AUTOBIOGRAPHICAL MEMORY, BEGINS AND ENDS WITH THE SELF

Autobiographical memory, Consciousness, the Influence of Stress and Neural Correlates

Dissertation

To achieve the doctoral grade

Of natural sciences

Of the university of Bielefeld

Marie Vandekerckhove

Bielefeld, 2004

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First mentor: **Professor Dr. Hans Markowitsch**

Second mentor: **Professor Dr. Robert Wicklund**

Presented by **Marie Vandekerckhove**

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INTRODUCTION

AUTOBIOGRAPHICAL MEMORY, CONSCIOUSNESS THE INFLUENCE OF STRESS AND NEURAL CORRELATES

Definitions and hypothetical theoretical constructs help us as starting points of empirical inquiry.

FOREWORD

The general purpose of this thesis is to study some fundamental, yet still open questions about autobiographical memory and related consciousness, the influence of early stress on the brain and autobiographical memory and its neural correlates. The goal is to make some progress in the definitory confusion and conceptual understanding of the relationship of these concepts starting from a developmental point of view. In the attempt to throw some light on what can fall under the sum of autobiographical memory-related themes, no overview or review of the existing answers will be given but rather, after extended research of the theoretical and empirical literature and own empirical work, a new clarifying point of view of the different phenomena. Considering the close relationship between the experience of the world, consciousness and autobiographical memory, the first question that becomes addressed in the theoretical part is how a child develops autobiographical memory and what Tulving entitles as associated ‘autonoetic consciousness’, a self-reflective mental state of awareness in time and space (Tulving, 1985; 2002). The second question is concerned with how early childhood can form the basal template in the buffering and facilitation of influences of stress on the brain and also on autobiographical memory, with psychogenic amnesia and altered autonoetic consciousness as a prototypical example. Autobiographical old memories are as a result of a high degree of anatomical interconnectivity and cognitive complexity most vulnerable to brain damage and other external and internal influences such as stress (Markowitsch, 1995; 1999; 2000; 2002; 2003; Tulving and Markowitsch, 1998). The second empirical part of the thesis, is primarily focused on the fundamental research of autobiographic memory, and its neural correlates. The different focuses within the chapters will bring up more questions for theoretical thinking and empirical research about the same complexity of which individuals are made of.

1. MEMORY, AUTONOETIC CONSCIOUSNESS AND THE SELF: Consciousness as a Continuum of States

The chapter about autonoeitic consciousness responds on a renewed need to understand the phenomenon of consciousness and subjective experience. Science is still far from understanding the relationship between consciousness, self-consciousness and memory, especially autobiographical memory. We notice a growing dissatisfaction with the Cartesian separation of body and mind, together with the desire to give the phenomenon of subjective experience a place in science, especially from an integrative view of neurophysiological, philosophical and psychological concepts. Departing from the theorizing of Tulving (1985, 2002) about semantic and episodic memory and cognitive child development of memory (Nelson, 2002, in press; Nelson & Fivush, 2001), the basic idea is that different levels of development of the self relate to the phylogenetic development of different states of consciousness of being in the world. A gradual distinction becomes suggested: from 1. a rudimentary state of autonomic awakeness or unknowing consciousness as a biological adaptive function or “anoeitic” consciousness, towards 2. "knowing consciousness”, including “noeitic” and “autonoeitic” consciousness based on semantic and episodic memory systems. Evidence from the influence of brain damage upon autobiographical memory, and from the effects of stress on autobiographical memory and related consciousness confirms the proposed framework insisting on the significance of different states of consciousness connected with different ways how the self becomes expressed in information processing and memory.

2. NEUROVULNERABILITY: The Influence of Early Stress on the Brain, the Self and Autobiographical Memory

This chapter primarily tries to contribute to the problem of different forms of early stress on the brain, and finally also on autobiographical memory and autonoeitic consciousness. I suggest that during early childhood, intimate care-taking constitutes the most important prerequisite for properly experiencing and processing stress later and in adulthood. Early, intense or chronic psychosocial stress may induce increased vulnerability on the neural and consequently also on the behavioral level. The phenomenon of what I call: neurovulnerability refers to a sensitivity or reactivity of the central nervous system at intracellular and biochemical to neurophysiological and psychological levels, facilitating the outbreak of severe and otherwise inexplicable functional disturbances. Psychogenic amnesia as a prototypical example is associated with an altered connection with the self and state of autonoeitic consciousness as an attempt to fulfil adaptive self-regulatory behavorial responses.

3. NEURAL CORRELATES OF AUTOBIOGRAPHICAL MEMORY: Engagement of Lateral and Medial Prefrontal Areas in the Ecphory of Negative and Positive Autobiographical Memory.

Autobiographical memory allows us to experience ourselves through subjective time associated with the awareness of the prior conscious event. Usually, autobiographical memory is affect-laden, whereby the main distinctions of affect are either of a positive or a negative valence. Based on previous (PET) findings on neural activations related to the ecphory of old autobiographical episodes a question of interest is whether in addition to a likely engagement of frontal lobe regions other brain areas are implicated differentially in the processing of sad versus happy old autobiographical memories. This study relates to quite earlier studies, implicating in particular the orbitofrontal portion of the prefrontal lobes in a number of emotion-related processing patterns.

This research about autobiographical memory will give us a deeper understanding of autobiographic memory, the interaction between emotion and memory and functional neuroanatomy.

4. BI-HEMISPHERIC ENGAGEMENT IN THE RETRIEVAL OF NEUTRAL, POSITIVE, NEGATIVE AND STRESSFUL AUTOBIOGRAPHICAL EPISODES

Autobiographical memory includes emotional memory ranging from neutral to negative, positive and stressful memories. Stress, as viewed here, is a quantitatively specifiable variable which almost superposes the positivity or negativity of an event. The inclusion of stressful memories is also considered to be important, since stressful incidents – if not coped properly – may lead to a block of autobiographical memory retrieval and may change the activity of specific brain regions most likely due to changes in brain metabolism such as an increased release of stress hormones and the block of receptor channels in memory sensitive areas (Markowitsch, 2002; 2003). Using functional magnetic resonance imaging (fMRI), the study addresses the question whether autobiographical memories of a positive, negative, stressful, or neutral character recruit similar or different neural networks. Obtained results will have implications for the classification of memory tasks with respect to memory systems and related autonoetic consciousness, the influence of different types of autobiographical memory, laterality and processes.

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CHAPTER 1

MEMORY, CONSCIOUSNESS AND THE SELF:

Consciousness as a Continuum of States

1. MEMORY, AUTONOETIC CONSCIOUSNESS AND THE SELF IN DEVELOPMENTAL PERSPECTIVE

James (1890) defined the basis of our identity as:„the knowing of the I who knows the bodily me, who has an image of myself and sense of identity over time."

Introduction

This chapter addresses some open questions about the self, development, consciousness and memory, especially episodic memory, and is meant to bring more clarity to the definitory confusion of these phenomena and especially the relationship between them. Though in the past many attempts were made for a deeper understanding of consciousness, science is still far from understanding the relationship between consciousness, self-consciousness and memory. Actually, a renewed need exists to understand phenomena of consciousness and subjective experience, especially from an integrative view of neurophysiological, philosophical and psychological concepts (Zeman, 2001).

Given the close relationship between the experience of the world, consciousness and memory, the first question that becomes posed is how children develop awareness of themselves as someone with specific semantic characteristics and as someone embedded in the dimensions of time and space. Although do not have the intention to solve the posed questions, the theorizing of Tulving (1985, 2002) about semantic and episodic memory and cognitive child development of memory teaches us to see how different levels of development of the self relate to the phylogenetic development of different states of consciousness of being in the world. A gradual conceptual distinction is suggested, starting from 1) a rudimentary state of autonomic awakeness or unknowing consciousness as a biological adaptive function - "anoetic" consciousness and self-consciousness relying on implicit and procedural memory - towards 2) "knowing consciousness", first "noetic", then "autonoetic" consciousness. Noetic consciousness is based on semantic memory, whereas autonoetic consciousness is based upon a self-reflective state of self-consciousness within time and other contextual dimensions.

In addition to actual theorizing, we also point to the importance of a first sort of 'self-experience' or self-consciousness already apparent at an anoetic level. Children, already very early in development, develop an implicit awareness of their own organism and of its influence on the surrounding world. Even when they are still not capable to reflect on the perceptual origin of their own knowledge, they possesses already very early, implicit experiential information about themselves ('anoetic self-consciousness'). Without this level we are not able to understand phenomena as experiencing oneself without explicit remembering time and context.

In the third part we continue to describe temptatively the neural correlates of the differential continuum of consciousness.

1.1. FROM UNKNOWING CONSCIOUSNESS...

Very early in development, children are aware of the presence of other human beings, through tactile, auditive, visual and other sensory experiences (Piaget, 1972). Babies smile „at" their mother, experience their emotions, but cannot observe or perceive them distinctly from the environment (Lewis & Brooks-Gunn, 1979). Even within a few hours of birth, infants display preferences for face-like stimuli (Goren et al., 1975, Gauthier & Nelson, 2001). Young children continuously look for social contact, warmth and intimacy to build a social form of comfort or agreeable situation. In this context, Nelson (2001) and Gauthier and Nelson (2001) found that at the age of 6 months, faces begin to be seen as a separate class of objects. For events with which infants are familiar, like a face they have often seen, infants at 3 months show recognition memory after short periods of exposure (Pascalis et al., 1998). However, even when there is a primary interest in the other person, anoetic consciousness is still essentially egocentric and without reflective awareness of that something. Anoetic consciousness is the simple awareness of the environment and the own organism almost exclusively based upon primary procedural and affective learning principles. At this level of consciousness, children "experience" themselves and the world without a reflective capacity. Little infants live in this affective/sensory-motoric relationship with the world and cannot refer to the feelings which they experience (Piaget, 1962). Also, the world may at first, at least partly, though being a point of controverse, be experienced as an extension of oneself. The caregiver functions rather as an external regulator of the children's' internal anoetic state of consciousness. He or she is actively involved in affective transactions with the infant influencing the growth of the brain structures involved in imprinting these affective experiences (Schore, 1994, 2000). These child-caregiver transactions result in early attachment relationships and are internalized and encoded at the level of procedural-affective memory (Amini et al., 1996). Development proceeds then to more and more sensitivity for the spatial environment and oneself, through one's own activities (Butterworth, 1995).

1.2. TO KNOWING CONSCIOUSNESS

During the first three months of life children seem to show a spontaneous interest in the image of other children, without explicitly differentiating between themselves and others. Between the age of three and eight months, however, children already recognize their own image in the mirror on the basis of contingent cues between their own body-movements and the movements in the mirror (Gallup, 1977; Butterworth, 1992). Children see themselves as the cause of the moving visual image. However, it has not yet been clarified whether babies know that the image is the image of themselves. Self-recognition arises at the moment the infant becomes personally touched by the recognition of him- or herself, not just by someone.

At about 8 to 9 months of age, children learn to manipulate or internalize the environment as an object of thought and begin to exhibit "joint attention" (Tomasello, 1988, 1993). When the mother attends to her child as an object of interaction, children become stimulated to do so as well. Children develop an awareness of themselves as an object of observation for others, and thus develop this awareness of the self as an object as well. Neisser (1995) stated that even very young children appear to perceive themselves as real objects embodied and embedded in the world.

This alteration of consciousness of oneself on a level of experience, towards the explicit 'awareness' of oneself as an object of attention, is dependent on a capacity to control attention (Posner, 1994). Between 13 and 15 months of age, research has shown that infants are also able to direct an adult's attention to a particular (distal) object and check whether the adult is attending to it (Tomasello, 1999, p. 65). That this requires knowing consciousness is convincing, while as Perner (2003) discusses, we never point out a particular object absentmindedly, and check whether another person attends to it.

1.2.1. NOETIC CONSCIOUSNESS AND SYMBOLISATION

At the age of one year, children show a remarkable shift in consciousness of how language may be used to locate and name objects and to express intentions (Carpenter et al., 1998). Within the theory of Piaget (1926) on the sequential appearance of different forms of mental representation., the earliest forms are called figurative; knowledge is assimilated in perceptual cues and the highest form of knowledge representation is the emergence of language, which he termed the "symbolic phase" (Piaget, 1926). Infants between 13-15 months of age, for instance, possess already a referential use of language (Perner & Dienes, 2002). While this use of language could first reflect imitated utterances, the genuine (non routinized) production of two-word should be a better indicator of what we understand by knowing consciousness (Perner & Dienes, 2002).

Also, at about the age of 8-12 months, children begin to become aware of categorial features of the self and to locate objects (Butterworth, 1995; Lewis, 1979). Experiments have shown that children of this age can now become aware of things, people, places and concepts that are not directly perceived (Piaget, 1926). They start to think about the world, their bodies and what they can do (Meltzoff, 1988); this co-incides, as we suggest, with an incepient functioning of the semantic memory system. The retrieval of this factual knowledge of the world, or semantic memory retrieval, is accompanied by what Tulving calls 'noetic consciousness', or the awareness of something in the world without temporal or contextual reference.

The Self and the World

Finally, between 12 and 24 months, children become more fully capable of differentiating between themselves and the environment (Kagan, 1981). Freud (1923) and Erikson (1963) saw this as the age where 'the I' or 'the ego' reach consciousness. Together with a heightened awareness for the distinction between the self and the world, children of about 18 months demonstrate the ability to recognize a picture of their face (Lewis, 1992), knowing that the picture belongs to themselves. Likewise then, children experience their feelings as distinctly personal.

Recognition of oneself as an autonomous being, though being a point of discussion in developmental science, might be indicated by the observation that infants are able to remove a dab of odorless rouge from their nose using the mirror reflection as a guide. Self-recognition in a mirror arises at the moment the infant becomes personally touched by the recognition of him- or herself, not just by someone. The capacity of independent movement of children at about 18 months of age stimulates the awareness of oneself as an independent subject (Butterworth, 1995; Neisser, 1995).

According to Lewis (1992), this seems to begin at about the age of 20 months, related to the awareness of being able to have an effect upon the world. One's own name begins to become associated with the self as a point of reference. Children can verbalize their own situation and the events seen, and begin to define and to formulate the causes of their own activities, such as "I play, I want to do this alone", etc. At this time point of development, children appear to develop the capacity to anticipate the consequences of their own behavior and inhibit specific behavioral responses (Posner, 2001).

The Other as Object

Experiences become internalized, whereby the other becomes manifest as an object externally from oneself. Children evolve more and more as social beings, capable of interacting voluntarily with the environment. Johnson (1982) reported a positive correlation between self-recognition in a mirror and prosocial behavior, as when children comfort their mother when she pretends to be distressed. Around the age of two years, children appear to be able to imitate how it would be to be someone else (Meltzoff, 1990). A capacity to manipulate the relationship between the inner and outer world by strategies develops, such as wanting to impress another person. Children achieve intersubjectivity based on jointly constructed meaning and communication through verbal and nonverbal symbols as well as in reciprocal attunement (Trevarthen, 1992). This sharing of verbal communication and facial expression serves as an essential prerequisite for the further development of perspective-taking, self-consciousness, other-consciousness and memory.

1.2.2. AUTONOETIC CONSCIOUSNESS

Verbal consciousness gains importance as it allows to describe one's own person and the environment. The self as a unit with events from past history within a specific frame and context in the world, or the remembered self in time and space progressively occupies more space in one's thoughts.

In studies on remembering, it has been concluded that between three and six years of age, children develop the ability to remember events as having been personally experienced (Perner & Ruffmann, 1995). But even if children of six can freely recall past events without much help, the question remains, whether they are really 'remembering' in the sense of Tulving's definition, thus within context and personal reflection or reference. Perner and Ruffmann (1995) suggested that children before the age of four years are not capable of encoding information in a personally explicit 'experienced' episodic way.

This means that before that age, children cannot be aware that something happened as a subjective experience which subsequently became integrated into the personal perspective of the rememberer (Wheeler et al., 1997). According to Tulving (1985), children should not be able to remember events as experienced before the age of three. In correspondence, Tulving theorized that before that age children do also not possess autonoetic consciousness which refers to the self-knowing capacity to imagine existence within subjective time and space. Autonoetic consciousness namely has to be distinguished from episodic memory, while, as we will discuss further, it can also refer to the awareness of an image of an event in the present and in the future.

When awareness is directed to the past in time and space, the recall of an episodic memory is required. Explicit memory is revealed when performance on a task requires conscious recollection of previous experiences (Schacter, 1987). Accordingly, this would not mean that children do not 'know' something about the past, including a great amount of details. But, the memories are without autonoetic consciousness.

In line with the theorizing of Tulving, if a child sees another child on the street, it is able to recognize the child on a 'semantic knowing' level, but it does not remember the child in a visual sense, within the context of time and space inherent in the recollection of the past in an episodic way (Wheeler et al., 1997; Tulving, 2001). In work from Perner and Ruffman (1995), children before the age of about 4 or 5 years do not understand why they say that they have seen an object, for example, an object which was put inside a box (*). Recollective experience implies the understanding of the ´origin´ or the 'source' of their knowledge, which appears to develop later and is connected with autonoetic consciousness. Perner (1990), too, defined what they call 'experiential awareness' in association with the understanding of the origin of one's knowledge in perception, as a form of autonoetic consciousness.

Eacott and Crawley (1998), however, only found evidence for episodic memory retrieval of children at the age of 21/2 years. Controlling for the fact that the information could come from other sources, they found that children at the age of two years remembered their sibling's birth, but significantly less well compared to those between 2 years and 4 months and 3 years and 3 months of age. In this context, Terr (1988) observed that children younger than 2 years and 4 months of age and up to 3 years with traumatic experiences show replaying of the events with toys and avoidance and fears of memories connected with the trauma, whereas infants older than 3 years at the time of the traumatic event are more likely to have verbal memories of the event. In these memories it is not sure, whether they remain on the level of semantically "knowing something" without involvement of autonoetic consciousness or whether they already implicate explicit recall within time and space.

Also, in this context, other experimental studies have even shown that children can recall events at their 13th month of life (Bauer & Wewerka, 1995). In these studies, recall of events becomes expressed in deferred imitation whereby infants produce actions they have seen previously (Mandler, 1990; Bauer et al., 1994). Meltzoff (1995), however, found that at the age of 9 months, children appear able to imitate a sequence of actions, even after delays of 24 hours to 1 month. By 9 months of age, infants are capable of demonstrating ordered recall under special circumstances; nevertheless, this recall is quite fragile in general (Wiebe et al., 2001; Bauer et al., 2001). Several studies from the laboratory of Bauer and colleagues have shown that if 9-month-old infants are given three exposures to a 2-step event, about half of the infants demonstrate ordered recall when tested one month later (e.g., Bauer et al., 2001; Carver & Bauer, 1999, 2001). Collie and Hayne (1999) observed for a number of specific conditions deferred imitation after a 24 hour delay in infants of merely 6 months.

However, as to the age at which remembering takes place, it is obvious that we still do not know exactly when children can consciously recollect the past in an (explicit) episodic way and when children are able to be autonoetically aware. Even if delayed imitation in its most simple form taps nonverbal declarative memory, based on a single event (third person view) (Hayne et al., 2000; Nelson, 1995), it is not sure whether it can be equated with a memory (knowledge) of that event as a single, past event within time and space.

In this context it is important to note that it is intuitively probable that before children are capable of being autonoetically aware of an event, they possess - aside from the capacity of semantic memory and associated noetic consciousness - already the capacity of encoding personally experienced events related on an implicit 'imaginative' and experiential level, as can be seen when children imitate experienced events very soon after birth. Schank and Abelson (1977), for instance, claimed that babies of 4 months of age may have "personal scripts". They stressed the memory of episodes or a standardized generalized episode which they termed a "script".

Children who are not yet capable of retrieving personal events on an explicit level, we suggest, possess imaginal, "experiential" information on an implicit level expressed as anoetic consciousness. These conclusions still need further empirical confirmation as even the neural circuits underlying the ability of declarative memory (as the recognition or recall of familiar information) are not yet known (Carver et. al., 2000; Hayne et al., 2000).

The Self as Object of Reflection

Together with a growing capacity for declarative remembering, children establish more and more distance towards themselves as an object of reflection. Verbal consciousness gains importance for describing one's own person and the environment. Outer and inner self-representations in memory form a reality at the age of about six (Selman, 1980). In the childhood period between two and twelve, the uniqueness of the subjective self becomes more and more relevant so that it is maximally actualized in early adolescence (Erickson, 1968). Slowly, children begin to formulate reflective questions about themselves and the world. They can now become aware of themselves as defined by factual personality characteristics, in a ´knowing´ or ´noetic´ sense, or episodically, in an ´autonoetic sense´.

The semantic self is represented with a sum of different traits, whereas the episodic self is represented with behavioral memories and autobiographical memory. We can describe our semantic self by definitions such as: "I am honest, difficult, intelligent and my birthday is the 28th of August, etc.", whereas to describe our episodic self we have to include more of our history, such as: "I am a person who had a nice youth, though sometimes when my father did not say anything for days, I got easily upset".

Based upon described developmental findings and conceptual descriptions, a continuum of consciousness will be outlined.

2. A CONTINUUM OF CONSCIOUSNESS: From Unconsciousness and Unknowing Consciousness Towards Knowing Consciousness

2.1. UNCONSCIOUSNESS AS PREREQUISITE FOR CONSCIOUSNESS

Unconsciousness refers, on the one hand, 1.to the preferences, related tendencies, thoughts, affects and cognitions that are not the object of the present state of awareness. The continuum of unconsciousness towards consciousness, involves a graded potentiality for an unconscious process to become aware. Freudian repressed memories (Freud, 1923), for example, might never come into consciousness, they might eventually be triggered by an associated situation or memory, or they may be masked in a transformed form. Mostly they work implicitly through (1) our ability to give meaning, (2) corresponding experiences and procedural memory and related anoetic and (3) noetic and autonoetic consciousness. Implicit processes such as non-declarative memory have a non-conscious influence on behavior (Squire & Zola-Morgan, 1991). These processes refer to every change in experience, thought and action that is attributable to a past event, such as priming effects, savings in relearning, or proactive and retroactive interference (Kihlstrom, 1993). In prosopagnosia, memories for a specific face are in a way preserved, but the patient cannot express it on a conscious level. Unconsciously they react with physiological responses to familiar and unfamiliar faces. Also, many people, who do not report verbally that they are threatened or stressed, show measurable responses on a physiological level.

2. The second sort of unconscious processes are those of encoding and storage of information and the strengthening of memories. We never become consciously aware of these neural processes. These are, in a way, automatic processes, whereas conscious awareness is a controlled process (Kihlstrom, 1996). Automatic processes work via specific input, independent of any intentionality of the subject, and they cannot be controlled or terminated. We have no introspective access to automatic procedures, or to their operations. These can only be known by inference (Kihlstrom, 1996). In this process of transition between unconsciousness and consciousness, selectivity is included. As

Zeman (2001) stated, there is always a foreground and a background determined by the limited capacity at a given moment.

2.2. "UNKNOWING CONSCIOUSNESS"

2.2.1. CONSCIOUSNESS

Consciousness refers to the level of access that one's awareness can take to some or many of the aspects of his or her own objective and subjective existence, the personal mental process and their variations (Bisiach, 1988). Consciousness is a mental state that permits us to have a phenomenological awareness of our experience (Moscovitsch, 2000). It is the capacity to become aware of something, whereby awareness is the manifestation or expression of this capacity. Awareness is always about something. Consciousness, also anoetic consciousness, is not directed at something specific, in opposition to awareness, which implies the attention to that something. Characterized by what Tononi and Edelman (1998) described as integration and differentiation; each conscious experience is a unified experience achieved in hundreds of milliseconds. The brain has namely the capacity to experience numerous different conscious states, within a short period of time. Consciousness, based on its capacity to form a memory trace, can be divided in different sorts of consciousness: from anoetic to noetic and autonoetic consciousness. The "higher" the level of consciousness on the continuum, the more integration of different senses is involved, affect, imagination, language and intentional planning. That integration is necessary, becomes illustrated by examples of states where it may fail, such as specific constellations in split brain patients, or states of dissociation.

2.2.2. ANOETIC CONSCIOUSNESS

Anoetic consciousness is a kind of procedural/affective sensory, and primary level consciousness on the continuum of consciousness. It is based on information that one can act upon without bringing it into explicit consciousness, which corresponds to the lack of awareness of the mental 'contents' of a task (Tulving, 2001).

As a pre-reflective state, anoetic consciousness does almost not become apparent in awareness, it is always present, as long as the person is not asleep or in a state of coma. Tt appears in experience as a result of sensory input which makes the difference between being awake, being conscious, and asleep. We feel that we are and know intuitively how to act upon the world. In parallel, in early childhood, as discussed before, the newborn lives almost in a state of sensory affective responsiveness with only limited directed attention and little selective capacity with respect to autonomic, sensory and motor functions. At first, babies possess a form of primary consciousness without explicit distinction between the I and the world. It is the state of small children before they become aware of themselves on a declarative level. There is little or no voluntary involvement. Information processing happens almost automatically, controlled by auditory and visual input (Baars, 1997; Posner & Raichle, 1994). As a state of being in the stream of consciousness it gives us a feeling of continuity. No reflective object involvement is implied, as opposed to higher levels of consciousness. Because it remains rudimentary, or global, and is the least complex level of consciousness; it does not involve a 'thinking' subject as is necessary for higher levels of consciousness. In very young children, as we mentioned above, and in adults, we see preferences for specific faces and situations, although the children do not know this on an explicit level (Zajonc, 1980, 2001).

Anoetic Self-Experience?

At a specific point in development, though this is difficult to determine, the child experiences that it exists as an organismic being. The first implicit awareness of oneself in interaction with the environment is a global state or a sense of self, or what we temptatively call 'anoetic self-experience'. Anoetic self-experience refers to the primary or pre-reflective experience of one's own self, based on being embodied in social and physical reality. The anoetic self is not the object of reflective thought and is developed early in the intimate dialogue between the mother and her child, probably even prenatally. This shared interaction, which postnatally includes the observation of facial expressions of the mother or caregiver is an essential prerequisite for developing anoetic self-experience and memory. It results from the first procedural representations of the confrontation with the world and associated affect.

This state goes also together with what Zeman (2001) defined as self-detection by the organism that can respond to stimuli impinging from outside and eventually change its behavior to handle them. Only a global, diffuse and experiential representation or awareness of existential experience exists.

In adulthood, access to one's anoetic self-experience can be compared with one's own felt sense (Gendlin, 1962). It gives us the possibility of having an experienced meaning of things, a meaning which may be reflected somatically. It is primarily preconceptual and can be differentiated into various affective, meaningful aspects influencing actual information processing.

In anoetic self-experience, the self is involved in interpreting something without being "self-aware" (Velmans, 1992). Anoetic consciousness constitutes a state of continuous implicit experiencing, associated directly with the self of the actual moment, or, indirectly, with the me of the past.

Anoetic Consciousness as an Immediate State of Experience

The direct, immediate realization of the world is enough to become anoetically aware. In accordance with Marcel (1983) and Bargh, and coworkers (2001), it is probable, that perceptual processes which give rise to a state of consciousness, immediately redescribe sensory data into representations accompanied by the automatic activation of implicit memory. Anoetic consciousness involves then the implicit complexity of the different contents or kinds of events that we continuously experience in the present and have experienced in the past. In this context, it is still an open question whether anoetic awareness as phenomenal awareness can be the direct reflection of perceptual awareness without the implicit activation of an underlying memory trace or representation.

Influencing Meaning, Symbolization and Behavior

Anoetic consciousness influences phenomenal experience and modulates "the tone of behavior" (Marcel, 1983). The phenomenal quality of this anoetic consciousness is influenced by social constructs, related meanings and the self that enters into the information processing producing this experience until an appropriate symbol has been found in the mind. Words can be used to refer to this sensorial or physiologically felt sense of existence in the world. Putting it in words transport this continuous experience into another one constructing and reconstructing the actual experience (cf. Gendlin, 1962).

The intersubjective dimension of consciousness is the capacity of a person to communicate this state, demonstrating a specific relation with oneself (Natsoulas, 1983). Language or gestures may become used to express consciousness of something. If put in words, explicit symbols or an image of the implicit meaning becomes apparent.

2.3. "KNOWING": NOETIC, AND AUTONOETIC CONSCIOUSNESS

"The mind knows that it knows" (James, 1890)

Reflective Consciousness

Inherent in being reflectively conscious is the potentiality for a direct awareness of the occurrence of something. Mostly, explicit object-related awareness springs into the foreground when the automaticity of being is not enough to handle the world. In the state of being awake, attentive processes towards something with a representation of that object occur (James, 1890; Baars, 1991; Velmans, 1999). Inherent in being reflectively conscious is the direct awareness of a representation at that moment. It is supposed to imply a cognitive relationship between the one who is aware and that of which he or she is aware.

Information that becomes processed in awareness then is at the focus of attention, selected from competing information. Every conscious state, with depending variance, involves attentive processing most obviously clear in explicit awareness. Direct reflective consciousness based on episodic memory informs us about the qualitative character of some of our retroconsciousness. Autonoetic consciousness includes a qualitative reflective experience of consciousness in opposition with unconsciousness that can never be unconsciously reflective (cf. Natsoulas, 1986).

2.3.1. NOETIC CONSCIOUSNESS

The semantic memory system represents symbolically representable knowledge which an individual has about the world. Though being by definition a presence-oriented memory system, it provides an individual the access to one's own past and the world, detached from personally colored experience. The mode of this access is one of 'knowing,' not 'remembering'; it is also without what James calls 'warmth and intimacy' (Gardiner, 1988, 2000; Gardiner & Java, 1993; James, 1890; Andreasen et al., 1995; Tulving & Markowitsch, 1998). It gives us a factual understanding of things. Also, thinking about the 'facts of the world' means being noetically aware of what one is thinking, as well as being aware of such awareness (Tulving, 2002).

2.3.2. AUTONOETIC CONSCIOUSNESS

Autonoetic consciousness is the capacity to mentally represent protracted existence, to possess and act with the sense of chronesthesia. As a self-generated, self-knowing state, attention in autonoetic consciousness can be directed to 1. the past in retrograde consciousness, 2. the present in "real-time" consciousness and 3. to the future in 'prospective' consciousness. Autonoetic consciousness can be (1) the explicit self-awareness, and/or (2) the explicit awareness of something or someone else in a specific time-space context. When attention is directed from the present to the past to re-experience personal past in subjective time, it makes use of episodic memory (Tulving, 2002).

Episodic Memory

Episodic memory is a past-oriented context-embedded memory system (Tulving, 1999, 2002). It makes up the most advanced and hierarchically highest memory system, allowing us the development of an integrated identity (Markowitsch, 2003b; Tulving and Markowitsch, 1998; Vargha-Khadem et al., 1997). Tulving (1985, 1999, 2001) defined episodic remembering as "cognitive, symbolic and representable". Episodic remembering involves the encoding of specific information of a particular occasion within a context and its reactivation and explicit representation on a subsequent occasion. It is the product of continuous construction and reconstruction of the individual's feelings, thoughts, goals and behavior, mediated by the actual self. The information the person is aware of includes information about the source from which prior information was learned as well as the temporal reference of an event. We are able to select an event as a reference point and to judge whether a recollected event came before or after this point of reference (Robinson, 1986).

Autonoetic Consciousness and the Awareness of Time and Memory

Autonoetic consciousness also involves the conscious awareness of subjective time ('chronesthesia', Tulving, 2002). The sense of subjective time in humans makes possible to engage in mental activities and attain goals that are not possible for an organism which does not possess this capacity. Autonoetic consciousness, however, is in opposition to episodic memory, not limited to the past. The individual can have an awareness of personal time, looking backward, in the present, as well as looking forward (Tulving, 2001; Wheeler et al., 1997). Autonoetic consciousness departs from the self in subjective time, whereas in chronesthesia, awareness of time in itself comes into the fore.

Autonoetic Consciousness and "The Feeling of Warmth and Intimacy"

Autonoetic consciousness confers to the phenomenal flavor of the remembering of past events (Tulving, 1985, p. 3). The flavor distinguishes remembering from other kinds of consciousness such as those characterizing perceiving, thinking, imaging or dreaming. James (1890) described 'remembrance' as related with a direct feeling; its object suffused with 'warmth and intimacy' which no object of mere conception ever attains to. Remembering is guided by a specific feeling of subjectivity specified by the internal and external situation in the past. It is embedded in embodied experiences, associated with feelings that give meaning to these experiences. These feelings are applied to form self-knowledge about oneself and other functional relationships as also to maintain a sense of well-being (Barclay, 1993).

3. CONSCIOUSNESS AND THE BRAIN

3.1. MANY SELVES, MANY STATES OF CONSCIOUSNESS

It is generally accepted now that the neural substrates of consciousness, the self, and self-consciousness, are distributed across the brain in toto (Markowitsch, 1999a). No single region in the brain is responsible for consciousness all the time. It is the brain that creates a functional unit out of the different sorts of consciousness and self-systems. Nevertheless, individual regions contribute differently to the creation of a united consciousness - starting from the asending reticular formation in the upper medulla and brain stem, and ending in the frontal lobes and limbic brain circuits.

Brain processes are spatiotemporally distributed, whereas from the internal point of view of the subject, they form a unified whole (Mitterauer, 1998). The functional organization of the brain is composed of multiple representational units of the neural network and processes interacting with each other, continuously integrating different information (Mesulam, 1990). The interconnection between the units is anatomically complex, entailing lateralized, hierarchical, cortical and subcortical integration (Stuss, 1995). A recurrent network in the brain integrates information from different sensory modalities into convergent modules (Damasio, 1989). The process of being aware, as Singer (1998) suggested, stems from meta-representations, which are implemented by the dynamic association of distributed neurons into functionally coherent assemblies rather than by individual specialized cells. Damasio and Damasio (1994), borrowing from Changeux (1983), referred to a 'neuronal self', capable of producing this experience of subjectivity or representing units. The brain might have many locations of (self-) consciousness. The self and associated consciousness represents a multiple system. These different selves are correlated with different states of consciousness, represented by parallel, distributed processing areas of neural networks (Rumelhart et al., 1986). As a distributed process, it has different levels of neural involvement, involving different brain areas (Raichle, 1998).

3.2. CONSCIOUSNESS AND THE BRAIN

Regarding the anatomical side of consciousness, anoetic consciousness, like sensorial awakeness or wakefulness, is as we suggest, primarily dependent on the ascending reticular activating system in the upper brainstem tegmentum, the locus coeruleus, midline and intralaminar nuclei of the thalamus, with extensions into the cerebral cortex providing feedback to the brainstem centers that play a role in arousal and alertness (Bogen, 1995, Frith et al. 1999, Llinas et al., 1998, Young & Pigott, 1999). The midline and intralaminar nuclei of the thalamus integrate (1) input arising from the spinal cord, cerebellum, brainstem and basal ganglia with reciprocally related inputs from the cerebral cortex and (2) exert control over functionally related areas of the striatum and prefrontal cortex (Mair et al., 1998). Lesions of the midline and intralaminar nuclei of the thalamus have been shown to reduce the capacity for delayed conditional discrimination across multiple sensory modalities (Mair et al., 1998). They also affect learning and memory related to the cortical-striatal systems which they innervate.

On the cortical level evidentially many regions participate. We will highlight here only those which have more special roles than merely integrating the sensory aspects of information. Among these, the retrosplenial cortex (the most caudal portion of the posterior cingulate cortex) receives input from regions importantly engaged in emotional processes (such as perceiving and evaluating emotional stimuli), as well as in autobiographical memory processing. Inputs from the amygdala to the entorhinal cortex and from the entorhinal to the retrosplenial cortex provide further feedback loops for emotion and memory (Andreasen et al., 1995; Tulving et al., 1999; Maguire et al., 2000; Markowitsch et al., 2003).

Anterior cingulate activity accompanies the representation and awareness of almost any stimuli (Shulman et al., 1997). In a study of Lane and coworkers (1998), for instance, measuring (emotional) awareness, subjects' level of emotional awareness during watching of emotional and neutral movies correlated with changes in anterior cingulate blood flow. This was interpreted by Posner and Rothbart (1998) as suggesting a possible connection between cingulate activity and awareness of the stimulus.

For the selection of information entering consciousness, the executive capacity of the prefrontal lobes is of major importance (Young & Pigott, 1999). The prefrontal lobes are regarded as the seat of the highest mental functions (Markowitsch, 1995, 2001; Stuss, 1991; Stuss et al., 2002). They have a central role in the representations of the self, the processes of being aware and in the capacity for self-reflection and attribution, and they play a prominent role in the higher levels of awareness, reflected by noetic and autonoetic consciousness (Henson et al., 1999; Moscovitsch & Melo, 1997; Tulving, 1993; Wheeler et al., 1997). The retrieval of episodic information, for instance, is dependent on a proper functioning of the prefrontal cortex (Fink et al., 1996; Fletcher & Henson, 2001; Markowitsch, 1995, 2001). The prefrontal lobes give us the possibility of having a feeling of oneself in a meaningful way. In parallel, in child development, the formation of conscious mental (self-) representations, the temporal regulation of behavior, and affective self-regulation require increasing involvement of the prefrontal lobes (Bush et al., 2000; MacDonald et al., 2000). Correspondingly, between the ages of two and four years, the prefrontal system appears to undergo important developments of associated abilities such as reflective capacities, effortful control, delay of gratification, and socially appropriate behavior (Posner, 2001).

Posterior dorsolateral and medial regions of the prefrontal cortex exercise executive functions such as maintening and organizing information in meaningful ways (Stuss, 1995;

Stuss et al., 2002), possibly particularly in the domain of knowing consciousness. Specific other areas of the frontal lobes such as the orbitofrontal cortex are involved in evaluative processes such as appraisal of information (Pribram, 1987), the direction of attention toward oneself and content-related aspects of consciousness (Goldenberg et al., 1989). The orbitofrontal cortex is intimately interconnected with the limbic area and has therefore been considered to be the "association cortex" for the subcortical forebrain (Pribram, 1981). It receives multimodal input from all sensory cortical areas and takes a unique position between the neocortical areas and the limbic system. Brain imaging studies emphasize the orbitofrontal cortex as a major trigger station for ecphorizing emotional autobiographical memory (Markowitsch et al., 2003). Moreover, Teasdale and coworkers (1999) described the orbitofrontal cortex as having access to preexisting representations of schematic mental models, related to the self and others.

The medial temporal lobes - with their intimate connection with the hippocampal formation, the adjacent lateral cortex, and diencephalic structures - have a role in the process of becoming aware of something when this leads to the establishment of a memory trace (Moscovitsch, 2000). The role of the medial temporal lobes, including their hippocampal and parahippocampal portions, for the formation and transfer of declarative information to long term storage has been so well established that it needs not to be expanded here.

Mentioning may be done of the amygdala which participates centrally in evaluating (LeDoux, 1996; Hamann, et al., 1999) the emotional tone and the meaning of information. Especially studies of Urbach-Wiethe patients, who have a bilateral severe calcification of the amygdala, have elucidated the esssential contribution of the amygdala in establishing a proper conscious binding of emotions and memory (Markowitsch et al., 1994; Cahill et al., 1995; Siebert et al., 2003).

The emergence of the qualitative character of an experience results from these capacities for convergence, producing both a subjective experience and the implicit consciousness of experiential being. Consciousness, accompanied by the capacity for propositional knowledge, as in noetic and autonoetic consciousness, is intimately dependent on a proper action of the amygdala, thalamocortical circuits, hippocampal and neocortical regions.

3.2.1. AUTONOETIC AND NOETIC CONSCIOUSNESS AND HEMISPHERIC LATERALITY

A large amount of evidence exists associating episodic and semantic memory processes to different cortical circuits. Starting in 1994 with the formulation of the HERA (hemispheric- encoding-retrieval-asymmetry) model by Tulving et al., according to which right prefrontal regions are differentially more involved in episodic memory retrieval than left regions, and left prefrontal regions more than right ones in encoding episodic and semantic and in retrieving semantic information, research on hemispheric asymmetries in information processing accumulated (Desgranges et al., 1998; Fletcher et al., 1995; Nyberg et al., 1996; Tulving et al., 1994; Shallice et al., 1994). Recent research from various groups (Markowitsch, et al., 2003; Lepage et al., 2000; Maguire et al., 2001; Piefke et al., 2003; Wagner et al., 1998a, b) however, questioned the idea of a strict left versus right asymmetry in the retrieval of semantic and autobiographic memory and instead emphasized a more differentiated bilateral perspective.

3.2.2. EVIDENCE FROM INDIVIDUALS WITH BRAIN DAMAGE

Lesion data suggested that an integrated prefronto-anterior temporal network is necessary for successful memory retrieval, including the indexing and triggering of recollection of personal past events. Damage to the anterior temporal lobes results in a failure of analysis or on-line maintenance of information concerning the self. Malfunctioning of these regions - either due to manifest tissue damage or due to psychogenic stress and trauma situations, disturbs self-consciousness and meta-consciousness. Anosognosia, emotional flattening and indifference may be the result (Markowitsch, 1996; Markowitsch et al., 1999, 2000). Self-knowledge becomes then reduced to the level of semantic knowing of personality characteristics or traits

(Markowitsch, 1999b). Patients seem to lack access to their own episodic self as reference to act, accompanied by a disturbed sense of time.

Memories remain peripheral without the central feeling of self instead, the feeling of a "foreign element" may exist in memory, impairing the sense of personal continuity, self-consciousness, and identity (Picton & Stuss, 1994). Feelings of warmth and intimacy, which often accompany a particular memory and thus individually determine the self-related quality of consciousness, might be missing (Wheeler et al., 1997). The capacity of healthy self-regulation, to plan into the future, to trust in the prospective execution of one's own goals is related to the experience of past learning episodes, or autonoetic consciousness. As a result, adaquate decision-making becomes disturbed. Behavior then becomes determined by irrelevant goals or inappropriate habits (Shallice & Burgess, 1993). Furthermore, brain damage possibly might lead to impairment in inhibitory control and novelty detection, causing distractibility, stimulus-driven behavior, reduced confidence in personal decisions and in reality-checking (Knight & Grabowecky, 2000). Persons with a malfunctioning prefrontal cortex may no longer be interested in or critical towards themselves. They become unsure, without an orientation point of inner reference, are bound by environmental stimuli and unable to suppress previous responses.

Damasio (1995) found, for example, that patients with bilateral ventromedial frontal damage show decision-making deficits in the personal and social domain, and do not have the normal ability to generate somatic responses to emotional stimuli.

4. UNCONSCIOUSNESS AND CONSCIOUSNESS: TWO STATES ON THE SAME CONTINUUM

A continuum of consciousness is elucidated, implying an increasing level of voluntary involvement, complexity, sharpness of representation, intensity and object-relatedness. Within this continuum from unconsciousness to consciousness, a graded potentiality for unconscious processes to become conscious is found.

4.1. UNCONSCIOUSNESS

Unconsciousness on the one hand, refers to the preferences, related tendencies, thoughts, affects, and cognitions that are not the object of the present state of consciousness. However they do have the potentiality to become aware. Implicit memory, or non-declarative memory, for instance, involves the non-conscious influence of experiences on behavior and preferences (Squire & Zola-Morgan, 1991).

4.2. ANOETIC CONSCIOUSNESS

As a stream of sensory and visceral consciousness, anoetic consciousness refers to the waking state of the organism in the absence of an explicit knowing of a content. It is a kind of procedural, pre-reflective sensory, and primary level consciousness within the continuum of consciousness. Anoetic self-experience, as the primary distinction between the I and the world, is the experience as a being in self-experience, without explicit content.

4.3. NOETIC CONSCIOUSNESS

This level of consciousness is associated with semantic memory. When a person is noetically aware of something, then he or she knows that specific facts have happened in the past, but without having access to subjective experience. Noetic self-consciousness is the consciousness of the own person in a semantic way, expressed in the awareness of personality traits and factual self-knowledge.

4.4. AUTONOETIC CONSCIOUSNESS

Autonoetic consciousness refers to the capacity to mentally represent protracted existence embedded in specific contexts. As a self-generated, self-reflective (knowing) state, attention in autonoetic awareness can be directed to the past, the present and the future. Autonoetic consciousness can be (1) the explicit self-awareness, and/or (2) the explicit awareness of something or someone else in the dimensions of time and space. When attention is directed from the present to the past to re-experience personal past in subjective time, it makes use of episodic memory (Tulving, 2002). Autonoetic consciousness has an affective quality characterized with 'warmth and intimacy" as opposed to noetic consciousness, the "cold" consciousness of a semantic fact.

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CHAPTER 2

NEUROVULNERABILITY

The Influence of Early Stress on the Brain, the Self and Biographical Memory

"The single most significant distinguishing feature of all nervous tissue - of neurons - is that they are designed to change in response to external signals. These molecular changes permit the storage of information by neurons and neural systems" (Perry, et al., 1995, p. 274).

1. THE ROLE OF THE DEVELOPMENTAL ENVIRONMENT IN SHAPING OUR CAPACITIES TO COPE WITH STRESSFUL EXPERIENCES

"The same soul governs the two bodies ... one will, one supreme desire, one fear that the mother has, or mental pain, has more power over the child than the mother, since frequently the child loses its life thereby". (Leonardi, unknown source).

Introduction

The intense interaction of a child with his or her environment is an essential prerequisite for healthy development of the brain and the sense of life, and for handling the continuous stream of tasks within the world. Environmental influences, in particular prenatal and postnatal life experiences with the mother and other caretakers influence the neural and neuroendocrine reactivity to the demands and stressors the child meets (Anisman, et al., 1998; Cicchetti & Tucker, 1994; Cicchetti & Toth, 2000). In this early period, brain tissue is still in a continuous state of growth and differentiation (Cicchetti & Tucker, 1994) whereby the maternal environment (e.g., prenatal stress, ambivalence toward the child) may lead to long-lasting alterations in brain morphology and functions, thereby making the neural networks vulnerable to further stressful influences. The present chapter aims at contributing some new thoughts to this topic and at clarifying the facets implicated in the expression neurovulnerability.

We think that many typical and atypical syndromes, such as psychogenic amnesia, chronic fatigue syndrome, unspecified affective disturbances, hypertension, immune-related disorders, dissociative states, depression, etc. may be caused by stress of psychosocial and biochemical origin, in association with a pre-existing vulnerability in the brain which develops after massive or recurrent stress situations, especially when these occur early in development. As we will discuss later, minor head injury, without identifiable structural brain damage, occasionally leads to retrograde amnesia for autobiographical memory which is otherwise difficult to account for (De Renzi & Lucchelli, 1995; De Renzi et al., 1997; Markowitsch, 2000). We will discuss these forms of "psychogenic amnesia" in the context of an acquired neurovulnerability within early childhood.

Stress

The concept of stress as created by Selye in 1956 signifies a reaction of the organism towards heightened demands from the environment. Basic stress reactions are a greater release of stress hormones (glucocorticoids), an rise in pulse, respiration and blood pressure and a narrowing of the pupils. Stress reactions help to control or eliminate dangers to the body or the mind to improve one's level of performance. At the same time, cognitive flexibility decreases and consequently the abilities to remember old material and to encode new information. This is especially the case when stress reactions follow in rapid sequence or when they cannot be controlled readily. Stress is controlled via the hypothalamo-hypophyseal-adrenal axis which regulates the release of stress hormones.

The experience of stress is common across human life. In such situations individuals enter into a state in which external and internal, biochemical and psychological resources become vulnerable; the subject cannot cope appropriately with the situation, or is overwhelmed by 'the demands of the world'. Biochemical and psychological homeostasis becomes disturbed.

In general terms responses towards stress are twofold: either the organism can cope with the incoming stressful input and restore homeostasis, or the organism is unable to do so. In situations which are experienced as stressful the organism's self is not strong enough to struggle appropriately with known and unknown influences. When stress becomes uncontrollable, it may easily threaten the health and well being of the person. On the one hand, stress situations stimulate the central and peripheral noradrenergic system through the activation of cortical and subcortical neuronal connections. As a consequence, learning processes such as discovering how to cope with stress, may be induced (Rothenberger & Hüther, 1997). This process is generally called 'experience-dependent' plasticity (Greenough et al., 1992). Uncontrollable stress, however, destabilizes neural pathways that have already been established and connection patterns with the consequence that it might endanger the actual integrity of a child directly and indirectly later in life such as in adulthood.

1.1. THE UNBORN CHILD

Early emotional experiences result in the establishment of enduring neuronal templates for the later processing of affective information. Especially during pregnancy, the child shares every emotion with the mother. Before birth, the infant needs physical and affective comfort, warmth and intimacy to build a form of comfortable situation. Early patterns of responsiveness to negative and positive emotions of the mother influence attachment related to the growth of the orbitofrontal area, the cortico-limbic system (Dawson et al., 1992; Schore, 1994) and general brain development of the unborn child. In the child's brain, pleasurable or non-pleasurable experiences change the way the infant processes other experiences and obtains knowledge (Trevarthen & Aitken, 1994). Massive stress of the mother, such as marital problems, the death of her husband, depression, etc., stress the psychological and structural neurological development of the infant (Lou et al., 1994) by fine or massive disturbances at the cellular and subcellular levels, induced by the release of stress hormones.

Elevated levels of stress hormones in the maternal plasma easily cross the placenta and enter the fetal circulatory and nervous systems. Glucocorticoid hormones influence neuronal activity, underlying the stress response system, and have long-term consequences for the organization of the stress response system. Several studies found out that even prenatal ambivalence toward the unborn child may cause stress and therefore be negative for later development. It may interfere with fetal development and result in a higher incidence of malformations, directly via psycho-endocrine or autonomous influences, or indirectly by the way in which the mother acts in this situation of stress, if, for example, she attempts to provoke abortion, neglects proper food intake, smokes excessively, or abuses alcohol or drugs (Blomberg, 1980).

1.2. THE NEWBORN CHILD

From mild, stimulating, to deteriorating and destroying stress

The experience of stress displays many variations, beginning from slight, mild stress which might even stimulate neuronal differentiation and development, to stress inhibiting developmental processes, and ranging up to massive destructive stress. These stress responses can be buffered or enhanced by influences from the direct social environment.

1.2.1. BUFFERING THE STRESSRESPONCE

Mutual Secure Interaction, the Formation of Motivational Preferences

Child development is characterized by a rapidly increasing interaction of the child with his or her social and material world. At birth the sensibility for stress is very high; even undressing and weighing the newborn elicit significant elevations of cortisol (Gunnar, 1992). Born with this sensibility, the newborn is highly dependent on the ontological security of the immediate environment and is continuously seeking affective support, tenderness and protective care. Very early within this development, it is aware of the presence of other human beings - through the sensorial perception of olfactory, gustatory, tactile, auditory, and visual experiences.

Even before the cerebral cortex is active, the fetus already seeks human contact. We can easily observe how the basis of motivational processes is already set up very early in embryogenic brain tissue. Infants sense the emotional and intersubjective meaning of expressive movements, they perceive from their caretakers, in a global Gestalt-like manner, without reflective distance. Slowly, in the dynamic exchange with their caretakers, children learn to understand the association between the production or the imitation of specific expressive behavior and their rewarding or negative effect on the significant other. The primary caretaker facilitates, by subtle or massive punishment or reward of the infant, the development of corresponding pathways (Meltzoff & Moore, 1992). The undifferentiated cells and pathways of the developing cortex and further brain structures are engaged in evaluating situations, contributing to the first base for the development of the formation of dynamic representations of others (Trevarthen & Aitken, 1994) and the world, becoming expressed in emotional preferences and behavioral tendencies of approach and avoidance. These mutual body and environmental influences continually stimulate cerebral structures.

Secure Attachment and Representation of the Self

Bowlby (1973) and Ainsworth and coworkers (1978) all strongly emphasized the importance of a secure caregiver and interaction-based attachment to the infant. If newborns and other young children are intuitively „understood", they consistently learn to trust the specific relation between them and their caregivers, their behavior and associated effects (Gunnar, 1998). Secure internal representations of relationships and attachment and of one's own self, appear to function as a buffer against stress, enabling the child to avoid being afraid when separated briefly from their mother. Positive, trustful early experiences lead to a permanent adaptation of stress receptors in the brain (Meaney et al., 1985). These stress-sensitive receptors are involved in terminating the response (Sapolsky, 1992), allowing stress levels to return to a baseline level after confrontation with new stimuli.

1.2.2. FACILITING THE STRESSRESPONSE

Lack of Interactional Reciprocity

The opposite of intuitive parenting - mismatching, unpredictable reactions - disorganizes the child and results in an increasingly insecure attachment (Bowlby, 1969). Before and after birth, inconsistent or ambivalent social interaction disturbs attachment, the experience and expression of warmth and intimacy. Particular aspects of parental behavior, such as intrusiveness, help to explain why insecure attachment does not "buffer" the stress response by related release of stress hormones (Gunnar, 1998). Mothers who do not intuit their children, for instance, persistently engage the infant even when he or she is looking away from her and attending to someone or something different (Tronick et al., 1982). Spitz (1965) spoke of 'psychotoxic maternal care'.

To react negatively upon or neglect the expressive attempts of the child (who cannot understand why this occurs), confuses and stresses him or her. Mothers with postnatal depression, for instance, do not reward positive expressions of their child. In several studies on affect production and perception by caregiver and infants, it was found that depressed mothers exhibit fewer animated faces and voices (e.g., Field et al., 1988). During interaction, there is less sharing of positive emotions, increased matching of negative emotional expressions and neglect of the emotional expressions of the child. When the mother shows an immobile face or starts looking away from the infant, the child first tries to restore contact by targeted gazing, making eye-contact and smiling. After trying a while, the child's face is less orientated towards the mother and may fall into a slumping position. Infants of depressed mothers manifest a preference for sad faces and voices. Speech of depressed mothers differs in content and emotional tone: it is less focused on the experiences of the child and if it is associated with the child, the mother is more critical and hostile and seems to refer less to the infant as an intentional being (Murray et al., 1993; Trevarthen & Aitken, 1994).

Separation from the Mother

During development, the child learns to exercise a variety of strategies to make the world predictable with respect to coping with the coming and going of the mother; separation and being left alone is a minor fear experience in this period of life (Bowlby, 1973), and extended separation leads to the potentiality of trauma and ingrained helplessness, when repeated cries of the infant do not bring the mother back. In this context, research of de Kloet, Korte, Rots, and Kruk (1996) on rats has shown that these animals indeed develop extreme reactions of distress caused by the separation from their mother. It was shown that longer periods (24 h) of separation of the rats' infants disrupt the stress-associated hyporesponsive period with a rise in corticosterone. Mother-deprivation of rats at the postnatal age of three days results in hypercorticism and increased nigrostratial dopamine responsiveness (Rots et al., 1996). In human infants, brain organization is apparently stimulated by repeated daily short maternal separations by the subsequent maternal care, which should facilitate maturation of specific neural limbic pathways (Meaney et al., 1994; Levine, 1994). Important here for an individual's development are the "reunion" phases after periods of stress (Ainsworth et al., 1978), indicating the quality of attachment, regulation and arousal (Stern, 1983). These reunion episodes - especially the anticipation phases - may act, as Stern (1989) suggested, as one of the first generators of the autobiographical experience of episodic memory.

However, if the mother-child interaction becomes uncontrollable and turns into irrepressible stress, it inhibits normal development and leads to an enhanced sensitization for subsequent stress (Rosenfeld et al., 1994; Levine, 1994).

Emotional Trauma

Many children witness violence, or are victim of abuse. Such experiences may be stressful and even traumatic. As traumatic experiences are learned in an extreme emotional context, they may lead to drastic changes in an infants' percept of his or her direct social environment and of the world as a whole, resulting in a hostile, stressful image of the world (Schore, 1994). A traumatized child is often in a state of low-level fear associated with hyperarousal or dissociation. The whole neural organization becomes mediated by such an experience or by prolonged series of experiences. In addition, the abusive caregiver often provides little protection against other potential abusers of the infant (Schore, 2001).

Posttraumatic stress disorder is one of the massive and severe expressions of the influence of very acute stress on the relation with one's own self.

Inhibition of Emotional Expression

Stress is a joint product of the individual and his or her environment. Certain conditions such as a positive relationship with the significant other have a preventive effect by facilitating verbal and nonverbal expression, whereas other conditions are inhibitory (Buck et al., 1992). Expressing experienced traumas helps to process and organize complex and painful experiences (Bremner, 1995). Pennebaker, Hughes and Oheeron (1987) and Pennebaker (1993), for example, found that adults, when asked to refrain from talking about traumatic experiences, exhibited higher levels of skin conductance, than when asked to describe these experiences verbally. While talking about traumatic experiences decreases the level of skin conductance, listening to traumatic experiences of others enhances skin conductance levels. As a consequence, some people tend to avoid listening to others and in correspondence to their children's problems, and then force the others, like their children in a subtle way to be silent about these problems. However, it has been shown that children who verbally inhibit their reaction to stress show significantly elevated systolic blood pressure, higher heart rates and levels of stress hormones (Fontana, Rosenberg, & Marcus, 1987). External inhibition of emotional expression by children might be explained as another kind of neglect, impatience, and social avoidance behavior (Pennebaker et al., 1987).

In line with the observation that listening to traumatic experiences may enhance the own level of stress, this effect might also be placed in the context where the child has to listen to their parents' emotional problems, stressing the child by burdening such psychologically painful experiences on them from early life.

Consequently, the way in which children and adults handle stressful emotional issues in their lives affects the development of their cognitive-affective brain functioning, their health and their immuno-responsiveness: neurovulnerability may be the consequence.

2. NEUROVULNERABILITY

Neurovulnerability leads to, and is caused by biochemical changes, in particular the release of stress hormones, resulting in fine or massive disturbances at the cellular and subcellular levels. This process is accompanied by structural and metabolic alterations in specific areas of the brain (Bremner, 2002; Sapolsky, 1994) The whole neural organization becomes mediated by the above described early experiences or prolonged series of experiences in childhood, going together with an accelerated loss of glia and nervous tissue, either cells as a whole or portions of them, such as presynaptic vesicles, axonal and dendritic arborizations, or synapses. As a result, cortical thickness may shrink, and seizure-like activity may develop, particularly in emotion and memory sensitive area.

Neurovulnerability is associated with reduced neuroplasticity, which later facilitates the development of psychopathological conditions and functional disturbances which are difficult to explain with standard medical and psychological frameworks. We postulate that many mental health problems share the same pathophysiological mechanism, a syndrome of subjective discomfort developed as the result of an early acquired enhanced sensitivity or reactivity of the central nervous system at psychological, biochemical, neurophysiological, and molecular levels (cf. Miller, 1997). The underlying explaining alterations can remain undetectable or without obvious effect on behavior for a prolonged time, but may lead to disturbances in neuronal functioning long-term.

As both a precedence and a consequence of neurovulnerability, we postulate biochemical, behavioral and psychological consequences of the negative influences we described in the first part of the text, including an increased reactivity to stress, an enhanced release of stress hormones, atrophy of specific brain regions and a heightened vulnerability of the self. Chronic or massive stress inhibits emotional learning and memory, and therefore the development of the self as a memory-dependent entity. It furthermore inhibits a situation-specific activation of the self, which is necessary in order to find optimal, need-based self-regulation.

2.1. INCREASED AFFECTIVE AND BEHAVIORAL STRESS RESPONSE

2.1.1. CONSEQUENCES OF PRENATAL STRESS

Our stress response system, shaped by genetic factors and life experiences, is most severely influenced by neonatal life events (de Kloet et al. 1996). Fetal brain development is changed and retarded by high levels of maternal stress hormones (Glynn, Wadhwa, & Sandman, 2000). In pups of rats, unpredictable gestational stress increases fearful stress responses, which may become overt in adulthood as behavioral problems to stressful and conflict-rich situations (Fride & Weinstock, 1988). If there is a long term enhancement in the level of stress, a variety of changes all over the central nervous system may be induced, altering physiological functions and behavior throughout the development of the organism. Studies in rats have shown that, after prolonged stress before birth, the offspring is more easily frightened, exhibits less exploratory behavior, demonstrates generally heightened tendencies of behavioral inhibition (Fride & Weinstock, 1988) and show reduced tendency for social interaction (Takahashi & Haglin, 1992). Fride and Weinstock (1988) for instance, administered synthetic stress hormones (dexamethasone) to pups of a few days in age. In pre-term maturation, they observed an acceleration of incisor eruption, eye opening and development of motor skills, and a retardation of body and brain growth. In support of our neurovulnerability hypothesis, they observed hyperactivity of these animals in adulthood with stereotypy and decreased adaptability and learning capacity in new situations. Averse stimuli especially cause enhanced emotional reactivity and transient, long-lasting or irreversible changes in neural function (Hayes & Dixon 1994; Hayes et al, 1992; Miller, 1997).

2.1.2. CONSEQUENCES OF POSTNATAL STRESS

Disturbed or impaired development of the brain as a consequence of major stress, caused by inappropriate interaction (e.g., deprivation) between caregiver and child, may later result in improper coping in various situations. Vice versa, especially during adolescence, empathy, attachment and the regulation of emotions depend to a large degree on proper regulation by structures of the limbic system.

A disturbed mother-infant attachment in childhood enhances the likeliness for the development of depressive pathology in the child (Cytryn et al., 1980). Zuckerman, Als, Bauchner, Parker, and Cabral (1990) found, for example, that newborn children of depressed mothers were less consolable and more disoriented than children of non-depressed mothers. Field and co-workers (Field, 1998a, b; Field et al., 1988) found that infants of depressed mothers vocalized less, displayed increased gaze, aversion and fussiness, and at the same time, had higher heart rates and decreased vagal tone. These children appeared outwardly calm, but were subjectively distressed in real. In the same way as depressed adults, they exhibited a dissociation between behavioral and physiological responses. On the one hand, there is the experience of stress accompanied by enhanced levels of stress hormones, and on the other hand, after the first response of stress the child learns to "behave" depressively as a result of imitating the mother's depressed behavior (Dawson, 1994). Neglected or maltreated children show globally enhanced levels of cortisol (Hertsgaard et al., 1995). If the mother is emotionally absent, the child cannot develop a common level of understanding with her (Murray et. al., 1993). Infants show insecure, resistant attachments as a reaction to a mother who is, in other words, 'physically, but not emotionally present'. Lack of reciprocity disengages attachment with the mother while the infant's confidence in his or her own effectiveness within the environment creates a conviction of helplessness. The infants of these mothers show helpless and dysregulated behavior and even delays in growth and development at twelve months of age (Field, 1998a).

In a traumatic environment, there is also the phenomenon that as a traumatized child encounters trauma-related information, the critical neural pathways related to the experience of the threat, will become reactivated, increasing thereby the probability for a disconnection of the self, as we will discuss farther below.

In later development, children exposed to traumatic situations (e.g., witnessing violence, having been abused or kidnapped) may manifest a wide range of posttraumatic stress disorder (PTSD) symptoms, behavioral disorders, phobias, anxieties and depressive disorders. The experience of cumulative traumatic stress results in the expression of different symptoms (Yehuda et al., 1997). Maltreated and abused children, for instance tend to become depressed and hyperactive ones and show conduct disorders (Cicchetti & Toth, 2000). Sexual abuse for example has a deep impact on personality development, inducing feelings of shame, anger, stigmatization, low self-esteem, social isolation, poor impulse control, and self-destructive behavior (Brown et al., 2000; Conaway & Hansen, 1989; Kendall-Tack et et al., 1993; Toro, 1982). As we can notice, in response to these chronic or massive stress situations, children and later adults typically display significant reductions in learning, perceptual, intellectual and memory capacities (Cicchetti et al., 1993).

These deprivation- or trauma-induced abnormalities affect the limbic system to an extent that the individual may become emotionally and socially "blind" and unable to perceive, process, or respond in a normal fashion to social and emotional stimulation (Cicchetti, 1989; Cicchetti & Rizley, 1981; Joseph, 1999).

Increased Stress Response

Stress during critical periods of development alters the brain's biochemistry. Two stress systems, the sympathetic adrenal-medullary system, and the neuroendocrine system, the hypothalamic-pituitary-adrenocortical system (HPA-axis) in the brain and periphery become activated (Davis et al., 1997; de Kloet et al., 1996; Henry & Stephens, 1977). They are described as the effort and distress systems, or the fight-flight and conservation-withdrawal systems. The sympathetic adrenal medullary system (SAM) is most strongly engaged in connection with strong emotional states, fear and anger, as in traumatic anxiety. After prolonged and repeated separations from a contact-aversive, non-attuning mother, the hyperaroused child is in a state of sympathethic-dominant agitated stress (Schore, 1994).

Hyperarousal of the traumatized child is characterized by an enhanced sympathetic nervous system and hypothalamic-pituitary adreno-corticothrophic activity, increased activation of the centrally controlled peripheral autonomic nervous system, which results in accelerated heart rate, blood pressure, respiration, the release of stored sugar, enhanced muscle tone and general hyper-vigilance for critical information (Perry et al., 1990). The HPA-axis is thought to function in connection with overwhelming threats (Henry & Stephens 1977). The hypothalamus in the brain releases corticotropin releasing hormone which stimulates the pituitary gland, immediately outside the brain barrier to release adrenocorticotrophine hormone (ACTH) which stimulates the adrenal gland in the periphery to release adrenal glucocorticoids. It is well documented that adreno-cortical hormones are involved in mediating the influence of stress on cognitive performances (McEwen, 1997; de Kloet et al., 1999; Roozendaal, 2000; Roozendaal et al., 2001). Enhanced or chronic levels of glucocorticoids result namely in cell elimination and neuronal death (Guilarte, 1998). Glucocorticoids mobilize energy by inhibiting the uptake and storage of energy substrates (Sapolsky, 1993, 1996, 2000). When the stressor is terminated, glucocorticoids are able to inhibit subsequent adreno-corticotrophine release from the adrenal cortex as a negative feedback loop (Meaney et al., 1994).

Inverted U

The effects of different intensities of stress are reflected by an inverted U: brief periods of stress can potentate memory formation, whereas more chronic or longer periods of stronger stress may disturb memory processes to the extent of a total blockade ("mnestic block syndrome"; Markowitsch et al., 1999b; Markowitsch et al., 1999c). On the neuronal level, a moderate duration of stress causes reversible atrophy of apical dendrites on pyramidal neurons, while basal dendrites remain unchanged. Chronic stress, as mentioned before, generally is potentially more dangerous than acute stress (Garmezy & Masten, 1994). Prolonged high concentrations of glucocorticoids may lead to hypertension, hyperglycemia, suppression of the immune system and brain cell death (Rosenfeld et al., 1993; Sapolsky, 1993; 1996; 2000). In chronically stressed rats, Magarinos and coworkers (Magarinos et al., 1997; Magarinos et al., 1997; McEwen, 1999) observed an altered vesicle distribution pattern with depletion of vesicles. The chronic influence of glucocorticoids on the hippocampus leads to damage, in the form of the loss of pyramidal neurons and decreased dendritic branching. Massive production of glucocorticoids changes and reorganizes synaptic connectivity in the hippocampus, leading to severe consequences in memory.

Hippocampal Atrophy and Memory Impairment

The hippocampal formation is a brain area specifically relevant for episodic, declarative and spatial learning and memory (Tulving & Markowitsch, 1997; Vargha-Khadem et al., 1997) and for the processing of stress (Bremner et al., 2000; Bremner et al., 1997; Bremner et al., 1999; Bremner et al., 2000). The hippocampus has the highest levels of two types of receptors for stress hormones, the mineralocorticoid and glucocorticoid receptors. Therefore, the highest accumulation of stress hormones occurs in the hippocampus and can cause atrophic processes (Porter & Landfield, 1998). Glucocorticoids especially impair episodic and declarative forms of memory (as defined in Tulving & Markowitsch, 1998), whereas they have no effect on procedural and priming forms of memory (McEwen & Sapolsky, 1995).

Stress experienced before birth, and then extending across the postnatal period, influences the maturation and volume of the hippocampus. The hippocampus is one of the few brain areas that continues to develop after birth and may even show neurogenesis (Van Praag, et aL., 2002). Maternal stress, for example, decreases the number of corticosterone receptors in the hippocampus, reducing the inhibition of the release of adreno-corticotrophic hormones mediated by the corticoid receptors. These adreno-corticotropines stimulate the release of adrenal glucocorticoids, possibly leading to neuronal cell death, as just mentioned.

Blockade or deficiency of mineralocorticoid receptors influence the capacity of selective attention and integration of sensory stimuli, whereas the impairment or blockade of glucocorticoid receptors affects the process of consolidation and retrieval of information. A particularly relevant study of Lemaire and coworkers (Lemaire et al., 2000) in rats showed that prenatal stress induces a reduction of hippocampal cell proliferation by approximately 45% in all age groups tested. The rats showed also delayed learning in a spatial memory task. In this context, Bremner. (1997, 1999, 2000; Bremner & Vermetten, 2001) found, for example, strong correlations between hippocampal volume and years of abuse or maltreatment. These studies show that stress causes a greater reduction in cell proliferation from adolescence to senescence with early stress exposure accelerating a reduction in hippocampal plasticity.

The Amygdala and the Cingulate Gyrus

Aside from the hippocampal region, other structures of the limbic system, particularly the amygdala and the cingulate gyrus, play an important role in the response to stress and appear to be especially sensitive to the destructive influences of stress hormones.

The amygdala, deep inside the antero-inferior region of the temporal lobe, connects with the hippocampus, the septal nuclei, the prefrontal area and the medial dorsal nucleus of the thalamus. These connections make it possible for the amygdala to play its important role on the mediation and control of stress and major affective processes. According to McGaugh, Cahill, Ferry, & Roozendaal, (2000), the amygdala is of essence in the mediation of effects of reward and punishment. As limbic area it is central in emotionally arousing processes of learning and explicit memory (Cahill et al., 2001; Markowitsch, 1998/99; Markowitsch et al., 1998; Siebert, et al., in press). Hereby, it should be the level of arousal and not the aversive nature that determines the involvement of the amygdala in long-term memory enhancement (Cahill & McGaugh, 1990).

In confrontation with dangerous information, the amygdala becomes triggered, giving rise to fear and anxiety which lead the organism into a stage of alertness, getting ready to flight or fight in function of self preservation. Stimulation of the amygdala by stress enhances the release of corticotropin-releasing factors and activates the hypothalamic-pituitary-adrenocortical system (Gabrieli et al., 1995). The receptors for the corticotrophin-releasing factor in the amygdala respond to stress by increasing corticosterone and adreno-corticoidtrophine hormone (ACTH) release. The basolateral nucleus of the amygdala especially appears to be a key nucleus in regulating hormonal effects on memory (Cahill et al., 2001; McGaugh et al., 2000; Roozendaal et al., 1998; Roozendaal et al., 2001).

The cingulate cortex, too, has an important number of cortisol receptors. Together with parts of the prefrontal cortex it mediates executive functions (Carter et al., 1998), such as effortful behavior, high-caliber attention, control of inhibitory acts (Fletcher et al., 1996; Markowitsch et al., 2003; Nieuwenhuis et al., 2003), and probably emotions in general. The posterior cingulate cortex is more involved in evaluative functions. The role of the anterior cingulate cortex role is multiple, and engagements are related to hypothesis testing, response selection, emotion processing, anticipation, arousal, visual imagery and re-experiencing (Cabeza & Nyberg, 1997; Fletcher et al., 1996; Markowitsch et al., 2000).

In a study with preschool-aged children with high levels of cortisol Gunnar, Tout, de Haan, Pierce, and Stansbury (1997) found, for example that glucocorticoids affect self-control and self-regulation that required strenuous effort, probably related to the influence of the stress hormones on the cingulate cortex.

Enhanced Affective Laterality

Hemispheric lateralization constitutes one of the most effective evolutionary advantages of the human brain: The right hemisphere has a global superiority for processing negative emotions, while the left hemisphere is mainly engaged in processing positive emotions (Borod et al., 1986; Davidson, 1992, 2000, 2002; Davidson & Irwin, 1999). The right hemisphere is also more directly involved in controlling the whole body, whereas the left one is central in the regulation of action (Trevarthen & Aitken, 1994). Functions such as emotional social self-regulation, for example the comprehension of prosody, appear to require an enhanced activation of the right side of the brain (Tucker, 1981). The right hemisphere is also preferentially active under stress conditions (Tucker, 1981; Bremner, 2002; Driessen et al., in subm.). For instance, posttraumatic stress disorder may be paralleled by right hemispheric dysfunction.

As we suggested above, the early neonatal and postnatal experience of emotions and stress affects hemispheric lateralization which in turn influences the manner of information processing. Measurements of resting frontal EEG activity have been found to predict the child's response to stress (Davidson & Fox, 1989). In a study by Davidson and Fox (1989), 10-month-old infants who demonstrated relative right anterior right prefrontal activation during a baseline period were more likely to cry when later separated from their mothers. Infants who showed relatively higher left anterior prefrontal activation during the baseline period were more likely not to cry in response to maternal separation. Fride and Weinstock (1989) also investigated the effects of maternal noise and light stress, applied during pregnancy, on the development of behavioral and neurochemical asymmetries in rat offspring, observing that stress effects extend into adulthood. The authors argued that their findings are consistent with the possibility that cerebral asymmetries induced by prenatal stress may offer an explanation for why the offspring show more difficulties in coping with anxiety provoking situations. The resting levels of laterality reflected differences in reactions towards negative emotion in stressful situations (Davidson & Fox, 1988).

Enhanced laterality can temporarily "switch" according to the tasks and functions the human being has to deal with. Children of mothers who were depressed during pregnancy tend to exhibit a characteristic pattern of enhanced right frontal EEG activity even until the age of three years (Field, 1998a, b). We assume that in accordance with these findings, enhanced right hemispheric laterality may be associated later with enhanced vulnerability for negative emotional stress associated with reactive inhibition systems. In correspondence with our neurovulnerability thesis, we hypothesize that later in development children with enhanced right hemispheric laterality may prove to be more insecure and oversensitive to social stress. Several studies found that avoidance behavior in children results from the negative emotional experience that they have been exposed to by hostile or over-stimulating reactions of the primary caregiver.

Traumatized individuals are unable to respond to stress in similar ways as normals, possibly due to an immature right brain development (Wittling, 1997). In adulthood, there may be an enhanced avoidance pattern in habitual coping strategies which facilitates dissociation and psychogenic memory problems. Vice versa: prenatal stress in adults might lead to a blunting of the stress response in the right and not in the left prefrontal cortex

(Brake et al., 2000). On the other hand, children with strong left hemispheric activation might be more actively engaged in the world, resulting from a tendency towards an autonomic experience of the self. By observing these phenomena, we may conclude again that an infant's affect may be predictors for later laterality, approach, impulsiveness and level of activity.

Vulnerability on the Level of the Self

The Self

We define the self as the base of identity and as self-confidence in this identity. The self is a conglomerate of need-related experiences and preference-related experiences, subsumed to the self, or in other words, summarized as the self. It helps us to direct our actions according to our emotional preferences and biological needs.

Impairment of integrated self-development

The development of the self is essentially associated with the trust within oneself and the environment. In early development, disturbed development of the self may be the result of a lack of understanding the trials and errors of the child's expressions to communicate its needs and preferences to the important other. Severe stress reduces the capacity of the self to connect via learning experiences with the environment. As a consequence of the influence of stress on various brain regions - such as the hippocampus and amygdala, involved in memory - chronic or massive stress inhibits learning, the development of representations of positive and negative experiences directly associated with the fulfillment of one's own basic needs, or self representations. Stress might inhibit the capacity to encode new, context-rich information on a deep emotional level activation of the self as a memory structure, and thus 2). the capacity to become involved with the self. Enhanced levels of stress hormones at a specific level, especially in the limbic area, inhibit the individual from developing this self by episodic learning experiences through a reduced capacity to encode or retrieve information. We suggest that exaggerated activity of the stress system, and the associated experience of negative emotion or stress, inhibit processing or retrieval of especially complex contextual episodic information in the right frontal brain. In correspondence, the right hemisphere appear to be relatively (see Keenan, Wheeler, Gallup, & Pascual-Leone, 2000; Markowitsch et al., 2003) more involved in self-referential cognition, the encoding and retrieval of autobiographical episodic memories, whereas the left hemisphere appear to be more involved in semantic memory processing (Fink et al., 1996; Markowitsch, 1998, 2000). The right hemisphere is also preferentially engaged under stress conditions (Tucker, 1981; Driessen et al., in subm.).

After learning, it may inhibit the activation of implicit preference-related self-representations accumulated by the self in accordance with the specificity of the actual situation. Later in life, when the self cannot become involved, or expressed in stress situations, then the encoding or retrieval of self-related material, especially episodic autobiographical information, becomes reduced. This may lead to conditions which resemble those of depression, helplessness, emotional flatness, indifference and cognitive impairment such as memory disturbance. In this context, it has been found that maltreated children perform more poorly on self-related emotion-recognition tasks than do non-maltreated children (Camras et al., 1983; Camras et al., 1988).

In such children, the self apparently can no longer work as the basis for need-related evaluation or as an 'inner point of reference'. This may give rise to reduced self-confidence too. Self-confidence highly influences the manner of handling stressful situations. Children with a low self-concept or those having been exposed to extreme stress, such as the experience of abuse, become easily estranged from the self. Flattening of affect occurs, and on the other hand, a state of over-vigilance is very common. Persons with posttraumatic stress disorders are very alert and hypervigilant to cues which remind them of the threatening situation. Traumatized children and adults are also likely to remain at a distance from the self, and to become partly disconnected from their own personal history especially by psychogenic episodic memory disturbances, depersonalization and derealization (Classen et al., 1998).

2.2. PSYCHOGENIC AMNESIA AS PROTOTYPICAL EXAMPLE OF NEUROVULNERABILITY

Psychological stress or minor brain injury may progress from minor to severe episodic autobiographical amnesia due to changes in brain metabolism such as increased release of stress hormones or the blocking of receptor channels in memory sensitive areas (Markowitsch, 1996, 1998, 2002; Markowitsch et al., 1999b; Markowitsch et al., 1999c, 2000). Even a single traumatic psychological shock or short-lasting, but massive stress can cause transient or even long-lasting "mnestic block syndromes" (Markowitsch, 2002). Markowitsch and coworkers (1997, 1999b, c) theorize that 'bottleneck structures' especially of the medial temporal lobe may become blocked due to stress-related biochemical alterations.

There is evidence that amnesias without a measurable morphological correlate (as inferred from the results of static brain imaging) do show functional neuroimaging correlates, and that these conditions can be explained by the early acquisition of neurovulnerability in memory-sensitive areas such as the hippocampal formation (Markowitsch, 1999a, b; Markowitsch, Kessler et al., 1998; Markowitsch et al., 2000). Individuals with a comparatively small hippocampal volume, caused by early stress, for example, are more vulnerable to develop functional disorders such as psychogenic amnesia due to their reduced capacity to handle stress. Furthermore, as described above, the development of the self depends on memory sensitive areas in the medial temporal and prefrontal regions (see also Keenan et al., 2000; B. Levine, 2000; B. Levine et al., 1998; B. Levine et al., 1999). In association with the estrangement of the self, we see that episodic amnesia - whether of direct organic or psychogenic origin - is characterized by an inability for re-experiencing episodic events as belonging to one's self (Markowitsch, 1999a; Markowitsch & Ewald, 1997; Markowitsch et al., 1993). Inhibited access to one's own self-representations is most likely a major cause for an impaired regulation of the self.

Case Examples With Psychogenic Amnesia

In correspondence with the neurovulnerability hypothesis, a few case studies may serve to understand the phenomenon of neurovulnerability in association with psychogenic or transient amnesia.

Case NN

Markowitsch, Fink, Thöne, Kessler, and Heiss (1997) described a patient, named NN, who showed permanent retrograde amnesia after a fugue condition. This condition commenced one morning when he was on his way to get some rolls from the near-by bakery. Instead of taking his bicycle to the bakery, he continued riding it for several days, without knowing who he was, or what the reason for his trip was.

After several days he entered a psychiatric clinic where he was diagnosed as having a fugue condition. NN did not show any brain abnormalities when investigated by static magnetic resonance imaging. Exposing him to his personal past while he was undergoing a positron emission tomograph revealed, however, that his brain did not process biographical episodes in the same manner as the brains of normal individuals do (Fink et al., 1996), but with a higher activation in the opposite, left hemisphere. (The left frontal hemisphere is usually engaged in processing neutral, semantic knowledge; De Renzi et al., 1987; Markowitsch, et al., 1999a.) We can hypothesize that this left hemispheric processing is caused by right hemispheric dysfunction, as described above. The basis for his behavior can be found in his childhood. After his birth, his mother did not accept, and in fact blatantly neglected, the fact that he was a boy. Later, he was told that he would ruin their firm, that he would be unable to lead a successful life and that he was worthless and unfit for a normal life. As an adult, he married a women with a similar temperament as his mother, putting considerable pressure on him by blaming him continuously that he did not make enough money, etc. An enhanced neurovulnerability and associated psychic vulnerability in combination with this renewed psychological stress condition can be seen as basic for the development of his psychogenic fugue condition. (In fact, he had had a few similar, though less severe episodes earlier in his life.) It can be concluded that his autobiographical information processing ability became totally disconnected from the self based especially on the right hemisphere as inner point of reference and thus he lost every contact to reality.

Case AMN

Another patient with a related background and a similar psychic condition was described by Markowitsch and coworkers (1998, 2000). Case AMN presented with psychogenic amnesia and a state of major brain hypometabolism, especially in regions sensitive to memory processing. He had experienced an early trauma as a four-year-old child, whereby he had seen how a man burnt to death in a car, and later at the age of 23 he survived a life-threatening fire at home. This fire in the cellar of his house in fact had been minor, but for him at was immediately life-threatening and resulted in an enduring mnestic block syndrome (Markowitsch, 1998; Markowitsch et al., 1998). He could not retrieve any autobiographical memories for the last six years, and was incapable of acquiring any new information. Positron emission-tomography (PET) showed a reduced glucose level in memory-sensitive areas of the temporal and diencephalic regions. He could not continue in his former position during the first year after the trauma; however, he did succeed in regaining memories after a long period of pharmacological and psychotherapeutic treatment that took more than 12 months.

In conformity with the neurovulnerability hypothesis, it can be inferred that the singular event of being exposed to a massive traumatic situation as a small child changed the hormonal and neurotransmitter sensitivity in his brain, leading to the release of a glucocorticoid cascade (O'Brien, 1997) when he was re-confronted with a precarious fire situation (Aldenhoff, 1997).

In evaluating these cases, we have to remark that every person responds differentially, and that every category of information processing, including memory consolidation, is a process of active construction work. The experience of stress is determined by the capacity of the organism to process stress-related stimuli but it is essentially influenced by appraisal and sensitization of the self for specific information (Bremner, 1995, 1999). Information processing and memory are active processes in which information is selected and filtered, but, significantly, at different levels of awareness we only attend to certain, discrete forms of information and not to others. The emotional state highly influences the specificity of the information that is selected for processing. The preceding functional state determines the following conscious state, and thereby the state of information processing as well.

Taken together, the phenomenon of neurovulnerability develops after repeated, early, chronic, or acute confrontation with stressful information, but especially when this confrontation occurs during the early critical phases in development. The concept refers directly to alterations at the neuronal level, after massive and/or repeated and/or prolonged stress. Neurovulnerability facilitates extreme responsiveness following stress-related stimuli.

A heightened behavioral response occurs as a more sensitive neural response is evoked by less intense stimuli, as is the case in traumatized children (Perry et al., 1995). In traumatized persons, even slight stressors easily sensitize responses such as hyperarousal, dissociation, or even psychogenic amnesia, possibly as a defense against the pain and helplessness engendered by the traumatic experience. There is an overactivation of the relevant neural networks. The nervous system becomes globally vulnerable with respect to its stress-processing capacity, and reacts in a hypersensitive way by the meaning predicated onto specific information.

2.3. PREVENTION

Buffering Stress

Prenatal

Future research will provide us with new methods and procedures for understanding the vulnerability of the brain, brain plasticity, psychopathology and prevention of damage conditions. Our awareness of the fetal sensory and emotional experiences has increased during the last decades, as has the interest in possibilities for stimulating the unborn fetus properly. In correspondence with the evidence described above for the neural and affective consequences of stress on the child, the environment should be actively involved in giving a mother the feeling of wellbeing and relaxation both during her pregnancy and after the birth of her child. In addition, techniques such as relaxation, techniques for the relief of fear and anxiety, can be recommended to modify stress hormone levels (Panthuraamphorn et al., 1998; Sudsuang et al., 1991).

Postnatal

For the newborn fetus, postnatal stimulation seems to have strong and long-lasting physiological consequences. Gentle stimulation of prenatal (multi-)sensory processes, for instance, should facilitate mother-child bonding (Meaney et al., 1994). It should facilitate the maturation of the brain, for example, which should find expression in an increase in the thickness of cortical tissue. It has been found that stimulated infants show a significantly larger head circumference which is traditionally seen as an outcome measure of brain growth. In addition, synaptic density should be higher and levels of vascularization more refined. Social interaction processes as well as motor development should be furthered by pre- and postnatal stimulation (Van de Carr & Lehrer, 1986). Touch and audition appear to be the principle senses through which mothers change neonatal state and brain activity (Field, 1981; Trevarthen & Aitken, 1994).

In rat pups, we observe that postnatal handling apparently protects the organism against age-related cognitive decline (Anisman et al., 1998). As we shortly mentioned before, maternal separation from the pups during the first 14-21 postnatal days may have positive effects on them when occurring for but short durations (about 15 min) but not for longer ones (3 h and more) (Meaney et al., 1991, 1996). Generally, removing rat pups from the nest and placing them in an empty cage for a brief period of time leads to fewer anxiety responses in adulthood. Postnatal handling may decrease neuroendocrine responses, age-related processes of cognitive degeneration and may alter central neurotransmitter activity caused by stressful influences. In addition, recovery in basal levels of glucocorticoids should occur more quickly (Meaney et al., 1991). The expected alteration would most probably also express itself in the reduction of hippocampal corticoid receptors and in an emotional reactivity in the behavioral expression of emotions in response of threatening situations. Several authors have described that some of the prenatal stress effects are reversible by early postnatal experimental handling. But, when mother-child separation becomes stressful and to what degree separation as natural postnatal handling can be generalized to human beings still has to be investigated.

Interactive Repair and Intuitive Parenting

Stress in the caregiver affects biological rhythm which is central for the bonding process. Important here is the process which Tronick (1989) named "interactive repair", which can take place after the child has been stressed. This process of short-term regulation of affect has long-term structural influences. Field, Schanberg, and Scafidi (1986) suggested that, for instance, massaging the infant is effective in reducing acute stress responses. Also, in order to function as a stress regulator for the infant, the primary caregiver must be able to regulate his or her own affect with some efficiency (Schore, 1994). The relaxation of the child through active means on the part of the parents certainly improves on the ability of the child for future attempts at self-relaxation to handle incoming stress. In this chain of relaxation-inducing strategies, the creation of a sense of sameness is vital for inducing the belief in predictability as well as basic trust which forms the basis of later stable identity and patterns of attachment. An intuitive, caring, and predictable environment should be the primary buffer against neurovulnerability. Only within a secure parent-child interaction can the neural basis be established for later potential resistance and protection against stress. If one of the parents is depressed, and is not able to show proper or adequate emotional readiness in favor of the child, the most natural buffers are the non-depressed partners and caregivers, as they provide an optimal stimulation and arousal modulation (Field, 1998b).

Whether parents convincingly express their readiness for an attachment to their children becomes obvious in their manifold expressions of acceptance, in their use of the voice, and in a broad spectrum of nonverbal behaviors (Schwartz, 1997). As we already stressed, various critical periods are most vulnerable, during which sensitivity and plasticity are highest. These are the prenatal period and the first years of the child's development. Imitative and contingent caring responsiveness, focused on the child, supports the infant's sense of efficacy and autonomy and therefore stimulates neural and thus cognitive and emotional development.

Psychotherapeutic Intervention

Psychotherapeutic intervention may prove necessary in children with traumatic experiences to provide emotional relief and to re-process some traumatic moments. As we described above, according to Pennebaker, Hughes, & Oheeron, (1987).), lack of emotional expressiveness or, vice versa, emotional stoicism will be harmful, whereas emotional expression should be helpful in strengthening immune functioning. Emotional expression in a psychotherapeutic context may consequently strengthen right hemispheric functioning which is necessary for emotional meaning and self-regulation. The possibility of expressing stress reactions openly within a socially supportive environment plays an important role in coping with stress. In further therapeutic interventions it may then become necessary to increase the capacity for readjusting the meaning of the original traumatic triggers, in order to learn how to relax and to restore personal integrity to one's self. Emotional support may be vitally necessary. Experiential psychotherapy (Greenberg, 2002; Leijssen et al., 2000) as well as basic methods of supportive psychotherapy are recommended here, whereas in cases of sexual abuse and physical maltreatment use of a behavioral approach may be more directly effective, for example, by strengthening parental skills within adult education programs.

For parents, interventions which target possibilities for mood altering, such as relaxation and music therapy, for instance could be appropriate, if they succeed in making parents more responsive to interactive coaching and to slight signs of improvement in their interactions (Field, 1998a, b). Parents might need to learn to anticipate and protect a child against possible external traumatic influences or even against the parents' own outbursts of aggression; in both cases, the parents should learn how to provide a sense of safety and security for the child. Family support, as from visiting nurses or home visiting parental aides, could be employed, as well as specific psycho-educative programs for the children about abuse, teaching them how to become self-assertive to molesting parents (Kaplan & Pinner, 1996).

Reversibility

The process of reversibility has a high degree of relevancy to this topic: We know that cognitive functioning improves when mood improves (Brown et al., 1999; Richardson et al., 1994). Alterations in the hippocampus may be made reversible by learning to alterate a person's mood and lowering his or her cortisol levels, which in addition should further reduce the effects of aging. In this connection, Nelson (2000) discussed the plasticity of the brain and the possibilities of cortical reorganization in the young and adult brain; motor stimulation by playing a stringed instrument (Elbert et al., 1995) and sensory stimulation of the face (Pons, 1995) were suggested as well.

Final Remarks

In the theoretical discussion between neuroscientists who stress nature's influence, and psychologists who stress the role of social nurturing, the interface between neurophysiological and psychological environments is particularly relevant (Cicchetti & Tucker, 1994). Plasticity is an outcome of the temporally changing and dynamic relation of nature and nurture and a feature of development. The basis for change, for plasticity and for constraints in development lies in the relations that exist among the multiple levels necessary for living: biological, social, sociocultural and psychological (Csikszentmihalyi, 1993).

Future research should elucidate further the fine mechanisms influencing just how stress influences our neural networks and information processing, and which stressors sustain effects on the healthy information processing of the individual. In this context, it should be both exciting and rewarding to explore in greater detail what kind of environmental influences strengthen our neural and psychological system in the encounter with the demands of the world. The more we discover about the fine psychological and physiological influences on the organism, the more we will realize how to protect infants from negative influences and how to ameliorate environmental influences. Plasticity of the brain refers to the potential for change, the possibilities for coping in an adaptive way with the negative influences we continuously meet in our environment. Many otherwise inexplicable mental and physiological phenomena could be prevented or eliminated if we were more aware of the sensibility of initial living.

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CHAPTER 3

ENGAGEMENT OF LATERAL AND MEDIAL PREFRONTAL AREAS IN THE ECPHORY OF NEGATIVE AND POSITIVE AUTOBIOGRAPHICAL MEMORY

1. INTRODUCTION

Memory is divided into several systems of which the episodic-autobiographic system requiring conscious reflection and allowing a mental time travel into the past (Tulving and Markowitsch, 1998). Autobiographical memory allows humans to re-experience our previous events associated with the awareness of the prior conscious event - a self-reflective mental state, defined as autonoetic consciousness by Tulving (1985, 2002).

As episodic-autobiographic system it requires conscious (self)-reflection and is considered to be the most complex (Tulving and Markowitsch, 1998). It gives individuals a sense of identity: we come to know who we are because of our past, the memory of your personal history. Due to its complexity, it is vulnerable to diverse forms of focal as well as diffuse brain damage and to various psychiatric problems, particularly in the field of stress, trauma, and dissociative disorders (Markowitsch, 1999, 2000).

Both results from brain damaged patients (Kroll et al., 1997; Levine et al., 1998) and functional imaging studies (Fink et al., 1996) have stressed the special role of portions of the prefrontal cortex in higher complex psychological functions of the human such as memory processing as well as in theory of mind (Stuss et al., 2001), empathy and consciousness (Henson, et al. 1999; Knight and Grabowecky, 2000; Wheeler et al., 1997), emotion processing (Baker et al., 1997), self-recognition and personal identity (Keenan et al., 2000).

This research relates to quite earlier studies, implicating in particular the orbitofrontal portion of the prefrontal lobes in a number of emotion-related processing patterns (Eslinger, 1999; Rolls, 1999), various personality dimensions (Harlow, 1848, 1869; Welt, 1888; Kleist, 1934) and processes such as directing attention to oneself (Goldenberg et al. 1999).

Autobiographical memory shares many of these functions as it is specifically self-centered, and concentrated towards the retrieval of past emotional happenings associated with a self-reflective state of consciousness or autonoetic consciousness (Tulving, 1985).

A question of interest is whether in addition to a likely engagement of frontal lobe regions other brain areas are implicated differentially in the processing of sad versus happy old autobiographical memories. Limbic area, like portions of the prefrontal/orbitofrontal cortex, the ventral striatum and the amygdala are considered to process emotional information (Davidson, 2000; Davidson and Irwin, 1999; Mesulam, 2000; Morris and Dolan, 2001).

Recent fMRI findings showed significant bilateral amygdala activations towards both positively and negatively valenced pictures but demonstrated that the arousal level modulated the amygdala response for negative but not for positive stimuli (Garavan et al., 2001). The amygdala receives preprocessed polysensory information and its left and right nuclear complexes respond differently to different aspects of emotional stimuli (Markowitsch, 1998/99). In a review of Markowitsch (1998/99) it was concluded that the left amygdala is more closely related to affective encoding with a higher affinity for pictorial or image-related material. The right amygdala may be also more strongly engaged than the left one in a fast and global analysis of affect-related information. Other memory-modulating area such as the hippocampus are expected to be activated. In a study of Fink and coworkers (1996) during the retrieval of old biographical memories, ventral prefrontal and temporal regions, including amygdalar and hippocampal areas were activated. Other area as the cingulated cortex (Fink et al. 1996; Markowitsch, 2000), the basal forebrain area and the precuneus may be activated (Fletcher et al. 2000; Shah et al. 2001).

We used functional magnetic resonance imaging (fMRI) in normal human subjects to address these questions of interaction between memory, emotion, and functional neuroanatomy.

2. METHODS

2.1. SUBJECTS

Subjects were 13 right-handed healthy volunteers (7 females, 7 males) from the Universities of Cologne and Frankfurt am Main. None had a history of previous neurological or psychiatric illnesses or syndromes. No gross brain abnormalities were found on magnetic resonance (MR) scans. All subjects were native German speakers. Informed consent was obtained from each subject prior to participation in this study.

2.2. PROCEDURE

Subjects were told that psychologists have been studying memory for many years, but that there is still a need for research on the brain representation of autobiographical memory about positive and negative experiences. They were asked to retrieve autobiographic episodes of a positive and a negative content, evoked by a fixed set of key words, from the following periods of their life: (1) the first 12 years, (2) the period between years 12-18, (3) and that from age 18 to the present. Subjects were encouraged to provide episodes of a most intense character for both mood conditions. They were told that the investigators were not interested in particulars of the content, but in the general way in which different experiences are re-activated and memorized.

The retrieved episodes were sorted with respect to the two conditions. Subjects were asked to rate and comment on the intensity of their positive or negative emotion for each provided episode. Subjects were asked to rate and comment on the intensity of their emotion for each provided episode. In spite of obviously differing in content between individuals, all episodes were carefully selected with respect to their emotionality and their prompt evocation. A mean intensity level of 7.8 for the positive- and a mean intensity level of 6.7 for the negative condition was obtained which is consistent with the study of

D´Argembeau et al. (2002), for instance. While studying the phenomenal characteristics of autobiographical memories, they found that positive autobiographical episodes were more easily accessed, and tend to be more elaborated and more rehearsed compared to negative autobiographical episodes. The authors interpreted their findings as consistent with the general positive view most people possess from themselves.

After the interview phase, subjects exercised using a computer program to become familiar with the key words and the time-constraints of the procedure.

For brain scanning, subjects were instructed imagine the same episodes as before. The key sentences used in the interview were presented for 5 s on a screen. The screen was darkened for the next 20 s. Following a box-car design, every task (imagination) period of 25 s alternated with a rest condition of the same length (5 scans each for rest and task). Aside from the two experimental conditions - ecphorizing negative and positive episodes - a third, control or baseline condition (REST), was used in addition. During REST, subjects had to fixate a small cross centered on the screen with light gray background (similarly as in the study of Fink et al., 1996). The higher luminance of the rest-screen indicated to the subjects to immediately stop their imaginations carried out in complete darkness. All 36 cues (18 negative, 18 positive) were arranged in 2 blocks, consisting of 6 successive items of the same quality (6 negative first, than 6 positive, in fixed order), and 3 sessions (childhood, adolescence, recent past). The sequence of sessions (120 scans each) was counterbalanced between subjects. Before starting a session, the display showed them the imaginative "life period"; "you are a child" (or "adolescent", or "adult"). The questions depicted in table I were used.

TABLE I

Questions Used to Trigger Emotive Episodes from the Past

A. Negative remembrances from childhood

1. The first negative memory in your life, you remember truly.
2. A situation in which you were very angry.
3. A situation wherein you experienced anxiety.
4. A situation where you were hurt.

5. A negative memory about a friend.

6. A sad memory.

<u>B. Positive remembrances from childhood</u>

1. The first positive memory in your life, you remember truly.

2. A positive event you can remember, for example a play situation.

3. A birthday in your childhood.

4. A positive memory about a good friend.

5. A nice memory wherein you played with others.

6. A nice holiday situation.

<u>C. Negative remembrances from adolescence</u>

1. A negative experience from your school-time.

2. A close contact with another person, which evoked very awkward feelings.

3. A very awkward situation wherein you were alone.

4. A negative experience evoking massive stress.

5. A shameful situation.

6. A conflict with someone close.

<u>D. Positive remembrances from adolescence</u>

1. Feelings of being in love.

2. A nice experience of success.

3. A cheerful amusing adventure.

4. A very agreeable situation with someone.

5. A nice holiday.

6. A very nice appointment.

<u>E. Negative remembrances from adulthood</u>

1. A situation wherein you worried a lot.

2. A moment of deep sadness.

3. The death of a beloved person.

4. A situation in which you were exploited.

5. A situation in which you were hurt.

6. A situation in which you were jealous.

F. Positive remembrances from adulthood

1. One of your nicest moments in the last years
2. A very motivating positive situation.
3. A happy moment.
4. A really joyful situation.
5. The memory of a very nice, intimate experience.
6. A situation which made you very enthusiastic.

2.3. MRI HARDWARE AND TECHNICAL PARAMETERS

Prior to the start of the experiment, subjects' brains were scanned with MRI to exclude morphological-pathological abnormalities. All fMRI measurements were performed on a 1.5 Tesla whole-body scanner (SIEMENS Vision) with standard head coil and using a standard EPI sequence (TR=5 s, TE= 66 ms, FA=90°, FoV=220; matrix 128 x 128, voxel size= 1.64 x 1.64 x 5, scan time 2 s for 15 slices, 5 mm slice thickness). All fMRI scans were realigned to the initial scan from to correct for any head movement. Between each of the 3 sessions of 125 scans each (first 5 discarded) a short break was necessary for technical reasons to restart the EPI sequence for the next 125 measurements. Subjects were instructed to hold their position unchanged over sessions. Data analysis was performed using SPM (Worsley and Friston, 1997). After realignment of all 360 scans to the first scan, and spatial normalization to standard stereotactic space (Friston et al. 1995), images were smoothed applying a Gaussian kernel of 15 mm FWHM. Statistical analysis was then carried out in two stages. First, a fixed effect (within-subject) model was applied to the time series of every individual subject. After filtering (high-pass: 100 s, low-pass: hrf), and proportional scaling the images to overall grand mean, t-statistic maps (height threshold: t=3.12) were generated for the contrasts (negative>rest), (positive>rest), (negative>positive) and (positive>negative) and a single contrast image was written out from the parameter estimates for each contrast and for every subject. Then, with one summary contrast 'scan' per subject, a second-level random effects analysis was conducted for these four contrasts, applying to a one-sample-t-test model. This approach takes the between subjects variability into account and extends inference from the subjects studied to the overall population effects. The resulting activation maps were superimposed to the MNI template brain of SPM 99 (Figs. 1-3).

2.3. IMAGE ANALYSIS

All possible permutations of each two of the three conditions negative, positive, rest were analyzed, applying contrast calculation within the general linear model approach provided by the SPM 99 software (two-level random effect analysis [Friston et al. 1995]). The most revealing comparisons were those between negative and positive episodes (negative>positive; positive>negative (Fig. 1).

3. RESULTS

The main results are a lateral orbitofrontal activation, when activating negative memory episodes, and a subcallosal-anterior cingulate activation, when activating positive ones. In literature, terminology used for these regions differs: Sometimes, they are referred to as limbic frontal or frontolimbic cortex, sometimes as orbitofrontal or basal frontal regions, and some authors use the term prefrontal even when addressing anterior cingulate and subcallosal regions (e.g., Gusnard et al., 2001; Simpson et al., 2001). The cingulate sulcus and para-cingulate gyrus are structurally variable, so that exact anatomical locations differ between subjects (cf. Paus et al., 1996). The negative>positive contrast (after random effect analysis) resulted in a major symmetrical activation of the lateral orbitofrontal cortices, possibly extending into the ventrolateral prefrontal cortices (see Table II), together with smaller activated regions in the right lateral temporal cortex and the left cerebellum (Figs. 1 and 3; Table II). Vice versa, the comparison of the retrieval of positive episodes with that of negative ones resulted in a major left hippocampal, a bilateral (with a preponderance to the right hemisphere, however) subgenual cingulate (Brodmann area 25) and a left dorsolateral-prefrontal activation (Table II). The medial subcallosal activation was exactly below the genu of the corpus callosum (Figs. 1 and 3). All these activations were highly significant (second-level random effects analysis; height threshold t=3.93, puncorrected <.0001). Comparisions of the activated conditions with the condition REST resulted (for second-level analyses) in several significant activations for the comparisons positive>rest and negative>rest (Table II; Fig. 2). Regions in the right posterior temporal and anterior cingulate cortex, in the left dorsolateral and orbital frontal cortex, the left precuneus, the right lenticular nucleus, the medial cerebellar and the left ventral pallidal - dorsal amygdalar region were activated (Table II; Fig. 2).

Table II

Areas activated in the condition of negative relative to positive autobiographic memory.

Region, Gyrus	x	y	z	z-statistics
Lateral orbitofrontal cortex, left	-52	24	-2	3.52
Lateral orbitofrontal cortex, right	54	34	-6	3.79
Lateral temporal cortex	64	-28	-12	3.90
Cerebellum, left	-10	-60	-24	3.99

Areas activated in the condition of positive relative to negative autobiographic memory.

Region, Gyrus	x	y	z	z-statistics
Medial orbifrontal cortex, R	14	26	-10	3.77
Medial orbifrontal cortex, L	-24	24	48	3.79
Hippocampal region, L	-30	-28	-16	4.10
Dorsolateral prefrontal cortex	-24	24	48	3.79

Areas activated in the condition of negative autobiographic memory relative to rest.

Region, Gyrus	x	y	z	z-statistics
Anterior cingulated gyrus (area 24/32), L	12	20	26	4.89
Lateral orbitofrontal cortex (area 47), L	-44	44	10	4.84
Lenticular nucleus, R	28	10	2	4.81
Cerebellum, medial	4	-48	-18	4.22

Areas activated in the condition of positive autobiographic memory relative to rest.

Region, Gyrus	x	y	z	z-statistics
Posterior temporal gyrus (area 37)	32	-56	2	5.99
Anterior cing. gyrus (area 24/32), R	14	16	28	5.37
Medial frontal gyrus, L	-16	20	48	5.19
Superior frontal gyrus, L	-12	-45	4	5.12
Precuneus, L	-26	-58	16	5.09
Ventral pallidal/dorsal amygd. Reg., L	-22	-4	-4	5.29

The main results are a differential orbitofrontal activation, which is lateral when activating negative memory episodes and medial when activating positive ones. All these activations were highly significant, after second-level random effects analysis (height threshold t=3.93, uncorrected< .0001). Figures 1, 2 and 3 illustrate our main results.

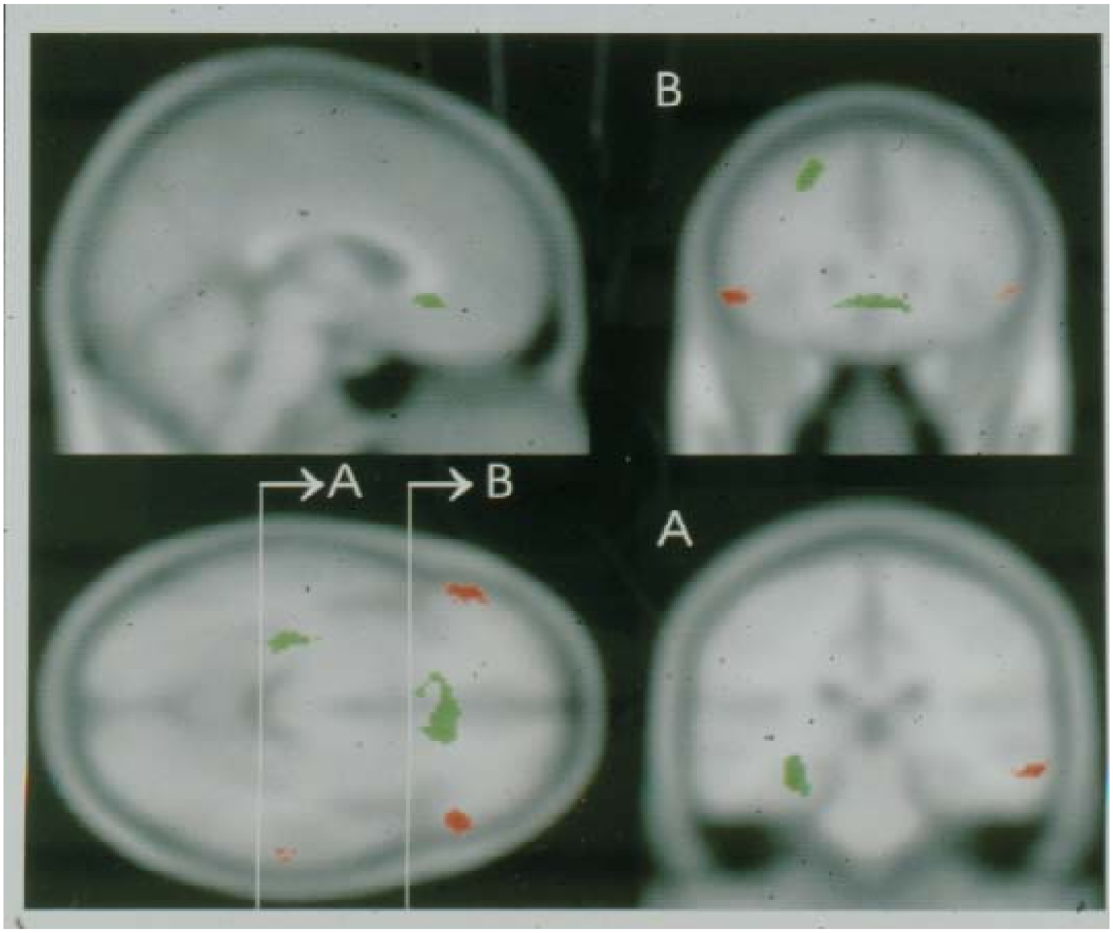

Figure 1. Functional anatomy of the negative>positive (red) and the positive>negative (green) comparisons. A coronal, sagittal, and transverse plane of an arbitrary magnetic resonance image is shown at the level providing the most significant activations. negative-positive activations are found bilaterally in the lateral orbitofrontal cortex and to a minor degree in the right temporal cortex. Vice versa, the positive>negative comparison led to a strong bilateral medial orbitofrontal activation, a left hippocampal and a left dorsolateral prefrontal activation.

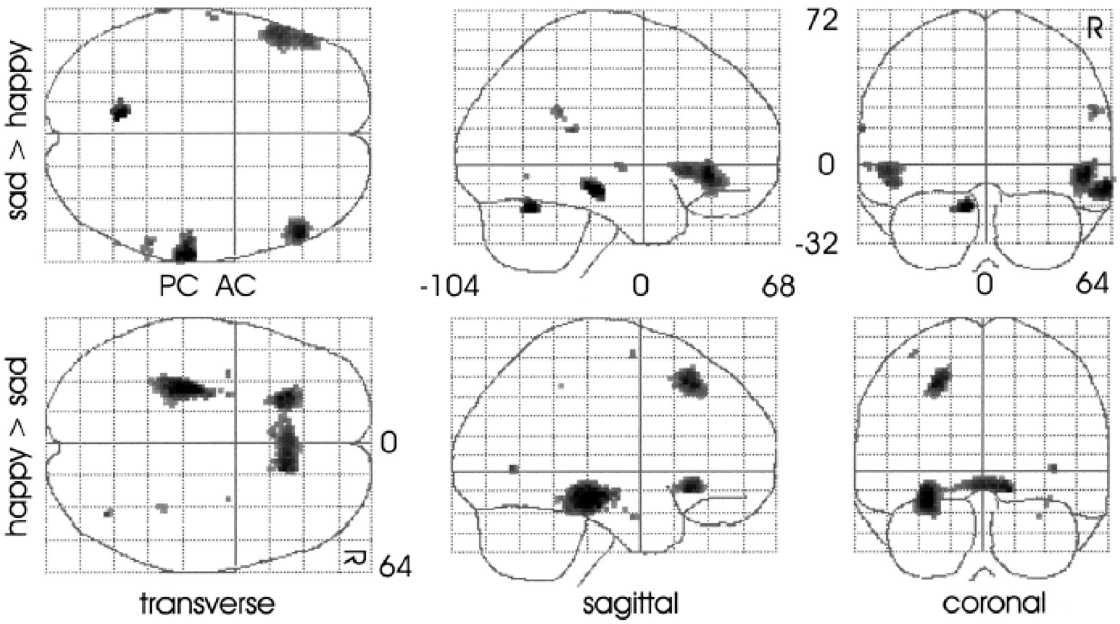

Figure 2. Projections of activations onto representations of the standard stereotactic space as defined by Talairach and Tournoux (1988) ("SPM-99 glass brains"). The top three maps show the activations for the negative>positive, and the bottom tree for the positive>negative comparison.

4. DISCUSSION

This study centers on old autobiographical memory retrieval and emphasizes the link between emotion and memory. The activity patterns are very distinct and differ considerably between negatively and positively experienced episodes. The activations are, with exception of the cerebellar one, all (cerebral) cortical and largely confined to limbic or paralimbic regions.

Especially, the orbitofrontal and subcallosal cortex turns out to be a major hub for the retrieval of emotional memories. Within this area there is a clear separation between regions engaged in the retrieval or ecphory of positive and negative episodes of the distant past.

4.1. Orbitofrontal-Subcallosal Area

The orbitofrontal cortex and its immediately adjacent prefrontal and anterior ventral cingulate regions are shown to be major trigger stations for ecphorizing emotionally colored episodes of the distant past. The orbitofrontal and adjacent subcallosal cortex receives input from (other) prefrontal and posterior cortical integration areas as well as from many limbic regions, representing the hierarchical apex of this system. As a consequence of intimate interconnection onto limbic area, it has been therefore conceived as an "association cortex" for the limbic forebrain (Pribram, 1981).

The orbitofrontal cortex has an important function in social knowing how to behave, the selection of appropriate behavior, or social and interpersonal selfregulation (Bechara et al., 2000; Esslinger et al. 1995; Rolls, 1999, 2000; Shammi & Stuss, 1999). Elliot, Dolan, and Frith, (2000) suggested that the orbitofrontal cortex signalizes the likely value or behavioral relevance of available choices of action, whereby it is not exactly known, how the functions become expressed. The sensitivity to the reward-relatedness of information of the orbitofrontal cortex plays a role in stimulus association learning, especially in unclear or unpredictable situations (Thorpe et al. 1983, Rolls, 1999). Furthermore, decoding and readjusting the reinforcement value of stimuli seems to be an important function of the orbitofrontal cortex (Rolls, 1999). This kind of general supervisory or controlling function was also stressed by Raine et al. (1998) in the interpretation of their findings of orbitofrontal changes in murderers. They, as well as other researchers (Bechara et al., 2000), assume the orbitofrontal cortex to be involved in high level judgment, implicating the anticipation of consequences, empathy and decision making.

Lateral and medial portions of this basal frontal cortex have different networks of connectivity. The medial sector is particularly related to hippocampal and parahippocampal regions, and the posterior cingulate and retrosplenial areas, while the lateral section has strong connections with the amygdala, sensory and premotor regions (Cavada et al., 2000). This division corresponds (a) to the selective medial subgenual (and left hippocampal) activation when ecphorizing positively valued episodes, and (b) to the selective lateral orbitofrontal activation, when remembering negative or sad episodes (it has repeatedly been stressed that the amygdala evaluates negative or particularly intense emotions to a higher degree than positive ones; (Canli et al., 2000; Markowitsch, 1998/99). Also the findings of Frey et al. (2000) of area 13 involvement in the processing of unpleasant auditory information and that of Simpson et al. (2001) of medial orbitofrontal/subgenual involvement during anticipatory anxiety are of relevance in this respect.

We cannot determine whether the activation in the two disparate loci reflects the triggering of the respective episodes or is used to influence (e.g., suppress) the respective other circuit. For this last hypothesis speak the findings of Zubieta et al. (1999), who found a medial frontal engagement in posttraumatic stress symptoms, and of Elliot et al. (2000), who suggested from their findings that activation of the lateral orbitofrontal cortex may reflect the suppression of previously rewarded responses. (However, they also referred to an activation of the lateral orbitofrontal cortex when viewing an angry face.) For the first hypothesis, on the other hand, speaks the result of Blood, et al. (1999) who found that emotional responses to pleasant music correlated with medial orbitofrontal activation. Price (1999) referred to PET data which showed increased blood flow in the lateral orbitofrontal cortex in patients with unipolar depression (compared to normals) and decreased blood flow in medial frontal regions in bipolar, manic-depressive patients, in their depressed phase, suggesting again a differential involvement of these two basal frontal sectors in emotional processing. Gusnard et al. (2001) hypothesized from their findings with functional magnetic resonance imaging that the region they term medial prefrontal cortex (and which with respect to anatomical co-ordinates closely resembles our medial anterior orbital/subcallosal area) is engaged in aspects of the self ("self-referentiual mental activity"), which they found when letting subjects determine which of presented pictures were pleasant or unpleasant. The interaction between memory and emotion consequently seems to be central for the self (Natsoulas, 1995, p. 318; Markowitsch, in press).

There are a few results which may be viewed as at variance with our findings of a medial anterior cingulate/subcallosal activation when ecphorizing positively valued episodes and a lateral orbitofrontal activation when ephorizing negatively valued ones: Mayberg and co-workers (Mayberg et al., 1999; Liotti et al., 2000) found in a PET-study sadness related activity increases in the subgenual cingulate cortex and Drevets et al. (1998) found that the subgenual prefrontal cortical volume is reduced in patients with major depressive disorder.

These observations might, however, indicate that this cortical region, in fact, processes positively valued information in normal, non-depressed subjects. Alternatively, or in addition, it could process both positively and negatively valued episodes, but with varying strength or engagement. Evidence for this view was provided by Rolls (2000) and Ochsner et al. (2001). Rolls (2000) reviewed neuroimaging results which showed that "areas of the orbitofrontal cortex (and connected subgenual cingulate cortex) are activated by pleasant touch, by painful touch, by rewarding and aversive taste, and by odor" (p. 284). Ochsner et al. (2001) suggested from their findings in a patient with bilateral anterior cingulotomy that one "of the anterior cingulate's roles may be to monitor on-line processing and signal the motivational significance of current actions or cognitions" (p. 219), indicating a more general role of this cortex in information processing.

Recently, the group of Tulving (Lepage et al., 2000) also found anterior cingulate activations during memory retrieval tasks and proposed that neuronal activity in this region is correlated with the maintenance of episodic memory retrieval mode, a condition necessary for remembering past episodes. In this article, they also provided a new interpretation of their HERA model (hemispheric encoding retrieval asymmetry) by writing that the previously assumed strict right hemispheric activation during episodic retrieval should be replaced by a bilateral, though more prominently right hemispheric activation - a revision fitting our present data. In conclusion, spatially different and distinct portions of the human basal frontal cortex seem to work as hubs within wider and primarily cortical nets engaged in ecphorizing old autobiographic episodes of a positive or negative character.

4.2. Dorsal Prefrontal Cortex

A left dorsolateral prefrontal activation (together with a left hippocampal one) during the retrieval of positive episodes was observed. The left dorsolateral prefrontal cortex is involved in a number of functions, above all, in the encoding of episodic and semantic information (Tulving et al., 1994; Nolde et al., 1998). In literature, it was also suggested that this region of the brain is engaged in 'working with meaning' (Kapur et al., 1994), an interpretation fitting the present design. The retrieval of episodes is accompanied by their re-encoding, which might be an explanation for the left dorsolateral activation. The selective activation under the condition positive memory- relative to negative memory retrieval is most likely related to the significance threshold set. Reduced activation of the dorsolateral prefrontal cortex has been found in several psychiatric diseases, as in schizophrenia (Selemon et al., 1999); furthermore, damage to the left dorsolateral prefrontal cortex is associated with clinical depression (Baxter, 1989; Martinot, 1990; Robinson, 1996).

4.3. Hippocampal Formation

The hippocampal formation is that brain area that becomes associated with memory. The role of the hippocampus in retrieval however, remains a topic of discussion (Maguire et al. 2001), especially as it is seems to be impossible to distinguish between mere retrieval and retrieval accompanied by the re-encoding of the retrieved information (Tulving and Markowitsch, 1997, 1998). This has to do with the largely unsolved nature of memory consolidation (Ambrogi Lorenzini, 1999; Knowlton and Fanselow, 1998; Lechner et al., 1999; McGaugh, 2000; Moscovitch and Nadel, 1998; Sara, 2000). Tulving and Markowitsch (1998) discusses the hippocampus as necessary in the acquisition and remembering of episodic memories, but not necessarily in the acquisition of semantic memories.

Psychiatric patients demonstrate anatomical deviations in the hippocampal region (Deicken et al., 1998; Whitworth et al., 1998). Heckers et al., (1998) found an impaired recruitment of the hippocampus during conscious recollection in schizophrenia and it is argued quite frequently that the disturbed cognitive functions in schizophrenia may be a result of fronto-hippocampal disconnection (Csernansky et al., 1998; Fletcher, 1998), an interpretation fitting the combined ventral prefrontal and hippocampal activation seen under the condition positive memories in comparison with negative memories. An interaction between ventral prefrontal and hippocampal regions has been proposed both from anatomical (Lavenex and Amaral, 2000) and functional (Mesulam, 2000) points of view. It seems therefore possible to consider the principal activation pattern as reflecting a neuronal circuitry for emotional evaluation of memorized episodes, possibly more so of those with a positive affective background. Alternatively and in addition, the hippocampal activation could indicate that this region is indeed involved in information retrieval, at least for a limited period of time. As we combined three time periods we could not determine whether there is a greater activation for the retrieval of more recent as opposed to more remote memories (cf. Moscovitch and Nadel, 1998). Possibly, the left hemisphere might became just significant, while the right hemisphere did not. Or that retrieving old episodes, positively valued episodes, engages the hippocampal formation of the left hemisphere.

Several factors do play a role in the issue of laterality. Nolde et al. (1998) suggested for instance that more demanding retrieval tasks of perceptually detailed information elicit left prefrontal activation as well, whereas simple memory retrieval tasks elicit right prefrontal activation. In a study of Ranganath et al. (2000), left activation was reliably engaged during retrieval trials of pictures and objects and increased with demands to retrieve perceptually detailed information about the studied items.

4.4. Cerebellum

The significant left hemispheric cerebellar activation corresponds to the findings of others, suggesting that particularly the left cerebellum is engaged in several nonmotor mental activities, among them episodic memory retrieval (Andreasen et al., 1999; Buckner and Tulving, 1995; Cabeza and Nyberg, 2000; Fink et al., 1996; Tulving et. al., 1994), and attribution or experience of emotion (Lane, 1996; Paradiso et al., 1999). The cerebellum appears to be generally involved in conscious processes (Edelman, 1989).

In the study of Andreasen et al. (1999) subjects intentionally recalled a specific past personal episodic memory. The authors suggested the participation of the cerebellum in an interactive cortical-cerebellar network initiating and monitoring the conscious retrieval of episodic memory. Probably cerebellar neurons provide a sequencing time code or a temporal programming to ecphorized events.

4.5. Lateral Temporal Cortex

The selective engagement of a right-hemispheric region of the lateral temporal gyrus during the retrieval of negative episodes may reflect a somewhat more controlled, less emotional access of negative compared to positive episodes. Also, in old work of Flor-Henry (1969) on patients with epilepsy, he found that psychotic behavior is more likely associated with dysfunction of the left, "dominant in his words", than of the right temporal lobe, which is associated with depressive behavior. The temporal region probably reflects the particular engagement of an actual storage places of the engrams (Chen et al., 1996; Miyashita et al., 1998; Sakai and Miyashita, 1994).

4.6. Amygdala

The amygdala can be viewed as that structure that gives episodic memory its emotional flavor (Sarter and Markowitsch, 1985). As a consequence, the amygdala might be expected to be activated during the retrieval of old autobiographical memories (Dolan et al., 2000; Fink et al., 1996; Markowitsch, 1998/99; Markowitsch et al., 2000). Indeed, this was found when comparing retrieval of positive memories with the rest condition. The comparisons of principal interest, however, namely positive- relative to negative and negative- relative to positive, apparently cancelled the amygdala activation out, which most likely existed in either condition (Fink et al., 1996; Markowitsch, 1998/99; Markowitsch et al., 2000). Different intertwined influences may be at work here: habituation (Wright, 2001), sexe differences in amygdaloid activation during memory retrieval (Cahill et al. 2001) and during sadness (Schneider et al. 2000). These factors may have resulted in this selective activation pattern in one condition and not in the others.

5. CONCLUSIONS

This study provided evidence for an engagement of portions of the orbitofrontal/ventral prefrontal cortex in the retrieval of retrograde emotional live-events. A differential activation is demonstrated towards past autobiographical events that were viewed as clearly positive in character and events that were viewed as clearly negative in character. The results complements earlier ones in which it was found that the retrieval of old episodes activates a temporo-frontal network of structures for which the expression "expanded limbic system" (Nauta, 1979) can be used (Fink et al., 1996; Markowitsch et al., 2000). Especially areas within the prefrontal lobe can be described as acting in a dynamic interplay between cognition and emotion (Simpson et al., 2001a, b). From our findings it can be concluded that different anatomical networks engage in the ecphory of positively and negatively rated biographical events. It can furthermore be concluded that cortical structures provide a significant contribution to the processing of affective memories.

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CHAPTER 4

BI-HEMISPHERIC ENGAGEMENT IN THE RETRIEVAL OF AUTOBIOGRAPHICAL NEUTRAL, STRESSFUL POSITIVE AND NEGATIVE EPISODES

AUTOBIOGRAPHIC MEMORY - PROTOTYPE OF EPISODIC MEMORY

1. INTRODUCTION

Episodic autobiographical memory concerns the recollection of specific life-events through subjective time the present, the past to the future. It is accompanied by a self-reflective mental state state of consciousness, entitled autonoetic consciousness by Tulving (1985, 2002). Tulving (2002) defined episodic memory as cognitive, symbolic and declaratively representable. Its operations depend on the underlying semantic memory systems. As the main subset of episodic memory, it is directed towards the ecphory of past emotional happenings. (Tulving, 1983, considers ecphory as the process whereby cues for retrieval interact with stored information so that an image or a representation of the information occurs.) Within autobiographical memory, a main emotional distinction exists between memories of positive versus negative valence (Markowitsch et al., 2003; Piefke, et al., 2003). In a functional magnetic resonance imaging study on neural correlates of happy and sad autobiographical memories circumscribed regions within the orbitofrontal cortex were found (Markowitsch et al., 2003). Piefke, Weiss, Zilles, Markowitsch, and Fink, (2003), studying the neural correlates of differential remoteness and emotional tone in autobiographical memory, found (irrespective of remoteness and emotional tone) bilateral activations in medial and lateral temporal, temporo-occipital, posterior cingulate and frontal cortices. The results also demonstrated a time-dependent involvement of the hippocampal region. Also, the orbitofrontal as well as the entorhinal cortex and adjacent medial temporobasal areas were observed to be differentially more active in positive compared to negative autobiographical memory retrieval.

In this context, it is still a controversially discussed question whether the right, compared to the left hemisphere contributes more intensely and more directly to the retrieval of affect-laden memories. Both the HERA-(hemispheric and encoding retrieval asymmetry) model (Tulving, et al., 1994) and a number of more recent findings, both from functional neuroimaging (Buckner, et al., 1998; Cabeza & Nyberg, 2000; Fletcher, et al., 1998; McDermott et al., 1999; Nyberg, et al., 1996; Habib et al., 2003) and from case reports of brain damaged patients (Eslinger, 1999; Markowitsch, 1995, 2000) all emphasize a stronger role of the right hemisphere. This would be in keeping with the idea of Stuss and Alexander (2000) to view the right hemisphere as a convergence zone of affect and cognition. The right frontal lobe, in interaction with the right temporal lobe, would serve as a specific convergence site for neural processes essential for affect-laden experiences of the self (Markowitsch, 2003a, 2003c).

Recent morphological measurements, in which a considerably larger right (compared to left) hemispheric interconnection between frontal and temporal regions via the uncinate fascicle was found, support this view further (Highley et al., 2002). Both the higher degree of anatomical interconnectivity and the cognitive richness and emotional value of autobiographical old memories make these more vulnerable to brain damage and other external and internal influences (Knowlton & Fanselow, 1998; Markowitsch, 1995, 2000, 2003b; Moscovitch & Nadel, 1998; Tulving & Markowitsch, 1998).

On the other hand, other authors emphasize a left-hemispheric contribution to episodic memory retrieval (Lee et al., 2002; Nolde et al., 1998). Our study aimed to contribute to a solution between these extremes by using memories of various valences, stressful and neutral memories, and additionally, by requiring the subjects to intensely imagine their autobiographical episodes.

Autobiographical memory includes emotional memory ranging from neutral towards negative, positive and stressful memories. Stress, as viewed here, is a quantitatively specifiable variable which superposes the positivity or negativity of an event. Phenomenological examples of states of stress or pressure situations are non-specific or specific time pressure (e.g., having to submit a paper before a deadline is reached) or the wish to have to be better than someone else (e.g., in a sport situation). The inclusion of stressful memories was also considered to be important, as stressful incidents may lead to a block of autobiographical memory retrieval and may change the activity of specific brain regions (Markowitsch et al., 1999; Markowitsch et al., 2000), most likely due to changes in brain metabolism such as an increased release of stress hormones and the block of receptor channels in memory sensitive areas (Markowitsch, 2002).

Using functional magnetic resonance imaging (fMRI), the present study addresses the question whether autobiographical memories of positive, negative, stressful, or neutral character recruit similar or different neural networks. Obtained results should have implications for the classification of memory tasks with respect to systems, laterality and processes.

2. METHODS

2.1. SUBJECTS

Subjects were 16 right-handed healthy women of 21 to 32 years of age. None had a history of previous neurological or psychiatric illnesses or syndromes. No brain abnormalities were found on magnetic resonance scans. All subjects were native German speakers. Informed consent was obtained from each subject prior to participation. Only female subjects participated in order to account for possible gender effects (Cahill et al., 2001; Nyberg et al., 2000; Schneider et al., 2000). On the behavioral level, Lang, Greenwald, Bradley, and Hamm (1993) found that women are more likely to report more intense emotional experiences and show more physiological reactivity in accordance with valence judgements than men do.

2.2. PROCEDURE

Prior to brain scanning, subjects were informed that psychologists have studied memory for decades, but that there would still be a need for research on the brain representation of autobiographical memory. They were then asked to retrieve autobiographic episodes, corresponding to the four conditions - neutralL, stressful, negative, and positive - evoked by a fixed set of 24 standard key sentences (6 sentences per category; questions are given in Table 1). To increase the basis for a similar intensity of the selected memories, three additional (reserve) cue-sentences were given. For neutral and stressful episodes, subjects were encouraged to provide events as neutral and as stressful as possible. For negative and positive episodes, they were encouraged to provide events with an emotional degree of intensity, vividness and detail as high as possible. They were told that the investigators were not interested in details of the content, but in generalizable explanations, how different experiences are re-activated and memorized in the brain.

Subjects practiced the recall of autobiographical memories by associating cue-words (specified before from their retrieved episodes) with the to-be-retrieved episodes. This procedure corresponds to the one used before in several of our functional imaging studies (Fink et al., 1996; Markowitsch et al., 2000, 2003; Piefke et al., 2003) and allowed individuals to familiarize with the procedure employed during scanning. Brain scanning was done on the day of the interview whereby subjects were instructed to re-imagine their original episodes by pairs of cue-words. These were presented acoustically in a completely darkened environment. Subjects were instructed to keep their eyes closed throughout the experimental session. To control for episodic "floating" during the condition of rest, subjects were instructed to imagine a cross the experimentator had shown before against a white background. Following an alternation ("boxcar") design, every task (imagination) period of 30 s alternated with a rest condition of the same length (6 scans each for rest and task). All 24 cues (each 6 neutral, stressful, positive, negative) were arranged in four blocks, consisting of six successive items of the same quality. The sequence of sessions was counterbalanced between the subjects, rather then randomized to avoid variable order artefacts.

TABLE I.

Questions Used to Trigger Emotive Episodes from the Past

<u>1. Neutral memories</u>

1. Gardening situation.
2. Shopping situation.
3. Lunch situation.
4. Working situation.
5. Cooking situation.
6. Cleaning situation.

<u>2. Stressful memories</u>

1. Stress situation.
2. Difficult examination.
3. Time pressure.
4. Important appointment.
5. Something lost.
6. Work stress.

<u>3. Negative memories</u>

1. Death of beloved person.
2. Sad situation.
3. Situation of loneliness.
4. Being hurt.
5. Situation of hopelessness.
6. Disappointment.

<u>4. Positive memories</u>

1. Being in love.
2. Happy moment.
3. Cheerful party.
4. Joyful situation.
5. Nice holiday.
6. Nice appointment.

Post-scan debriefing

After scanning, to ascertain the remembering of the cue-sentences and related association of the respective memory enduring the scan-measurements, subjects were again asked to fill out a questionnaire with feature characteristics defined in the following items: how emotional, positive, experiental vivid each episode was, and in what visual detail they remembered the episodes. These characteristics had to be rated on scales from 1=not at all, 2=scarcely, 3=slightly, 4=fairly, 5=much so, 6=very much so. Subjects were paid for their participation.

2.3. MRI HARDWARE AND TECHNICAL PARAMETERS

MRI scans were carried out using a 1.5 T scanner (Siemens MAGNETOM Symphony, Erlangen, Germany) equipped with a standard head coil and with echoplanar imaging capability. To position the axial T2*-weighted images along the AC-PC line, scout and sagittal T1-weighted images were obtained in every subject. Functional imaging volumes were acquired according to a block paradigm, where a baseline condition was alternated with a stimulus condition. During each block which was lasting 30 s, 10 sets of 16 axial T2*-weighted MR-slices with a slice thickness of 7 mm were obtained using a standard EPI sequence (TR = 1600 ms, TE = 50 ms, field of view (FOV) 192 mm, matrix 64x64). The volumes covered the whole brain. To provide an anatomical reference and to exclude gross brain pathology, a T1-weighted 3D-sequence (MPRAGE, TR = 11.08 ms, TE = 4.3 ms, slice thickness 1.5 mm, FOV 201x230 mm, matrix 224 x 256) was obtained in every subject.

2.4. STATISTICAL ANALYSIS

All images were exported from the measurement console to a SUN workstation. Before intra-run realignment of the functional data sets, the first two images were skipped to account for T1 saturation effects during the first scans. The remaining images were analyzed using SPM99, which was used for image pre-processing as well as for a voxel-based statistical analysis within the context of the General Linear Model (GLM). To correct for head movements, the images were realigned using the SPM99 default algorithm. Prior to group comparisons, anatomical differences were compensated for by means of a spatial normalization using the SPM99 default settings and the standard stereotactic space, i.e. the MNI brain (Montreal Neurological Institute). Then a spatial smoothing was carried on with a Gaussian kernel of 10 mm full-width-half-maximum (FWHM), to increase both signal and anatomical conformity.

A fixed-effects statistical analysis for all permutations of the four conditions (neutral, positive, negative, stress) was done on a voxel-by-voxel basis. Differences between conditions were assessed individually as well as for the group of subjects. After filtering (high-pass: 120 s, low-pass: hrf) t-statistic maps were generated for all contrasts and a single contrast image was generated from the parameter estimates for each contrast and for every subject. Then, with such a single summary image per subject, a random effects analysis was conducted for the contrasts (neutral-rest, stressful-rest, negative-rest, positive-rest, neutral, negative, positive-rest and neutral, stressful, negative, positive-rest), applying to a one sample t-test model. This approach takes into account the inter-subject variability and extends inference from the subjects studied to overall population effects. The resulting activation maps were superimposed to the MNI brain template of SPM99. Activations were projected onto representations of the standard stereotactic space as defined by Talairach and Tournoux (1988) ("SPM-99 glass brains").

3. RESULTS

Brain activations

The four different types of autobiographical memory - neutral, stressful, negative and positive memories - were compared with each other and with rest. Comparisons between the different autobiographical memory types did not reveal significant results, probably due to the shared emotional and self-referential character of autobiographical memory per se. (A second possibility is that to get significant differences for four conditions, more memories per condition are needed. The latter option was not possible given the length of the task and the strong task demands the subjects already had to fulfil.)

The random effect analysis with rest showed the following results (cf. Table 2):

1. In neutral memory compared to rest, prefrontal areas were active: the inferior and middle frontal gyri, the orbitofrontal and the dorsolateral cortex. Aside from prefrontal activations, the anterior and posterior cingulate gyrus, the parietal lobes and the occipital cortex were activated on the left side.

2. The contrast of stressful autobiographical memory compared to rest revealed left prefrontal activations (inferior, middle and superior frontal cortex), as well as activations of the right anterior and left posterior cingulate cortex and the left parietal lobes. In this condition - but not in the comparison of neutral memory vs. rest - the lateral temporal lobes were activated bilaterally.

3. The comparison of negative memory with rest resulted in major bilateral contributions of the prefrontal and temporal lobes (Fig. 1). Within the prefrontal cortex, left orbitofrontal and dorsolateral cortex as well as bilateral anterior medial to superior frontal cortical regions were activated. In the temporal lobe, activity was observed in the lateral lobes (left middle and bilaterally the superior anterior temporal gyrus), and within the medial temporal lobes, the parahippocampal/hippocampal area. As for neutral and stressful memory conditions (compared to rest), activity was observed in the left parietal lobes, with activations in both posterior and anterior areas, and also in the left anterior cingulate area.

4. Positive memory relative to rest resulted in major contributions of the bilateral prefrontal cortex and temporal lobes. Within the prefrontal cortex, the inferior-orbitofrontal, dorsolateral and anterior medial-to-superior frontal cortices were activated bilaterally. In the temporal lobe, activity was observed in the lateral lobes within the left middle and, bilaterally, the superior anterior temporal gyri. Within the medial temporal lobes, parahippocampal/hippocampal areas were activated. As in neutral and stressful memory, both posterior and anterior areas of the left parietal lobes were engaged. Also, the left cingulate gyrus became active.

5. In the combined condition (neutral, negative and positive autobiographical memory) versus rest, again a common pattern of bilateral prefrontal and temporal lobe activations was found. Within the prefrontal lobe, activation was found bilaterally in the inferior-orbitofrontal cortex, the left dorsolateral cortex and, again bilaterally, in the anterior medial-to-superior frontal cortex. Within the lateral temporal lobe, the left middle and both superior anterior temporal gyri were activated. Within the medial temporal lobes, the left parahippocampal/hippocampal areas were active. As in the single conditions of neutral, stressful, negative and positive memory, there was involvement of the left inferior parietal lobes, left posterior cingulate cortex and right cerebellum.

6. For the combination of negative, positive, and stressful autobiographical memory versus rest, prefrontal and temporal lobe activations were dominant. Within the prefrontal lobe, as in the preceding condition (neutral, negative and positive memories relative to rest), activation was found bilaterally in the inferior-orbitofrontal cortex, the left dorsolateral cortex and, again bilaterally, in the anterior medial-to-superior frontal cortex. Within the medial temporal lobes, the left hippocampus, and the right parahippocampus were active. As in the other conditions, the left inferior parietal lobes, the left posterior cingulate gyrus and the cerebellum were active bilaterally.

7. Comparisons of the combination of every type of memory (neutral, stressful, negative and positive) resulted in a similar activation pattern with bilateral inferior frontal, left middle frontal/dorsolateral and right superior frontal lobe engagements. Within the lateral temporal lobes, the left middle and both superior anterior temporal lobes were active. Within the medial temporal lobes, the left parahippocampus and hippocampus were

activated. Also, the left anterior and posterior cingulate, the left inferior and posterior parietal lobes, and the right cerebellum were active.

Table II.

Areas activated in the condition of *neutral* autobiographic memory relative to rest. .

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus	(44)	-39	13	27	5.12
Middle frontal gyrus	(8)	-33	11	47	5.63
Middle ,, ,,	(6,8)	-30	23	44	4.87
Orbitofrontal cortex	(11/47)	-36	40	-15	6.03
Dorsolateral cortex	(46)	-48	27	24	4.56
Posterior cingulate gyrus	(23/30)	-9	-55	10	5.62
Anterior ,, ,,	(32)	-6	19	39	5.36
Parietal lobes, precuneus	(7)	-15	-70	49	5.65
,, ,,	(7)	-27	-71	46	5.57
Inferior parietal lobes	(40)	-36	-71	41	5.47
Superior occipital cortex	(19)	-36	-80	29	4.67

Areas activated in the condition of *stressful* autobiographic memory relative to rest

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus/ orbitofr.	(47)	-45	23	-4	Inf.
Orbitofrontal cortex	(11)	-36	43	-15	5.21
Middle frontal gyrus	(9)	-45	5	38	Inf
,, ,,	(47)	-48	40	-7	4.75
Superior ,, ,,	(10)	-36	58	-3	6.11
Dorsolateral cortex	(6)	-6	17	45	Inf
Anterior cingulate gyrus	(32)	12	22	38	5.74
Posterior ,, ,	(23)	-6	-55	10	5.70
Medial temporal lobe	(21)	24	-8	22	6.99
Middle temporal lobes	(21)	-48	-38	-6	4.92
,, ,,	(21)	-36	-44	0	5.23
Parietal Lobe, precuneus	(39)	-36	-74	34	4.87

Areas activated in the condition of *negative* autobiographic memory relative to rest.

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus/ orbitofr.	(47)	-48	26	-6	Inf.
Middle frontal gyrus/sup. Dorsol.g.	(8)	-36	14	47	Inf.
,, ,,	(9)	-42	14	42	Inf
,, ,,	(10)	-30	61	-3	7.67
	(10)	-27	56	20	6.36
Superior frontal gyrus	(9/10)	-9	60	27	6.79
,, ,,	(10)	-6	65	17	5.65
,, ,,	(8)	-21	43	38	5.13
,, ,,	(9/10)	12	60	27	4.85
,, ,,	(10)	9	65	22	4.59
Medial temporal lobe	(21)	-56	-7	-20	6.11
	(21)	-33	-8	-23	4.91
Superior anterior temporal g.	(38)	-45	10	-31	7.12
,, ,,	(38)	36	10	-36	4.54
,, ,,	(38)	-45	16	-31	5.59
Parahippoca,mp. G./Hippocampus	(36)	-24	-46	-27	5.33
,, ,,	(28/36)	-39	-65	36	5.49
Posterior parietal lobe	(23/31)	-6	-54	23	5.03
Anterior cingulated gyrus	(32)	-6	17	42	Inf

Areas activated in the condition of *positive* autobiographic memory relative to rest.

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus	(47)	45	26	-7	5.27
Orbitofrontal gyrus	(11)	24	43	-16	5.64
,, ,,	(47/11)	-48	43	-10	4.54
Middle frontal gyrus	(6/8)	-36	14	47	Inf
,, ,,	(10)	-39	55	0	5.47
Middle frontal gyrus/dorsolat. g.	(6/8)	-3	20	44	Inf
,, ,,	(9)	45	19	34	7.75
,, ,,	(10)	-6	52	-5	Inf
,, ,,	(10)	-6	55	2	7.68
Superior frontal gyrus	(10)	-12	60	25	6.21
,, ,,	(10)	-27	56	17	5.13
,, ,,	(9/10)	12	60	27	5.83
Inferior temporal gyrus	(20/36)	-33	-10	-32	5.24
,, ,,	(20)	-53	-19	-22	4.61
Middle temporal gyrus	(21)	-53	-7	-20	6.25
Hippocampus/parahippocampus	(28)	-15	-18	-17	6.23
Superior anterior temporal g.	(38)	45	19	-29	6.02
,, ,,	(38)	-39	16	-34	5.63
Cingulate gyrus (ant.-post.)	(23/30)	-6	-51	20	5.68
Anterior parietal lobus, precuneus	(39)	-39	-71	36	6.59

,, ,,	(39)	-50	-63	23	5.88
Cerebellum, posterior		9	-86	-21	5.00

Areas activated in the combined condition of *positive, negative, stressful* autobiographic memory relative to rest. .

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus	(47)	-45	26	-6	Inf
,, ,,	(47)	53	29	-7	4.79
Dorsolateral gyrus	(6/8)	-6	17	42	Inf.
Superior frontal gyrus	(9/10)	-6	54	23	Inf
,, ,,	(9)	12	60	27	6.30
Middle temporal gyrus	(39)	-50	-63	23	Inf
,, ,,	(21)	-56	-7	-20	6.50
,, ,,	(21)	-50	-35	-8	4.72
Hippocampus	(28)	-18	-18	-17	Inf
Parahippocampal gyrus	(28/36)	21	-16	-27	5.52
,, ,,	(36)	27	-10	-33	5.17
,, ,,	(36)	18	-39	-26	5.35
Superior anterior temporal gyrus	(38)	45	19	-31	6.78
Posterior cingulate gyrus	(23)	-6	-55	13	6.92
Inferior parrietal lobe	(39)	-39	-68	36	Inf
Cuneus	(17)	6	-93	2	4.69
Cerebellum		-18	-42	-23	6.94

Cerebellum		6	-82	-18	5.76

Areas activated in the combined condition of *neutral, positive, negative, stressful* autobiographic memory relative to rest.

Region, Gyrus	BA	x	y	z	z-statistics
Inferior frontal gyrus	(47)	-36	25	-6	Inf
,, ,,	(47)	-45	26	-6	Inf
,, ,,	(47)	53	29	-7	6.17
,, ,,	(47)	45	26	-4	6.08
Middle frontal gyrus/dorsol. g.	(10/ 46)	-39	45	20	4.61
Superior frontal lobe	(9)	15	57	28	5.55
Middle temporal gyrus	(21)	-53	-7	-22	7.46
,, ,,	(21)	-48	-38	-8	5.96
Parahippocampal gyrus	(28)	-18	-18	-17	6.54
Hippocampus		-27	-13	-17	5.29
Superior anterior temporal g.	(38)	48	16	-28	6.10
,, ,,	(38)	-39	16	-34	5.51
Anterior cingulate gyrus	(32)	-6	20	42	Inf
Posterior	(23)	-6	-58	10	Inf
Inferior parietal lobe, precuneus	(39)	-39	-68	36	Inf
,, ,,	(39)	-48	-63	23	6.14
Posterior parietal lobe, precuneus	(7)	-15	-70	49	5.65
Cerebellum, posterior lobe		6	-83	-21	5.13

All these activations were significant at a threshold of t= 4.54 with an uncorrected p<0.001.

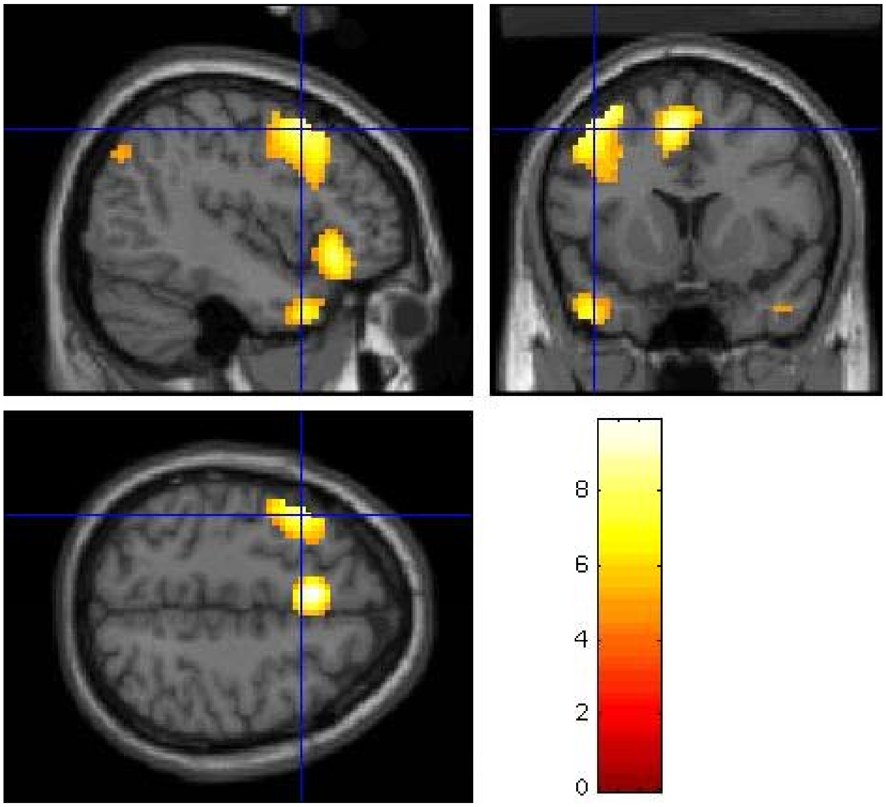

Figure 1. Relative increases in neural activity associated with negative remembrances (compared to rest) superimposed on MRI sections to depict the functional anatomy of the activations and their relationship to the underlying structural anatomy.

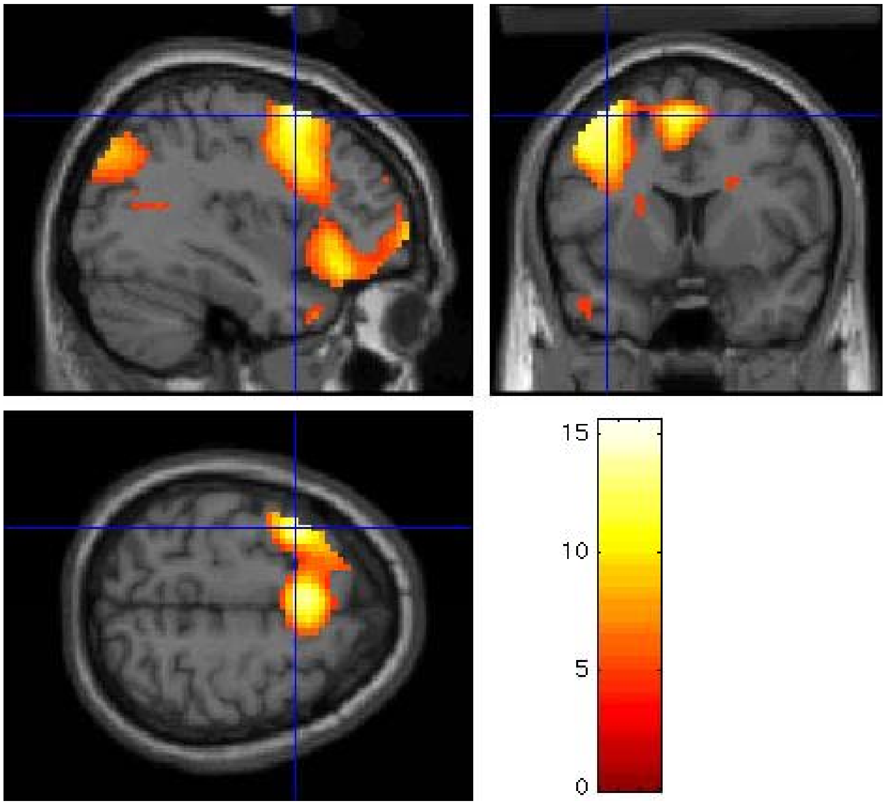

Figure 2. Relative increases in neural activity associated with positive, negative, and stressful remembrances (compared to rest) superimposed on MRI sections to depict the functional anatomy of the activations and their relationship to the underlying structural anatomy.

Behavioral Results

The results of the questionnaire concerned with the phenomenal characteristics of the different types of autobiographical memory were analyzed employing a one-way analysis of variance (one-way ANOVA) with post-hoc Duncan-Multiple Range analysis. A significant effect of the conditions 1. Neutral, 2. Stress, 3. Positive and 4. Negative autobiographical memory was found for all the variables; emotionality $F(3,332)=91.95$, $p < 0.001$ (df=amount of memories); intensity, $F(3, 332)=20.59$, $p < 0.001$; experiential vividness, $F(3, 329)=7.097$, $p < 0.001$; and visual detail, $F(3, 330)=2.76$, $p<00.05$ (see Table 3).

Duncan's post-hoc analysis was applied to detect whether the types of autobiographical memory differed significantly ($p<0.05$) from each other with respect to the different phenomenal characteristics. Duncan's multiple range test involves the pairwise comparisons of the means of a specific variable over the different types of autobiographical memory and builds homogenous groups when not differing significantly from each other. Homogeneous groups are indicated in the cells by the same indicators [(a), (b), (c), (d)] (see Table 3).

Considering the variable emotionality, (a) negative memory was experienced as most emotional then came (b) positive, (c) stressful and at the end (d) neutral memory. The most intense type of memory was (a) positive memory, building a second homogeneous group with (a) negative memory. Then came stressful memory (b), whereas the least intense group was (c) neutral memory. In correspondence, positive memory was experienced as the most (a) vivid, building a homogeneous group together with negative and stressful memory, while (b) neutral memory was experienced as the least vivid memory.

Considering the amount of visual detail in the remembering of memories, (a) neutral memory was associated among the memories with the highest level of detail, (which was due to the fact that the subjects became instructed to choose their memories among more daily life events, which were naturally more recent) building a group with (a) negative and (a) positive memory. In line with the hypothesis that stress may inhibit the remembering of memories, stressful memories (b) were associated with the fewest remembering of detail.

Table III. One-way ANOVA and Duncan Multiple Range Test results of rates on phenomenal characteristics over the four types of autobiographical memory (means and standard deviations; s.d.).

		NEUTRAL	STRESS	NEGATIVE	POSITIVE	F(3,329-332)
Emotion	Mean	2.01(d)	3.9 (c)	4.8 (a)	4.4. (b)	91.95**
	s.d.	1.2	1.3	1.0	1.0	
Intensity	Mean	2.4 (c)	3.3 (b)	-3.7 (a)	3.9 (a)	20.95**
	s.d.	1.3	1.3	1.3	1.3	
Experiential Vividness	Mean	3.5 (b)	4.0 (a)	4.2 (a)	4.3 (a)	7.097 **
	s.d.	1.4	1.3	1.1	1.1	
Visual Detail	Mean	4.5 (a)	3.9. (b)	4.4 (a)	4.4 (a)	2.76*
	s.d.	1.5	1.6	1.5	1.5	

N=83-84, *=0.05%, **=0.001% Note: The letters following the means for each group represent the results of the Duncan Multiple Range test. Means with different letters differ significantly at $p<0.05$.

4. DISCUSSION

This study centered on different types of autobiographic memory. Relative to rest, the different retrieval conditions induced significant neuronal activation patterns; the comparisons between the various retrieval conditions, however, did not result in statistically significant activations. While one could argue that the conditions - retrieving events with positive, negative or stress-related backgrounds - were too similar to each other, a more likely cause can be seen in the limited amount of memories retrieved by the subjects in each condition (which was due to the overall length of the experiment).

The brain regions activated in each memory condition and the totality of the conditions relative to rest corresponds to the known networks supporting episodic memory retrieval. The activations were almost all bilateral with a preponderance to the left hemisphere. The principal activated regions we found were the lateral medial temporal lobes, including the hippocampal and parahippocampal areas, the medial, inferior and superior prefrontal cortex as well as the orbitofrontal cortex, the anterior and posterior cingulate gyrus, including the retrosplenial cortex, parietal lobes, precuneus and cerebellum. The active areas within the conditions share a common pattern, correspondending with the outcome of the review of Cabeza and Nyberg (1997) in episodic memory retrieval. They found despite all the differences in tasks and material, five relevant brain regions: prefrontal cortex, anterior cingulate cortex, posterior midline area (including the posterior cingulate, retrosplenial, precuneus and cuneus regions), parietal cortex and cerebellum (see also Tulving et al., 1999; Gabrieli, 2001). Closely corresponding findings were also seen in a study on episodic memory retrieval, where activations were noted in the right lateral cerebellum, the medial and left orbitofrontal cortex, the anterior cingulate and the parietal region (Andreasen et al., 1999).

The overlapping network of activations may be explainable by the common features in the retrieval of autobiographical memory, namely meaningfulness and the self-referential character of each type of autobiographical memory. In comparison to neutral memories where the activation was seen primarily in the left prefrontal lobes, stressful memory activated, aside from the prefrontal engagement, the lateral temporal lobes, reflecting the more experiential nature of stressful memory in comparison to neutral memory as we will discuss more deeply below. This is even much more so for the emotional types of negative and positive memory, where in comparison to stressful memory, not only the lateral, but also the medial temporal lobes were active, supporting the sensory and emotional richness of autobiographical memories. The exclusive left hemispheric involvement in neutral memory is consistent with its role in more "cold" semantic processes, whereas the inclusion of the right hemispheric engagement is consistent with its role in emotional processes (Markowitsch, 2003a-c; Davidson, 2002; Schore, 2002; Braun, et al., 2003).

Taken together, the bilaterally rather symmetrical activation is partly in contradiction to the traditional HERA-concept, but corresponds to the outcome of our previous studies (Markowitsch et al., 2000, 2003) and that of several other studies on episodic memory retrieval (Andreasen et al., 1999; Conway, 2000, 2001, 2003; Maguire & Mummery, 1999; Piefke et al., 2003), which have led to competing theories regarding the contributions of the left and right hemisphere and prefrontal regions to memory formation and retrieval. The results of all these studies suggest that laterality within the brain is more complex than previously suggested, especially with respect to autobiographic memory processing, and that the veridificacy of existing models needs to be further nuancated and assessed, an issue allowing us to further specify the role of the left hemisphere in episodic autobiographical memory.

4.1. PREFRONTAL LOBES

The hypothesis that different prefrontal regions implement different functions with respect to long-term memory processing has been confirmed by our as well as by previous neuroimaging results (Buckner & Petersen, 1996; Nyberg et al., 2000; Nolde et al., 1998; Wagner, 1999). For memory retrieval, prefrontal activation may be evoked by processes of monitoring, verification and initiation (Fletcher et al., 1995; Markowitsch, 1995).

Inferior, medial and superior prefrontal regions were active during the retrieval of all four types of autobiographical memory (neutral, stressful, negative and positive) and (consequently) also, when combining them. Especially, the anterior medial-to-superior frontal lobe activation within Brodmann area 10 (BA 10), active in every memory condition, except neutral memory retrieval, may reflect processing of meaning consistent with the overall meaningfulness of (especially emotional) autobiographical recall.

Moreover, in accordance with the self-reflecting character of autobiographical memory retrieval, the anterior prefrontal lobes have been associated with self-awareness and reflection in general (Johnson et al., 2002) and more specifically with judgment, the appropriateness of social interactions and planning (Prigatano & Schacter, 1991).

The activation of the inferior prefrontal ventral cortex (BA 47) is in accordance with its importance in the selection of a memory of an event within associated competing memories, thereby filtering out irrelevant information (Jonides, 2000), as well as with its role in retrieval success (McIntosh et al., 1997). Activations of the medial and superior prefrontal cortex will be commented on under the headings of the frontodorsolateral and orbitofrontal cortex.

Our finding of an important contribution of the left prefrontal lobe corresponds to other recent results (Conway, 2000, 2001; Nolde et al., 1998; Piefke et al. 2003, for a review see Lee et al., 2002) and provokes the question, whether and how the right hemisphere processes information differently from the left, and in what manner the left hemisphere contributes to the retrieval of autobiographic memories. Variables that may additionally contribute to the laterality effects are inherent processes such as re-consolidation and strategic search, the global and specific experimental context and procedure, as well as the distinct characteristics of the stimuli - in particular emotionality and easiness of availability. Subject variables such as age and level of motivation have to be considered as well.

4.1.1. LEFT PREFRONTAL INVOLVEMENT

Inferential and Re-consolidation Processes

The spontaneous analysis and evaluation of the to be recalled events and feelings during the scan-measurements of the memory retrieval task may have evoked a stream of feelings, thought inferences and generalization processes which may have become a substrate for further encoding and re-consolidation processes of the activated information, processes relying centrally on the left prefrontal lobes (e.g. Buckner & Tulving, 1995; Cabeza et al., 2003; James, 1890; Sara, 2000; Markowitsch et al., 2003).

Strategic Search

The prefrontal lobes are especially engaged in the retrieval of autobiographical memory when executive functions are required (Greene et al., 1995). The highly complex demands of the retrieval task in combination with the high motivation and probable pressure subjects put on themselves may have enhanced primary search, systemic self-cueing processes and the initiation of selection processes of an appropriate memory event.

Correspondingly, the right prefrontal lobe has been theorized as more responsible for the easy or automatic activation of information, whereas the left prefrontal cortex goes a step further, by rehearsing specific memory characteristics initiating strategies, and generating cues for retrieving inactive information, all processes critical for accurate episodic remembering (Burgess & Shallice, 1996; Ranganath et al., 2000).

This may also explain why Fink et al. (1996) and Markowitsch et al. (2003) found relatively more right-hemispheric activation in comparison to our results. In both studies, subjects evoked their memories by listening to a whole sentence extracted from a memory episode they had retrieved before. In this present study, the subjects were presented with recall by (two) single central cue-words which leaves more freedom to choose another memory event, and stimulates strategic search and selection processes among competing responses relying on the left prefrontal cortex (Lee et al., 2000).

High Level of Detail

Related to these findings is the fact that subjects reported high experiential vividness and high visual detail which may stimulate left prefrontal areas (Nolde et al., 1998). Nolde and coworkers found that simple memory retrieval tasks elicit right prefrontal activation whereas more demanding retrieval tasks of perceptually detailed information elicit left prefrontal activation as well. Left prefrontal activation is thus related to more reflective processing and additional recall of event information. In a study of Ranganath et al. (2000), activation of the left anterior prefrontal cortex (BA 10/46) was reliably activated during retrieval trials of pictures and objects whereby activation in this region increased with demands to retrieve perceptually detailed information about the studied items.

Visual Clarity and Experiential Vividness

Neutral memory - related to a high level of reported visual detail - showed increased involvement of the left prefrontal cortex, whereas stressful, negative and positive memory - related to the report of experiential vividness - was associated with bilateral prefrontal and medial temporal lobe involvement and an overall participation of the left hemisphere across the conditions.

These findings correspond to the results of Conway, Pleydell-Pearce, Whitecross, and Sharpe (2003) who found principally more left prefrontal activity associated with imagined events, more temporal activation related to experienced (cf. experiential) events and an overall activation of the left hemisphere when generating imagined and experienced kinds of memory.

4.1.2. ORBITOFRONTAL CORTEX

The orbitofrontal engagement is consistent with its apparent important role in the retrieval of autobiographical memories (Markowitsch, 1995; Markowitsch et al., 2003; Piefke et al., 2003). As site of convergence for intero- and exteroceptive information, it receives multimodal input from all sensory cortical areas and has a unique position between subcortical and cortical regions, linking affect and memory (Derryberry & Tucker, 1992; Price et al., 1996; Goel & Dolan, 2001; Rolls, 1999, 2000). The orbitofrontal cortex is engaged in processes of both negative and positive emotional valence; in emotional responses to pleasant music (Blood et al., 1999), as well as in unipolar depression (see Price, 1999, for a discussion).

Furthermore, orbitofrontal activations confirm its access to preexisting representations of schematic mental models, related to self and others (Teasdale et al., 1999). A finding which is in conformity with its role in social, emotional, motivational, self-regulatory and autobiographical processes. The orbitofrontal cortex signalizes the likely value or behavioral relevance of available choices of action (Rolls, 1999; Elliot, Dolan, & Frith, 2000) and selects appropriate behavioral strategies (Eslinger, 1999). The intimate connection between emotion, memory and the self in functions such as conscious reflection (Wheeler et al., 1997), theory of mind attributions (Stuss et al., 2001), and those of self-recognition and personal identity (Keenan et al., 2000) are linked to the ventral frontal lobe.

The idea of Kleist (1934) of the orbitofrontal cortex as representing the self, among other personality variables, and collective ego, moral actions and moral dispositions, finally receives late support from actual neuroimaging studies.

4.1.3. DORSAL PREFRONTAL CORTEX

The role of the frontodorsolateral cortex in memory functions such as temporal order retrieval (Cabeza et al., 1997), in perception (temporal perception, order perception) (Cabeza & Nyberg, 2000), and in active maintenance, operating processes of verbal information that was already stored in memory (Fletcher & Henson, 2001; Petrides, 1998), may explain its generalized activation in every type of autobiographical memory and in the combinations of the different types of memory. The executive demands of the task may also be expressed in other typical dorsolateral functions such as task switching, "willed action", and inhibition of previously successful responses (Markowitsch, 1988; cf. Kapur et al., 1994). In episodic memory, the dorsolateral cortex typically has also been related to conceptual and spatial working memory (Goldman-Rakic, 1987). The left hemispheric activations found in our study may consequently reflect functions like encoding, re-encoding and reconsolidation (Tulving et al., 1994; Nolde et al., 1998; Sara, 2000).

4.2. PARIETAL LOBES

The parietal lobes have a major role in various aspects of behavior monitoring and their medial portions are involved in mental imagery. Processes of successful memory retrieval may be modulated by parietal activity (Bernard et al., 2001, Fletcher et al., 1995; Cabeza, 2000; Wilding & Rugg, 1997). The activation of the gyri angularis (BA 39) and supramarginalis (BA 40) in all memory conditions, except in stressful memory, probably (due to its inhibiting influence: see above) may reflect the integration of stimulus characteristics or of relations between context and abstract symbolic representation.

4.3. LATERAL TEMPORAL LOBES

Consistent with several functional imaging studies on episodic memory (Gabrieli et al., 1997; Rugg et al., 1997; Schacter et al., 1996; Eldridge et al., 2000), and autobiographical memory in particular (Fink et al., 1996; Markowitsch et al., 2002, 2003), we found generalized temporal activation, except for the condition of neutral memories. [For neutral autobiographic memory, activations were only found at a low threshold of 3.09; (-36, -55, 11), (T: 5, 63) (Z=5,62)]. This activation pattern was strongly related to 1the higher experiential richness of negative and positive memories compared to the lesser richness of stressful memories.

Left temporal activations are in line with our previous research, demonstrating that autobiographic memory retrieval uses a network of right hemispheric ventral prefrontal and temporopolar regions and left hemispheric lateral temporal regions (Markowitsch et al., 2000, 2003). Furthermore, the observation that for language, semantic memory retrieval, and episodic memory encoding, left prefrontal and temporal regions are typically engaged (Cabeza & Nyberg, 2000; Markowitsch, 1995), may again stress processes of re-encoding and reconsolidation during the retrieval of episodic memory (Markowitsch et al., 2003; Sara, 2000) - especially under emotionally rich memory conditions. That the temporal lobes were not active in the neutral, fact-like memory condition, suggests again the rich experiential autonoetic character of the retrieval of negative, positive and stressful memories in our study. Lateral and anterior temporal activations, especially in Brodmann areas 21 and 38, correspond to activations observed in previous studies on lifelike events and autobiographical memory (Burgess et al., 2001; Fink et al., 1996; Maguire & Mummery, 1999). Essential in episodic autobiographical memory is the sense of self, made by the mental experience of an event, or by autonoetic consciousness. The importance of certain brain structures in autonoetic consciousness - especially portions of the inferior prefrontal and the anterior temporal cortex (Markowitsch, 2003c) - is confirmed by the corresponding activations observed presently and previously (Fink et al., 1996; Menon et al., 2002).

4.4. MEDIAL TEMPORAL LOBES

Neuroimaging studies confirm the role of the medial temporal lobes in memory and learning (Wagner et al., 1998; Markowitsch, 2000), the conscious successful ecphory of episodic events and their sensory-perceptual details (Aggleton & Brown, 1999; Vargha-Khadem et al., 1997; Conway et al., 2001). Increased activations of the medial temporal lobes - the hippocampus and the parahippocampus - was observed for stressful, negative, and positive memories as well as for the combination of all memory types together. The left activations correspond to those obtained in the study of Düzel et al., 1997) who found that episodically retrieved old items were associated with increased blood flow in the left medial temporal lobe. Furthermore, possible processes of re-encoding and re-consolidation processes may play a role here, particular in the more emotion loaded memories with the exception of stressful memories, for which the experienced stress may inhibit of block re-encoding and retrieval processes (Markowitsch et al., 1999, 2000).

4.4.1. HIPPOCAMPAL FORMATION

Tulving and Markowitsch (1998) discussed the hippocampus proper as necessary for the acquisition and remembering of episodic, but not of semantic memories. Engagement of the hippocampus in negative, positive and combined conditions of autobiographic memory corresponds to its function in autobiographic information processing (Vargha-Khadem et al., 1997; Maguire & Mummery, 1999; Maguire et al., 2000) and conscious recollection (Heckers et al., 1998). Control of this result by lowing the threshold to 3.09, shows that the hippocampus is slightly, though not significantly, activated in the stressful condition. The left sided dominance is consistent with the left hippocampal findings in the retrieval of autobiographical memory (Maguire & Mummery, 1999; Maguire et al., 2000; Markowitsch et al., 2003). It may again partly be involved, aside from its role in verbal memory (Strange et al., 1999), in possible re-encoding and re-consolidation processes during retrieval.

Furthermore, Maguire and Mummery (1999) observed enhanced activity for the retrieval of personally relevant, time-specific memories in the left hippocampus and left medial prefrontal cortex. Also, Buckner (2000) described hippocampal involvement in the recognition of time and context-related episodic memory, but not in other forms of recognition. Particularly the left hippocampal lateralization should point to context-dependent episodic memory (Maguire et al., 1998; Burgess et al., 2001).

4.4.2. PARAHIPPOCAMPAL REGION

Together with the hippocampal engagement, processing of complex event memories likely involves the association of information from multiple brain regions. One such contributing region, activated in our study, is the perirhinal-parahippocampal cortex with its dense, reciprocal connections with the hippocampus (Gaffan & Parker, 1996; Zola-Morgan & Squire, 1990; Lavenex & Amaral, 2000), receiving convergent input from association cortices of various sensory modalities.

In our study, activations were primarily confined to the entorhinal cortex which is by far the largest field of the parahippocampal gyrus. Similar as in the hippocampal activation pattern, we could not directly observe parahippocampal activation in the stressful and neutral conditions, fitting the hypothesis that the limbic medial temporal regions are especially involved in experiential, autonoetic memories (Sarter & Markowitsch, 1985; Cahill et al., 1995; Burgess et al., 2001). Maguire (2001) reported increased effective connectivity between parahippocampal and hippocampal cortex for the recollection of autobiographical memory. Also in line with the complex experiential autonoetic character of particularly negative and positive memory, Epstein, Harris, Stanley, and Kanwisher (1999) obtained parahippocampal activation when subjects viewed complex contextual scenes such as rooms, landscapes and city streets, rather then when they viewed photographs of single and more simple objects.

4.5. ANTERIOR CINGULATE CORTEX

Consistent with the present results of an overall activation of the anterior cingulate gyrus (BA 32), Markowitsch et al. (2003) and Lepage, Ghaffar, Nyberg, and Tulving, (2000) found anterior cingulate activations during episodic memory retrieval tasks probably as correlates of executive processes like the maintenance of episodic memory retrieval mode and response selection (Botvinick, et al., 2001; Cabeza & Nyberg, 1997; D'Esposito et al., 1998). Also other processes, attributed to the anterior cingulate region, such as visual imagery, arousal modulation, re-experiencing of emotion and emotional and behavioral inhibition processes may play a role here (Fletcher, et al., 1996; Markowitsch et al., 2000). The lack of activation in positive memories might be explained by the less executive and selective engagement that is needed to retrieve a very vivid positive episode. Experimental research has found that positive episodes in comparison to negative ones in general tend to be more elaborated and more easily accessed (Larsen, 1998).

4.6. RETROSPLENIAL CORTEX

The retrosplenial cortex receives input from regions importantly engaged in emotional processes such as perceiving and evaluating emotional stimuli. Inputs from the amygdala to the entorhinal cortex and from the entorhinal to the retrosplenial cortex can be seen as prerequisites for successful memory processing (Van Hoesen et al., 1993; Cabeza & Nyberg, 1997; Düzel et al., 1999; Tulving, et al., 1999; Maguire et al., 2000; Maguire, 2001; Gabrieli, 2001; Piefke et al., 2003; Markowitsch et al., 2003). The posterior cingulate area, particularly the retrosplenial cortex, was engaged in every single and every combined condition of our experiment, in line with the findings of Maddock's (1999) review, in which it was stated that the retrosplenial cortex was consistently activated when emotional materials were processed and remembered. Also, the life-like contextual (Burgess et al., 2001), the self-reflective (Johnson et al., 2002) and the familiar characters

(Shah et al., 2001) of autobiographical memory may add to the retrosplenial involvement in our study.

Taken together, the retrosplenial cortex has recently been implicated in emotional salience and episodic memory and now also seems to be a hub area involved in autobiographical memory confirming its role as mediator between memory and affect.

4.7. CEREBELLUM

The role of the cerebellum is multiple, vague and inviting for exploration. Aside from its traditional role in motor activity control, cerebellar regions more recently were related to cognitive (and even emotional) tasks (Lane et al., 1998; Paradiso et al., 1999; Cabeza & Nyberg, 1997; Desgranges et al., 1998; Tulving et al., 1999; Wiggs, et al., 1999; Gabrieli, 2001; Fink et al., 1996; Fletcher & Henson, 2001; Markowitsch et al., 2003). The observed cerebellar activations in our study may reflect its participation in initiating and monitoring conscious retrieval of episodic memory, as well as the maintaining and coordination or ongoing updating of the entire retrieval process (Andreasen et al., 1999).

Clinical neuropsychological data have also demonstrated that cerebellar lesions can produce a blunting effect (Schmahmann & Sherman, 1998), which may aid in explaining the cerebellar activation in conditions of positive memory retrieval. As noted before, the behavioral reports of our subjects showed us that positive memory is associated with the most vivid and intense memories, which may have stimulated cerebellar activation.

D´Argembeau, Complain and Van der Linden (2002), who studied the phenomenologic characteristics of autobiographical memories behaviorally, found that positive autobiographical episodes were more easily accessed, and tended to be more elaborated and more frequently rehearsed than negative autobiographical episodes. The authors interpreted their findings as consistent with the general positive view most people possess from themselves.

5. CONCLUSIONS

The principally activated brain regions in every single type of autobiographical memory overlapped considerably and constituted an interactive network of temporal and prefrontal lobes defined as structures of the extended limbic system connecting affect and cognition (Nauta, 1979; Simpson et al., 2001a, b). As in our previous work, these cortical structures appear to be highly important in the recall of autobiographical memory (Fink et al., 1996; Markowitsch et al., 2003).

The main bilateral activations with left sided preponderance refer to enhanced levels of complex self-related information of a high level of experienced detailed imagination of multimodal contextual and perceptual qualities. The primary search and systematic self-cueing processes involving a detailed, deliberative analysis of activated information and the initiation of enhanced selection processes due to the diverse conditions employed in this study, have to be acknowledged here. Due to its rich contextual nature, autobiographical memory contains both episodic (event-based) and semantic aspects. The contribution of both episodic and semantic systems can contribute in parallel and with different weights to the actual outcome of autobiographical episodes (Tulving, 1995, 2002; Tulving & Markowitsch, 1998). Episodic memory retrieval may consequently benefit from recruiting resources of both hemispheres. A dynamic functional interaction between left and right hemispheric functions, and semantic and episodic processes has consequently to be acknowledged as contributing to autobiographical memory retrieval. Consequently, variables such as task demands, subject variables and contexts contribute dynamically and may activate both hemispheres to various degrees (Lepage et al., 2000).

Thinking in distributed networks consequently is more than ever necessary in order to account for the recall mechanisms of functions as complex as autobiographical memory retrieval.

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GENERAL DISCUSSION

AUTOBIOGRAPHICAL MEMORY, BEGINS AND ENDS WITH THE SELF

Autobiographical Memory, Consciousness, the Influence of Stress and its Neural Correlates

1. MEMORY, AUTONOETIC CONSCIOUSNESS AND THE SELF: Consciousness as a Continuum of States

A renewed attempt is made for a deeper understanding of the relationship between memory and consciousness, relying on neurophysiological, philosophical and psychological concepts. Departing from the theory of Tulving (1985, 2002), about semantic and episodic memory and cognitive child psychology the question was posed how children develop awareness of themselves as someone with specific semantic characteristics and as someone embedded in time and space. The assumption is that different levels of development of the self relate to the phylogenetic development of different states of consciousness of being in the world. A gradual conceptual distinction is outlined: 1). a rudimentary state of autonomic awakeness or 'unknowing consciousness' as a biological adaptive function or “anoetic” consciousness relying on implicit and procedural memory. As a state of anoetic consciousness, a first sort of 'self-experience' or self-consciousness became suggested: children, already very early in development, develop an implicit awareness of their own organism and of its influence on the surrounding world. Even when they are still not capable to reflect on the perceptual origin of their own knowledge, they possesses already very early, implicit experiential information about themselves. Without this level we are not able to understand phenomena as experiencing oneself without explicit remembering time and space. 2) 'Knowing consciousness'; or "noetic", and "autonoetic" consciousness. Noetic consciousness is based on semantic memory without having access to subjective experience, whereas autonoetic consciousness is based upon a self-reflective state within time and other contextual dimensions. The mode of access in autonoetic consciousness is associated with what James calls 'warmth and intimacy'. As a self-generated, self-knowing state, attention in autonoetic consciousness can be directed to the past in retrograde consciousness, the present in "real-time" consciousness and to the future in 'prospective' consciousness. Autonoetic consciousness can also be (1) the explicit self-awareness, and/or (2) the explicit awareness of something or someone else in a specific time-space context. When attention is directed from the present to the past to re-experience personal past in subjective time, it makes use of episodic memory (Tulving, 2002).

In the third part of the text, suggestions about the neural correlates of the consciousness as a continuum of states with evidence from brain damage became proposed. Also, evidence from lesion data suggested that an integrated prefronto-anterior temporal network is necessary for successful memory retrieval. Malfunctioning of these regions - either due to manifest tissue damage or due to psychogenic stress and trauma situations, disturbs self-consciousness and autonoetic consciousness.

Due to its complexity, the higher degree of anatomical interconnectivity, autobiographical memory and associated autonoetic consciousness, is more vulnerable to diverse forms of focal as well as diffuse brain damage and other external and internal influences such as stress and neurovulnerability. Anosognosia, emotional flattening and indifference may be the result. Considering the conceptualizing of different levels upon a continuum, empirical studies will be more able to tease different levels of consciousness and memory apart, like unconscious and conscious level of processes and to control the measurements of one level in comparison with another level.

2. NEUROVULNERABILITY: the Influence of Stress on Memory and Autobiographical Memory

I argued that during early childhood intimate care-taking constitutes the most important prerequisite for properly experiencing and processing stress. The intimate interaction of a child with his or her environment is an essential prerequisite for healthy development of the brain and sense of life, and for handling the continuous stream of tasks within the environment. Environmental influences, in particular prenatal and postnatal life experiences with the mother and other caretakers influence the neural and neuroendocrine reactivity to the demands and stressors the child meets.

The present chapter aimed at contributing new thoughts to this topic and at clarifying the facets implicated in the expression neurovulnerability. In early childhood, brain tissue is then still in a continuous state of growth and differentiation whereby environmental stress may lead to long-lasting alterations in brain morphology and functions by reduced neuronal maturation and enhanced neuronal degeneration. As a result, neural networks becomes more vulnerable to further stressful influences. I suppose that many mental health problems share pathophysiological mechanisms originating*f* from subjective discomfort, which in turn leads to enhanced neurovulnerability; a sensitivity or reactivity of the central nervous system at various levels -- from intracellular and biochemical to neurophysiological and psychological ones. Intense or chronic psychosocial stress may induce increased vulnerability on the neural and consequently also on the behavioral level, resulting in the facilitation of the subsequent development of functional disturbances, with psychogenic amnesia and altered autonoetic consciousness being a particularly poignant example.

Future studies should further explore the mechanisms influencing just how stress weakens our neural networks and information processing, and which stressors have strenghtening effects on the healthy information processing and state of autonoetic consciousness of the individual.

4. ENGAGEMENT OF LATERAL AND MEDIAL PREFRONTAL AREAS IN THE ECPHORY OF NEGATIVE AND POSITIVE AUTOBIOGRAPHICAL MEMORY

As the subset of episodic memory, episodic autobiographical memory is accompanied by a self-reflective mental state of consciousness or autonoetic consciousness (Tulving, 1985; 2002). It is directed towards the ecphory of past emotional happenings, usually affect-laden, either positively or negatively. Using functional magnetic resonance imaging (fMRI), the question of interest was whether in addition to a likely engagement of frontal lobe regions other brain areas are implicated differentially in the processing of negative versus positive old autobiographical memories. Limbic area, like portions of the prefrontal/orbitofrontal cortex, the ventral striatum and the amygdala are considered to process emotional information (Davidson, 2000; 2002; Davidson and Irwin, 1999; Mesulam, 2000; Morris and Dolan, 2001).

In this context, it is still a controversially discussed question whether the right, compared to the left hemisphere contributes more intensely and more directly to the retrieval of affect-laden memories.

The results provided evidence for an engagement of portions of the orbitofrontal/ventral prefrontal cortex in the retrieval of old, emotionally colored episodes. These findings point to the importance of the orbitofrontal cortex for affect-laden information processing in autobiographical memory and autonoetic consciousness and to the existence of distinct neural nets for the re-activation of positively and negatively viewed autobiographic episodes.

1. Comparing the retrieval of sad with that of positive episodes activated both lateral orbital cortices symmetrically, together with a small region in the right lateral temporal cortex and the left cerebellum were activated.

2. Comparing the retrieval of positive with that of negative episodes a major left hippocampal and a bilateral (but more strongly right-sided) medial orbitofrontal/subgenual cingulate and a left dorsolateral prefrontal activation. These findings point to the importance of the orbitofrontal cortex for affect-laden information processing and associated autonoetic consciousness and to the existence of distinct neural nets for the re-activation of positively and negatively viewed autobiographic episodes.

4. BI-HEMISPHERIC ENGAGEMENT IN THE RETRIEVAL OF AUTOBIOGRAPHICAL NEUTRAL, STRESSFUL, POSITIVE AND NEGATIVE EPISODES.

The second study went a step further by using memories of various valences, positive, negative, stressful and neutral memories, and additionally, by extra requiring the subjects to intensely imagine their autobiographical episodes. The inclusion of stressful memories was considered to be important in answer upon the question how stressful incidents may change the activity of specific brain region by increased hormones resulting in the inhibition or blockade of receptor channels in memory sensitive areas. Using functional magnetic resonance imaging (fMRI), this study addressed the question whether autobiographical memories of positive, negative, stressful, or neutral character recruit similar or different neural networks. Obtained results have implications for the classification of memory tasks with respect to systems, laterality and processes.

Moreover, in the context of the precedent chapters, I will now re-analyse and re-discuss this study about the retrieval of neutral, stressful, positive and negative episodes with as background 1). the theorizing about autonoetic consciousness, its experiential quality and its neural correlates, 2). the question whether the subjective phenomenal characteristics will help us to understand the different activations and 3). the question whether the ecphory of stressful memories changes the activity of specific brain regions, information retrieval and autonoetic consciousness. Not only uncontrollable stress when coping mechanisms fail, can be destabilizing but also the recall of "daily" stressful events may change, inhibit or even destabilize neural processing, information processing and autonoetic consciousness.

The pattern of cerebral activations revealed significant results of the different conditions relative to rest, reflecting a pattern of shared activation of brain area. Activated areas that correspond to the known networks supporting autobiographic memory retrieval are: 1. the medial temporal lobes, including the hippocampal and parahippocampal area, 2. the medial, inferior and superior prefrontal cortex as well as the orbitofrontal cortex and the dorsolateral cortex, 3. the anterior and posterior cingulate gyrus, including the retrosplenial cortex, 4. parietal lobes and the precuneus and 5. the cerebellum.

The four different types of autobiographical memory - neutral, stressful, negative and positive memories - were compared with each other and with rest. The overlapping network of activations may be explained by the common features in the retrieval of autobiographical memory, namely meaningfulness and the self-referential character of each type of autobiographical memory. Only the most important area becomes discussed.

Prefrontal Area

Inferior, medial and superior prefrontal area were active during the retrieval of all four types of autobiographical memory (neutral, stressful, negative and positive) and (consequently) also, when combining them, reflecting their importance in autobiographical memory retrieval. The anterior medial-to-superior frontal lobe activation within Brodmann area 10 (BA, 10), however active in every memory condition, was not active in neutral memory retrieval, which may reflect enhanced meaningfulness of more experiential autobiographical memories. The prefrontal lobes are regarded as the seat of the highest mental functions with a central role in the representations of the self and in the capacity of self-reflection and attribution. Prefrontal lobes play a prominent role in higher levels of awareness, reflected in noetic consciousness and particular in autonoetic consciousness. As in the first study about positive and negative autobiographical memory, the intimate connection between orbitofrontal activation, emotion, memory and the self becomes confirmed here. The orbitofrontal cortex is also involved in evaluative processes such as appraisal of information (Pribram, 1987), the direction of attention toward oneself and content-related aspects of consciousness and memory (Goldenberg et al., 1989).

Medial and Lateral Temporal Area

In comparison to neutral memories, the more experiential memories, like stressful memories activated, aside from the prefrontal engagement, also the lateral temporal lobes. This was even much more so for the still more emotional types of negative and positive memory, where, not only the lateral, but also the medial temporal lobes - the hippocampus and the parahippocampus - were active (as well as for the combination of all memory types together). The role of the medial temporal lobes in memory and learning becomes confirmed in the conscious, successful ecphory of episodic events and their sensory-perceptual details (Aggleton & Brown, 1999; Vargha-Khadem et al., 1997; Conway et al., 2001). Damage to the temporal lobes results in a failure of analysis or on-line maintenance of information concerning the self.

Similar as in the hippocampal activation pattern, we could not directly observe parahippocampal activation in stressful and neutral conditions, fitting the hypothesis that the limbic medial temporal regions are especially involved in more experiential, autonoetic memories (Sarter & Markowitsch, 1985; Cahill et al., 1995; Burgess et al., 2001). This result is in line with the behavioural results, where, considering for instance, the variable emotionality, negative memory, and then positive memory was experienced as most emotional, followed by stressful memory and then neutral memory. The fact that stressful memories, considered by the subjects as emotional, did not activate hippocampal and parahippocampal area may reflect the inhibiting influence of processing stressful information on brain metabolism and related brain activation. In correspondence, stressful memories were associated with the fewest remembering of detail.

Parietal Area

Even though the parietal area is not the most specifically relevant region for episodic-autobiographical memory, it is interesting to observe that the gyri angularis (BA 39) and supramarginalis (BA 40) associated with the integration of stimulus characteristics of relations between context and abstract symbolic representation, were active in all memory conditions except in stressful memories.

Anterior cingulated cortex and retrosplenial cortex

Consistent with the present results, anterior cingulated gyrus is active during episodic memory retrieval (Markowitsch et al. 2003) and in the representation and awareness of almost any stimuli (Shulman et al., 1997). The posterior cingulate area, particularly the retrosplenial cortex, was engaged in every single and every combined condition of our experiment. Life-like contextual (Burgess et al., 2001), emotional (Maddock, 1999), self-reflective (Johnson et al., 2002) and the familiar characters (Shah et al., 2001) of autobiographical memory may have contributed to the retrosplenial involvement in our study.

Hemispheric Laterality

The overall left sided preponderance, also in the most emotional conditions, probably refers to enhanced levels of complex self-related information with high levels of experienced detailed imagination of multimodal contextual and perceptual qualities of the event. The primary search and systematic self-cueing processes, and the initiation of enhanced selection process due to different conditions in the study of an appropriate autobiographical event, have to considered here (Burgess & Shallice, 1996; Ranganath et al., 2000).

The exclusive left hemispheric involvement in neutral memory is consistent with its role in more "cold" semantic processes and its possible enhanced level of perceptual detail due to the more recent character (as became clear in the debriefing) of the neutral memories. The inclusion of the right hemispheric engagement in stressful, negative, positive and combined conditions is consistent with its role in emotional processes and the quality of autonoetic consciousness as characterized with 'warmth and intimacy'.

Considering the problem of episodic-autobiographical memory retrieval and laterality, a dynamic functional interaction between left and right hemispheric functions and resources, as well as semantic and episodic processes has to be considered.

The strict left, right prefrontal laterality in the retrieval of semantic and episodic autobiographic memory, as we see in traditional models of emotional processing may largely be understood in terms of the distribution and activity of areas over the whole brain.

Final Remarks

Both studies of autobiographical memory episodes showed activation of a temporo-frontal network of structures. The principally activated brain regions in both studies of autobiographical memory overlapped considerably, and constituted of an interactive network of temporal and prefrontal lobes defined as structures of the extended limbic system linking affect with cognition. Autobiographical memory and autonoetic consciousness, is intimately dependent on a proper action of the described circuits, prefrontal, medial and lateral temporal lobes and regions.

Psychogenic stress leads to a changed metabolism of the brain and neurovulnerability which may disturb autobiographical memory retrieval, self-consciousness and autonoetic consciousness. Autobiographical memory about the own self or self-knowledge may then become reduced to the level of semantic knowing of personality characteristics or traits, accompanied by an inhibited disturbed sense of time and autonoetic consciousness. Feelings of warmth and intimacy, which determine the self-related quality of autonoetic consciousness become inhibited or impaired. Evidentially, empirical confirmation of the neurovulnerability hypothesis needs longitudinal studies too, studies with large groups of subjects who had a stressful or traumatic childhood, as well as within-subject studies where subjects have to process stressful information before and after they experience something traumatic or before and after a period of traumatic stress. The question is whether they react differently and become more vulnerable to develop functional disturbances, such as changed, inhibited or blocked information processing and autobiographical memory. As well, the understanding of autobiographical memory and autonoetic consciousness needs further exploration of the fine mechanisms determining one level of consciousness and memory in comparison to another level of consciousness and memory, brain metabolism and lateralization.

To conclude, described theorizing and studies as done in this dissertation; mean an exploring, renewed, and confirmatory step further in the continuing debate on autobiographical memory, consciousness, and its neural correlates, as well as a preliminary step in the understanding of the phenomenon of neurovulnerability.

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Affirmation:

I affirm that this doctoral thesis is my own independent work and that it is exclusively submitted at the faculty of psychology of the university of Bielefeld.

Marie Vandekerckhove