Picture Category (F(2.84) =25.67, 20.6, 22.19, respectively for each time window). Post-hoc analyses revealed higher amplitudes in response to arousing pictures (pleasant and unpleasant) compared to neutral content. Furthermore, emotional valence had an effect on late potentials with pleasant pictures producing higher amplitudes than unpleasant slides (post-hoc: p< .001, p< .001, p< .05 respectively for each time window).

Emotional modulation differed also regarding electrode clusters, as revealed by significant interactions between Category and Site. Compared to frontal and posterior sites, at temporal areas voltage differences between arousing and neutral slides were more pronounced, especially in the late interval from 650 ms to 1 s (see Figure 4.1.6.). Whereas at temporal sites arousing pictures yielded more positivity compared to neutral slides (post-hoc p< .01), emotional content did not significantly modulate voltage changes in frontal and parieto-occipital scalp areas.

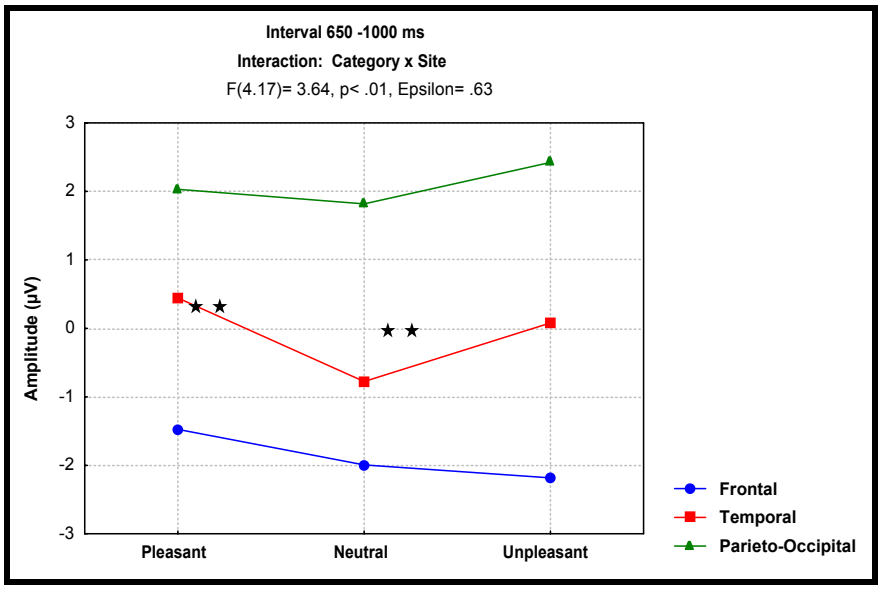

Fig.4.1.6 Mean amplitudes at frontal, temporal and parieto-occipital electrode clusters for each picture category

*(** indicate statistically significant (p< .01) post-hoc comparisons)*

Overall electrocortical responses to visual stimuli were slightly lateralized with enhanced amplitudes in the right hemisphere compared to mean voltage over the left hemisphere. In the 450-550 ms time window the main effect of hemisphere was significant (F(1.42) = 5.91, p< ,05) whereas in the following two time windows the effect reached only statistical trend level (p< .09 for the 550-650 ms area, p< .08 for the 650-1000 ms area). To get a detailed overview on amplitudes in the 450 – 1000 ms time windows, Table 4.1.2. lists mean voltages for pleasant, neutral and unpleasant picture content at each site of the left and right hemisphere.

Tab. 4.1.2. Mean Voltages (μV; and Standard Error) in the 450-550ms, 550-650ms and 650-1000ms time windows, at three regions in the left and right hemisphere for each of the three picture categories

	LEFT HEMISPHERE			RIGHT HEMISPHERE		
	Pleasant	Neutral	Unpleasant	Pleasant	Neutral	Unpleasant
450-550 ms						
Frontal	-2.82 (0.46)	-3.44 (0.42)	-3.80 (0.47)	-2.12 (0.45)	-2.96 (0.51)	-2.82 (0.39)
Temporal	-1.94 (0.38)	-3.24 (0.33)	-2.66 (0.36)	-1.48 (0.44)	-2.14 (0.40)	-1.74 (0.36)
Parieto-occipital	3.58 (0.57)	3.43 (0.53)	3.99 (0.50)	4.04 (0.48)	4.34 (0.40)	4.73 (0.50)
550-650 ms						
Frontal	-3.55 (0.54)	-4.04 (0.48)	-4.31 (0.55)	-3.06 (0.47)	-3.42 (0.50)	-3.90 (0.47
Temporal	-1.19 (0.30)	-2.72 (0.36)	-1.85 (0.41)	-1.04 (0.39)	-1.63 (0.37)	-1.26 (0,31)
Parieto-occipital	3.77 (0.56)	3.33 (0.50)	4.0 (0.52)	4.06 (0.54)	4.08 (0.41)	4.38 (0.53)
650-1000 ms						
Frontal	-1.69 (0.42)	-2.29 (0.40)	-2.54 (0.45)	-1.26 (0.43)	-1.70 (0.38	-1.83 (0.38)
Temporal	0.26 (0.35)	-1.16 (0.29)	-0.26 (0.37)	0.62 (0.37)	-0.39 (0.24)	0.42 (0.27)
Parieto-occipital	1.94 (0.44)	1.62 (0.35)	2.38 (0.42)	2.13 (0.44)	2.01 (0.33)	2.47 (0.46)

Differences between subject groups appeared in the very late time window from 650-1000 ms, (Group x Site interaction: $F(2.84)= 4.78$, $p< .05$, $\Sigma= .60$). At frontal sites, patients showed slightly reduced amplitudes compared to healthy subjects whereas their mean voltage at posterior sites was enhanced. Amplitudes at temporal sites did not discern between groups. Emotional picture content had an effect on groups mean amplitudes, as illustrated in Figure 4.1.7. Whereas responses to neutral slides did not differ between groups at any site, processing of arousing visual stimuli resulted in a diverse pattern for the two subject groups. Prominent differences resulted at frontal areas with patients showing an increased negativity during viewing of unpleasant slides ($p< .001$) and at parieto-occipital areas, where patients' mean voltages after pleasant ($p< .005$) and unpleasant pictures ($p< .001$) were visibly enhanced compared to responses of healthy subjects.

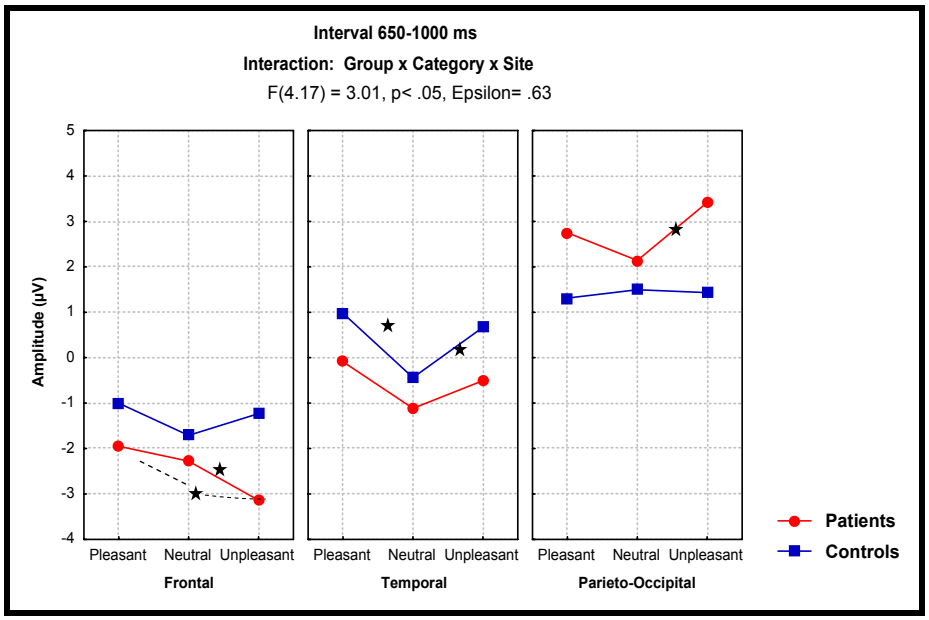

Fig.4.1.7. Mean amplitudes of patients and controls at frontal, temporal and parieto-occipital sites for each picture category (indicate statistically significant differences between categories within each group)*

At temporal sites, controls showed the typical activity pattern with enhanced amplitudes in response to arousing pictures compared to neutral ones ($p < .05$), whereas patients' mean voltages did not statistically differ between picture categories.

Time interval 1 – 4 s

For the analysis of the last three seconds of picture presentation, separate ANOVAs on mean voltages in time windows 1-2 s, 2-3 s and 3-4 s were conducted. As for earlier temporal areas, we again found the main effect of Picture Category ($F(2.84) = 14.27, 12.65, 8.18$, respectively for each time window). During the entire picture-viewing period, arousing pictures (pleasant and unpleasant) were followed by enhanced amplitudes compared to neutral content. In this very late stage of slide processing, valence had no effect on overall mean voltages, though emotional modulation differed with respect to recording site. Over the whole 3 s period, the interaction between Category and Site remained significant ($p < .0001$ for each time window). At temporal sites, pleasant and unpleasant pictures yielded a much greater positivity than neutral slides (post-hoc $p < .001$). At frontal areas, this effect resulted only for pleasant pictures in the 2-3 s time window, whereas at posterior sites voltage differences between picture categories never reached significance.

Hemisphere effects became increasingly evident during the last three seconds of picture presentation. Table 4.1.3. provides an overview on mean voltages in the three latest time windows for each condition and electrode cluster, separately for left and right hemisphere.

Tab. 4.1.3. Mean Voltages(μV; and Standard Errors) in the 1-2 s, 2-3 s, 3-4 s time windows, at three regions in the left and right hemisphere for each of the three picture categories

	LEFT HEMISPHERE			**RIGHT HEMISPHERE**		
	Pleasant	Neutral	Unpleasant	Pleasant	Neutral	Unpleasant
450-550 ms						
Frontal	-0.05 (0.32)	-0.91 (0.37)	-0.72 (0.35)	0.65 (0.32)	-0.07 (0.33)	0.21 (0.39)
Temporal	0.93 (0.35)	-0.47 (0.28)	1.05 (0.35)	1.50 (0.30)	0.32 (0.24)	1.58 (0.27)
Parieto-occipital	0.06 (0.29)	0.46 (0.27)	0.43 (0.27)	0.05 (0.35)	0.49 (0.28)	0.01 (0.39)
550-650 ms						
Frontal	0.29 (0.39)	-0.59 (0.46)	-0.19 (0.39)	1.37 (0.37)	0.44 (0.45)	0.70 (0.46)
Temporal	1.18 (0.37)	-0.41 (0.35)	1.58 80.40)	1.89 (0.35)	0.64 (0.28)	0.31 (1.43)
Parieto-occipital	-0.41 (0.32)	0.13 (0.30)	-0.11 (0.27)	-0.66 (0.33)	-0.15 (0.35)	-0.81 (0.43)
650-1000 ms						
Frontal	0.36 (0.52)	-0.57 (0.50)	-0.22 (0.44)	-0.74 (0.37)	0.93 (0.52)	0.73 (0.52)
Temporal	1.90 (0.43)	-0.56 (0.40)	1.65 (0.47)	1.46 (0.34)	0.87 (0.32)	2.39 (0.35)
Parieto-occipital	-0.74 (0.38)	-0.12 (0.33)	-0.22 (0.35)	2.19 (0.40)	-0.38 (0.38)	-0.95 (0.45)

A significant Hemisphere x Site interaction resulted for each of the 1s time windows ($F(2.84) = 3.65, 4.98, 4.86$, respectively for single intervals). Post-hoc analyses revealed that both at frontal and temporal sites amplitudes over the right hemisphere were enhanced compared to left

hemisphere voltage means, whereas no such lateralization became apparent at parieto-occipital areas.

During this very late stage of picture presentation differences related to the processing of distinct emotional contents were clearly evident between TBI patients and healthy subjects. The interaction between Group, Picture Category and Site remained significant over the whole 3 s period (see Figure 4.1.9. for statistical details). Post-hoc analyses revealed that most prominent differences resulted at parieto-occipital sites, where only control's mean amplitudes were modulated by emotional content. In response to unpleasant and pleasant pictures, healthy subjects showed an enhanced negativity compared to neutral slides, whereas no distinctions between picture categories became evident for patients. This effect is also visible in Figure 4.1.8, which maps surface activity for each group and picture condition in the 1-2 s time window.

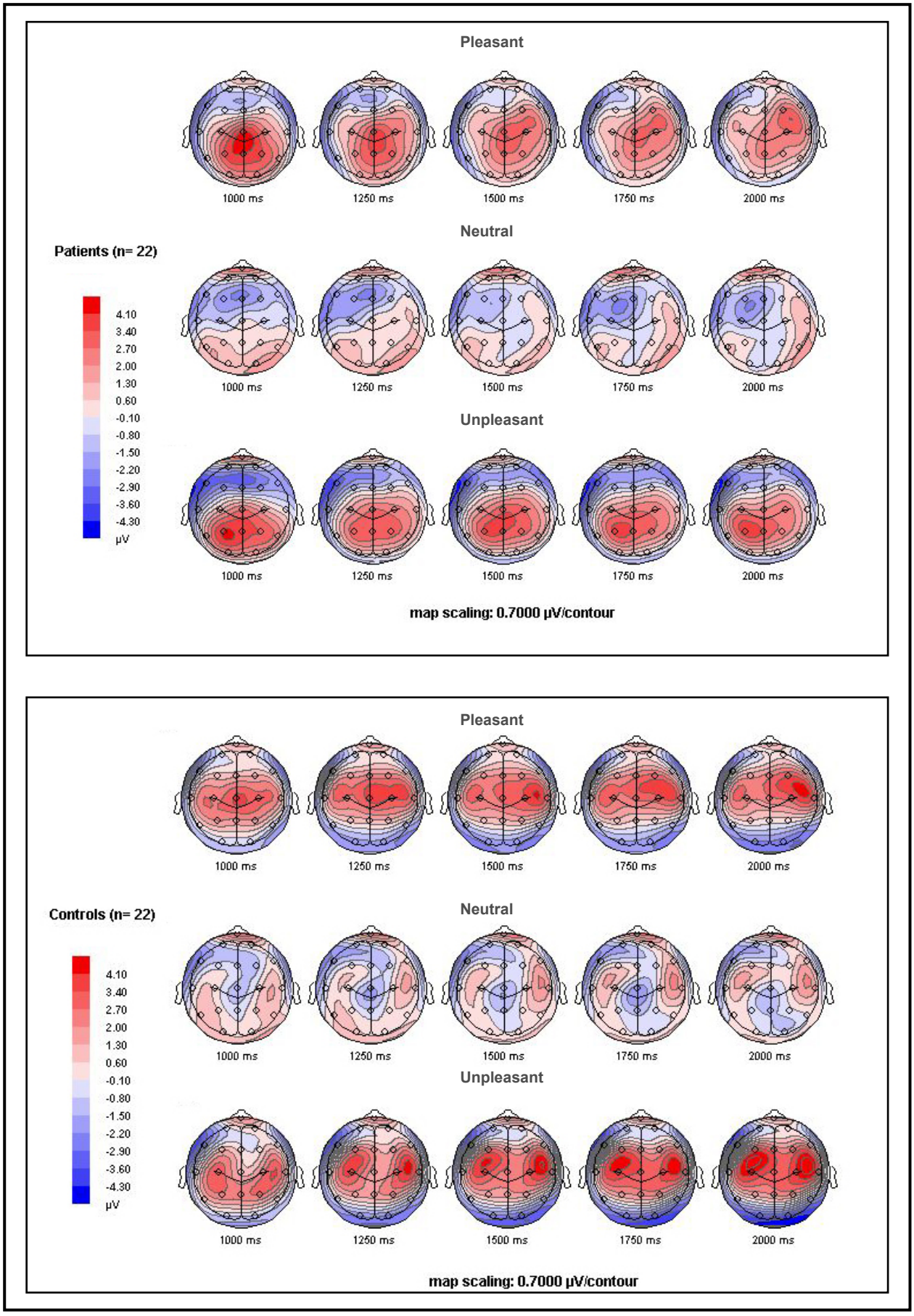

Fig 4.1.8. 1-2 s following picture onset: Grand mean topography of surface activity for pleasant, neutral and unpleasant picture content, shown separately for patients (on top) and controls

At frontal sites, differences between categories did not reach statistical significance, whereas clear group related distinction are visible (see Fig. 4.1.8). Controls showed an enhanced late positivity during viewing of arousing slides, whereas patients exhibited this effect to a minor extent only for pleasant pictures, but not for unpleasant slides. In fact, the only relevant difference between groups at this scalp area resulted for unpleasant content, where patients showed a noticeably reduced positivity compared to controls (post-hoc p< .01).

At temporal sites, both subject groups showed a rather similar pattern of emotional processing exhibiting a significantly larger negativity in response to arousing stimuli compared to neutral content. Group differences at this area resulted for pleasant and unpleasant categories with patients showing less positive amplitudes compared to healthy persons (post-hoc p< .05). It is important to note, that in no time window and at no site groups differed with respect to neutral content. Figure 1.4.9. provides a graphical overview on groups' processing of distinct emotional contents at each site in the three latest time windows.

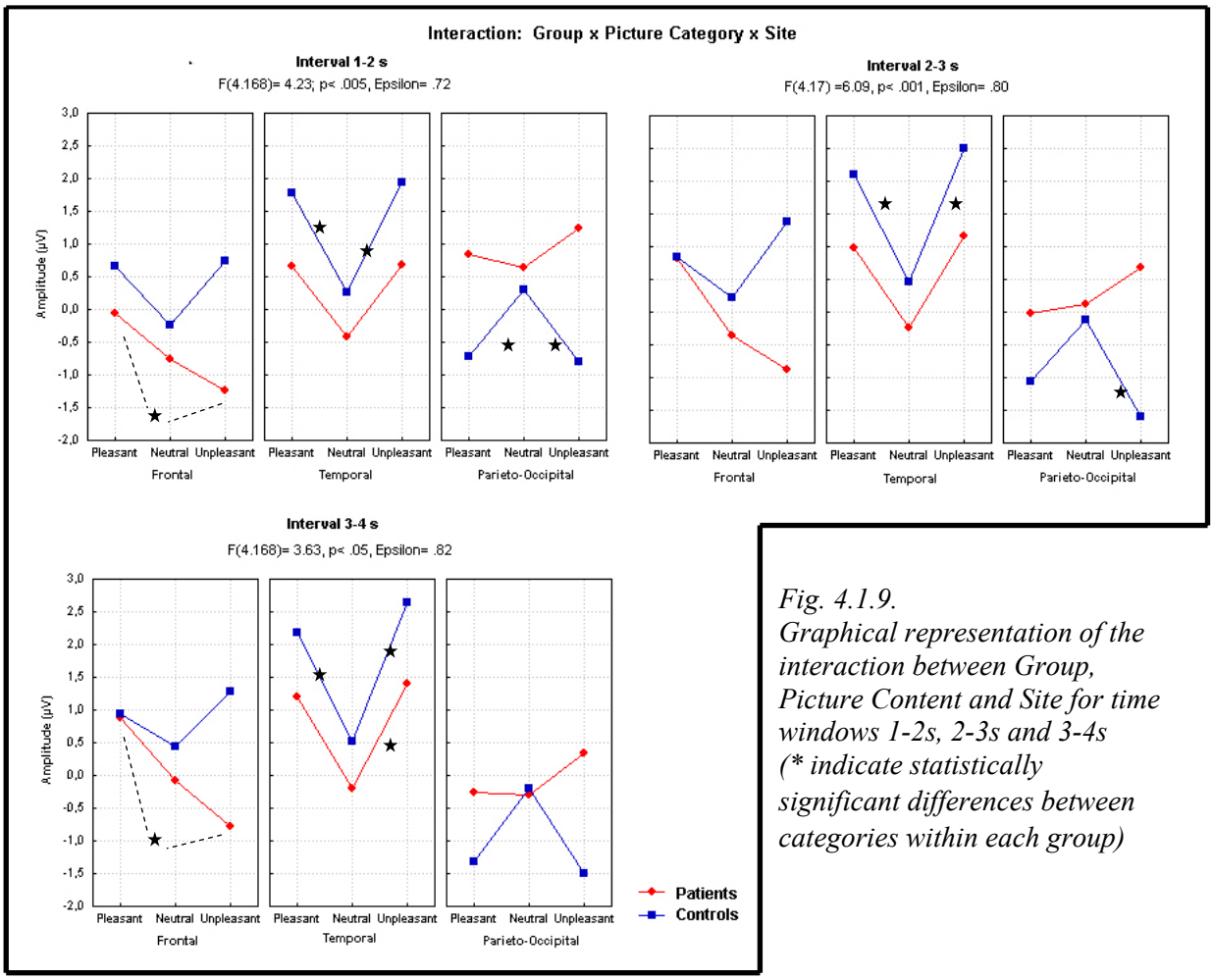

Fig. 4.1.9. Graphical representation of the interaction between Group, Picture Content and Site for time windows 1-2s, 2-3s and 3-4s (indicate statistically significant differences between categories within each group)*

In summary, ERPs during affective picture viewing showed that the early differentiation between arousing and neutrals slides did not differ between TBI patients and healthy subjects. Later components including P3 and slow wave were, instead, characterized by prominent differences between the two participant groups. The P3 amplitude enhancement in response to arousing slides was more pronounced in control subjects compared to patients. Furthermore, the P3 was generally reduced in brain injured subjects and, at frontal sites, did not show any significant enhancement for unpleasant pictures. Slow wave potentials revealed differences between patients and controls that were strongly related to emotional relevance of stimuli. Later electrocortical responses of TBI patients showed a consistent lack of arousal-related modulation, over parieto-temporal regions as well as at posterior sites where no voltage differences between emotionally salient and neutral pictures could be found. The frontal slow wave of brain injured subjects was modulated by emotional valence with only pleasant pictures evoking a similar sustained late positivity as in healthy subject.

Discussion

The early selective discrimination of emotionally arousing stimuli from less affective content over posterior areas is in line with a finding by Junghöfer et al. (2001) who reported an enhanced N260 peak for arousing pictures compared to neutral slides. Studies by Keil et al. (2001, 2002) and Pizzagalli, Regard and Lehmann (1999) revealed that emotion discrimination occurred at even earlier stages of picture processing at around 100-150 ms following stimulus presentation. The present data thus provides further evidence for a very rapid allocation of motivated attention as proposed by Lang (1994). In previous studies, these early ERP differences were found to be either unaffected by stimulus valence or more associated with pleasant stimuli (Keil et al., 2002; Pizzagalli et al., 1999). However, in the present investigation, unpleasant pictures evoked the strongest negative shift. Considering that rapid recognition of emotionally salient cues in the environment plays a decisive role in evolutionary adaptation, a faster detection of unpleasant or threat-related stimuli would make sense. A rapid and appropriate identification of dangerous cues is, in fact, more essential for survival compared to the recognition of equally arousing pleasant cues. This view is supported by some earlier human studies demonstrating that perception of threatening and fearful stimuli can take place outside the realm of consciousness, in an automatic and pre-attentive way (Hansen & Hansen, 1988; Öhman & Soares, 1994). One might also argue that the early emotion discrimination is due to formal visual characteristics, such as brightness and complexity of the different picture categories. However, Junghöfer et al. (2001) demonstrated that

ERP differences were independent of formal properties of IAPS pictures, including color, brightness, complexity and spatial frequency. The fact that early potentials revealed no differences between TBI patients and healthy controls indicates that the ability to discriminate emotions at this very early stage of visual processing is not impaired following traumatic brain damage. However, because the present thesis is the first study to record ERPs to emotional pictures in TBI patients, this interpretation should be regarded with some caution. Replication in further samples of brain injured patients is necessary before one can draw a valid conclusion.

P3 activity in healthy subjects, replicated comparable studies with arousing pictures evoking an enhanced positivity compared to neutral content (Cuthbert et al., 2000; Palomba et al., 1997; Schupp et al., 2000). Although overall P3 amplitudes were most prominent over the parietal region, the arousal-modulated effect was strongest over fronto-central sites. This finding can be interpreted in terms of motivated attention: Intensification of the P3 component reflects the allocation of more attentional resources to motivationally relevant stimuli whereas less attention is directed to neutral stimuli that are of minor significance. As emotional valence did not affect P3 activity, the mobilization of resources to arousing pictures at this stage seems to take place regardless of whether the motivational direction is appetitive or aversive.

With respect to this processing phase, two main results emerged from the comparison between TBI patients and healthy subjects. First, P3 amplitudes were generally lower in patients, independently of emotional arousal and valence. Second, brain injured subjects showed a poorer discrimination of unpleasant pictures as indicated by the missing amplitude enhancement for this slide category over frontal areas. The result that overall P3 activity was attenuated in the patient group is consistent with a number of studies reporting a decrease in P3 amplitude in head injured patients (Curry, 1980; Pratap-Chand et al., 1988, Rugg et al, 1988). Given that the P3 component indexes the allocation of attentional resources to stimulus evaluation, these findings suggest that attention speed and resources are limited in patients with TBI, irrespective of whether the specific stimuli are motivationally relevant or not. This indication of lowered attentional capacities in the present clinical sample may seem rather surprising given that the neuropsychological screening did not reveal such a deficit. However, both of the cognitive tasks that were used here to assess attention measured graphomotor speed and visual search capacities, are not well comparable to the aspect of attention the P3 component refers to and, thus, may result in contradictory performances.

Patients did not show the typical P3 pattern at frontal sites: there was a specific impairment in discriminating unpleasant pictures. This is a first indication of an emotion processing deficit associated with TBI that became even more visible during later stages of picture processing. The

specific P3 reduction in response to only unpleasant slides suggests that traumatic brain lesions can affect elaboration of pleasant and unpleasant pictures in a discriminatory manner. In consideration of the fact that orbitofrontal cortices were particularly damaged in the present patient group, the impaired responses to unpleasant pictures are in accordance with functional imaging studies arguing for a stronger involvement of the orbitofrontal cortex in the processing of unpleasant stimuli compared to pleasant ones (George et al., 1995; Northoff et al., 2000). Both of these experiments showed that enhanced brain activation evoked by positive stimulation was localized in the lateral prefrontal cortex. Thus, in our clinical sample, responses to pleasant pictures might be less affected because lateral prefrontal areas were damaged to a minor extent.

Late potentials and slow-wave activity confirmed the main effect for the P3 component with emotional pictures prompting a pronounced late positive potential maintained during the entire period of picture presentation (4s). For non-emotional slides, such an enhanced positivity was not observed. This result agrees with previous studies reporting a sustained positive slow wave selectively in response to arousing pictures (Cuthbert et al., 2000; Diedrich et al., 1997; Schupp et. al., 2000). Similar to Cuthbert et al. (2000), in the present research, slow positive potentials increased from frontal to temporo-parietal sites and, thus, might be interpreted as depending on the same neural generator which mediates the parietal P3. Thus, the present findings do not support the hypothesis of Diedrich et al. (1997) that P3 and the positive slow wave showing a maximum at frontal sites reflect distinct aspects of information processing. Rather, it can be assumed that the sustained positivity seen here indexes continued perceptual processing which is strongly modulated by emotional salience. This conclusion is supported by Schupp and co-workers who recorded ERPs to brief noise probes presented during presentation of affective pictures (Schupp, Cuthbert, Bradley, Birbaumer & Lang, 1997). The authors reported that P3 magnitude to acoustic probes was larger during neutral than during arousing pictures thus indicating that more attentional resources were dedicated to emotionally salient pictures during the entire picture presentation period of 6 s.
In addition to the arousal effect on the late positive potential, ERPs were also affected by stimulus valence with pleasant pictures evoking greater positivity compared to unpleasant slides for most of the first second after picture onset. Cuthbert et al. (2000) could reveal a similar effect, whereas most of the mentioned studies did not find a slow wave modulation by affective valence.

A stable hempisheric asymmetry for the fronto-central positive potential was found that remained sustained during the whole late picture viewing epoch (500 ms- 4s). Over right hemispheric sites, late positivity during picture viewing was generally enhanced compared to the left hemisphere. This

right hemispheric preponderance for emotional as well as neutral pictures was also reported by Keil et al. (2002) and can be interpreted as being related to picture perception per se rather than to the affective relevance of stimuli. Therefore, the present result can not provide any evidence for the assumption of a particular hemispheric specialization for emotion as stated, for example, by the right hemisphere theory (Borod, 1992) or the valence hypothesis (Davidson et al., 1994). Rather, our data argue for unspecific right-hemisperic dominance in attentional perceptual processing. Support for this view comes from studies proposing a predominant role of the right hemisphere, relative to the left, in the network mediating attention (Posner & Dehaene, 1994).

At occipital sites, a sustained negative slow wave was observed during the last three seconds of picture viewing that was evidently enhanced for arousing compared to neutral slides. This enhanced posterior activation selectively in response to emotional stimulation is strongly supported by other ERP investigations (Keil et al., 2002) as well as studies using fMRI during affective picture processing (Lane et al., 1997; Lang et al., 1998). The latter experiments found the greatest activity for emotional slides in the occipito-temporal cortex, suggesting that, given the low temporal resolution of fMRI, these signals may primarily reflect slow wave EEG activity. These results, together with the evidence from the present study, indicate that modulation of the posterior negative slow wave by emotional arousal may reflect sustained visual processing which is strongly influenced by the allocation of attention to emotionally salient stimuli.

Slow wave potentials revealed prominent differences between TBI patients and healthy controls arguing for an impaired discrimination of emotional pictures in the clinical sample. For the entire late picture viewing period from 650 ms – 4s, the late positive potential over parieto-temporal areas which in healthy subjects was greatly enhanced for arousing slides, did not show significant differences between affective and calm pictures in patients. From this, it can be concluded that, whereas healthy subjects continued to allocate attentional resources to affective pictures during the entire picture presentation period, brain injured patients failed to show a sustained attentional processing modulated by emotional salience. The absent enhancement of the late negativity over posterior areas in the TBI group provides further evidence for this assumption. Compared to healthy subjects, brain injured patients showed a greatly reduced level of visual processing for emotionally arousing and motivationally salient slides.

TBI patients' frontal slow waves reflect the pattern that was already evident for the P3 component. Whereas pleasant pictures evoked an enhanced positivity, no such effect could be observed for

unpleasant slides, thus providing further evidence for the assumption that TBI patients with mostly orbitofrontal lesions have a particularly severe deficit in processing unpleasant stimuli.

Thus, P3 component and the subsequent slow wave differ in TBI patients, but not early ERP patterns. One possible explanation for this discrepancy may be that early and later event related responses reflect qualitatively distinct processing stages that are related to specific neuroanatomical substrates and, as a consequence, are differently vulnerable to traumatic brain lesions. Although early (around 200 ms) ERPs discriminate between emotional and neutral stimuli, they may reflect some initial, pre-attentive processing limited to conceptual stimulus features. This assumption is supported by the fact that in the present study, early effects were recorded at posterior sites over the visual cortex. Other studies who located the activity sources for this early activity in the primary and secondary visual cortices, confirm this finding (Junghöfer et al., 2001). It is further presumed that early perceptual processes are particularly modulated by the amygdala, since this brain structure receives reciprocal connections from the visual cortex (see Figure 4.1.10.). Evidence from human lesion studies revealed that after amygdala damage, a visual perceptual enhancement for emotional items is abolished (Anderson & Phelps, 2001). The fact that in the present patient group, the amygdala was not found to be affected by the traumatic brain damage might account for the intact early ERP discrimination of emotional stimuli in our patient group.

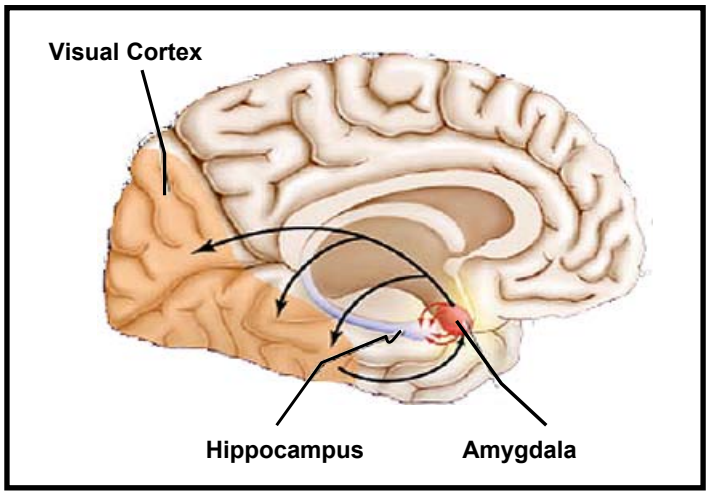

Fig. 4.1.10. Emotional-perceptual circuit in the human brain. Through extensive connections to the visual cortex, the amygdala has a modulatory effect on ***early*** *object perceptual processing.*

(adapted from Dolan, 2002)

Later EEG components like P3 and slow wave, are assumed to index conscious cognitive analysis whereby attention is selectively directed towards emotionally salient environmental cues. Several imaging studies have demonstrated the importance of orbitofrontal/prefrontal cortex during conscious processing of pleasant and unpleasant stimuli (Lane et al. 1997; Northoff et al., 2000; Reiman et al., 1997). These areas of the frontal lobe seem especially important in relating

information about external sensory stimuli to interoceptive information that represents emotional significance. Consistent with this, there is evidence from animal research showing that responses of prefrontal areas in monkeys are modulated on the basis of the rewarding stimulus, independent of its perceptual features (Rolls, 1999). Taken together, this supports the assumption that slow wave EEG activity in response to emotional pictures might be especially modulated by prefrontal/orbitofrontal cortical areas.

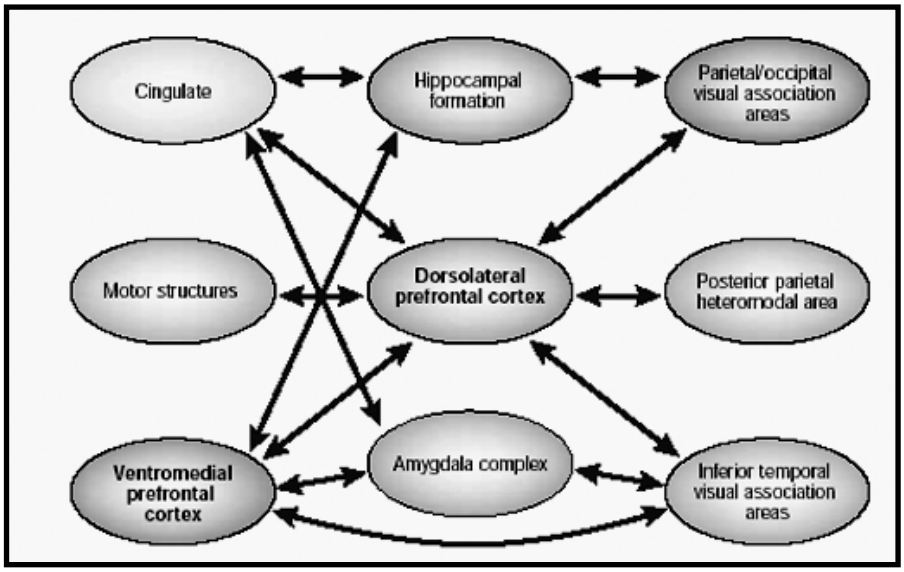

Fig. 4.1.11. Connectivity between prefrontal cortex and other brain regions; Both dorsolateral and ventromedial prefrontal areas are reciprocally connected with visual association areas.

(adapted from Wood & Grafman, 2003)

Given the extensive reciprocal connections between the prefrontal cortex and visual cortex, as illustrated in figure 4.1.11., this modulation may also influence the visual processing pattern recorded over the visual cortex (for a review, see Wood & Grafman, 2003). Thus, the consideration that all patients of the present clinical group showed prefrontal lesions which in most cases were rather extensive, may account for their substantial deficit to differentiate between emotionally relevant pictures and neutral content as indicated by late ERPs findings.

4.2. Skin Conductance Response

Electrodermal activity represented by maximum and mean skin conductance response to each slide was averaged across stimuli belonging to the same picture category (pleasant, neutral, unpleasant). Resulting mean scores were analyzed by an ANOVA with the between factor group (patients and controls) and the repeated measurement factor picture category. Only the first 48 trials were included with the intention to exclude habituation to affective slide contents. Data from 7 control subjects and 2 patients had to be excluded from analyses as a result of instrument and processing problems during SC-recordings.

Mean Skin Conductance Response

For mean skin conductance response a main effect of picture category was observed with emotional slides eliciting higher SCR-Amplitudes than neutral ones (see Fig. 4.2.1.). Post hoc tests revealed statistically significant differences between pleasant and neutral pictures ($p < .005$) and between unpleasant and neutral stimuli ($p < .05$). Although pleasant slides seemed to elicit a higher SC response than unpleasant ones, this discrepancy did not reach significance ($p < .08$).

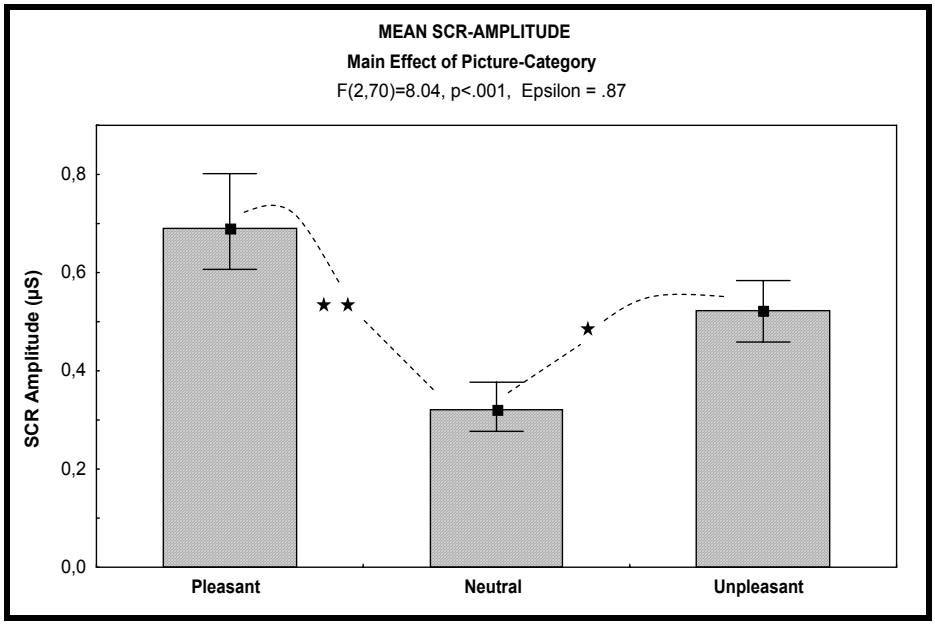

Fig 4.2.1. Mean Amplitude of skin conductance response (SCR) for each picture category (mean +/- standard error)
*(* indicate post-hoc significance p< .05; ** indicate significance p< .01)*

Mean amplitude of skin conductance responses did not significantly differ between the two participant groups. Scatterplots in Figure 4.2.2. illustrate SCR amplitudes of individual patients and controls elicited by each stimulus condition. Except for single outliers, data of the two groups show a quite similar distribution, irrespective of picture category.

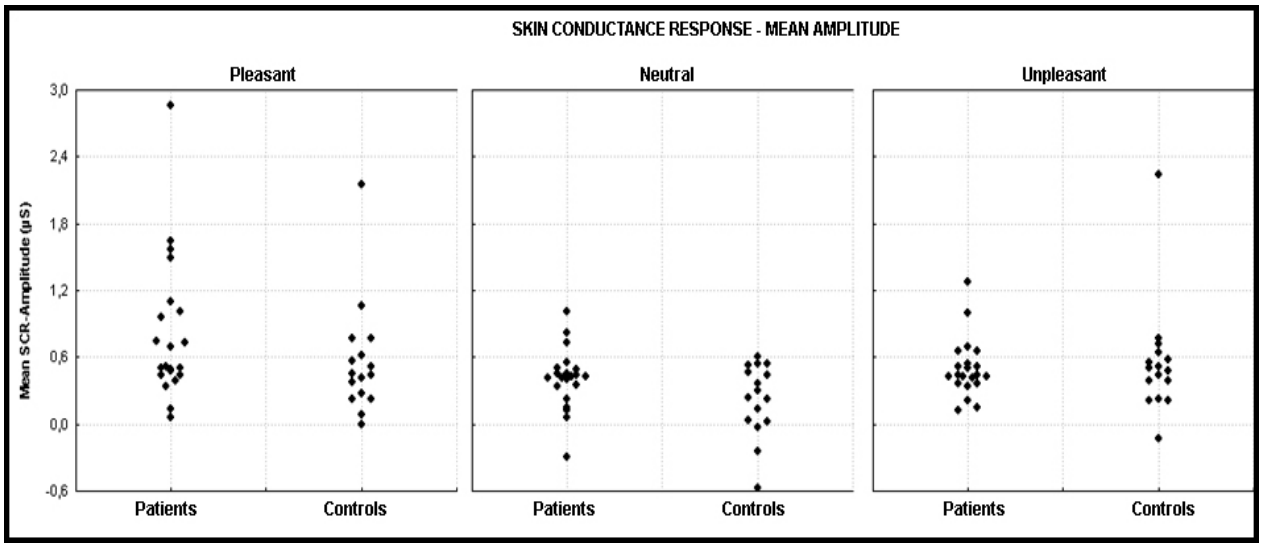

Fig. 4.2.2. Mean SCR-Amplitude for individual subjects in each group. Values are separately presented for each picture category (pleasant, neutral, unpleasant)

Maximal Skin Conductance Amplitude

The peak of skin conductance amplitude during the 1 to 5 s post stimulus period significantly differed between picture categories ($F(2.70)= 6.64$; $p< .005$) with pleasant slides eliciting a higher peak amplitude than neutral (post-hoc: $p< .005$) and unpleasant pictures ($p< .05$). Although a difference can be observed between maximal skin conductance response to unpleasant pictures (mean: 1.44 µS) and neutral slides (mean: 1.16 µS), it does not reach statistical significance ($p< .09$). No significant effects including the variable "group" could be found. Table 4.2.1. provides an overview on peak SCR amplitudes of patients and controls obtained for each of the three picture categories.

Table 4.2.1. Maximal SCR-Amplitudes (and standard errors) of participant groups for each condition

	Peak SCR-Amplitude		
	Pleasant Pictures	**Neutral Pictures**	**Unpleasant Pictures**
Patients (N = 21)	1.98 (0.39)	1.35 (0.27)	1.42 (0 .27)
Controls (N = 16)	1.67 (0.35)	.91 (0.21)	1.48 (0.30)

Thus, SC responses did not reveal any differences between TBI patients and healthy subjects. In both groups, mean and maximal skin conductance responses (SCRs) were substantially larger for emotionally salient pictures (pleasant and unpleasant) as compared to neutral stimuli.

Discussion

The present data confirm a series of studies reporting that the magnitude of SCR, which indexes sympathetic nervous system activation, is significantly influenced by the arousal level of the presented pictures (Bradley et al., 2001; Codispoti et al., 2001; Cuthbert et al., 1996). With respect to the importance of stimulus valence for electrodermal responses, empirical evidence is rather equivocal. The present findings suggest that pleasant stimuli evoke stronger SC responses than unpleasant picture, which is in agreement with a recent finding by Cuthbert and colleagues (2001). Furthermore, in the present thesis, stronger processing of pleasant slides was also indicated by a larger late positive potential for this stimulus category. Other investigations have revealed an opposite pattern with unpleasant slides eliciting the largest skin conductance changes (e.g. Bradley et al., 2001). The latter study also investigated different content groups within the category of pleasant pictures and came to the conclusion that only very explicit erotic contents, such as erotic couples and opposite-sex erotica, led to noticeably enhanced SC responses. Thus, the fact that in the present investigation, 14 out of the 25 pleasant IAPS pictures involved erotic stimuli (see Appendix A), could be a possible reason for the large increment of electrodermal responses to pleasant slides. In terms of Lang's model on emotion, these findings on appetitive motivation suggest that a specific threshold of motivational activation is necessary before greater sympathetic activity is initiated and that personally highly relevant cues, such as erotic stimuli, may be needed to prompt strong sympathetic engagement. Consistent with this notion, Bradley et al. (2001) demonstrated that other pleasant picture contents rated as similarly arousing (e.g. adventure, extreme sports) failed to evoke equally large SC responses. Furthermore, given that the present sample contained nearly only males, an influence of gender can be assumed to account for the valence effect with men showing more aroused responses to pleasant, especially erotic content. This view is consistent with recent fMRI study that revealed more pronounced cortical activation during presentation of pleasant material in men compared to women (Lang et al., 1998; Wrase, Klein, Gruesser, Hermann et al., 2003).

Contrary to our predictions, TBI patients did not show an attenuated SCR during viewing of arousing slides. Though no similar experiment with a comparable clinical sample of traumatic brain injured patients has been published so far, evidence from human lesion studies argues in favor of an impairment of SC activation following damage to the frontal lobes. Tranel and Damasio (1994) and Zahn et al. (1999) investigated electrodermal responses to IAPS pictures in patients with lesions of various parts of the frontal cortices and revealed that patients' SC responses to arousing stimuli were evidently attenuated or even completely absent. An analogous finding was described by

Angrilli and co-workers (1999) who reported a lower autonomic response to emotional pictures in a single TBI patient with a circumscribed damage to the right orbitofrontal and anterior cingulate cortex.

A possible explanation to the discrepancy between these results and the unimpaired electrodermal activation in TBI patients found in the present investigation could be the important differences regarding the exact lesion location in the respective clinical samples. Whereas patients in the Tranel and Damasio study (1994) and the Zahn et al. (1999) study had lesions comprising the anterior cingulate cortex, in no single patient was the anterior cingulate gyrus affected in the present investigation. Even more importantly, both earlier studies came to the conclusion that bilateral and unilateral lesions of the anterior cingulate cortex were particularly effective in producing deficits of SC responding. Findings demonstrated that neither ventromedial prefrontal nor orbitofrontal lesions alone were sufficient enough to cause electrodermal hyporesponsivity to emotional pictures. In light of these considerations, the unimpaired SC response of patients in the present study provides further evidence for the assumption that the anterior cingulate cortex plays a decisive role in SC modulation.

4.3. Subjective evaluation and recall of emotional material

SAM-ratings and performance on the incidental free-recall task were analyzed with a repeated measurement analysis of variance (ANOVA) including picture category (pleasant, neutral and unpleasant) as repeated measurement factor and "group" as between factor.

Self Assessment Manikin (SAM) Ratings

Data from three patients could not be utilized for analyses as their errors during questionnaire completion made scoring impossible.

SAM-Arousal ratings differed as a function of picture content ($F(2.82) = 101.39$, $p < .0001$, $\Sigma = .82$) with higher ratings for both pleasant pictures and unpleasant pictures than for neutral pictures (post hoc $p < .0001$). Emotional valence did not show any effect on arousal ratings; unpleasant and pleasant slides yielded similar scores. Patients generally rated pictures as less arousing than controls ($F(1.41 = 6.13$, $p < .05$) with brain injured subjects attaining an average rating score of 4.35 (S.E. = .21) and healthy subjects realizing an average of 5.05 (S.E.= .19). As illustrated in Figure 4.3.1., the two groups particularly differed with respect to unpleasant pictures (post-hoc $p < .01$), although the interaction between group and picture category did not reach clear statistical significance ($p<.057$).

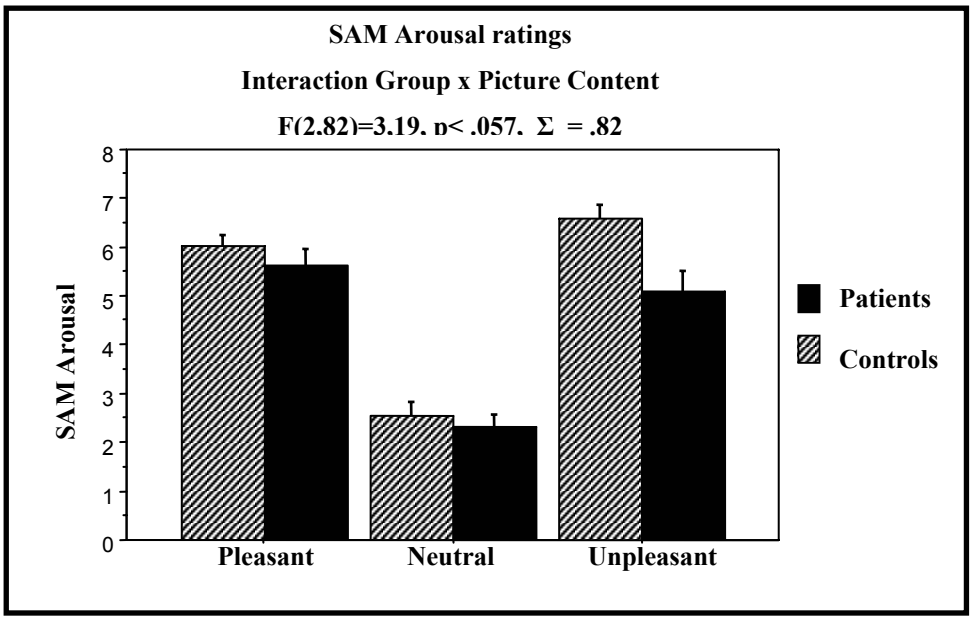

Fig. 4.3.1 . Mean SAM Arousal ratings (and standard errors) of participant groups for each picture category

With regard to SAM valence ratings, the expected main effect for picture category could be observed (F(2.82) = 181.65, p< .0001, Σ = .96). Unpleasant pictures were judged to be significantly less pleasant than neutral pictures (post-hoc p< .0005), which were in turn rated less positively than pleasant pictures (post-hoc p< .0005). Patients scored slides as less pleasant than controls (F(1.41)=5.12, p< .05), independently of the specific picture category. Figure 4.3.2. gives an overview on mean scorings for the different slide conditions separately for each of the two participant groups.

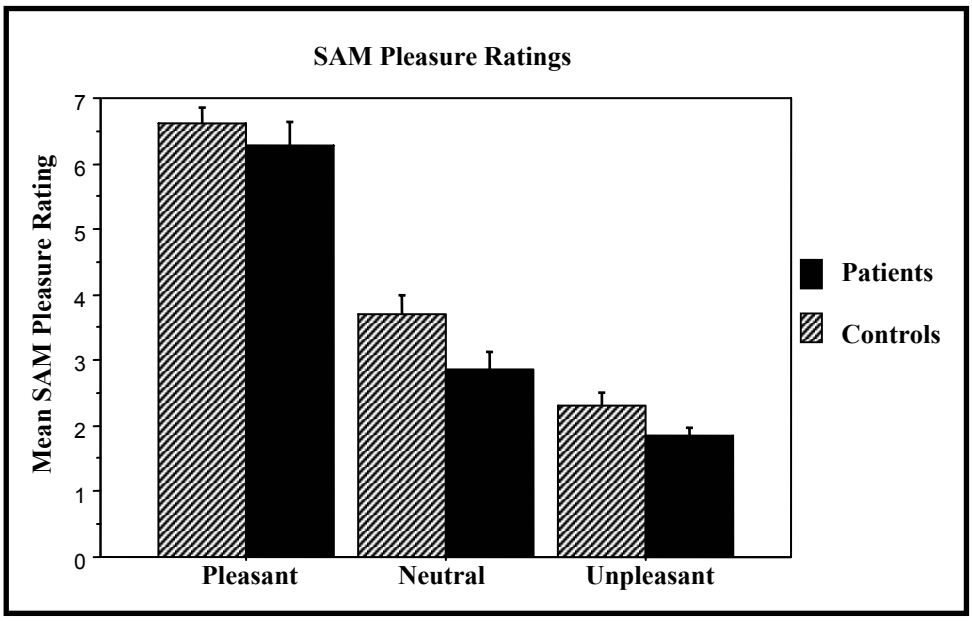

Fig. 4.3.2 . Mean SAM Pleasure ratings (and standard errors) of participant groups for each picture category

Slide Recall

Picture Category had a significant effect on immediate memory performance (see Figure.4.3.3.). Newman-Keuls post hoc comparisons indicated that both pleasant slides ($p < .0005$) and unpleasant slides ($p < .0005$) were remembered better than neutral pictures. Pleasantness of stimuli also influenced memory performance with unpleasant slides being recalled more often than pleasant pictures ($p < .05$).

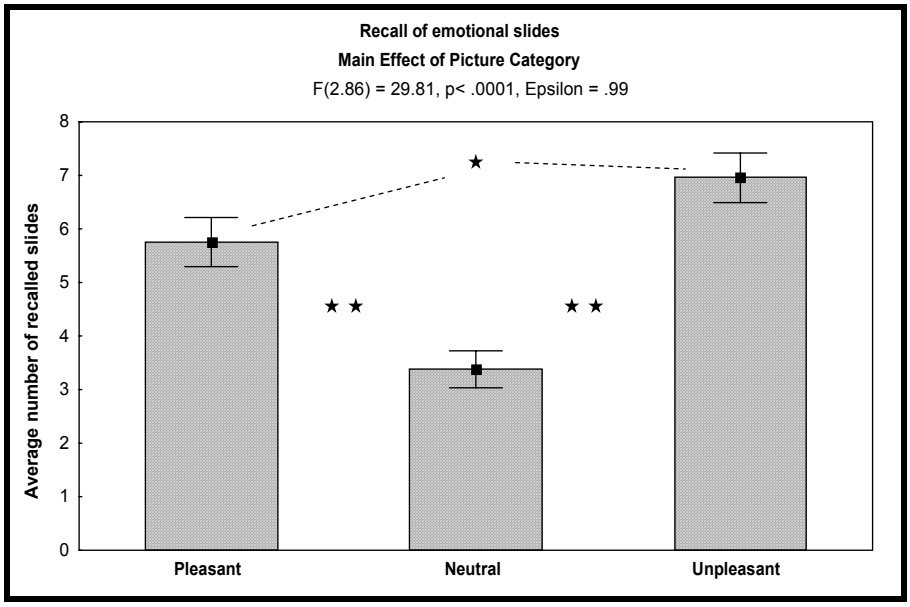

Fig 4.3.3. Number of correctly recalled pictures for each category (mean +/- standard error)

A main effect of group ($F(1.38) = 40.68$; $p < .001$) confirmed that healthy subjects (mean: 6.7, St.error: 0.42) recalled better than brain injured patients (mean: 3.9, St.error: 0.28), whereas specific picture characteristics did not influence memory performance of different participant groups.

Relationship between clinical variables and behavioral data

Pearson correlation coefficients were used to explore the relationship between coma duration and time elapsed since acquisition of brain injury and subjective data (SAM scores and recall of prior presented slides) in patients.

Overall ratings for Arousal and Pleasure as well as single ratings for each picture category (pleasant, neutral and unpleasant) were correlated with coma duration. None of these relationships resulted significant.

Overall recall of emotional slides was found to correlate with coma duration ($r = -.55$, $p < .01$). Fig. 4.3.4. illustrates that longer coma duration was associated with poorer recall, but not with recall of any specific picture category.

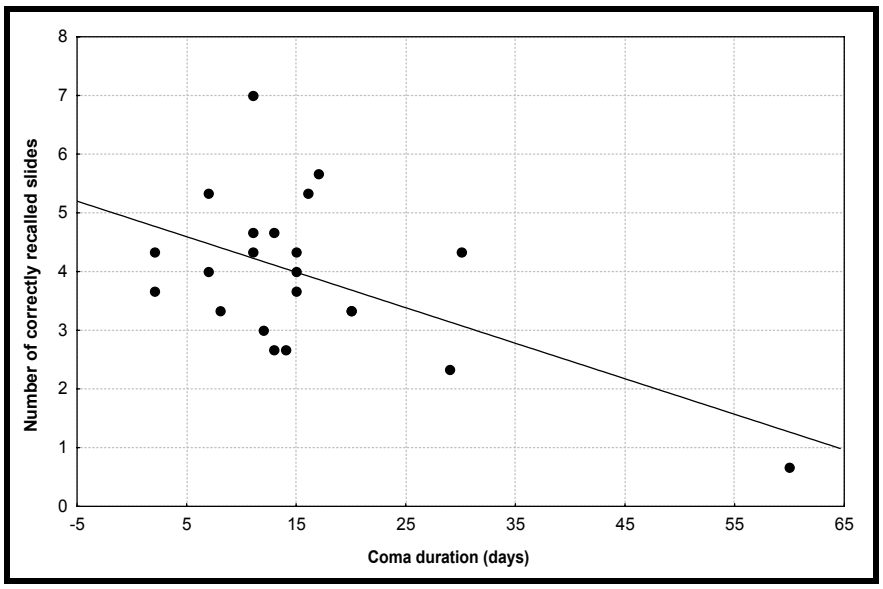

Fig. 4.3.4. Correlation between coma duration and overall slide recall

Note: Correlation is still significant when outlier is excluded from analysis ($p < .05$)

The variable "time elapsed since acquisition of head trauma" did not correlate neither with recall of affective slides nor with SAM ratings.

Discussion

The Self-Assessment Manikin (SAM) was used to measure subjective emotional responses to affective pictures in terms of emotional arousal and emotional valence. Mean ratings of all participants reflected the original selection criteria based on these two dimensions. Unpleasant and pleasant pictures were judged as more arousing compared to neutral slides and also ratings of pleasantness were similar to those provided by the norms (CSEA, 1999).

TBI patients showed an overall decrease of self-reported arousal which was particularly evident in response to unpleasant pictures. A similar effect was obtained for valence ratings, where patients, again, attained an overall reduced score when compared to healthy controls. However, this tendency to perceive the presented picture as less pleasant was not influenced by picture category. The fact that, despite differing to some aspects from healthy subjects, patients' self assessment of emotional pictures reflected the typical rating pattern, indicate that on a behavioral level, the present TBI patients characterized by extensive frontal brain damage are not completely impaired in their ability to distinguish between different fundamental emotional categories or to adequately report the subjective emotional experience related to them. This point is further supported by patients' performance in the free recall test where they showed a memory pattern for emotional material that

was similar to the one found in the control group; both pleasant and unpleasant pictures resulted in better memory performance as compared to neutral slides. This is in line with findings from previous studies using a comparable paradigm with healthy subjects (Bradley et al., 1992; Dolcos & Cabeza, 2002; Palomba et al., 1997). No effect of valence on recall could be observed in these earlier studies. Instead, unpleasant pictures were remembered more often than pleasant ones in the present experiment. Better memory for unpleasant events is assumed in "Flashbulb" theories of memory (Brown & Kulik, 1977) which propose that exposure to traumatic events creates a very strong and vivid memory representation. Empirical evidence for this supposition comes from paradigms that mainly assessed memory for unpleasant events compared to neutral ones (e.g. Christianson & Loftus, 1987), but rarely investigated both types of emotional valence. The recall advantage for unpleasant pictures in the present investigation may support the assumption of "flashbulb memories", however further studies are needed to explore the relationship of emotion to memory by using affective stimuli that vary along both emotional dimensions valence and arousal.
Although TBI patients showed the typical recall pattern with a better memory for highly arousing pictures, their overall memory performance was evidently impaired. This finding is not unexpected, in light of the fact that the neuropsychological profile of the patient group demonstrated a slight deficit of incidental memory. The free recall of prior presented pictures represented, as well, an incidental memory task as subjects had not previously been informed about the upcoming test. The present result that poorer overall slide recall was associated with longer coma duration together with the correlation found between some neuropsychological test results and coma length are in line with the assumption of this clinical variable as a good predictor of cognitive impairments (Cattelani et al., 2002). However, the fact that coma length was neither related to memory performance for any specific picture category nor to ratings of affective arousal and valence clearly indicates that this variable may be a reliable index for merely cognitive capacities but not for alterations in emotional elaboration.

4.4. Elaboration of affective pictures in TBI patients – General discussion

Event related potentials, skin conductance response and subjective evaluation served here as different indices of emotional elaboration in TBI patients. By comparing the results of these three parameters we can see that some of the findings confirm each other, whereas other do not provide univocal evidence for a common deficit. These conflicting results raise the question of whether different neuroanatomical substrates underlie specific parameters of affective processing that,

consequently, are variably affected by the predominant prefrontal lesions in the present clinical sample.

Selective impairments of elaboration of arousing slides as indicated by late EEG activity are not reflected by skin conductance responses of TBI patients which showed the typical enhancement after unpleasant and pleasant pictures. Instead, self-ratings of affective arousal partly agree with ERP findings, as both parameters indicate a specific reduction in processing unpleasant stimuli compared to healthy controls. This might suggest that late ERPs to emotional pictures and subjective ratings are modulated by a network that involves similar neuroanatomical structures whereas SCR is, at least to some extent, under the control of a different neuroanatomical substrate. Both patients' performance in the present investigation, along with evidence from previous studies, lead to the assumption that late EEG activity in response to affective pictures (Lane et al. 1997; Reinman et al., 1997) and self evaluation of these pictures (Angrilli et al., 1996) reflect higher order cognitive processes mediated mainly by a cortical network which includes the orbitofrontal cortex as a key structure. In this regard, present ERP findings and SAM ratings suggest that orbitofrontal lesions may be related to a greater deficit of elaboration for unpleasant compared with pleasant emotions. This conclusion would be in line with recent evidence from functional imaging experiments (Northoff et al., 2000) as well as human lesion studies (Angrilli et al., 1999).
Intact SC responses in the present patient sample argue against a crucial involvement of orbitofrontal areas in the skin conductance mediating network. Cortical areas that previously have been shown to play a decisive role for the emotional modulation of electrodermal activity are the anterior cingulate gyrus (Zahn et al., 1999) and the right inferior parietal region (Tranel and Damasio, 1994). Thus, in light of the fact that these specific brain regions were not damaged in any of the present brain injured patients, the finding of unimpaired SC responses seems plausible. The question in how far subcortical structures, such as the amygdala, are involved in higher modulation of skin conductance responses cannot be answered here. On the basis of the available lesion information, damage of the amygdala could not be established in our patients, even if lesions of the temporal cortical areas were present in half of the patients. However, several lines of evidence indicate that the amygdala plays a major role in the central mediation of autonomic responses, in particular with regard to emotional behavior (see Aggleton, 1992 for an overview). Only recently, Kubota et al. (2000) reported reduced electrodermal activity following unpleasant pictures in patients with unilateral temporal lobectomies suggesting that medial temporal structures seem to be part of the neural substrate that modulates autonomic processing of emotions.

Our finding that patients had overall reduced P3 amplitudes irrespective of stimulus category is in line with their performance on the free recall task and the SAM ratings showing a generally reduced level of self experienced arousal and poor recall for all picture contents. A close connection between cortical positivity and stimulus arousal was reported in previous studies revealing a positive relationship of SAM arousal ratings with the P3 component (Palomba et al., 1997) and with the positive slow wave (Cuthbert et al., 2000). It is assumed that because of their motivational significance, emotionally arousing slides are selected by the brain for sustained attentive processing. In this regard, P3 amplitude has been interpreted as manifestation of processes related to the allocation of attentional resources to stimulus evaluation, and furthermore, to the updating of representations in working memory (Donkin & Coles, 1988). Thus, the tendency of TBI patients to generally perceive the presented pictures as less arousing results in a less deep stimulus elaboration with fewer attentional resources dedicated to this process. This is further confirmed by the evidently impaired slide recall in patients that can be regarded as direct consequence of a less efficient stimulus encoding. The effect of stimulus processing depth, as indicated by P3 amplitude, on later memory performance ("Dm" effect) has been reported by a variety of studies (Johnson, Pfefferbaum & Kopell, 1985; Noldy, Stelmack & Campbell, 1990).

In summary, we demonstrated that elaboration of affective picture is strongly influenced by emotional relevance of stimuli with both psychophysiological indices, i.e. ERPs and SCR, as well as behavioral measures, i.e. subjective evaluation and recall, showing prominent differences between responses to neutral pictures and those to unpleasant and pleasant slides. This thesis has, for the first time, provided evidence that emotional picture processing is significantly affected in TBI patients with predominantly prefrontal lesions as indicated by their event-related cortical responses and subjective variables that differed from data of healthy subjects. First, these differences argue for a generally less efficient processing of pictorial stimuli with less attentional resources allocated to picture evaluation and poorer recall for these stimuli in patients. Second, results suggest a specific impairment of the present brain injured group for the elaboration of unpleasant pictures indicating an important involvement of prefrontal brain areas in modulation of responses to negative emotional stimulation.

5. INFLUENCE OF LESION EXTENT AND LOCATION ON AFFECTIVE PICTURE PROCESSING

The influence of lesion extent and location on patients' performance was examined by dividing patients into subgroups along their specific lesion characteristics. Three brain areas of interest were determined: (1) the ventromedial prefrontal cortex (VMPFC), (2) the residual frontal cortex, and (3) the temporal cortex. For each of these areas, the extent of lesioned brain tissue was estimated by again counting the number of marked pixels on the horizontal template of every patient. Figure 5.1. illustrates the horizontal standard templates with colored marked parts indicating the three cortical regions of interest. Subsequently, the size of lesion in each of the three areas was calculated as a percentage of overall brain tissue. This calculation was accomplished separately for each hemisphere and for the whole brain. One patient had to be excluded from the analyses because his original CT-scans provided by the hospital were not complete.

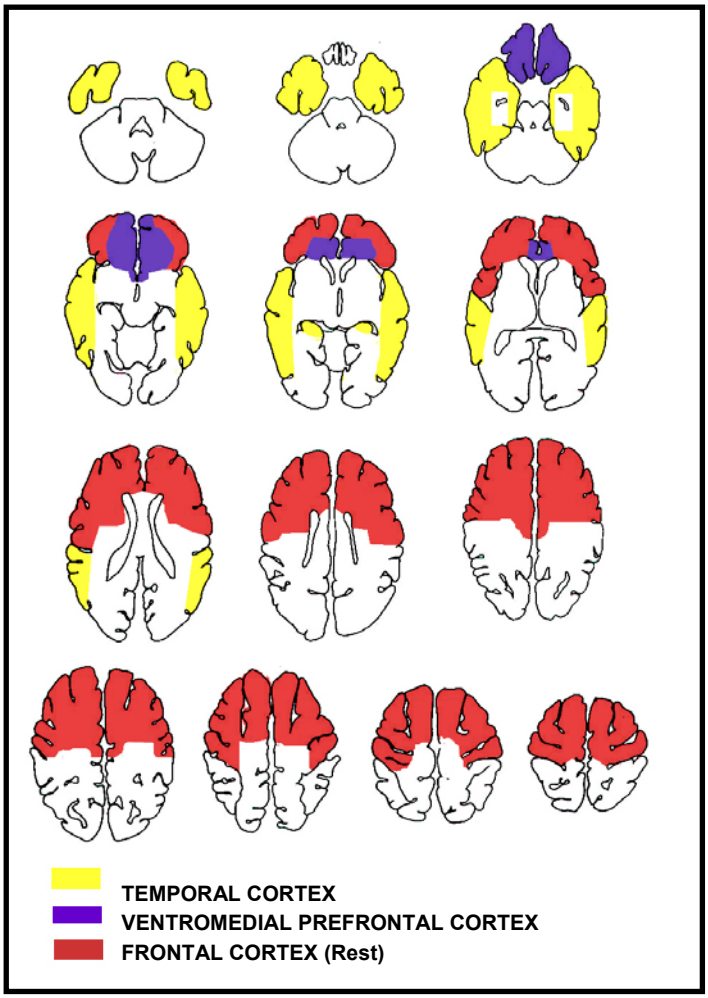

Fig. 5.1.
Horizontal standard template with colored markings indicating the neuroanatomical areas used for the definition of lesion subgroups

***Temporal cortex** (yellow):*
Brodmann areas 20-22,28,36, 37, 41,42

***VMPFC** (blue):*
Brodmann areas 11,12, 47 and anterior part of 10 & 24

***Frontal cortex** (except for ventromedial aspects):*
Brodmann areas 1-4, 6,8,9, 44-46

Subgroups were defined by:

(1) *Size of the frontal lobe lesions (large or small);* ventromedial prefrontal areas were excluded here, since they constituted their own region of interest. Patients with frontal lobe damage amounting to more than 1% of overall brain tissue were included in the subgroup "Large frontal lesion".

(2) *Presence or absence of lesions of ventromedial prefrontal areas* (VMPFC); to maintain the balance of the size of each subgroup, only patients with VMPFC lesions amounting to more than 0.2 % of overall brain tissue were included in the subgroup "with VMPFC lesion"

(3) *Presence or absence of lesions of the temporal lobe;* here, temporal lobe lesions amounting to more than 0.1% of overall brain tissue were included in the subgroup "with temporal lobe lesion"

Table 5.1. provides an overview of lesion extent within the respective area of interest and overall lesion volume for each subgroup.

Table 5.1. Details on mean lesion volume (and range) for different subgroups (indications for specific area of interest, single hemisphere and whole brain)

Subgroups "Large frontal lesions " vs. "Small frontal lesions"					
	N	**Volume of frontal lesion** (as percentage of overall brain tissue)	**Total lesion volume** (as percentage of overall brain tissue)	**Total volume of lesions in the left hem.** (as percentage of brain tissue in the left hemisphere)	**Total volume of lesions in the right hem.** (as percentage of brain tissue in the right hemisphere)
Large Frontal Lesions	**10**	2.57 (1.09 – 4.55)	4.64 (1.74 – 9.45)	5.91 (1.46 – 12.7)	3.37 (0 - 9.16)
Small Frontal Lesions	**11**	0.35 (0.03 – 0.6)	1.41 (0.23 – 3.99)	1.43 (0.05 – 5)	1.3 (0.4 – 2.98)
Subgroups "VMPFC lesion" vs. "No VMPFC lesion"					
	N	**Volume of VMPFC lesion**	**Total lesion volume**	**Total volume of lesions in the left hem.**	**Total volume of lesions in the right hem.**
Patients with VMPFC- lesions	**10**	0.58 (0.25 – 1.16)	4.04 (0.83 – 9.45)	4.59 (0.35 – 12.7)	3.50 (1.31 – 9.16)
Patients without VMPFC - lesions	**11**	0.05 (0 – 0.18)	1.95 (0.23 – 4.65)	2.63 (0.05 – 9.3)	1.18 (0.23 – 4.65)
Subgroups "Temporal lobe lesion" vs. "No temporal lobe lesion"					
	N	**Volume of temporal lesion**	**Total lesion volume**	**Total volume of lesions in the left hem.**	**Total volume of lesions in the right hem.**
Patients with temporal lobe lesions	**11**	0.86 (0.15 – 3.39)	4.19 (1.46 – 9.45)	5.06 (1.08 – 12.7)	3.23 (9.16)
Patients without temporal lobe lesions	**10**	0.03 (0 – 0.09)	1.58 (0.23 – 4.65)	1.92 (0.05 – 9.3)	1.24 (0 – 3.35)

Most patients had bilateral brain damage (as already mentioned in chapter 2.2.). Table 5.1. shows that patients with substantial damage in the right hemisphere also presented with similarly extended lesions in the left hemisphere. Pearson correlation coefficients were used to explore the relationship between lesion volume in each hemisphere and the extent of overall lesion. This analysis was accomplished separately for lesions within the three different areas of interest as well as for total lesion size. All correlations were found to be highly significant with at least $r = .6$ and $p<.001$ for all comparisons. Therefore, a further division of patients into subgroups with predominantly right and left hemispheric brain damage was not possible for the present clinical sample.

The comparison between psychophysiological data of the respective lesion subgroups was accomplished using the identical procedure we previously employed for the comparison between patients and controls. With respect to the analysis of ERP data, the same time windows with their respective electrode clusters were used (see section 4.1.). Statistical analyses comprised repeated measurement analyses of variance (ANOVA) including group (2 lesion subgroups) as the between factor. Repeated measurement factors were picture content (3 levels: pleasant, neutral, unpleasant), hemisphere (2 levels: left, right) and recording site (2 or 3 levels, depending on the chosen electrodes for the specific time window).
Electrodermal activity was analyzed as mean skin conductance response to each slide and averaged across pictures belonging to the same category (pleasant, neutral and unpleasant). Statistical comparisons were accomplished by applying an ANOVA with between factor group (2 lesion subgroups) and repeated measurement factor picture category (see section 4.2).
Only significant effects including factor group will be reported here since performance across all subjects has been sufficiently illustrated in chapter 4.

5.1. Comparison between patients with large and with small frontal lobe lesions

Neuropsychological performance

Differences between patients and healthy subjects on various neuropsychological tests were analyzed with two-tailed t-tests for independent populations. Although group profiles, as illustrated in Figure 5.1.1., appear to be quite distinct, differences in performance on single tests failed to reach statistical significance.

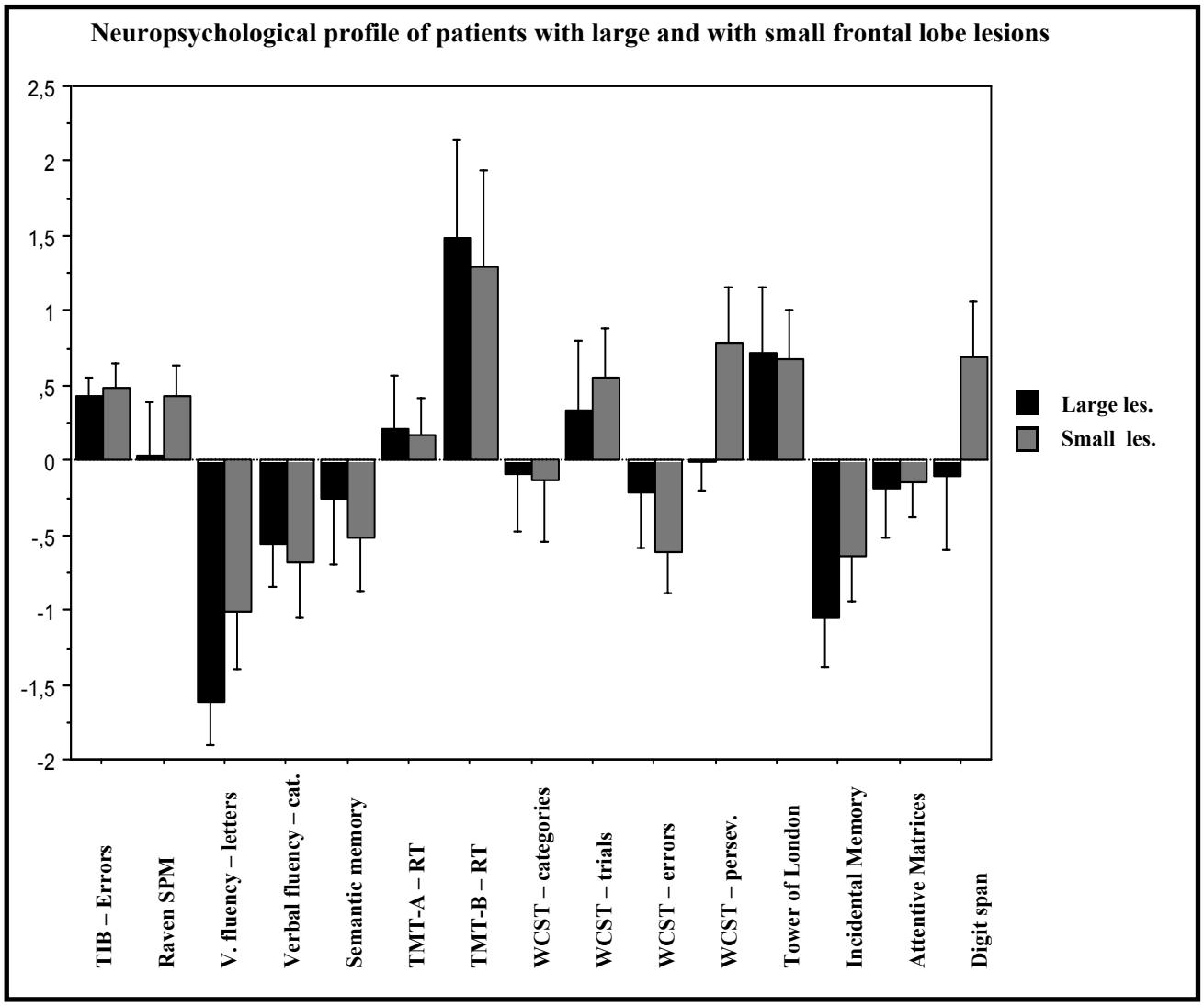

Fig.5.1.1. Neuropsychological profile of patients with frontal lobe lesions of different size (means of z-transformed values and standard errors are shown)

If we have a more "clinical" look at test results in terms of abnormal outcome, patients with large frontal lesions show three scores that differ from the respective norm by more than one standard deviation: "verbal fluency –letters", "TMT-Part B" and "Incidental memory". Patients with small damage to the frontal lobes only reveal one important deviation from the norm, namely their performance on the TMT – Part B.

Visual evoked potentials

EEG data revealed no subgroup differences for the early components (time windows 160-220ms and 220ms–280 ms). In both the early (280-350 ms) and the late (350-420 ms) P300 time windows a significant Group x Site effect could be found (early window: $F(2.38)= 4.22$, $p< .05$, $\Sigma= .65$; Later window: $F(2.38)= 4.74$, $p< .05$, $\Sigma= .68$). Both patient groups showed the highest amplitudes at parietal sites (see Table 5.1.1.), although voltage differences between sites were less marked for

patients with large frontal lesions (post hoc: p< .01) compared to patients with smaller lesions (p< .001). In fact, post-hoc analyses revealed significant group differences at frontal sites, where patients with more severe damage to the frontal lobes had less negative amplitudes (p< .05).

Tab. 5.1.1. Mean Voltages (μV; and Standard Errors) in the two P3 windows, at 3 sites, for each patient group

	Time window: 280-350 ms			**Time window: 350-420 ms**		
	Frontal	**Central**	**Parietal**	**Frontal**	**Central**	**Parietal**
Large frontal lesion	-1.47 (SE= 0.71)	-1.29 (SE= 0.72)	1.03 (SE= 0.63)	-2.37 (SE= 0.86)	-2.26 (SE= 0.90)	1.78 (SE= 0.88)
Small frontal lesion	-2.88 (SE= 0.61)	-2.81 (SE= 0.55)	2.06 (SE= 0.55)	-4.61 (SE= 0.74)	-4.66 (SE = 0.79)	3.38 (SE= 0.76)

The Group x Site effect was also visible in the following time interval from 450-650 ms (F(2.38)= 4.61, p< .05, Σ= .61) whereas in the 650-1000 ms window, it only reached statistical trend level (p< .06).

For ERP data from 450 ms on, an ANOVA on mean voltages averaged across selected electrode clusters (see chapter 4) was accomplished. Time window 450-550 ms exhibited a Group x Hemisphere effect (F(1.19)= 5.22, p< .05) revealing that patients with large frontal lesions showed a marked lateralization for ERPs whereas mean amplitudes of patients with small damage to the frontal lobe did not differ between hemispheres (see Table 5.1.2).

Table 5.1.2. 450-550 ms: mean Voltages (μV) in each hemisphere for patients with small and large frontal lesions

	Left Hemisphere	**Right Hemisphere**
Large frontal lesion	-1.29 (SE= 0.44)	0.86 (0.43)
Small frontal lesion	-0.65 (SE= 0.38)	-0.48 (0.38)

In addition, the 450-550 time window was the only interval that showed signs of a different elaboration of specific picture content in the two patient groups. Figure 5.1.2. depicts the Group x Picture Category effect, that nearly reached statistical significance (F(2.38)= 2.87, p< .07, Σ= .91). Patients with small frontal lobe lesions showed higher amplitudes in response to arousing stimuli (pleasant: p< .05 and unpleasant: p< .05) compared to the response elicited by neutral slides. Amplitudes of patients with large frontal lesions were influenced by emotional valence with more positive voltage means after pleasant slides compared to unpleasant pictures (p< .001). On the

other hand, differences between visually evoked responses to unpleasant picture and those to neutral slides did not reach statistical significance in this group.

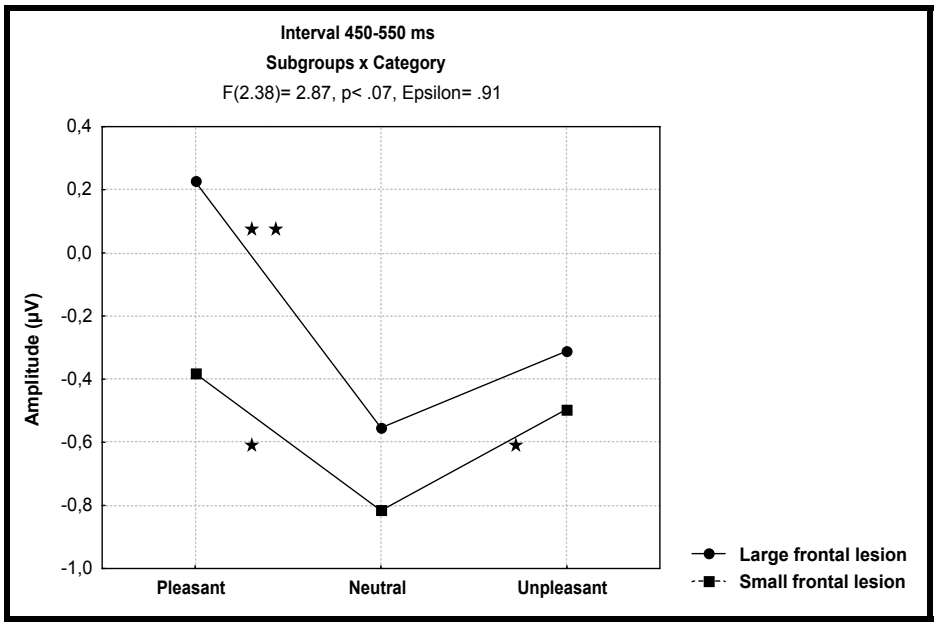

Fig. 5.1.2. *Mean amplitudes of different lesion groups for each picture category (* indicate significant differences between picture categories within each group)*

In none of the following time windows, covering the period from 650 ms to 4s post stimulus onset, important differences between the two patient groups became apparent.

Skin conductance response

Statistical analyses on mean skin conductance amplitude in response to presented slides revealed an important main effect of group.

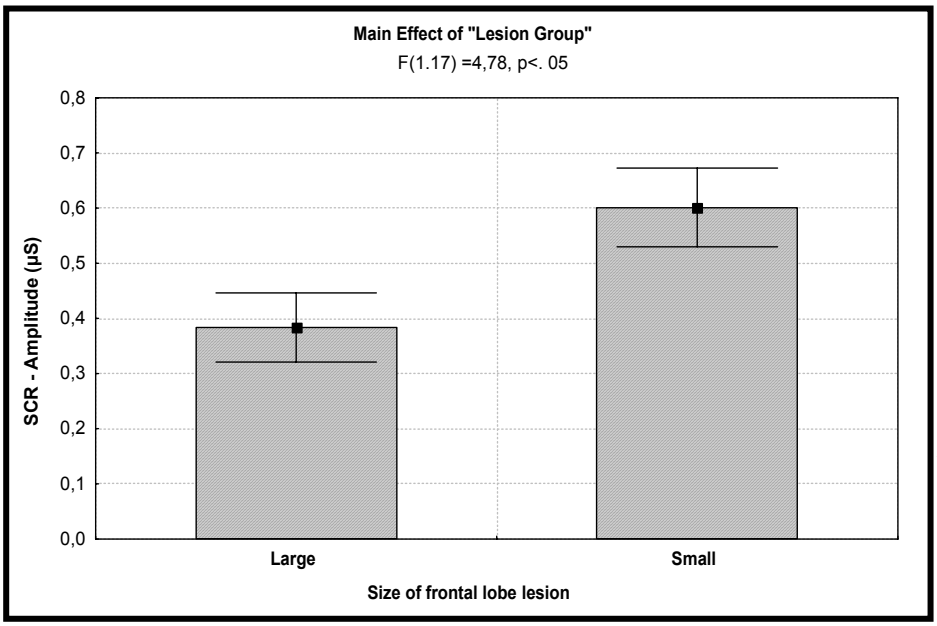

Fig. 5.1.3. *Mean amplitude of skin conductance response (SCR) in patients with large and with small frontal lobe lesions. (mean +/- Standard Error)*

Patients with large frontal lobe lesions showed a reduced overall skin conductance response compared to patients with less damage to the frontal lobes. This was found to be independent of emotional content, since no further effect including picture category emerged.

Subjective evaluation and recall of emotional material

SAM-ratings and performance on the incidental free-recall task were analyzed with a repeated measurement analysis of variance (ANOVA) including picture category (pleasant, neutral and unpleasant) as repeated measurement factor and "group" (large vs. small frontal lobe lesions) as between factor.

With respect to SAM Arousal ratings, no significant effect including factor group could be observed. Self perceived arousal during viewing of emotional slides was similar in patients with large frontal lesions and those with less damage to the frontal lobes. Pleasure ratings, instead, differed between the two clinical samples as a function of picture content. Figure 5.1.4. illustrates the significant Group x Picture Category effect ($F(2.36) = 3.79$, $p < .05$, $\Sigma = .81$).

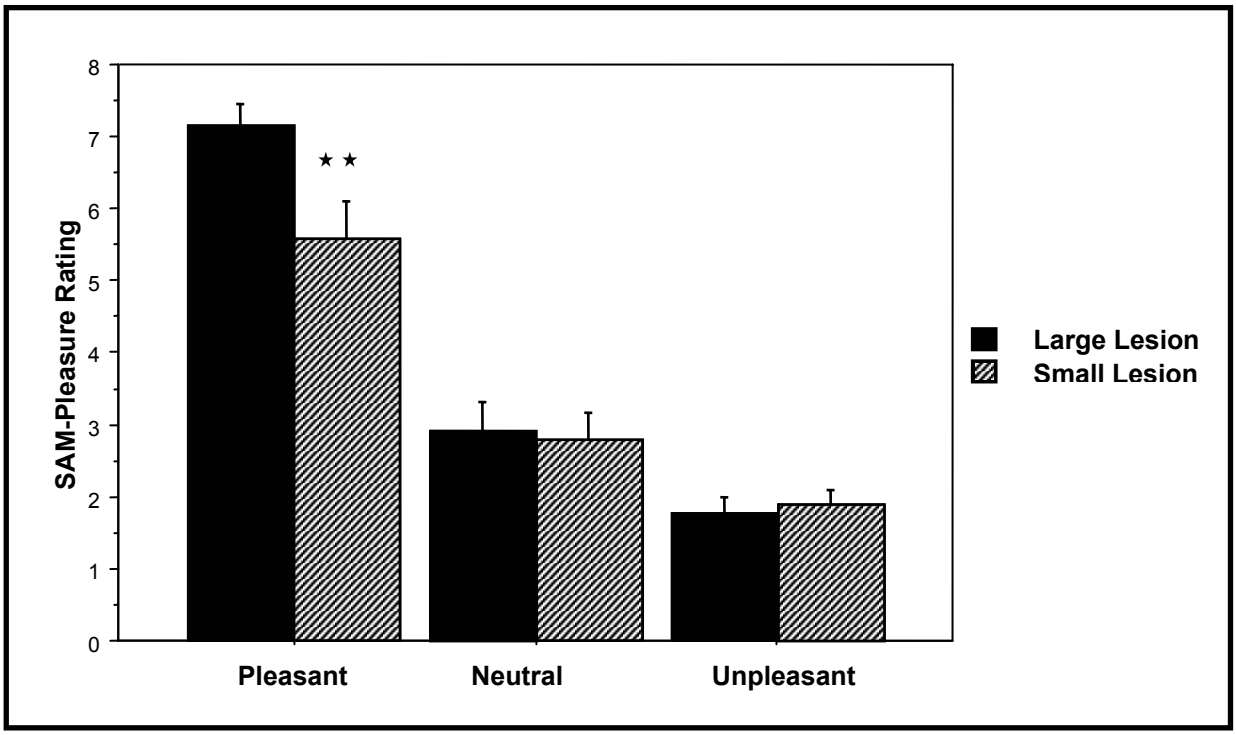

Fig. 5.1.4. *Mean SAM Pleasure ratings (and standard errors) of participant groups for each picture category*

As revealed by post-hoc analyses, patients with large frontal lesions scored pleasant pictures as significantly more pleasant compared to patients with small lesions in this cortical area ($p < .01$), whereas ratings in response to unpleasant and neutral content were very similar in both clinical

samples. Slide recall, instead did not reveal any significant difference between patients with large and with small frontal lesions.

Discussion

The comparison between data of patients with large frontal lobe lesions and those of subjects with smaller damage to the frontal lobes indicates that the severity of deficits of emotional elaboration is affected by the extent of frontal lobe damage. Even more important, the size of frontal lesions has an influence on different parameters of affective processing as suggested by findings from evoked cortical potentials, autonomic responses (i.e. SCR) and subjective measures (i.e. SAM).

Discrimination of arousing pictures from neutral content differed between the two subgroups with only patients with smaller frontal lesions showing the typical late positivity enhancement selectively for emotionally salient slides in the time window 450 – 550 ms. Instead, processing pattern of patients with large frontal damage was influenced by emotional valence. Whereas elaboration of unpleasant slides did not differ from neutral content, pleasant pictures were followed by a very pronounced amplitude enhancement that was even greater compared to the group with small frontal damage. These findings lead to the assumption that larger frontal lesions are associated with impaired processing of unpleasant stimuli whereas attentional resources allocated to the evaluation of pleasant stimuli are remarkably extensive. The strong involvement of prefrontal areas in the elaboration of affective stimuli has been confirmed by a large body of research. However, to date, it is not clear whether this involvement is valence specific, as indicated by the present results, or whether the prefrontal cortex is related to a more general function of emotion processing. In this regard, most of the studies investigating neuroanatomical correlates of affective picture viewing reported similar activation loci in the prefrontal cortex for pleasant and unpleasant pictures (Lane et al., 1997; Lang et al., 1998). Instead, evidence for a stronger contribution of the prefrontal cortex to the elaboration of unpleasant emotions comes from a single case study of a patient with a well-defined right orbitofrontal lesion (Angrilli et al., 1999). A subdivision of prefrontal regions into functionally different areas was proposed by Northoff et al. (2000) who showed that negative processing was characterized by strong medial prefrontal activation whereas positive emotional processing was related to a rather strong activation in lateral prefrontal cortex.

The finding that patients with extensive frontal lesions showed a particularly intense elaboration of pleasant stimuli when compared to patients with smaller frontal damage, might be related to the fact that this specific picture category mainly consisted of pictures with very explicit erotic content. Several studies have revealed altered sexual behavior as a consequence of traumatic brain lesions in the frontal cortex (Gray, 1966; Miller, Cummings, McIntyre, Ebers & Grode, 1986; Sandel,

Williams, Dellapietra & Derogatis, 1996) demonstrating that patients with frontal lesions were characterized by sexual disinhibition and hypersexuality. Thus, erotic stimuli may have had a stronger motivational relevance for patients with large frontal lesions compared to the group with smaller damage and were, therefore, more efficiently processed. The assumption of an increased susceptibility/reactivity to erotic stimuli in patients with extensive frontal brain damage is further supported by evidence from subjective evaluation of presented pictures where patients with larger frontal lesions scored pleasant slides as noticeably more pleasant compared to subjects with small frontal lesions.

A pronounced hemispheric asymmetry of the beginning late positive potential (450-550 ms) was found in patients with extensive frontal lesions, whereas subject with smaller lesions in this area showed similar amplitudes over both hemispheres. As in the former group, overall lesions showed an evidently lateralized distribution with 5.91 % of brain tissue damaged in the left hemisphere compared to only 3.37 % in the right hemisphere; hemispheric ERP asymmetries may reflect this lesion lateralization. In fact, in patients with small frontal lesions, both localization of brain damage and late ERP potential showed a rather symmetric distribution with respect to hemispheres. However, as this effect of hemisphere appeared only in one single time window, it did not seem to imply a systematic functionality for picture processing.

Overall skin conductance responsiveness to visual stimuli was reduced in the subgroup with extensive damage to the frontal lobes. Although this finding may suggest a critical role for the prefrontal cortex in regulation of electrodermal activity, it fails to support evidence from prior studies indicating a more specific involvement of prefrontal cortical areas in modulation of only emotionally salient stimuli (Angrilli et al., 1999; Tranel et al., 1994). These investigations have shown that patients with prefrontal cortical lesions did not display the skin conductance enhancement in response to arousing pictures compared to neutral content. Damasio and co-workers (for a review, see Damasio, 1994) have studied a variety of patients with damage to the prefrontal cortex and not only found a consistent lack of skin conductance responses to emotionally relevant stimuli in those patients, but also unaltered electrodermal activity during anticipation of presumably disadvantageous future outcome. The present findings, instead, suggest that very extensive damage to the prefrontal cortices may be related to a more general reduction of autonomic responsiveness to pictorial stimuli.

5.2. Comparison between patients with and without ventromedial prefrontal lesions

Neuropsychological performance

Two-tailed t-tests did not reveal any significant difference between the two clinical groups. Again, neuropsychological profiles of patient groups are shown to provide an overview on their performance on single tests.

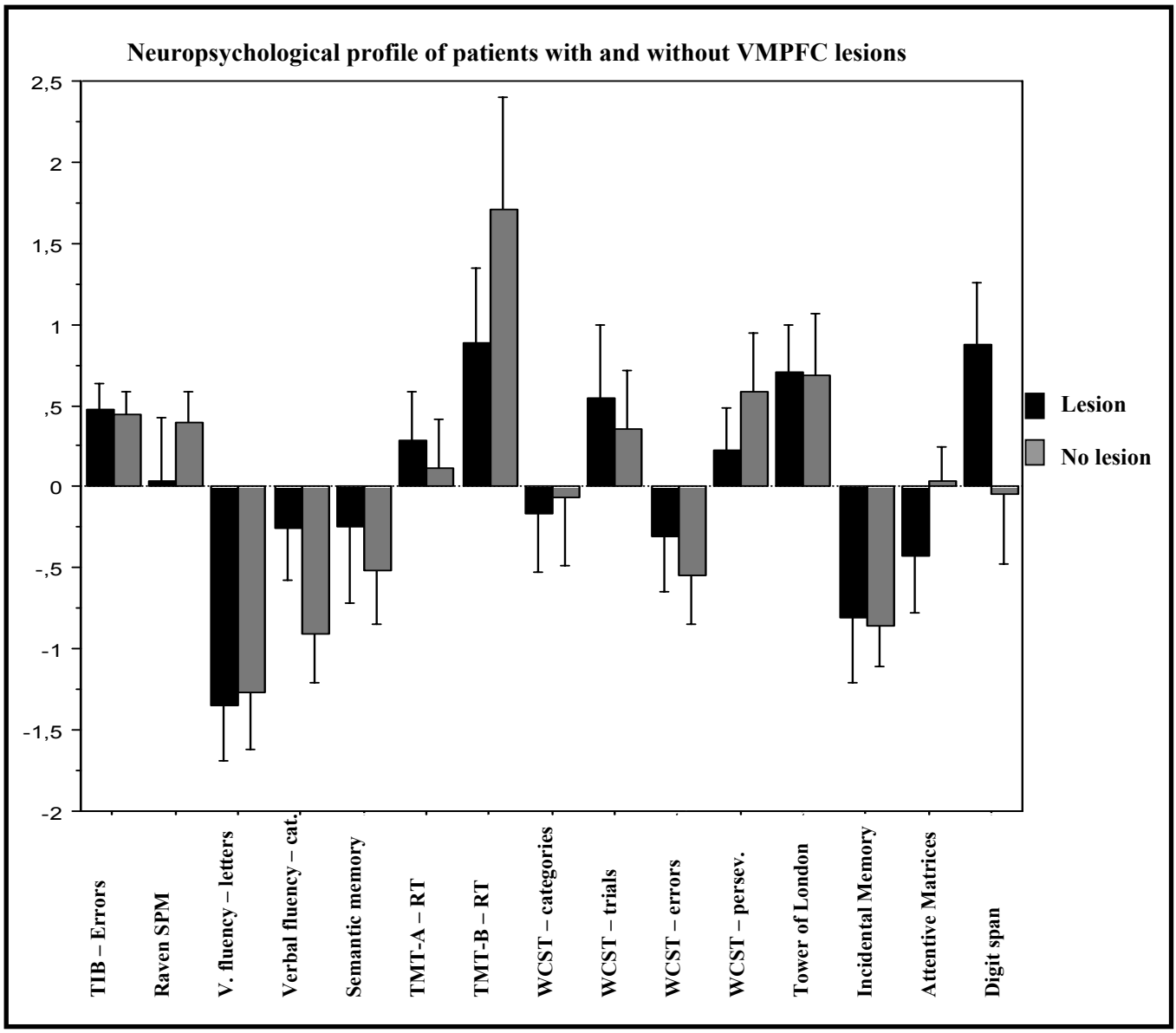

Fig.5.21. Neuropsychological test performance of patients with and without VMPFC lesions means of z- transformed values and standard errors are shown)

Visual evoked potentials

Differences between patients with and without VMPFC-lesions became already evident in the earliest time window (160-220ms) that revealed a significant Group x Category x Hemisphere effect. Figure 5.2.2. illustrates that stimulus processing in the right hemisphere, compared to the left hemisphere, showed marked differences with respect to picture content and clinical sample. Both patient groups differentiated between arousing and non arousing (pleasant and unpleasant) pictures, but their response pattern was very dissimilar. Whereas patients with no VMPFC lesion exhibited the expected response with a negative going deflection during viewing of arousing slides compared to neutral pictures, patients with VMPFC lesions show a nearly reverse picture with an enhanced positivity in response to arousing slides, in particular after unpleasant stimuli, which also elicited higher amplitudes than pleasant pictures.

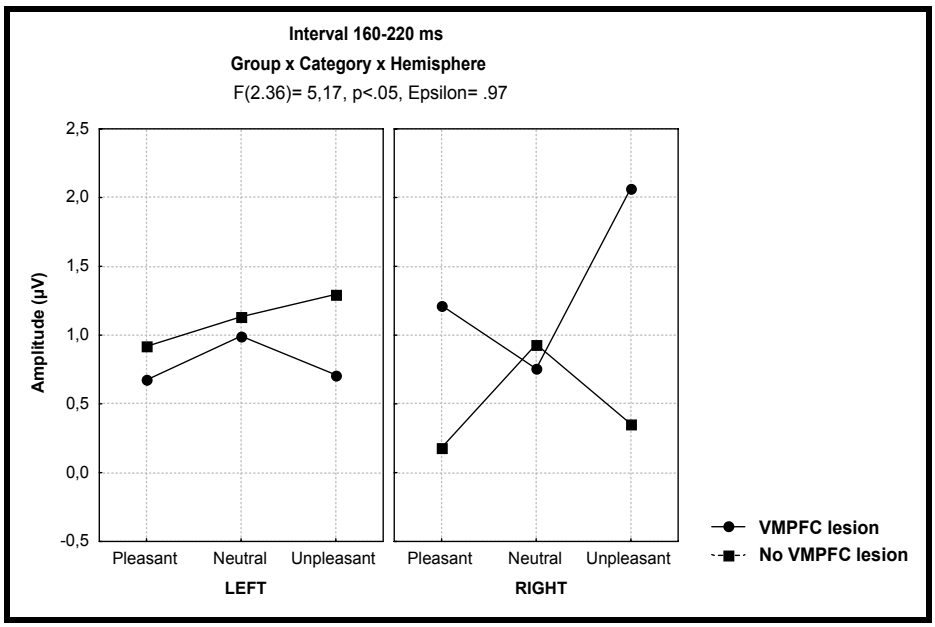

Fig. 5.2.2. Left- and right-hemispheric parieto-occipital sites: mean amplitudes in response to different emotional picture content

This effect persisted till the subsequent time window from 220 to 280 ms, but became weaker and thus failed to reach statistical significance ($F(2.36= 2.81, p< .08, \Sigma= .92)$.

Both P300 time intervals did not exhibit any important effect including "group". Further group differences became evident only with respect to the late slow wave starting from 650 ms after stimulus onset. Figure 5.2.3. illustrates late picture processing in patients with and without damage to the VMPC by mapping surface activity for each group and picture condition in the 1-3 s time interval. Maps indicate differences in the activity pattern of the two patient groups in response to specific emotional content. Patients without VMPFC lesions show more positivity (red color) to both pleasant and unpleasant pictures compared to neutral stimuli, whereas patients with damage to

the VMPFC seem to show this enhanced positivity only to pleasant slides. Their surface activity following unpleasant pictures looks quite similar to the one elicited by neutral slides.

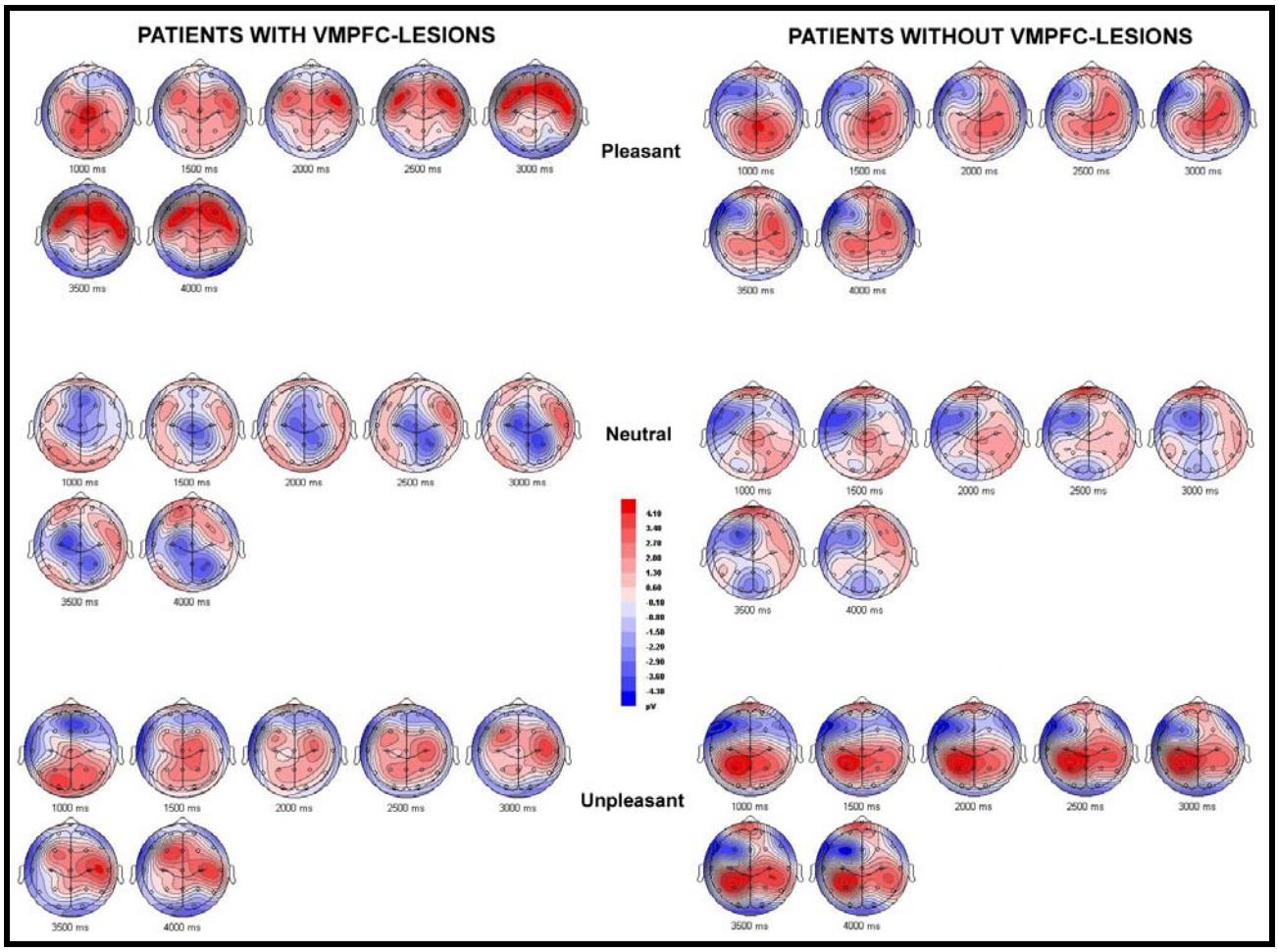

Fig 5.2.3. 1-4 s following picture onset:
Grand mean topography of surface activity for pleasant, neutral and unpleasant picture content, shown separately for patients with and without VMPFC-lesions
(map scaling: 0.7000 µV/contour)

This impression is confirmed by statistical analyses. A very stable Group x Category interaction, lasting up to the end of picture presentation, resulted for each of the four late time windows: 650 - 1000ms ($F(2.38)= 2.80$, $p< .08$, $\Sigma= .76$), 1-2s ($F(2.38= 4.18$, $p< .05$, $\Sigma= .68$) , 2-3s ($F(2.38)= 4.1$, $p< .05$, $\Sigma= .93$), 3-4s ($F(2.38)= 3.86$, $p< ,05$, $\Sigma= .73$). To exemplify this dynamic, figure 5.2.4. illustrates the interaction found in the time window 1-2 s. Post-hoc conducted analyses revealed that patients with damage to the VMPC showed higher amplitudes to unpleasant and neutral slides compared to patients without lesions in this specific cortical area ($p< .01$). Even more interesting is the result, that in patients with VMPFC lesions, mean amplitudes in response to unpleasant slides did not differ from amplitudes yielded by neutral stimuli, whereas the difference between mean voltages during viewing of neutral slides and pleasant pictures was pronounced ($p< .01$). Patients

without VMPFC lesions, instead, exhibited overall enhanced amplitudes to both types of arousing slides compared to neutral content ($p < .01$).

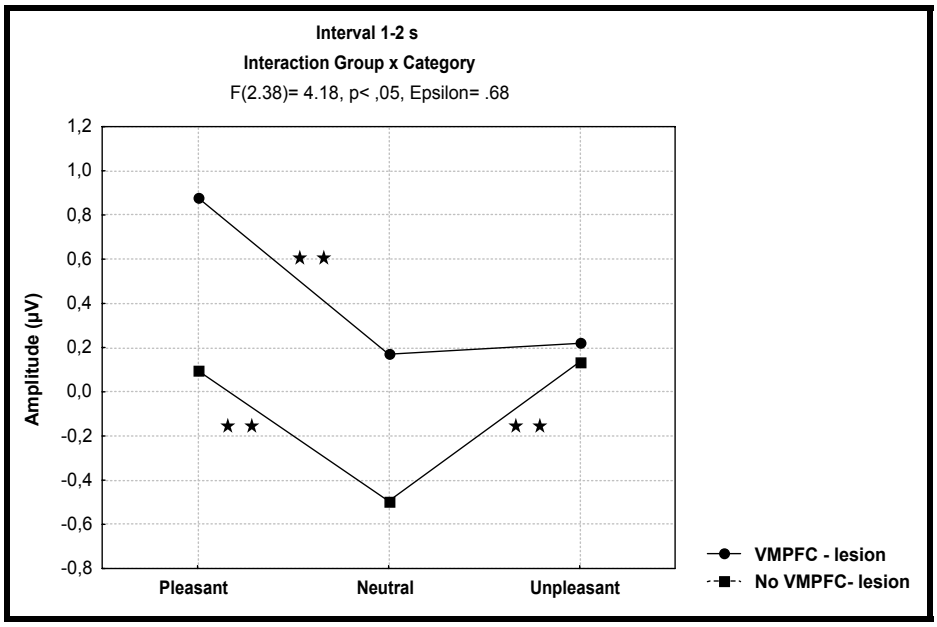

Fig. 5.2.4. Mean voltages of patients with and without VMPFC lesions, for each picture category

*(** indicate significant ($p < .01$) post-hoc differences between categories within each group)*

The illustration of surface activity also seems to reveal some differences with respect to laterality of emotional processing. For example, in response to pleasant pictures, patients without lesions of the VMPFC appear to show more positive activity in the right hemisphere compared to the left hemisphere (see Figure 5.2.3), whereas patients with VMPFC lesions seem to be less lateralized. Surprisingly, statistical analyses did not lead to any effect including the factor hemisphere.

Skin conductance response

No significant differences between patients with and without VMPFC lesions resulted for mean amplitude of skin conductance response.

Subjective evaluation and recall of emotional material

With respect to both SAM Arousal and SAM Pleasure ratings, no important effects including factor group could be observed. Also the recall of prior presented pictures was similar in both patients with and without damage of the VMPFC.

Discussion

A series of lesion and functional imaging studies in humans (Bechara et al., 2000; Elliot et al., 2000), as well as neurophysiological studies in nonhuman primates (Schönbaum, Chiba & Gallagher, 1998), have emphasized the role of the ventromedial prefrontal cortex in representing the

emotional value of sensory stimuli. In particular, the VMPFC is assumed to constitute part of the circuitry via which associations are formed between visual cues and the actions or choices that they specify. The VMPFC would, therefore, represent a cortical area that can represent cues, responses, and outcomes.

The present comparison between patients with and without lesions of the VMPFC revealed that damage to this cortical area was associated with more severely impaired elaboration of unpleasant stimuli as indicated by findings from event-related potentials. At a very early cortical processing stage (160-220 ms), only patients without VMPFC lesions displayed the typical ERP pattern with a relative negative deflection over right occipital areas in response to arousing slides. Patients with lesions to ventromedial cortices, instead, showed an enhanced positivity over right posterior areas during viewing of emotionally salient slides. Considering that early activity over visual cortices repeatedly has been assumed to index rapid allocation of motivated attention towards relevant stimuli (Keil, 2001; Pizzagalli et al., 1999), the atypical positivity found after VMPFC lesions might reflect less efficient processing of emotional pictures. Thus, the present result suggests that an intact right VMPFC is necessary to successfully modulate early affective encoding of visual stimuli. This conclusion is in line with recent evidence from single-unit recordings obtained in human right VMPFC in response to facial expression of fear and happiness (Kawasaki, Adolphs, Kaufmann, Damasio et al., 2001); neuronal discrimination between the two valence types already appeared after 120 -170 ms. It can be assumed that the right-hemispheric ventromedial prefrontal cortex exerts, the right-hemispheric ventromedial prefrontal, can be assumed to exert an important top-down influence on early visual processing of emotionally relevant cues.

Furthermore, the VMPFC appears to have a decisive role for affective modulation during later stages of stimulus elaboration, as well. In fact, the late potential consistently differed between patients with and those without damage to this particular area of the frontal lobe demonstrating that only patients with intact VMPFC discriminated unpleasant and pleasant slides from neutral content. Instead, from 650 ms up to the end of picture presentation, patients with VMPFC lesions displayed more positive amplitudes only in response to pleasant stimuli, whereas the slow wave during viewing of unpleasant slides did not differ from late processing of neutral pictures. This result is in accordance with previous studies reporting a stronger involvement of the ventromedial part of the frontal lobe in the recognition and elaboration of negative stimuli. In this regard, Harmer and co-workers found that disruption of processing within medial prefrontal cortex with transcranial magnetic stimulation produces longer reaction times in response to angry faces but not in response to happy facial expressions (Harmer, Thilo, Rothwell & Goodwin, 2001). Furthermore, Northoff et al. (2000) combined fMRI and MEG to investigate spatiotemporal activation of different prefrontal

subdivisions during emotional stimulation and revealed that negative affective processing generates activation in ventromedial frontal areas whereas elaboration of positive stimuli is more related to lateral prefrontal cortex.

In sum, the present ERP findings distinguished patients with and those without VMPFC lesions by showing that damage to this particular frontal area is associated with an abnormal modulation of rapid visual processing of emotional content and with an impaired discrimination of unpleasant stimuli during later stages of attentional visual elaboration. Surprisingly, these deficits were not reflected by any other indicator of affective stimulus processing; neither skin conductance responses nor subjective evaluation of pictures nor memory performance could reveal any differences between patients with and those without damage to the VMPFC.

5.3. Comparison between patients with and without temporal lobe lesions

Neuropsychological performance

As it was already the case with the prior discussed lesion subgroups, neuropsychological performance did not reveal any statistical differences between patients with and without temporal lobe lesions. Neuropsychological profiles of patient groups are shown to provide an overview on patients' performance on single tests. Considering abnormal outcome, represented by important deviations of performance from the respective normative data, we can see, that patients with temporal lobe lesions show a particular deficit on the TMT-Part B, whereas z-scores of patients without lesions in this cortical area remain within the normal range.

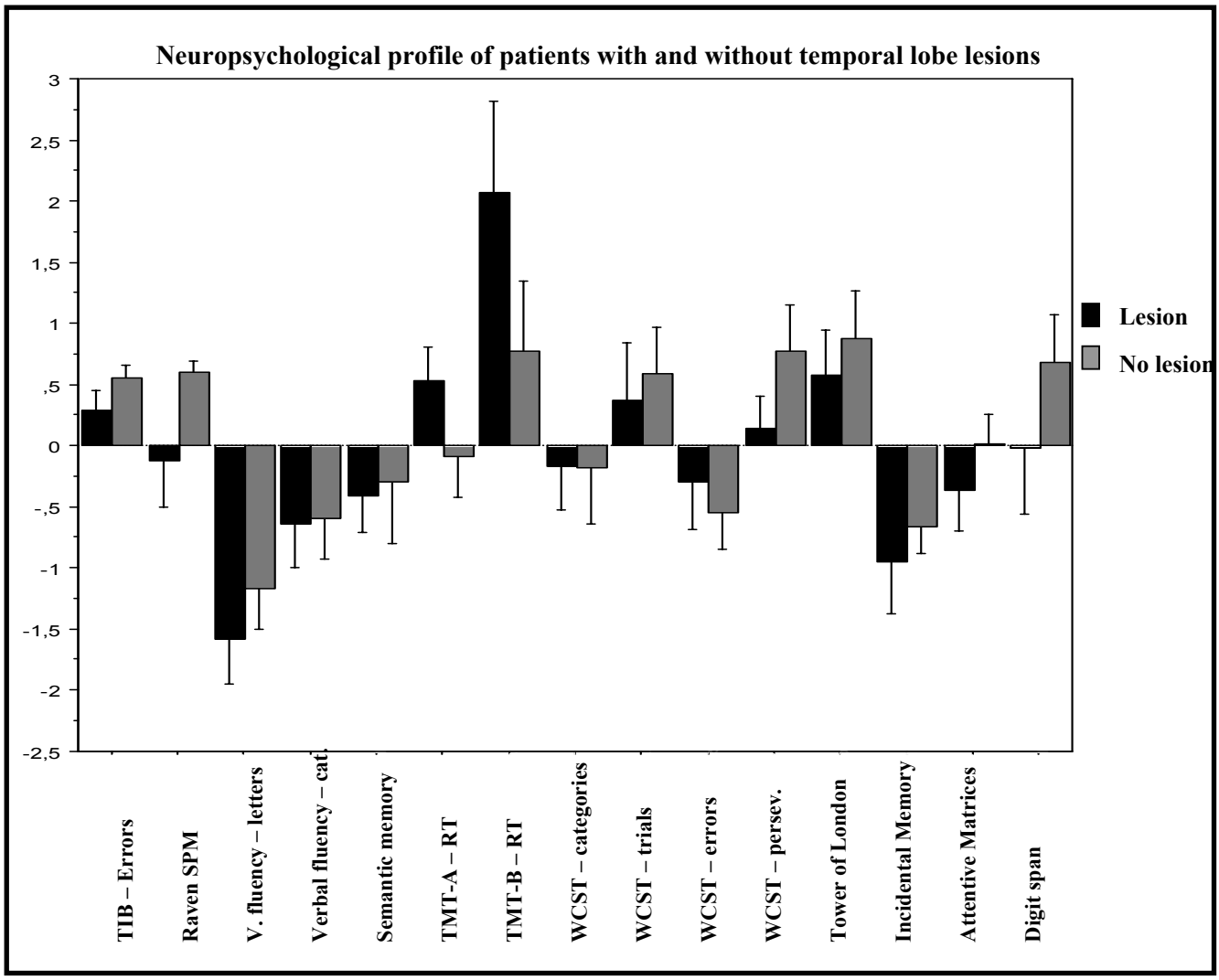

Fig.5.3.1. Neuropsychological test performance of patients with and without temporal lobe lesions (means of z- transformed values and standard errors are shown)

Visual evoked potentials

Prominent differences between patients with and without temporal lobe lesions became visible after 280 ms. In the early P300 window (280-350 ms), an interaction between Group, Category and Site could be found ($F(4.72) = 3.77$, $p < .05$, $\Sigma = .51$), that became even more pronounced in the subsequent late P300 interval (350-420 ms; $F(4.72) = 6.78$, $p < .005$, $\Sigma = .50$). Figure 5.3.2. depicts groups' mean amplitudes in the late P300 window at each of the three analyzed sites for single slide categories. Most evident differences between the two patient groups resulted at parietal sites, where the P300 reached its highest amplitude. Patients without temporal lesions showed the typical amplitude enhancement for arousing pictures compared to neutral content (post hoc: $p < .01$), whereas patients with damage to the temporal lobe did not differ at all between emotional picture categories. At frontal sites, instead, patients with temporal lesions exhibited a pronounced relative positivity for arousing sites ($p < .01$), whereas patients without damage to this specific cortical area

showed a rather unsystematic pattern with only unpleasant and pleasant sites differing from each other ($p < .01$).

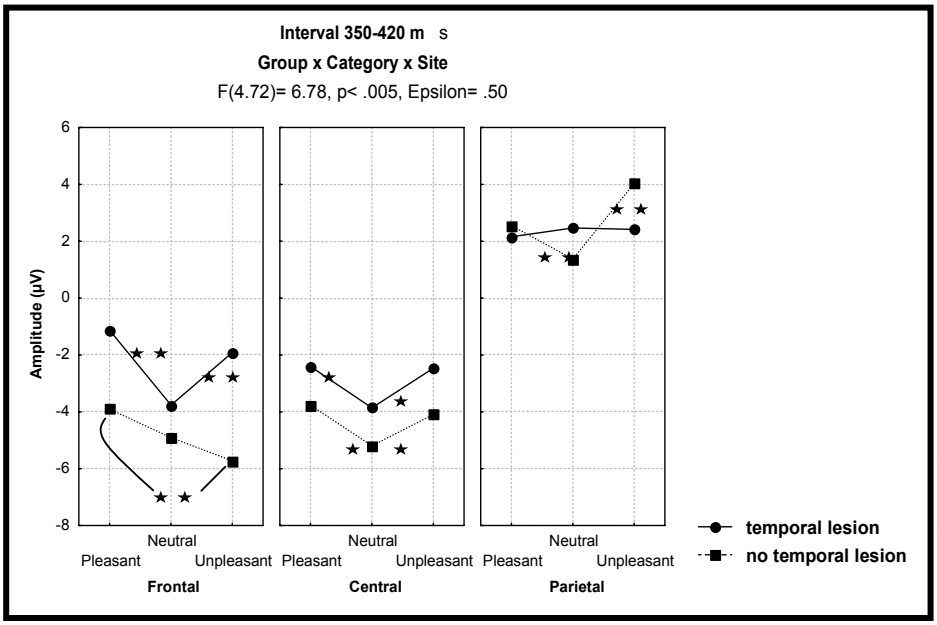

Fig. 5.3.2.
Late P3 window: mean amplitudes of patients with and without temporal lobe lesions at 3 sites for pleasant, unpleasant and neutral pictures
(indicate significant post-hoc differences between categories within each group)*

With regard to divergences between voltage group means, it is important to note, that at no site, voltage amplitudes in response to neutral content differed between the two clinical samples. The most stable group differences resulted for processing of unpleasant slides: At all electrode sites, mean amplitudes of patients with temporal lobe lesions differed from those of patients without damage to the temporal cortex ($p < .05$).

Also during later stages of visual processing, very distinct ERP patterns resulted for the two clinical samples. ANOVAs computed on regional means and electrode clusters revealed that the interaction between Group, Picture Category and Site remained significant until 2 s after stimulus onset (550-650 ms: $F(4.72)= 3.63$, $p <.05$, $\Sigma= .38$; 650-1000 ms: $F(4.72)= 3.98$; $p< .05$, $\Sigma= .46$; 1-2 s: $F(4.72)= 3.43$, $p< .05$, $\Sigma= .56$). Figure 5.3.3. provides an overview on grand mean event related activity during the first two seconds of picture presentation. Lateral waveforms depict the average activity of channels that have been grouped into electrode clusters (frontal, temporal and parieto-occipital), whereas midline waveforms display the activity of single electrodes (Nz, Fz, Cz, Pz).

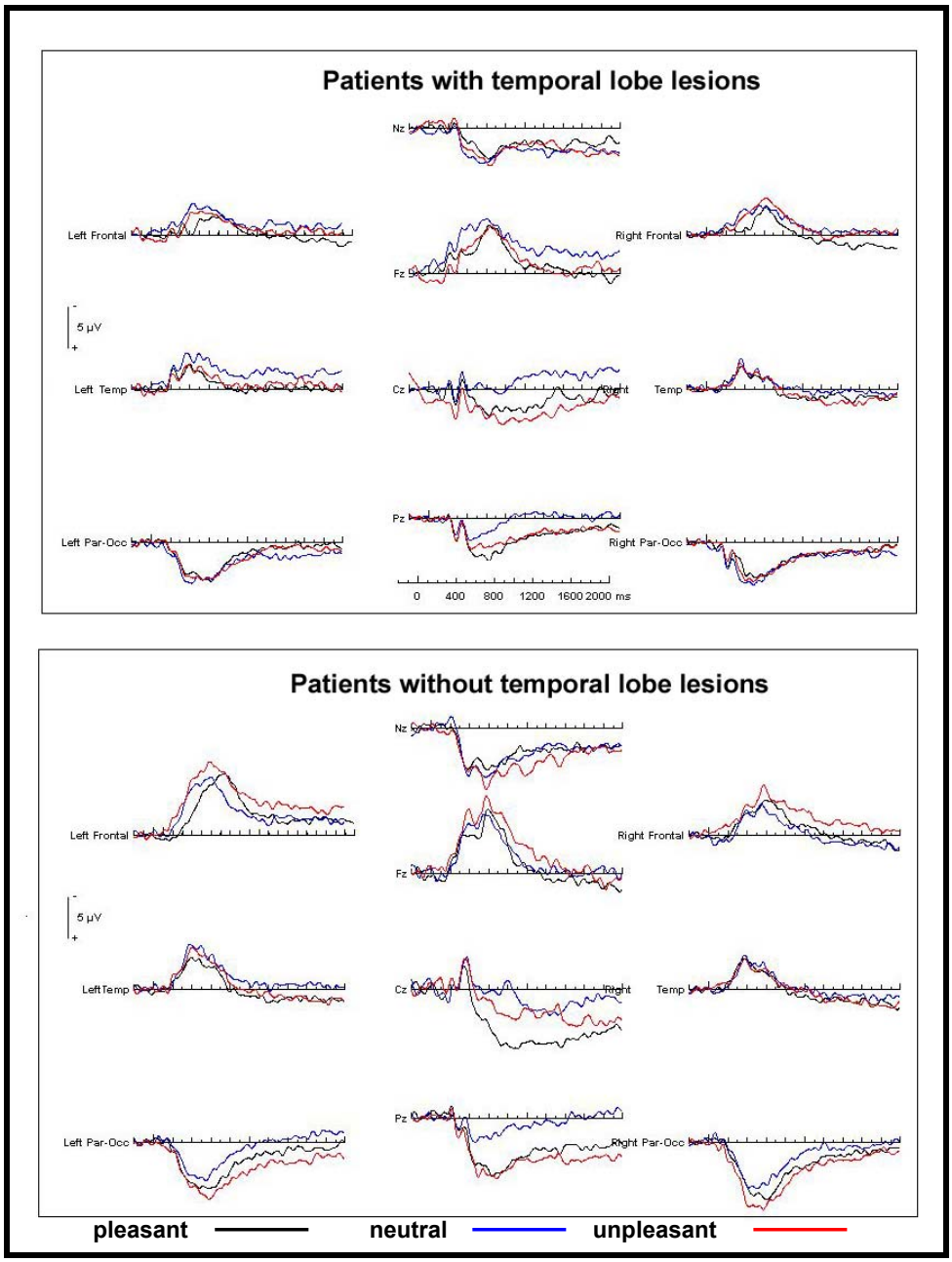

Fig. 5.3.3. Grand mean event related potentials (-200 to 2s) at lateral electrode clusters (averaged across grouped channels) and at four midline sites Note: Positive is down.

In particular waveform at posterior sites lead to the suggestion, that grand mean activity of patients with damage to the temporal lobe does not differ between picture content, whereas in patients without this type of lesions, activity in response to neutral slides (marked by blue color) clearly differs from activity elicited by highly arousing pictures. Post-hoc analyses conducted in these specific time windows, confirm this impression. Post-hoc tests in both time window 550-650 and 650 -1000 ms revealed that at no site, voltage means of patients with temporal lobe lesions were influenced by emotional content. Amplitudes in response to pleasant, neutral and unpleasant pictures did not statistically differ from each other. Patients without temporal lobe damage, instead, showed voltage means that were clearly affected by stimulus category. At temporal sites, these

patients exhibited higher amplitudes in response to arousing slides ($p < .01$), whereas at frontal sites, an enhanced negativity following unpleasant slides, compared to neutral pictures, became evident ($p < .01$). To get an overview on exact mean amplitudes in the discussed time windows, Table 5.3.1. lists the voltage means of each patient group for each condition and electrode cluster.

Table 5.3.1. Voltage mean(and SE in μV) of each patient group in three subsequent time windows, at 3 sites, for pleasant, unpleasant and neutral picture content

	Patients with temporal lobe lesions			**Patients without temporal lobe lesions**		
	Pleasant	**Neutral**	**Unpleasant**	**Pleasant**	**Neutral**	**Unpleasant**
550-650ms						
Frontal	-2.28 (0.97)	-2.94 (0.90)	-3.03 (0-83)	-5.15 (0.97)	-4.50 (0.90)	-6.42 (0.84)
Temporal	-1.13 (0.71)	-2.04 (0.53)	-1.35 (0.62)	-2.0 (0.71)	-2.83 (0.53)	-2.56 (0.62)
Parieto-occipital	3.72 (1.10)	3.81 (0.83)	3.69 (1.06)	5.63 (1.10)	4.01 (0.83)	6.55 (1.06)
650-1000 ms						
Frontal	-8.53 (0.77)	-1.77 (0.63)	-1.74 (0.54)	-3.03 (0.77)	-2.29 (0.63)	-4.41 (0.54)
Temporal	0.17 (0.71)	-0.92 (0.40)	-0.26 (0.55)	-0.10 (0.71)	-0.98 (0.40)	-0.64 (0.55)
Parieto-occipital	2.06 (0.85)	2.25 (0.46)	2.42 (0.70)	3.36 (0.85)	1.81 (0.46)	4.37 (0.70)
1-2 s						
Frontal	0.64 (0.48)	-0.70 (0.62)	-0.31 (0.47)	-0.68 (0.48)	-0.42 (0.63)	-2.07 (0.47)
Temporal	0.37 (0.66)	-0.64 (0.37)	0.36 (0.56)	1.17 (0.66)	0.10 (0.37)	1.07 (0.56)
Parieto-occipital	0.64 (0.66)	1.27 (0.40)	0.75 (0.55)	1.01 (0.66)	-0.09 (0.40)	1.81 (0.55)

Skin conductance response

No significant differences between patients with and without temporal lobe lesions resulted for mean amplitude of skin conductance response.

Subjective evaluation and recall of emotional material

Self evaluation of emotional material as assessed by the SAM did not reveal any differences between the two patient groups, neither regarding self perceived arousal nor with respect to scorings of picture pleasantness.

With respect to immediate recall of emotional pictures, ANOVA results did not exhibit significant effects including factor group. For this reason, we employed univariate testing (contrast analyses) of

memory performance for slides of different emotional content within each of the two patient groups. Contrast analyses revealed that patients with temporal lobe lesions remembered more unpleasant slides than pleasant and neutral pictures ($p < .01$ for both contrasts), whereas their performance did not differ between pleasant and neutral slides. On the other hand, patient without damage to the temporal lobes showed the typical pattern of recall of emotional material with neutral stimuli being remembered less often compared to pleasant ($p < .01$) and unpleasant ($p < .01$) pictures. The different recall pattern of the two lesion subgroups is illustrated in Figure 5.3.4.

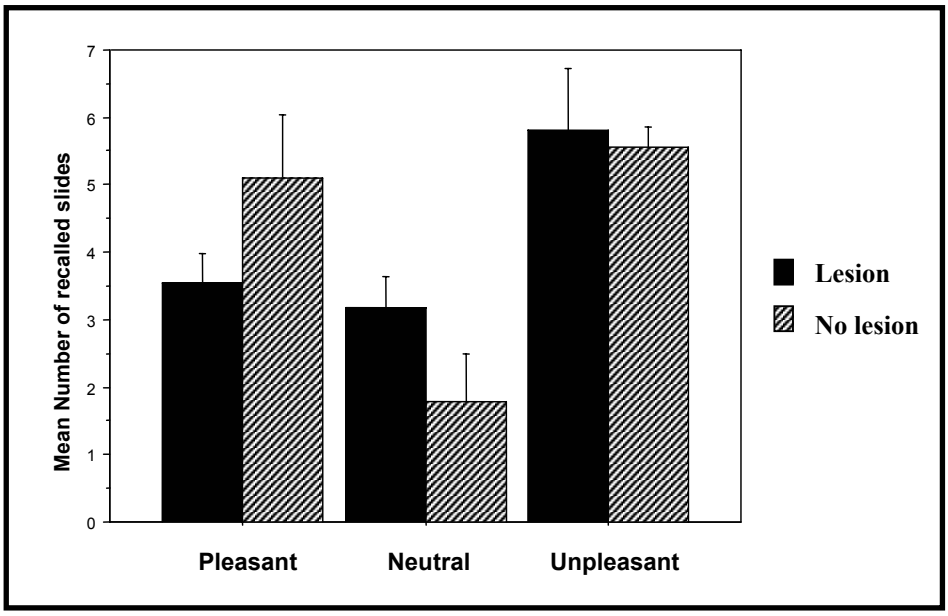

Fig. 5.3.4. Mean number of correctly recalled pleasant, neutral and unpleasant picture, in patients with and without temporal lobe lesions

Discussion

In research on emotion, consequences of temporal lobe lesions are typically discussed in reference to an assumed damage of the amygdala. In fact, several lesion studies aiming at investigating specific functions of the amygdala use patients with, for instance, temporal lobectomy or temporal epilepsy as clinical sample (Kubota et al., 2000). To date, only very few human studies exist that clearly distinguish effects of pure temporal lobe lesions from damage that exclusively comprises the amygdala. As far as the present clinical sample is concerned, we could determine from CT- and MR-scans of patients with lesions to the temporal lobes that their brain damage was restricted to cortical areas and did not affect the amygdala. Therefore, the deficits of emotional elaboration that were found here in subjects with temporal lesions, are not regarded as reflecting impairments provoked by lesion of the amygdala.

ERP findings consistently demonstrated that in patients with temporal lobe lesions, processing of affective highly arousing stimuli was clearly affected. Differences between the two subgroups

became apparent for the P3 activity over parietal areas with only patients without temporal lesions showing the increased positivity for emotionally salient slides. Amplitudes of patients with damage to temporal cortices did not differ at all between affective stimulus categories over this area, although affect discrimination was visible over the frontal cortex with enhanced positivity in response to arousing compared to neutral pictures. With respect to later EEG activity (550-1s), the impairment in discriminating between emotionally arousing and calm pictures was even more evident in patients with temporal lobe lesions. The late potential of this clinical subgroup did not seem to be modulated as a function of stimulus arousal with mean amplitudes not significantly differing between unpleasant, pleasant and neutral content.

Taken together, findings suggest that temporal lobe lesions do not affect the very early stages of visual processing. Instead, they seem to impair the correct functioning of the network that modulates later stages of affective elaboration where attention is selectively directed towards motivationally salient stimuli. In particular, the fact that slow wave potentials from 500ms-1s recorded over visual cortices did not differentiate between arousing and neutral pictures in patients with temporal lobe lesions argues for a top-down influence of temporal cortical areas on visual processing of emotional stimuli. Recent fMRI studies reported activation in the superior temporal gyrus during processing of negative facial expression of, for instance, fear and disgust (Iidaka, Omori, Murata, Kosaka & Yonekura, 2001; Phillips, Young, Scott, Calder et al., 1998). Considering that in our patient subgroup, lesions of the temporal lobe mainly affected the superior and middle temporal gyri, the present evidence would argue for a comparable role of these brain structures in processing of emotional pictures showing other motifs, as well. Further support for this conclusion comes from an fMRI study that employed both pleasant and unpleasant IAPS pictures as stimulus material and revealed enhanced activity in temporal gyri in response to both types of affective slides (Kuniecki, Urbanik, Sobiecka, Kozub & Binder, 2003).

In contrast to event-related potentials, neither skin conductance responses nor subjective ratings of emotional arousal and valence revealed any differences between patients with and those without temporal lobe lesions. This would be in line with the assumption that temporal lobe structures damaged in the present clinical sample, namely superior and middle temporal gyri, do not play a decisive role for modulation of autonomic arousal. So far, there is very little experimental evidence from available literature arguing for or against an involvement of temporal lobe structure in regulation of electrodermal activation. As mentioned before, this is partly due to the fact that first, patients with selective temporal lobe lesions are rarely studied, and second, eventual deficits of autonomic regulation provoked by damage of temporal cortices are typically discussed in terms of

an assumed amygdala dysfunction. An investigation that revealed similar findings to those presented here was conducted by LaBar and Phelps (1998). The authors examined skin conductance responses in patients with temporal lobectomy while they were rating emotionally arousing words and found that, like healthy controls, patients generated enhanced SCRs and arousal ratings for the arousing words compared to neutral stimuli. However, an important difference between the groups resulted for later recall of verbal material with only healthy subjects showing a better memory for arousing words, whereas recall of patients with temporal lobectomy did not differ between emotionally salient and neutral words. These results were interpreted in terms of an important role of temporal lobe structures in memory consolidation for arousing events. Findings of the present thesis partly support this conclusion by showing that only patients without temporal lobe lesions demonstrated the typical memory enhancement for emotionally salient pictures. Patients with damage to the temporal cortex, instead, demonstrated better recall for only unpleasant slides, whereas pleasant pictures were not remembered more often than neutral stimuli. This result may lead to the question whether the temporal lobe is particularly involved in memory consolidation for positive emotional material. In this regard, further studies that investigate larger samples of patients with well localized temporal lesions are necessary to draw a reliable conclusion.

5.4. Influence of lesion extent and location – General discussion

To determine how far the elaboration of affective pictures in TBI patients was influenced by lesion extent and location, data of clinical subgroups with specific lesion characteristics were compared. Areas of interest were those that have previously been linked to emotional processing: (1) the ventromedial prefrontal cortex (VMPFC), (2) the residual frontal cortex (mainly orbitofrontal), and (3) the temporal cortex). When discussing the results of these subgroup comparisons, it is important to keep in mind that due to the great lesion overlap in TBI patients, we were not able to build groups with completely delimited lesions. In the previous section, we have already reported noticeable alteration of emotional processing in the whole group of TBI patients, with respect to psychophysiological as well as subjective data. By employing the rather explorative approach of comparing patients subgroups with each other, we tried to further investigate if lesions of specific areas were associated with particular deficits in elaborating emotional stimuli.

TBI patients subgroups along the criteria “extent of frontal lesion”, “presence of VMPFC damage”, and “presence of temporal lobe lesions” did not differ in cognitive performance. Only when interpreting neuropsychological results in terms of abnormal outcome did the extent of frontal

lesions seem to have at least some impact on severity of impairments in that patients with large lesions showed more test results that deviate from the norm compared to patients with smaller frontal lesions. Thus, a greater extent of frontal brain damage might be related to a more general decline of cognitive functioning rather than to specific neuropsychological impairments.

Of course, the small sample size of patients' subgroups may serve as an explanation to the difficulty of determining differences in cognitive functioning between the groups. However, other studies with head injured patients also failed to demonstrate a significant relationship between neuroanatomical variables, such as lesion size and precise location, and neuropsychological and behavioral outcome (Fletcher, Levin, Lachar, Kusnerik et al., 1996; Hofman, Stapert, van Kroonenburgh, Jolles et al., 2001; Müller, Machado & Knight, 2002). In most of these studies, the absence of association between lesion characteristics and impairments was attributed to fact that a head injury usually implies, apart from focal lesions, diffuse brain damage and extensive axonal tearing that may also account for neurocognitive deficits.

The selection of TBI patients may be related to the problem of revealing significant differences in cognitive performance between lesion subgroups. In the present study, the clinical sample included was selected such as to form a rather homogeneous group in terms of head injury severity and neurobehavioral status. More importantly, TBI patients represented a uniform sample with respect to neuroanatomical aspects of their traumatic brain damage. Although the subgroups were distinct with respect to specific lesion features, there was still a considerable lesion overlap between the clinical samples that were compared with each other.

Aside from these methodological considerations, it is generally assumed that it is more reasonable to establish a correlation between measures that represent the overall severity of brain damage and neuropsychological functioning. As we mentioned earlier, coma duration represents the most reliable index of injury severity and a good predictor of cognitive impairments.(Cattelani et al., 2002). This was also the case in the present study where length of coma was found to significantly correlate with a few neuropsychological test results as well as with slide recall.

The comparison between patient subgroups revealed that the extent of frontal lesions as well as the presence of VMPFC or temporal lobe lesions lobe does affect specific aspects of emotional picture processing, thus suggesting an important role of these brain areas in modulation of affective elaboration. In particular, ERP findings provided insights regarding the involvement of the different brain structures during specific stages within the time course of emotional processing.

A large area of the prefrontal cortex can be assumed to be involved in attention modulated processing of particularly unpleasant stimuli. Both patient groups with VMPFC lesions and those

with especially large prefrontal damage showed a reduced late positivity in response to unpleasant pictures compared to their less damaged counterparts. This finding was interpreted in terms of fewer attentional resources allocated to negative stimuli, thus leading to a less efficient and deep elaboration of this type of affective stimulation. In addition, there was evidence for a very early top-down influence of only ventromedial prefrontal areas on visual affective processing, as ERPs of patient with lesions of these brain regions did not display the typical occipital negativity in response to arousing slides. Neither the extent of frontal lesions nor the occurrence of temporal lobe damage seem to play such a decisive role for the rapid visual discrimination between emotionally salient and neutral stimuli. Instead, patients with lesions of the temporal cortex displayed a specific deficit for recall of emotional material, thus confirming, to some extent, the importance for memory encoding that is habitually attributed to the temporal lobes (for a review, see Alvarez & Squire, 1994; Sakai & Miyashita, 1993).

A rather unexpected finding from subgroups comparisons was that, except for a general reduction in skin conductance responsiveness in patients with very extensive frontal lobe lesions, no patient group showed a defective electrodermal activation in response to specifically arousing pictures. Evidence from previous studies has suggested that lesions of prefrontal structures, in particular of the ventromedial prefrontal area, may be related to a lack of autonomic response to emotional stimulation (Angrilli et al., 1999; Bechara et al., 1996; Damasio, Tranel & Damasio, 1991). In fact, Damasio and colleagues advanced a coherent hypothesis on precisely this empirical evidence by stating that autonomic activation provides the covert information related to past emotional experience which is necessary to adequately respond to social situations and to find a solution to complex problems (Somatic Marker Hypothesis, see part 1.2.2.). According to this theory, prefrontal areas play an especially important role in the modulation of electrodermal responses to emotionally salient stimuli. However, the present result that neither patients with very extensive damage of the frontal lobe nor the group with lesion of the VMPFC showed an impaired skin conductance responses to arousing slides, disagrees with the assumption of a "somatic marker" deficit following prefrontal brain damage. We have already dealt with this contradictory evidence in the preceding chapter when discussing mean SC responses of the entire group of TBI patients (see section 4.4.). As a possible explanation, the fact was considered that in most studies reporting SC impairments to affective stimulation in subjects with prefrontal damage, lesions always included the anterior cingulate cortex (Angrilli et al., 1999; Zahn et al., 1999), whereas in the present thesis, this brain structure was not damaged in any patient. Furthermore, Tranel came to the conclusion that "*ventromedial damage is necessary but not sufficient to produce SCR impairment. In subjects with*

ventromedial damage but lacking damage to anterior cingulate and dorsolateral regions, SCRs were unimpaired" (Tranel & Damasio, 1994). Therefore, the present finding that patients with and those without VMPFC lesions did not differ with respect to electrodermal activity during viewing of affective slides, would be in line with this notion.
In summary, SCR results hint that it may be misleading to treat the frontal cortex as a whole and to associate the deficit in generating appropriate somatic markers to frontal lobe lesions, in general. Instead, by showing that even lesions covering extensive proportions of the prefrontal cortex are not sufficient to produce this impairment, the present evidence suggests that specific areas within the frontal lobe, such as the VMPFC or the anterior cingulate gyrus, may have quite different functions in emotion modulation that should be separately taken into account.

Whereas event related potentials, in particular the positive slow wave, revealed prominent differences between respective subgroups, these effects were not reflected by subjective arousal ratings that were similar in all patients, thus apparently unaffected by lesion location and extent. Together, these findings disagree with the close relationship between cortical positivity and self-perceived stimulus arousal that has been reported in previous studies (Cuthbert et al., 2000; Palomba et al, 1997). These authors concluded that pictures judged as more arousing represent motivationally more relevant cues that are selected by the brain for a particularly deep processing that is characterized by more attentional resources directed towards these relevant stimuli. The present results indicate that, although patients with large frontal lesions and those with VMPFC perceive affective pictures as variably arousing, their brain potentials are not consistently modulated by these differences. Thus, it may be assumed that the SAM affect scale probably represents a means of evaluation which is under the control of brain structures that, at least to some extent, differ from those involved in the network which regulates central processing of emotional stimuli. As indicated by EEG and SAM data of the whole group of TBI patients (see part 4.5.), the prefrontal cortex appeared to play a role for both arousal modulated processing of emotional pictures and self evaluation of these stimuli. However, as pointed out by the present comparison of patients with different lesion features, cortical potentials in response to emotional stimulation seem to be modulated by a more extensive network which involves more prefrontal structures, and, as a consequence, is more likely to be affected by lesions of the frontal lobe.

Of course, in view of the small sample size of the different lesion groups, the present findings need to be replicated by additional studies before drawing a definitive conclusion. As mentioned before, it has to be considered that the present approach of comparing subdivisions of patients with diverse

lesions had some methodological limitations given the substantial lesion overlap between the clinical subgroups. Furthermore, lesion size did not only differentiate between the group with large and the one with small frontal lesions, but also had an impact on other subdivisions. For instance, patients with very extensive frontal lesions were more likely to have some additional damage to the temporal lobes, as well. Since the present findings provides promising evidence for the specific role of prefrontal cortical regions in affective picture processing, further studies would be desirable that investigate, for instance, larger samples of patients with well-localized lesions of only one particular area within the frontal lobe.

6. CONCLUSIONS AND OUTLOOK

The present thesis addressed several hypotheses and experimental questions regarding psychophysiological and subjective correlates of affective stimulus elaboration in TBI patients with mainly orbitofrontal lesions. Furthermore, the study aimed at investigating whether the extent of prefrontal brain damage and the presence of lesions in ventromedial prefrontal areas or in temporal lobe regions were associated with specific impairments in processing emotionally relevant contents. This last section summarizes main findings of the present investigation by emphasizing their relevance for the initial hypotheses and experimental aims. The contribution of these findings to the understanding of the neuroanatomical basis of emotional evaluation is discussed, together with the implications they have for the assumptions of current theories of emotion.

Elaboration of emotional stimuli in TBI patients differed in many aspects from that of healthy persons pointing to an impaired discrimination between emotionally salient and neutral contents in these patients. Patients' ERPs showed a reduced cortical positivity in response to all pictorial stimuli, and furthermore, were not consistently modulated as a function of emotional arousal. The general attenuation of the P3 component and of the subsequent late positive potential suggests an impaired ability to direct and maintain sufficient attentional resources on picture processing, irrespectively of the emotional relevance of stimuli. Another facet of this impairment may be the severe memory deficit for previously presented pictures. Beside this unspecific impairment in picture elaboration, findings also confirmed the reduced ERP discrimination between arousing and neutral stimuli in brain injured patients that characterized the entire late picture processing stage (650ms – 4s). In particular, the missing enhancement of late negativity over occipital areas in response to highly arousing stimuli suggests that, in patients, emotional slides were not associated with a more intense level of visual elaboration, when compared to less relevant pictures.

Patients' evoked potentials at frontal sites beyond P3 did not differentiate between unpleasant and neutral pictures, whereas pleasant slides elicited an enhanced cortical positivity. This specific abnormality in evaluating unpleasant stimuli was further reflected by subjective data with patients' SAM arousal ratings for unpleasant pictures being noticeably reduced compared to scorings of healthy subjects. Considering that the lesions of the present head injured patients were mainly localized in orbitofrontal cortical areas, the particular impairment for the elaboration of negative emotional contents found here is not completely unexpected. Both functional imaging studies (George et al., 1995; Northoff et al., 2000) and a single case study of a frontal injured patient

(Angrilli et al., 1999) argue for a stronger involvement of orbitofrontal brain regions in processing of unpleasant stimuli, compared to pleasant ones. Taken together with the present findings, this evidence indicates that elaboration of unpleasant compared to pleasant emotions underlies, at least to some extent, different neuroanatomical substrates.

Evidence from the present subgroup comparisons provided further support for the assumption that prefrontal areas play a key role in the processing of unpleasant stimuli. In fact, both the presence of ventromedial prefrontal lesions and the extent of frontal brain damage were associated with a more prominent reduction of late event related positivity during viewing of unpleasant pictures. Instead, the P3 component and subsequent slow wave potentials were not modulated as a function of stimulus arousal in patients with temporal lobe lesions. Together, these finding suggest that whereas temporal areas seem to have an equally important top down influence on visual processing of both unpleasant and pleasant stimuli, the relevance of orbitofrontal areas for the emotion modulating network appears to be mainly related to negative stimulation. This conclusion would be in line with evidence from functional imaging studies that attribute similar roles to temporal (Kuniecki et al., 2003) and orbitofrontal cortical areas (Lane et al., 1997; Northoff et al., 2000) in visual affective processing. With respect to the influence of the size of frontal lesions, initially, it was assumed that very extensive lesions would be associated with a rather unspecific impairment of cognitive capacities and subjective and psychophysiological indices of emotional elaboration The comparison between patients with large and small frontal lesions has confirmed this hypothesis by revealing that subjects with more extensive brain damage showed, beside their specific deficit in processing unpleasant stimuli, signs of a more general decline of cognitive as well as physiological measures. In fact, patients with large frontal lesions, compared to the less damaged subgroup, were characterized by greater impairments of incidental memory and cognitive fluency and by generally reduced skin conductance responsiveness to pictorial stimuli.

In general, the present findings on skin conductance reactions were not able to confirm the experimental hypothesis assuming reduced SC responses to emotionally salient stimuli in patients with frontal brain lesions. Our contradictory evidence has been extensively discussed in preceding chapters where the suggestion has already been introduced in which the intact electrodermal performance in patients might be related to the fact that the anterior cingulate cortex, known as a key structure in modulating SC responses to emotional cues, was not damaged in the present clinical sample. However, considering the fact that both evoked potentials and subjective arousal ratings revealed abnormal responses to emotional stimuli in brain lesioned patients, one might also

argue that skin conductance responsiveness may not be such a reliable indicator of emotional impairment as previously assumed.

Damasio and colleagues have repeatedly emphasized the lack of SC responses to affective cues as a key deficit in patients with frontal lesions. In fact, Damasio considered his "*unequivoca*l" results (Damasio, 1994, p. 209) as the main confirming evidence for his "somatic marker theory". The specific SCR impairment in frontal patients was interpreted as the incapacity of those patients, when being presented with an emotional stimulus, to retrieve past emotional experience which should lead to a physiological activation appropriate to the emotional cue. In Damasio's words, they "*could not produce a somatic state or, in the very least, a somatic state of which they could be aware*" (Damasio, 1994, p.211). In the present thesis, the skin conductance findings along with evidence from ERP and subjective data argues against the assumption of the complete failure in frontally damaged patients to adequately respond to affective stimuli. Even though in patients with prefrontal lesions, both parameters revealed prominent impairments in elaborating emotionally relevant pictures, it is important to note that neither the whole patient group nor any of the lesion subgroups showed an entirely abolished distinction between affective and neutral stimuli. In particular, the ratings of self-experienced arousal reveal that, although emotional stimuli, especially unpleasant ones, were perceived as less exciting, frontally lesioned patients were still able to experience an emotional state. Thus, the term "somatic marker deficit" should be used with caution and, in particular, should not be generally applied to all frontal lobe patients. Evidence from the present study suggests that distinct areas within the frontal lobe, for instance the VMPFC, might be related to specific impairments of emotional elaboration. In this regard it would be interesting for future studies to investigate affective stimulus processing in frontally damaged patients with and without damage of the anterior cingulate cortex.

An alternative explanation for patients' particular impairment of emotional elaboration could be provided by referring to the motivational organization of emotion as proposed by Lang (Lang, 1998; Lang et al., 1997). In this regard, both physiological and subjective data would argue for a specific impairment in frontally damaged patients to adequately direct motivated attention towards emotionally relevant stimuli. Very early ERP responses that differ between arousing and neutral pictures and the capacity to produce adequate SCRs indicate that patients are principally able to differentiate between emotional and neutral contents. However, the consistent impairments during later stages of stimulus elaboration together with the reduction in self-perceived arousal suggest that emotional pictures are considered by patients as motivationally less relevant. As a consequence, less attentional resources are allocated to these stimuli which leads to a less deep and efficient cognitive

elaboration process. Our data further show that this attention-related deficit in patients with prefrontal lesions might be more pronounced with respect to aversive emotional motivation compared to appetitive motivation.

Besides revealing that traumatic brain lesions lead to significant deficits of affective stimulus evaluation, the present findings provide important insights with respect to temporal aspects of emotional elaboration by allowing conclusions about which brain structures are involved at what specific processing stage. Our ERP results strongly support the assumption of a network of various neuroanatomical structures associated with the elaboration of emotionally relevant stimuli. In agreement with previous functional imaging studies, our evidence suggests that this network recruits medial temporal areas as the superior and middle temporal gyrus (Iidaka et al., 2001) and parts of the prefrontal cortex, namely ventromedial prefrontal areas (Northoff et al., 2000) and the orbitofrontal cortex (Keightley, Winocur, Graham, Mayberg et al., 2002). Since amygdala lesions could not be detected in the brain injured patients, it was not possible to investigate the specific effect of such lesions on affective elaboration and draw reliable conclusions about the role of limbic structures in emotion modulation. However, the finding that very rapid discrimination between arousing and calm pictures was not affected in the TBI patient group might be an indication that at this early processing stage, the amygdala may play an especially important role whereas orbitofrontal areas are not involved. This assumption is supported by studies arguing for a modulatory effect of the amygdala on early affective perceptual processing (Anderson & Phelps, 2001) and the amygdala's implication in non-conscious monitoring of emotional stimuli (Whalen et al., 1998). Future clinical investigations should address this issue by studying rapid EEG responses to emotional stimuli in patients with well defined amygdala lesions.
In addition to the amygdala, evidence from the lesion group comparisons suggests the ventromedial prefrontal cortex as a further brain structure associated with rapid picture processing. In fact, the 160-220 ms ERP pattern of patients with VMPFC lesions was found to reflect less efficient visual encoding of highly arousing slides compared to patients without lesions in this brain structure. This leads to the suggestion that ventromedial prefrontal areas may be able to modulate even relatively early aspects of perceptual processing of emotional stimuli via top-down influences on the visual cortex. Support for this notion comes from single-unit recordings in human VMPFC in response to presentation of affective facial expression (Kawasaki et al., 2001).

Conscious cognitive processing of affective stimuli as indexed by the P3 and subsequent slow potentials was found to be noticeably affected by prefrontal (ventromedial and orbitofrontal) and

temporal cortical lesions. The middle and superior temporal gyri that receive bilateral projections from the amygdala, and prefrontal regions which are reciprocally connected with visual association areas have already been reported to be part of a network that modulates evaluation of facial expression and emotional pictures (Iidaka et al., 2001; Kuniecki et al., 2003). The present evidence would therefore fit the idea that once a stimulus is initially identified as emotionally salient, prefrontal contribute to stimulus relevance by relating information about the external visual cue to interoceptive information. If the stimulus is categorized as motivationally relevant, the prefrontal cortex may trigger the allocation of attentional resources towards this stimulus and finally, through his reciprocal connections with visual association areas in the temporal lobe (see Figure 6.1.), prime the visual cortex for further perceptual processing. This top-down influence of the prefrontal cortex is also described by Lang (1998) who explains that the "*increased activity…in perceptual processing areas for emotional … stimuli implies reentrant processing from sites more anterior in the brain*". Our data furthermore indicate, that the modulatory effect of frontal brain areas might depend on stimulus valence; the specific impairment at later processing stages in differentiating between unpleasant and neutral pictures that was found for the whole patient group and also for the subgroup with VMPFC lesions would argue for a particular involvement of prefrontal areas in evaluating unpleasant emotional stimuli.

My conclusion follows with a graphical illustration (Figure 6.1.) adapted from a recent review by Adolphs (2002) who has summarized various literature on perceptual processing of emotion. Although his conclusions were mainly based on studies on recognition of emotional facial expressions, they offer several similarities to the evidence found in the present thesis with respect to both temporal as well as neuroanatomical aspects of visual affective processing. Figure 6.1. shows, on the left, Adolph's schematic illustration of the initial stages of emotional stimulus elaboration and, on the right, the respective supporting evidence from the present thesis.

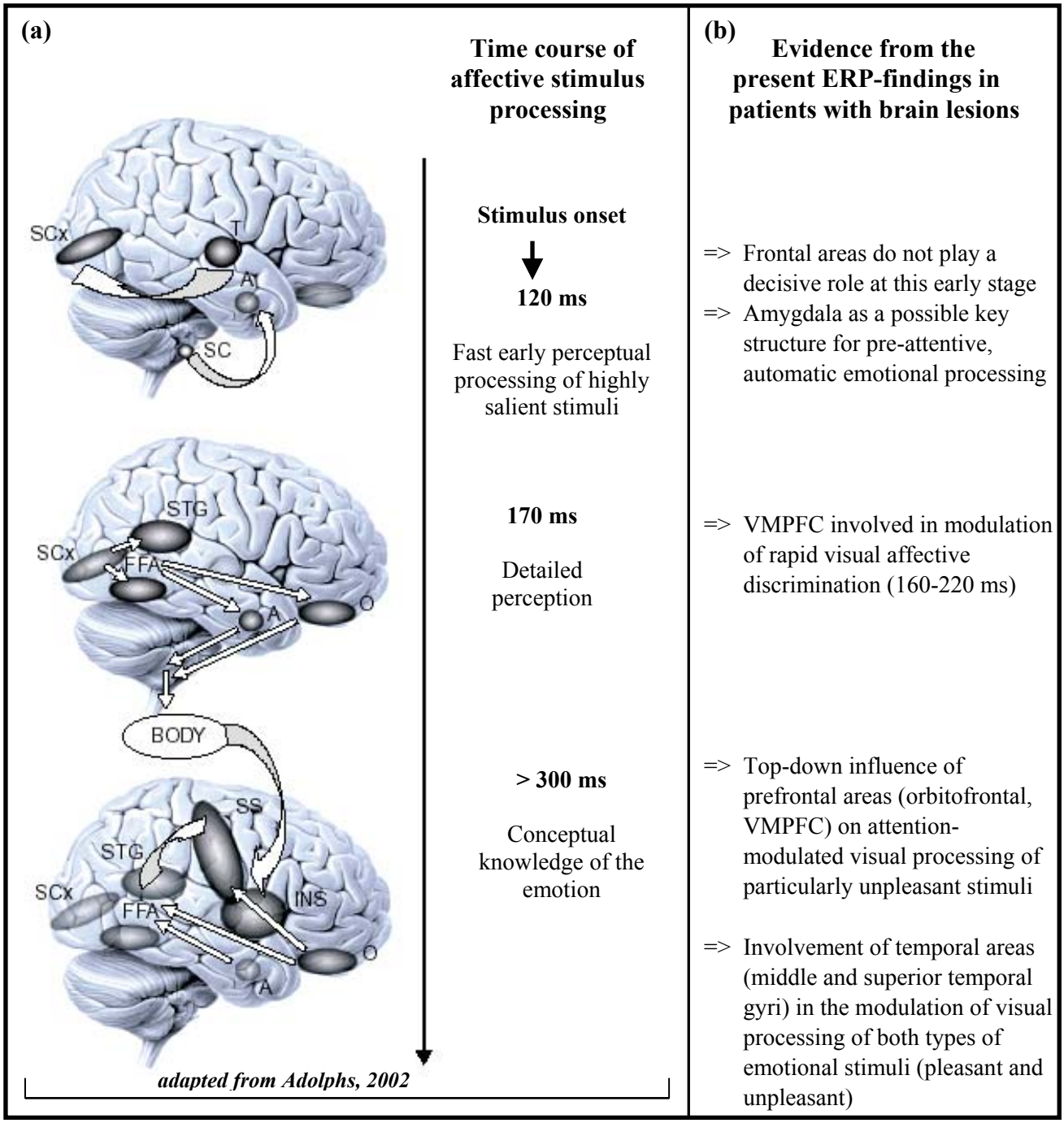

Fig. 6.1. Time course and neuroanatomical correlates of visual affective processing

(a) *Processing of emotional facial expression as a function of time, and brain structures involved at various time points; model proposed by Adolphs (2002) (**A=Amygdala**, FFA: fusiform face area; INS: insula; **O: orbitofrontal cortex**; SC: superior colliculus; **SCx: striate cortex**; SS: somatosensory cortex; **STG: superior temporal gyrus**; T: Thalamus)*

(b) *Evidence from the present investigation argues for similar temporal and neuro-anatomical mechanisms in the processing of visual affective stimuli other than faces*

Outlook

This thesis aimed, for the first time, at investigating deficits of emotional processing in TBI patients by systematically studying physiological and subjective responses to standardized emotional visual stimuli in a representative sample of head injured patients with mainly frontal lesions. Results support a model of an impaired discrimination between neutral and emotionally relevant stimuli in these patients and point to a specific role of prefrontal brain areas in affective picture processing.

Methodological limitations of the present study should provide recommendations for further research on brain injured patients:

The clinical sample was selected to be homogeneous with respect to rehabilitation status and brain lesion characteristics in that all TBI patients had predominantly orbitofrontal lesions and showed no substantial impairment of those basic cognitive functions (orientation, perception, and language comprehension) necessary to understand the experimental procedure. This homogeneity was advantageous when comparing the whole patient sample with a control group. It implied, however, some problems regarding the generation of subgroups. It was not possible to divide patients into small groups with completely distinguished lesions; instead, there was still a substantial lesion overlap between subgroups that were compared with each other. The absence of differences between two clinical samples, for instance, on neuropsychological measures and skin conductance responses, might, be related to their shared neuroanatomical and basic cognitive characteristics. To draw a reliable conclusion about the specific effect of a given brain structure on affective stimulus processing, future studies should compare representative samples of different head injured groups characterized by well defined lesions. Ideally, patients with circumscribed lesions of the amygdala and the anterior cingulate gyrus should also be included, as the consequences of damage to these brain areas that are assumed to play an important role for emotional elaboration, could not be investigated in the present patient group. A further issue which could not be addressed concerns the impact of lesion lateralization on affective stimulus evaluation. As our patients had all suffered bilateral, rather symmetrical brain damage, a further subdivision into groups with left and right hemispheric lesions was not possible. Future research on patients with unilateral lesions would be particularly useful to gain important insights in hemispheric specialization for emotional processing.

The ERP methodology employed for the present experimental paradigm provides an excellent temporal resolution and is particularly suited for studying cortical activity changes by relating them to different stages during picture viewing. To obtain more information on spatial characteristics of emotional processing, further EEG-studies should use high-density electrode arrays, together with a distributed source analysis procedure to reliably estimate the cortical sources of changes in the

scalp-recorded ERP. Another recommendable approach would be the use of whole head Magnetoencephalography (MEG) where localization of activity sources is possible even with greater confidence.

Recent research has demonstrated that high-speed presentation of up to 5Hz already leads to rapid detection and perceptual processing of emotionally salient stimuli (Junghöfer et al., 2001). Such a rapid projection of standardized pictures could be advantageous for future studies with brain injured patients as well as other clinical populations. First, many pictures can be presented in a very brief period, thus abbreviating the experimental session, and second, the investigation of emotional processing may be possible without having to fully activate potentially distressing affective responses in patients.

When discussing future research directions, implications for TBI rehabilitation programs should be taken into account. The present study showed that neuropsychological deficits are not necessarily severely impaired after brain damage, whereas the elaboration of emotional stimuli is characterized by consistent alterations compared to healthy persons. If further clinical investigations will be able to come to similar conclusions and provide additional knowledge about the quality and the neuroanatomical etiology of emotional alterations in TBI patients, important insights into effective treatment approaches may be gained. Instead of focusing – as it is the case today - mainly on the rehabilitation of cognitive skills, optimal treatment of brain injured individuals rather should consist of an integrated approach to the wide spectrum of possible neuropsychological, emotional, and behavioral dysfunctions. In addition, relatives of the patients should be included in treatment programs, as the daily family life or the relationship with a partner are often particularly affected by emotional alterations that follow a TBI. Enhanced knowledge about consequences that specific lesions have for emotional behavior might increase the awareness of patients and their family about changed ways of reacting to certain stimuli and situations in brain injured individuals. Furthermore, on the basis of this knowledge, individualized rehabilitation programs might be designed which enhance the probability that a TBI patient will be able to regain his cognitive, social and professional functionality.

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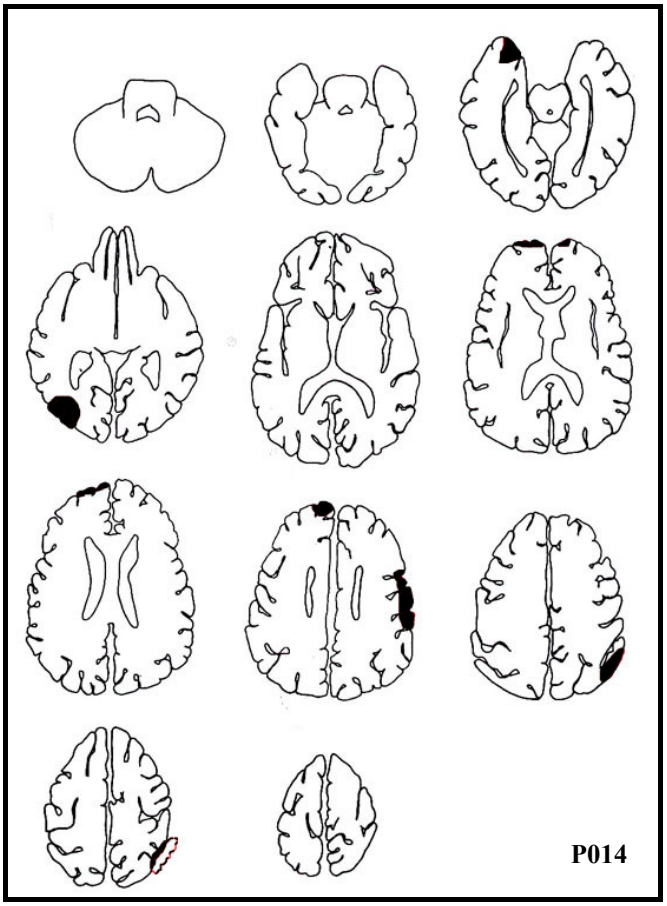
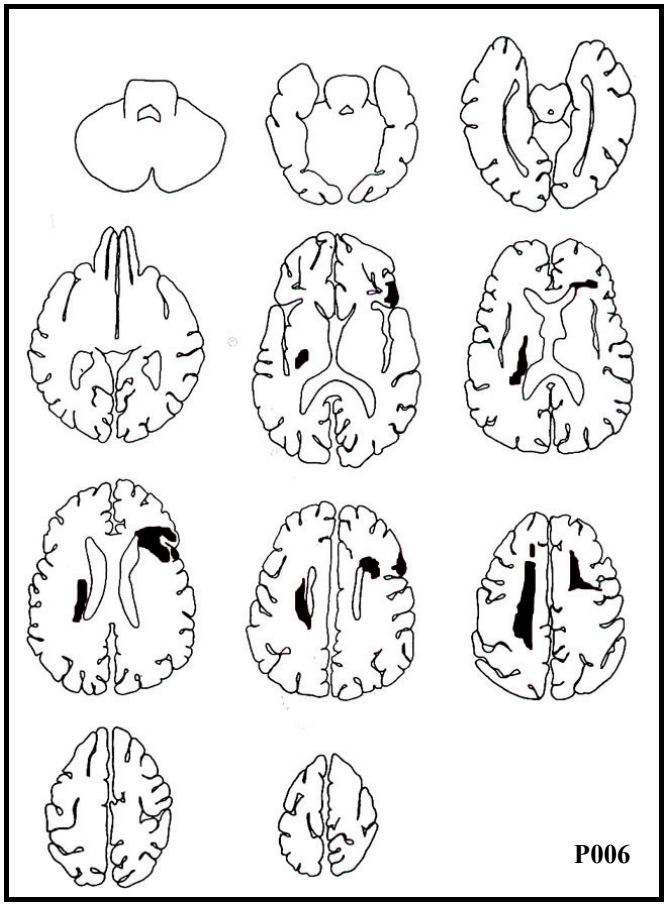
APPENDIX A

Horizontal standard template with marked brain lesion for each patient

(A1-A4 indicate types of cuts obtained with different angles to the inferior orbitomeatal line, e.g. A1 referring to the most horizontal incidence parallel to this same line.)

A1





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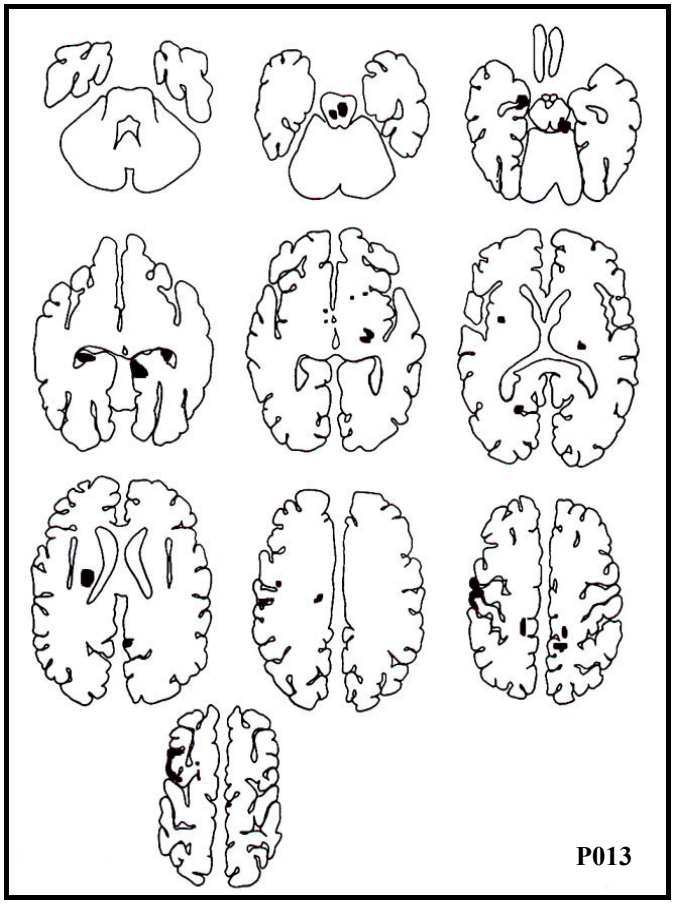

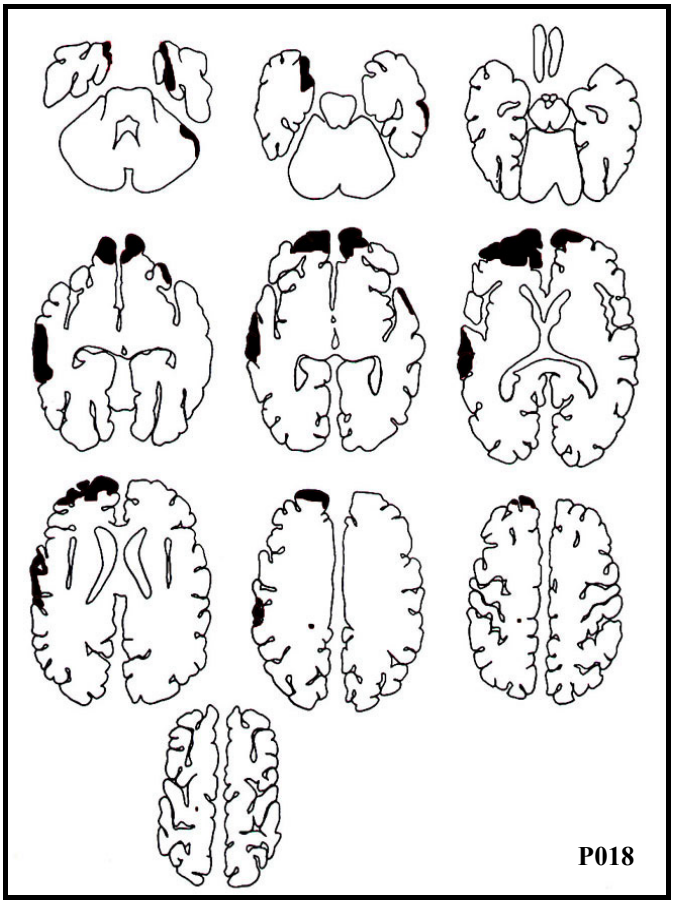

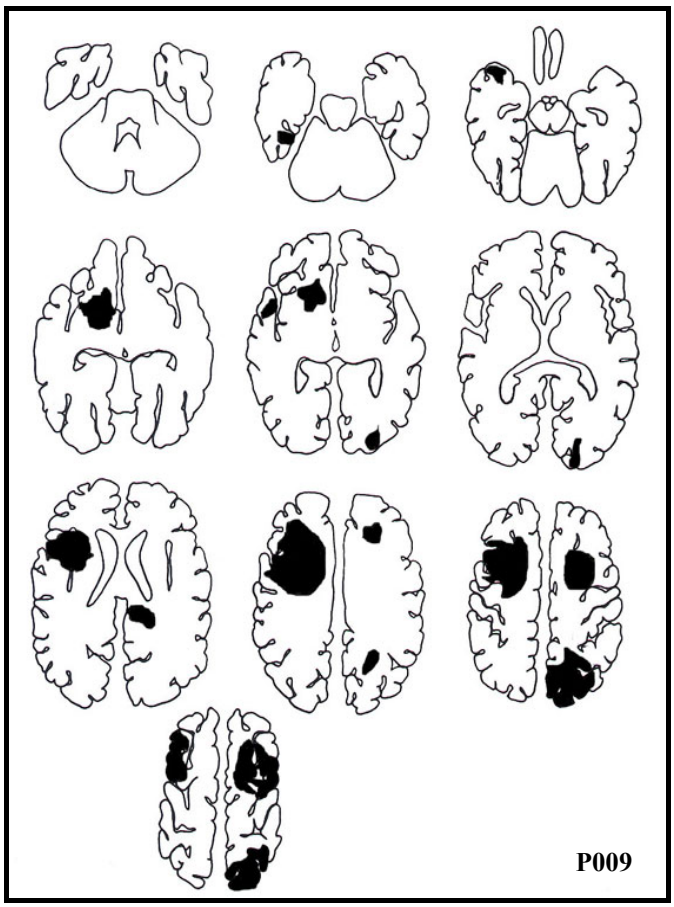

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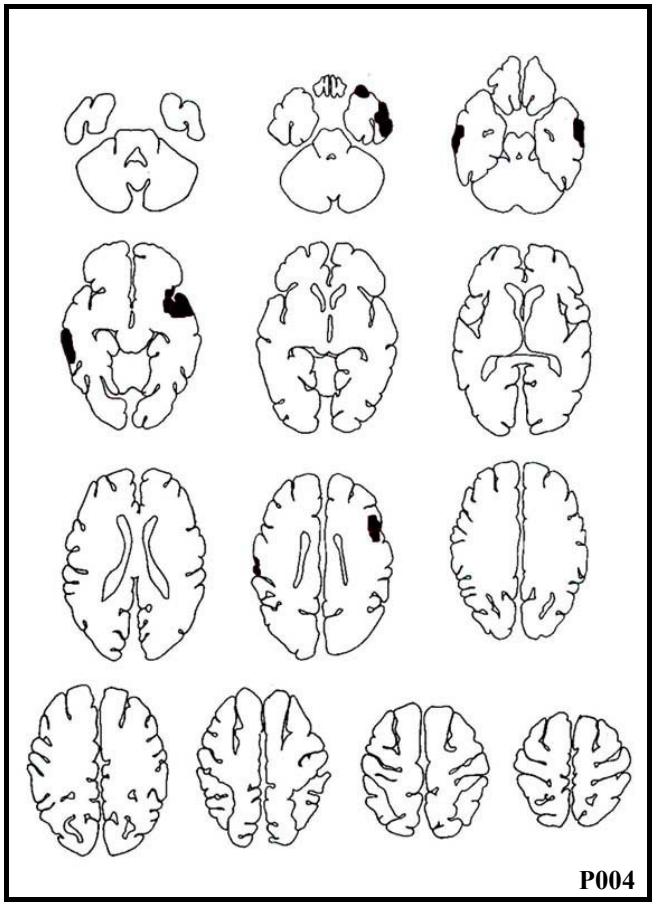

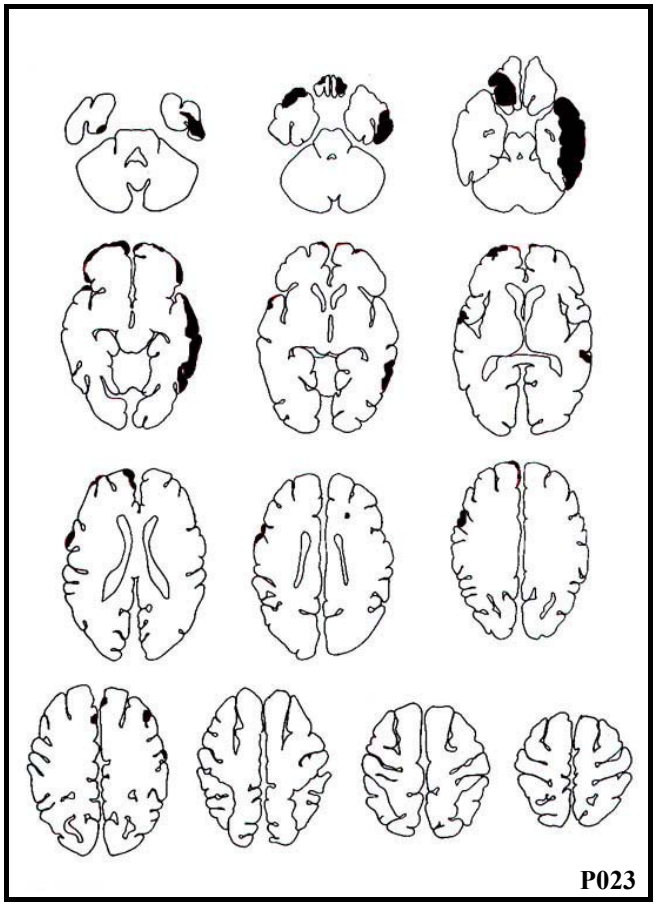

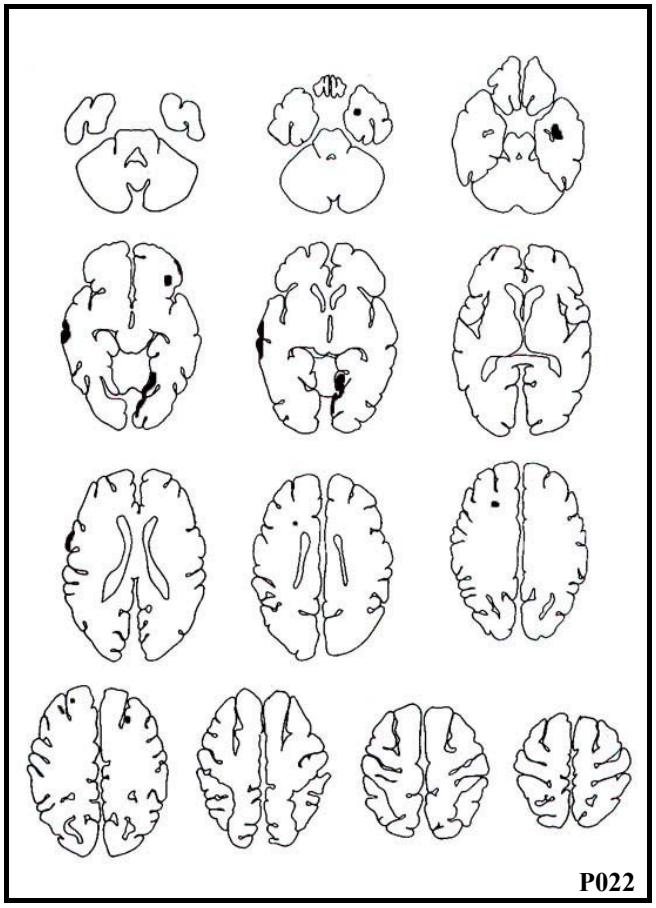

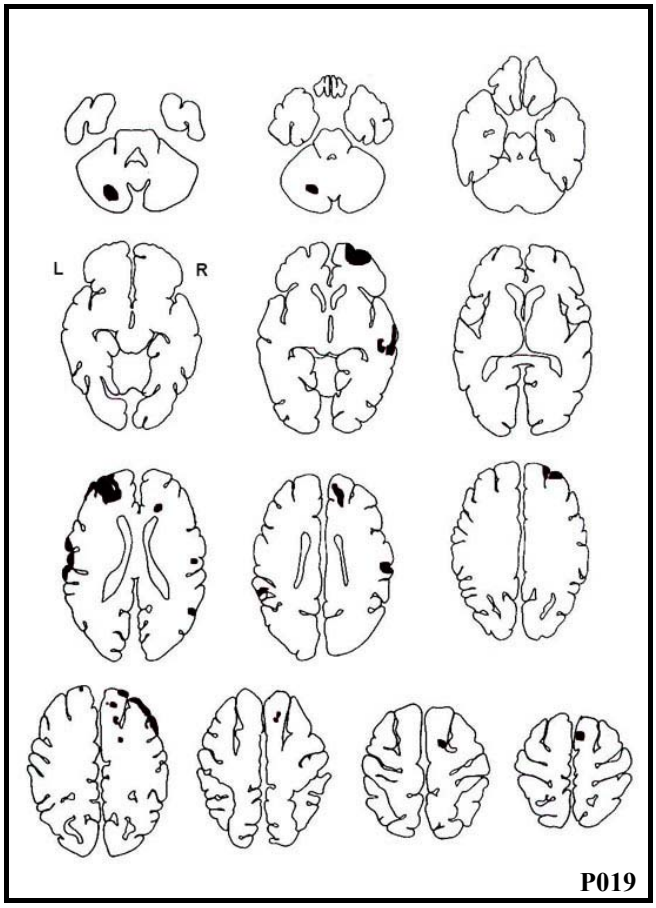

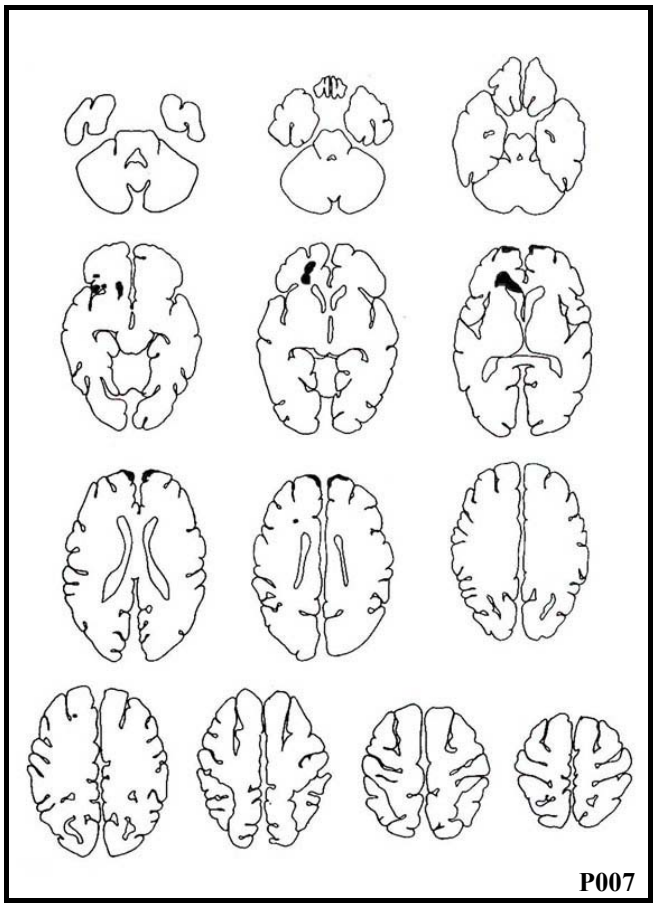
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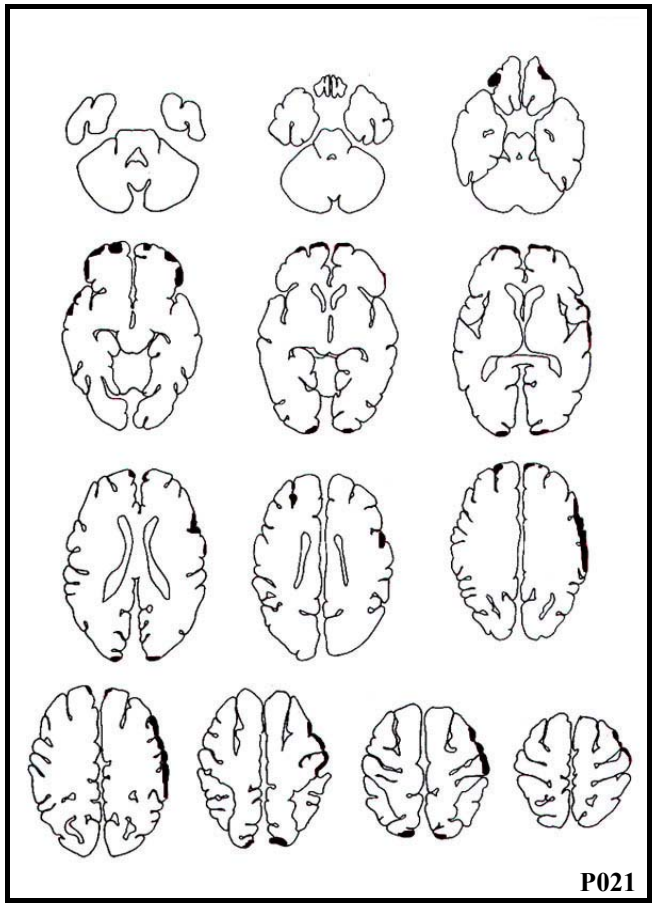
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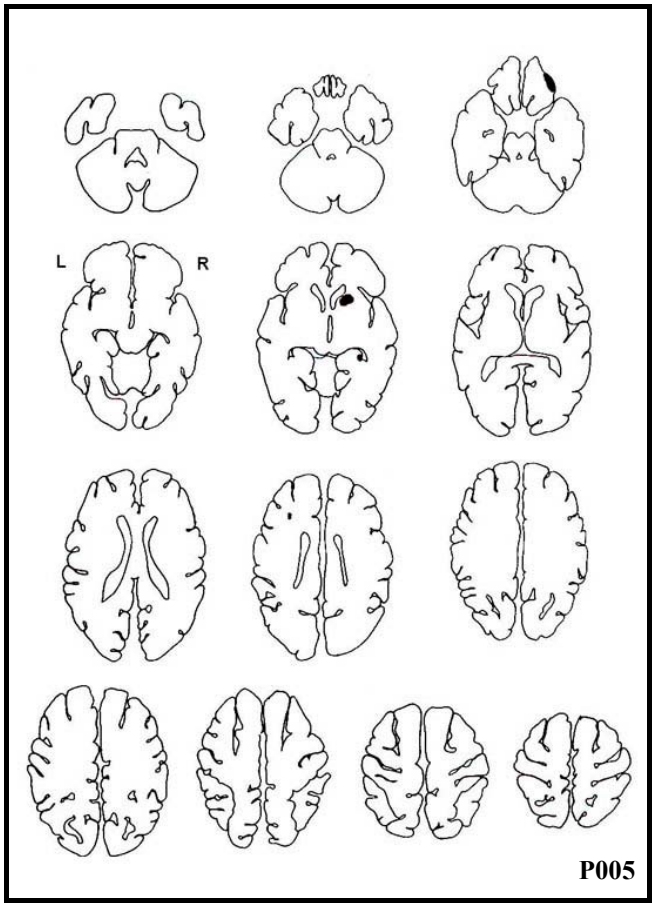
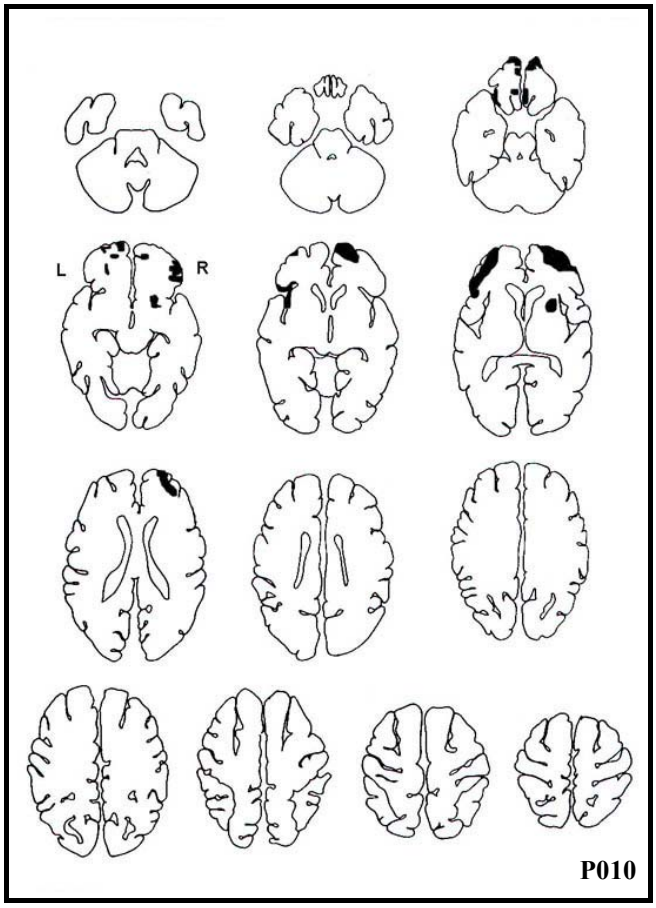

L
R
P005


L
R
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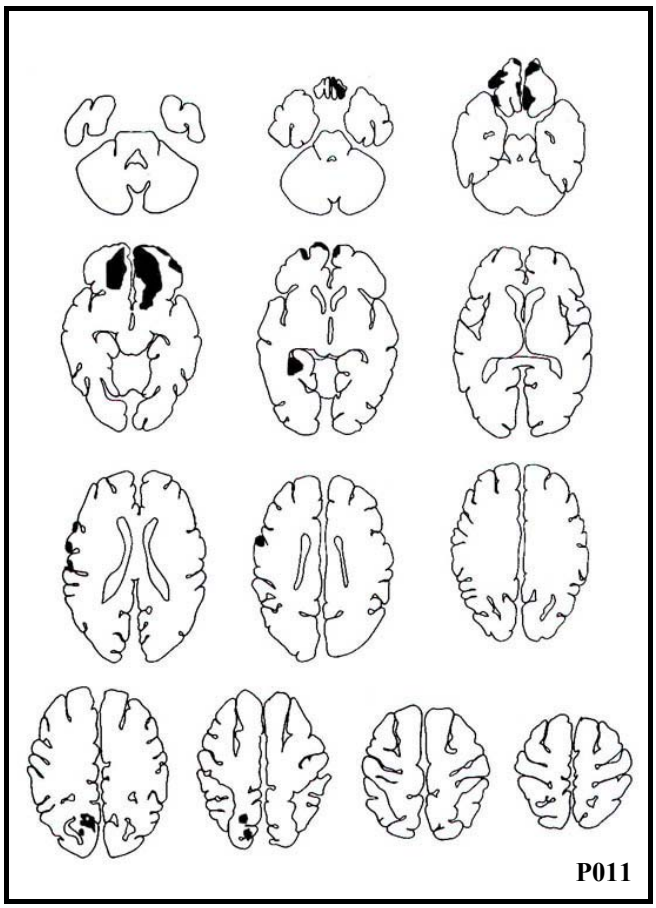

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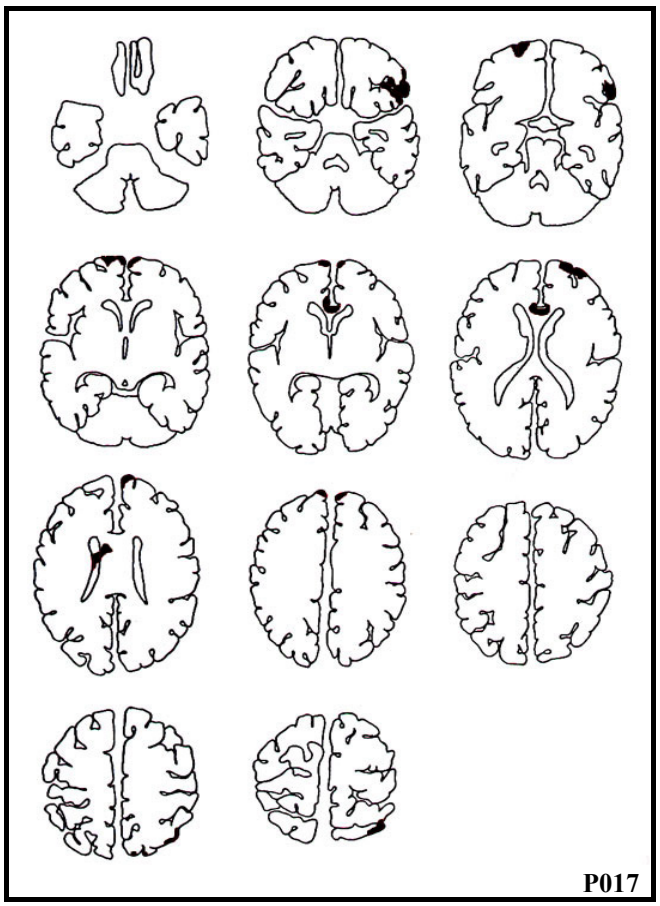

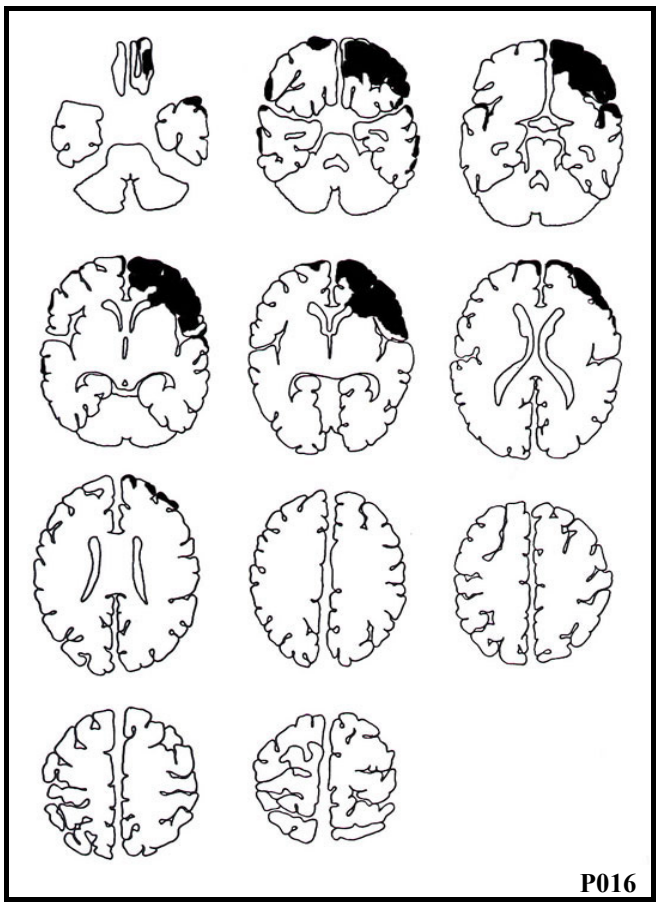

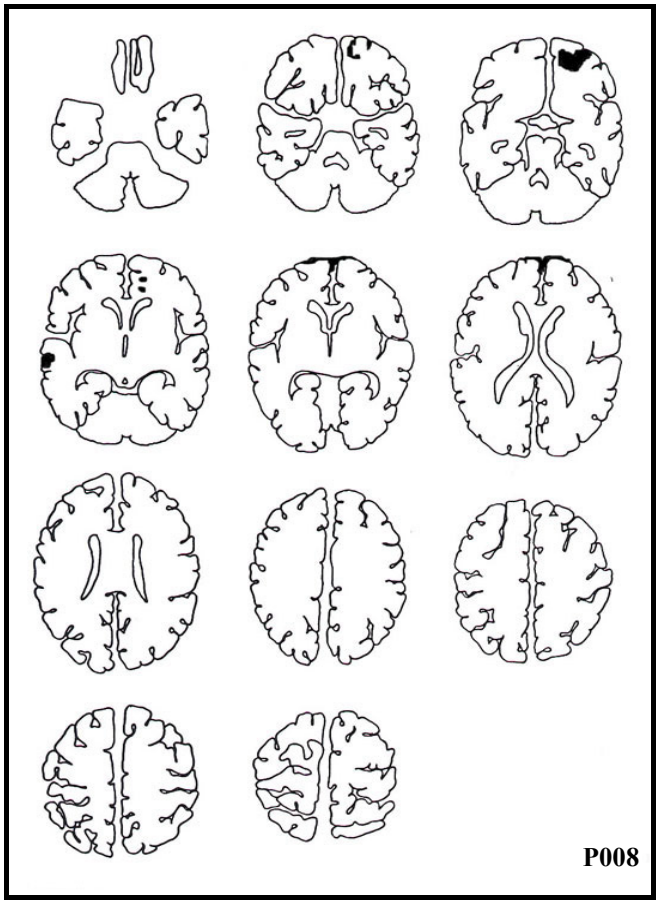
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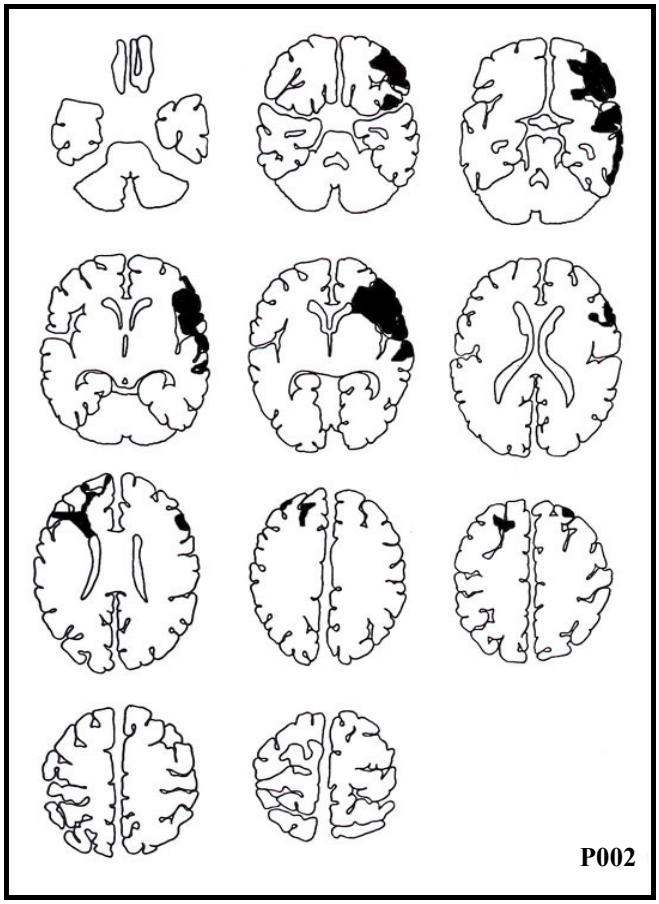
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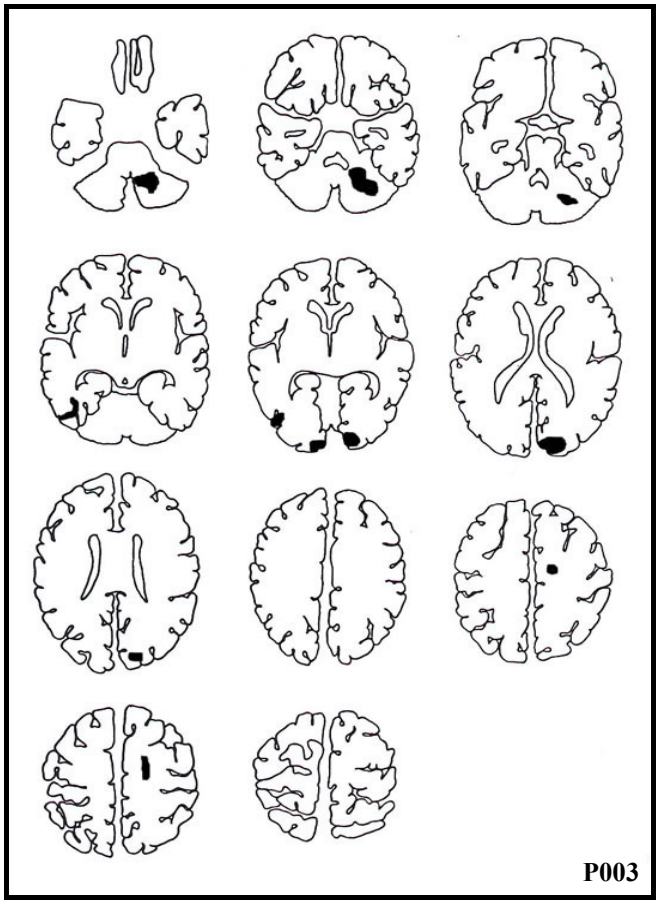
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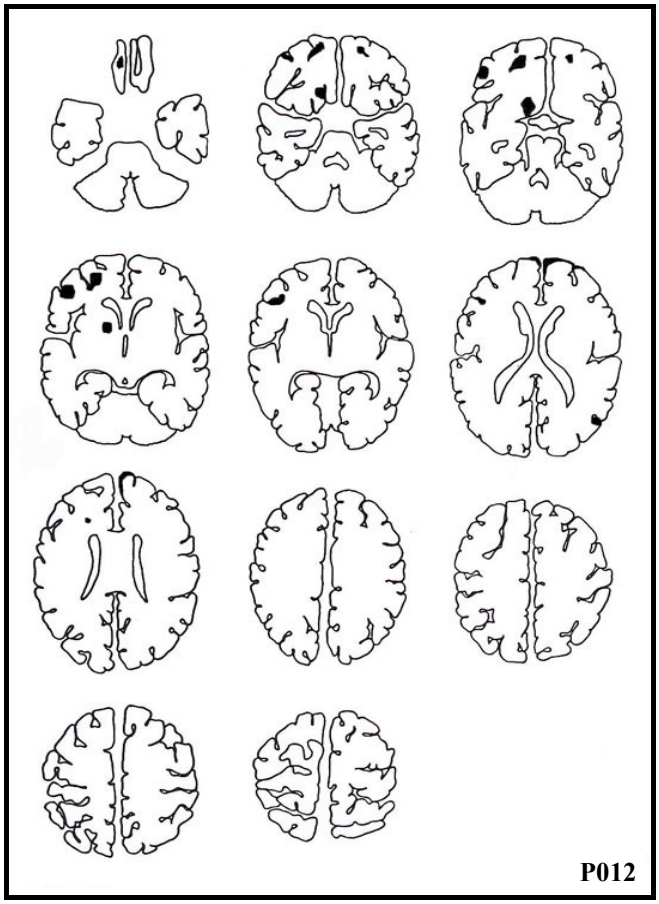
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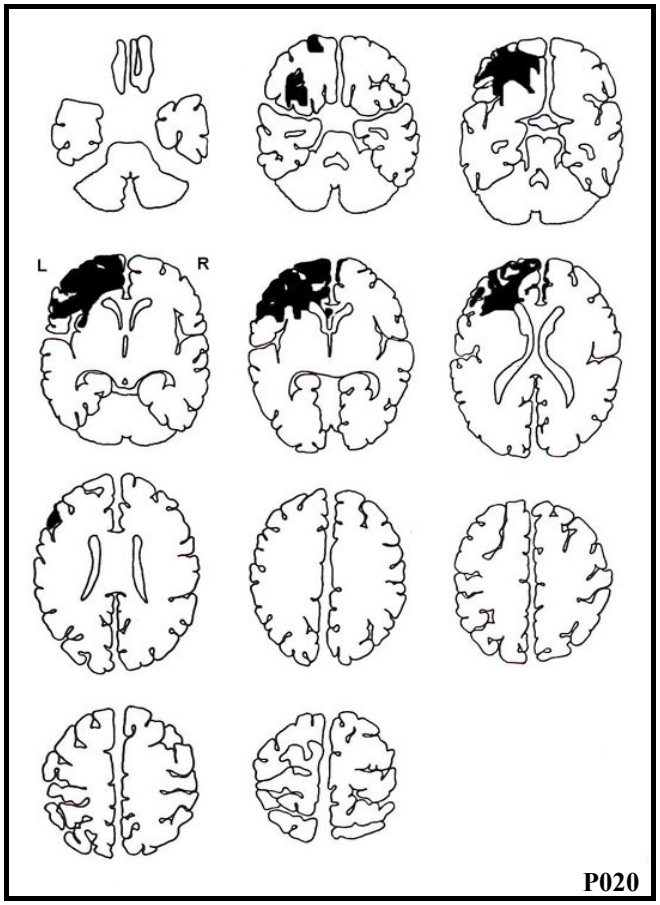
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R
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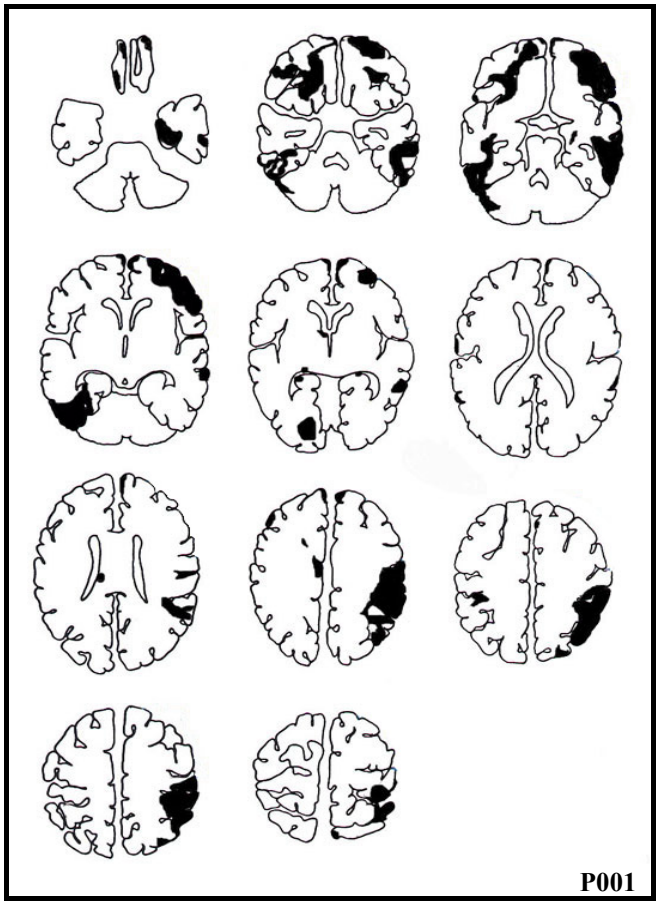

P001

APPENDIX B

IAPS pictures used in the experiment (normative affective ratings for individual slides)

NEUTRAL PICTURES

Examples

2190

7500

7100

Description	IAPS slide number	arousal	valence
Book	7090	2,61	5,19
Umbrella	7150	2,61	4,72
Hair-dryer	7050	2,75	4,43
Fork	7080	2,32	5,27
Rolling-Pin	7000	2,42	5,0
Trash-Can	7060	2,55	4,43
Light-Bulb	7170	3,21	5,14
Building	7500	3,26	5,33
Bus	7140	2,92	5,5
Fire-hydrant	7100	2,89	5,24
Chair	7235	2,84	4,96
Mug	7035	2,66	4,98
Fire cabinets	7224	2,81	4,45
Plate	7233	2,77	5,09
Stool	7025	2,71	4,63
Freeway	7560	5,24	4,47
Ironing-board	7234	2,96	4,23
Mug	7009	3,01	4,93
Basket	7010	1,76	4,94
Shoes	7031	2,03	4,52
Hammer	7110	2,27	4,55
Abstract	7187	2,3	5,07
Fan	7020	2,17	4,97
Man	2190	2,41	4,83
Building	7491	2,39	4,82

PLEASANT PICTURES

Examples

4607

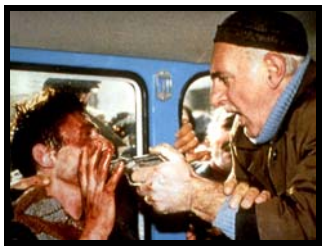
8490

8200

Description	IAPS slide number	arousal	valence
Nudes	4690	6,06	6,83
Nudes	4680	6,02	7,25
Couple	4660	6,58	7,4
Sky-divers	5621	6,99	7,57
Couple	4652	6,62	6,79
Cliff-divers	8180	6,59	7,12
Couple	4607	6,34	7,03
Couple	4664	6,72	6,61
Sex	4800	7,07	6,44
Erotic Female	4220	7,17	8,02
Erotic Female	4290	7,2	7,61
Erotic Couple	4608	6,47	7,07
Erotic Couple	4611	6,04	6,62
Erotic Couple	4670	6,74	6,99
Erotic Couple	4658	6,47	6,62
Erotic Couple	4656	6,41	6,73
Jaguar	1650	6,23	6,65
Skier	8190	6,28	8,10
Water skier	8200	6,35	7,54
Skier	8030	7,35	7,33
Skydiver	8185	7,27	7,57
Sailing	8080	6,65	7,73
Erotic Couple	4681	6,68	6,69
Roller	8490	6,68	7,2
Erotic Couple	4659	6,93	6,87

UNPLEASANT PICTURES

Examples


3530


9420


1300

Description	IAPS slide number	arousal	valence
Babytumor	3170	7,21	1,46
Mutilation	3000	7,26	1,45
Dead Body	3120	6,84	1,56
Dead Body	3140	6,36	1,83
Pit Bull	1300	6,79	3,55
Snake	1120	6,93	3,79
Soldier	9420	5,69	2,31
Mafia-Hit	3010	7,26	1,79
Aimed-Gun	6230	7,35	2,37
Burn victim	3053	6,91	1,31
Burn victim	3102	6,58	1,4
Attack	3530	6,82	1,8
Attack	3500	6,99	2,21
Mutilation	3060	7,12	1,79
Mutilation	3071	6,86	1,88
Mutilation	3080	7,22	1,48
Attack	6313	6,94	1,98
Attack	6540	6,83	2,19
Dead Body	9252	6,64	1,98
Sliced hand	9405	6,08	1,83
Dog	9570	6,14	1,68
Snake	1050	6,87	3,46
Injury	3266	6,79	1,56
Plane Crash	9050	6,36	2,43
Soldier	9410	7,07	1,51