The Influence of Early Life Stress on Affective Functioning:

An Investigation of Behavior, Brain Structure and Music-Induced Emotional Brain Responses

Dissertation

zur Erlangung des akademischen Grades
Doktor(in) der Philosophie (Dr. phil.)
Doctor of Philosophy (Ph.D.)

vorgelegt von
Dipl.-Psych. Sabine Aust
in Berlin, 2013
Erstgutachter:
Prof. Dr. Malek Bajbouj

Zweitgutachter:
Prof. Dr. Stefan Koelsch

Tag der Disputation: 20. Juni 2013
Acknowledgements

Special thanks to...

… my supervisor team, especially Malek Bajbouj, Stefan Koelsch, Hauke Heekeran, Isabella Heuser and Gisela Klann-Delius

… my ANEM colleagues, especially Simone Grimm, Anne Weigand, Melanie Feeser, Matti Gärtner and Yan Fan

… my colleagues from the LoE Graduate School, particularly Corinna Pehrs, Daniela Schönele, André Hoever and Aline Vater

… my colleagues from Freie Universität and Charité Berlin, namely Elif Alkan Härtwig, Stavros Skouras, Isabel Bohn, the team of the D.I.N.E. and all the other lovely people who discussed my projects with me, proofread my manuscripts, provided technical support or just joined me for lunch or a beer after work.

Very special thanks to...

… Lars

… Frédéric, Martin, Anne Kristin, Stephan, Hannes, Verena and Franco

… Renate & Wolfgang

… Gabi & Werner
Table of Contents

English Summary ....................................................... 1
Deutsche Zusammenfassung ......................................... 2

List of Figures ............................................................. 4
List of Tables ............................................................... 5
List of Abbreviations .................................................... 6

1. Introduction
   1.1 Emotions and Emotional Development ....................... 8
   1.2 The Influence of Early Life Stress .......................... 9
   1.3 One possible outcome: Alexithymia .......................... 10
   1.4 Another possible outcome: Major Depression ............... 12
   1.5 Aims of the Dissertation Project ........................... 13

2. The Role of Early Emotional Neglect in Alexithymia
   2.0 Abstract .............................................................. 15
   2.1 Introduction .......................................................... 16
   2.2 Materials and Methods .......................................... 17
      2.2.1 Participants .................................................... 17
      2.2.2 Procedure ....................................................... 17
      2.2.3 Measures ........................................................ 18
      2.2.4 Data Analysis .................................................. 20
   2.3 Results ............................................................... 21
      2.3.1 Descriptive Statistics ......................................... 21
      2.3.2 Relationship between Alexithymia and Early Life Stress . 21
      2.3.3 Reported emotional functioning in Alexithymia as a .......... 23
               function of Early Emotional Neglect
   2.4 Discussion .......................................................... 24
   2.5 Acknowledgements ............................................... 28

3. Development of a task to assess Neural and Behavioral Correlates
   of Emotional Experiences
   3.1 Introduction .......................................................... 29
3.2 Materials and Methods ........................................ 31
  3.2.1 Participants ................................................. 31
  3.2.2 Procedure .................................................. 31
  3.2.3 Measures ................................................... 31
  3.2.4 Behavioral Emotion Induction Task ....................... 32
  3.2.5 Data Analysis .............................................. 34
3.3 Results .......................................................... 34
  3.3.1 Descriptive Statistics ...................................... 34
  3.3.2 Effects of Stimulus Valence ............................... 35
  3.3.3 Effects of Stimulus Modality ............................. 35
  3.3.4 Effects of Alexithymia, Depression and Anxiety on Emotional Responses 36
3.4 Discussion ...................................................... 37

4. Introduction to Neuroimaging Methods
  4.1 Magnetic Resonance Imaging (MRI) ......................... 39
  4.2 Functional Magnetic Resonance Imaging (fMRI) ............ 40

5. How Emotional Abilities modulate the Influence of Early Life Stress on Hippocampal Functioning
  5.0 Abstract ....................................................... 41
  5.1 Introduction .................................................. 42
  5.2 Material and Methods ....................................... 44
    5.2.1 Participants ............................................ 44
    5.2.2 Procedure ............................................... 44
    5.2.3 Measures ............................................... 45
    5.2.4 Functional Magnetic Resonance Imaging (fMRI) ......... 46
    5.2.5 Data Analysis ........................................... 48
  5.3 Results ...................................................... 48
    5.3.1 Descriptive Statistics .................................. 48
    5.3.2 Subjective Rating of Emotional Experience ............. 50
    5.3.3 Physiological Results .................................. 50
    5.3.4 fMRI Results ............................................ 51
  5.4 Discussion .................................................. 53
  5.5 Acknowledgements .......................................... 58
6. Differential Effects of Early Life Stress on Hippocampus and Amygdala Volume as a Function of Emotional Abilities

<table>
<thead>
<tr>
<th>Section</th>
<th>Name</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>Abstract</td>
<td>59</td>
</tr>
<tr>
<td>6.1</td>
<td>Introduction</td>
<td>60</td>
</tr>
<tr>
<td>6.2</td>
<td>Material and Methods</td>
<td>61</td>
</tr>
<tr>
<td>6.2.1</td>
<td>Participants</td>
<td>61</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Procedure</td>
<td>61</td>
</tr>
<tr>
<td>6.2.3</td>
<td>Measures</td>
<td>62</td>
</tr>
<tr>
<td>6.2.4</td>
<td>Magnetic Resonance Imaging (MRI)</td>
<td>63</td>
</tr>
<tr>
<td>5.2.5</td>
<td>Data Analysis</td>
<td>63</td>
</tr>
<tr>
<td>6.3</td>
<td>Results</td>
<td>64</td>
</tr>
<tr>
<td>6.3.1</td>
<td>Descriptive Statistics</td>
<td>64</td>
</tr>
<tr>
<td>6.3.2</td>
<td>Results of Volumetric Analyses</td>
<td>64</td>
</tr>
<tr>
<td>6.4</td>
<td>Discussion</td>
<td>66</td>
</tr>
<tr>
<td>6.5</td>
<td>Acknowledgements</td>
<td>70</td>
</tr>
</tbody>
</table>

7. Music in Depression: Neural Correlates of Emotional Experiences in Remitted Depression

<table>
<thead>
<tr>
<th>Section</th>
<th>Name</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td>Abstract</td>
<td>71</td>
</tr>
<tr>
<td>7.1</td>
<td>Introduction</td>
<td>72</td>
</tr>
<tr>
<td>7.2</td>
<td>Material and Methods</td>
<td>73</td>
</tr>
<tr>
<td>7.2.1</td>
<td>Participants</td>
<td>73</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Procedure</td>
<td>73</td>
</tr>
<tr>
<td>7.2.3</td>
<td>Measures</td>
<td>74</td>
</tr>
<tr>
<td>7.2.4</td>
<td>Functional Magnetic Resonance Imaging (fMRI)</td>
<td>75</td>
</tr>
<tr>
<td>7.2.5</td>
<td>Data Analysis</td>
<td>77</td>
</tr>
<tr>
<td>7.3</td>
<td>Results</td>
<td>77</td>
</tr>
<tr>
<td>7.3.1</td>
<td>Descriptive Statistics</td>
<td>77</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Subjective Ratings of Emotional Experience</td>
<td>79</td>
</tr>
<tr>
<td>7.3.3</td>
<td>fMRI Results</td>
<td>79</td>
</tr>
<tr>
<td>7.4</td>
<td>Discussion</td>
<td>81</td>
</tr>
<tr>
<td>7.5</td>
<td>Acknowledgements</td>
<td>85</td>
</tr>
</tbody>
</table>

8. General Discussion

<table>
<thead>
<tr>
<th>Section</th>
<th>Name</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>Summary of Empirical Studies and Further Thoughts</td>
<td>86</td>
</tr>
<tr>
<td>8.2</td>
<td>From music-induced Emotions to music-based Interventions</td>
<td>89</td>
</tr>
</tbody>
</table>
9. References 92

Appendix:

Lebenslauf 113

Selbständigkeitserklärung 114
**English Summary**

The overall aim of the present dissertation project was to investigate how early stress exposure modulates emotional abilities as well as function and structure of emotion processing circuits in the brain. To capture individual degrees of emotional ability, healthy individuals with high and low levels of alexithymia as well as participants with and without a history of major depression were investigated. The goal was to explore the influence of early life stress under different “basic emotional configurations” to gain some insight into individual processes of adaptation to early experiences of stress, such as emotional and physical abuse or neglect. To investigate emotional brain functioning as validly as possible, we designed an experiment using musical stimuli to induce strong emotional experiences in the participants, which were measured via functional magnetic resonance imaging (fMRI). Furthermore, the volume of emotion-relevant brain areas, such as hippocampus and amygdala, was measured via MRI to explore the effects of early life stress on a structural level. The main results are:

1) The experience of early life stress is associated with altered emotional abilities in adulthood (i.e. high degrees of alexithymia) in healthy individuals.

2) Early life stress modulates brain responses to audio-visually induced pleasant emotional experiences as a function of alexithymia.

3) How early life stress affects the volume of emotion processing areas in the brain significantly depends on an individual’s degree of alexithymia.

4) Reduced pregenual anterior cingulate cortex reactivity to audiovisual emotional stimuli in remitted depressed individuals is modulated by the experience of early life stress and represents a neural marker for depression vulnerability.

In short, the present studies corroborate previous findings that early life stress has considerable effects on brain development, affective functioning and, in the broader sense, to mental health. However, our studies are the first to reveal that different degrees of emotional functioning can modulate individual neural and behavioral adaptations to early stress exposure. The results indicate that the development of emotional abilities in children and young adults exposed to ELS are crucial and need to be promoted in the context of prevention and intervention. Finally, we discuss the role music could play in therapeutic interventions promoting emotional functioning.
Deutsche Zusammenfassung


1) Das Erleben früher traumatischer Lebensereignisse geht mit veränderten emotionalen Fähigkeiten im Erwachsenenalter, wie beispielsweise einer hohen alexithymen Ausprägung, einher.

2) Frühe Stresserfahrungen verändern neuronale Antworten auf audiovisuell induzierte, als angenehm empfundene emotionale Erfahrungen in Abhängigkeit von Alexithymie.

3) Die Art und Weise, wie sich frühe Stresserfahrungen auf das Volumen emotionsverarbeitender Gehirnareale auswirken, hängt ebenfalls von der individuellen alexithymen Ausprägung ab.

4) Remittierte depressive Patienten zeigen eine reduzierte Aktivierung des prägenualen anterioren Cingulums in Reaktion auf audiovisuell induzierte emotionale Erfahrungen. Das Ausmaß dieser Aktivierungsreduktion wird durch frühe Stresserfahrungen moduliert und stellt einen neuronalen Marker für Depressionsvulnerabilität dar.
List of Figures

3.2.4 Behavioral emotion induction task with eight rating options ........... 33
3.3.2 Effects of stimulus valence on self-rated emotional experiences ....... 35
3.3.3 Effects of stimulus modality in the pleasant and unpleasant
condition .................................................................................... 36
5.2.4 fMRI design to audio-visually induce pleasant and unpleasant
emotional experiences ................................................................. 47
5.3.4 Early life stress modulates hippocampal responses to pleasant
(> neutral) stimuli in h-ALEX individuals ...................................... 52
6.3.2 The influence of ELS on hippocampus and amygdala volume
in individuals with high and low degrees of alexithymia ................. 66
7.3.3.1 Reduced pgACC activation in response to pleasant (> neutral)
stimuli in remitted depressed patients as compared to healthy
controls ....................................................................................... 81
7.3.3.2 Hippocampal activation in response to unpleasant (> neutral)
stimuli explained by trait anxiety in remitted depression ............... 82
8.1 Summary of main findings ....................................................... 88
## List of Tables

2.3.1 Test of group differences regarding alexithymia \((N=90)\) .......................... 22

2.3.2 Test of group differences regarding early life stress \((N=90)\) ....................... 22

2.3.3 The relationship between alexithymia and early life stress
\((N=90; \text{controlled for age})\) ................................................................. 23

5.3.1 Test of group differences regarding age, years of education,
alexithymia, early life stress and depression \((N=50)\) ............................ 49

5.3.4.1 Brain regions activated in response to pleasant \(>\) neutral
stimuli \((N=50)\) .......................................................................................... 51

5.3.4.2 Brain regions activated in response to unpleasant \(>\) neutral
stimuli \((N=50)\) .......................................................................................... 52

6.3.1 Test of group differences regarding age, years of education,
alexithymia, early life stress, depression and trait anxiety \((N=50)\) .... 65

7.3.1 Test of group differences regarding age, depression, early
life stress and personality variables ......................................................... 78

7.3.3.1 Brain regions activated in response to pleasant \(>\) neutral
stimuli \((N=28)\) .......................................................................................... 80

7.3.3.2 Brain regions activated in response to unpleasant \(>\) neutral
stimuli \((N=28)\) .......................................................................................... 80
List of Abbreviations

AC – anterior commissure
pgACC – pregenual anterior cingulate cortex
BA – Brodman area
BDI – Beck depression inventory
BOLD – blood oxygen level dependent
BVAQ – Bermond-Vorst alexithymia questionnaire
CISS – Coping Inventory for Stressful Situations
CTQ – childhood trauma questionnaire
DFG – German Research Foundation
DSM-IV – Diagnostic and Statistic Manual of Mental Disorders
ELS – early life stress
EN – emotional neglect
EPI – echo-planar imaging
ETI – early trauma inventory
FDR – false discovery rate
fMRI – functional magnetic resonance imaging
GSR – galvanic skin response
h-ALEX – high alexithymic
HAMD – Hamilton Depression Rating Scale
IAPS – International Affective Picture System
l-ALEX – low alexithymic
M – arithmetic mean
MADRS – Montgomery-Asberg Depression Rating Scale
MDD – major depressive disorder
M.I.N.I. – Mini-International Neuropsychiatric Inventory
MNI – Montreal Neurological Institute
n.s. – not significant
PC – posterior commissure
PTSD – posttraumatic stress disorder
RD – remitted depressed
SEE – Skalen zum Erleben von Emotionen
SD – standard deviation
SPM – Statistical Parametric Mapping
SPSS – Statistical Package for the Social Sciences
SSRI – selective serotonin reuptake inhibitor
STAI – state trait anxiety inventory
TAS-20 – Toronto Alexithymia Scale 20-item version
TE – echo time
TR – repetition time
TSIA – Toronto Structured Interview for Alexithymia
Chapter 1

Introduction

Emotions are essential for human life. Emotions exert influence on what we think, what we remember, what we forget, how we behave, which decisions we make. Emotions are the basis of interpersonal relationships and the key to communication; they are the source of literature, music and art. Consequently, the scientific investigation of emotions and their development has become increasingly relevant. In recent years, emotions were eventually integrated in the fields of psychology, sociology, even computer science and neurology, giving rise to interesting new fields of research such as affective computing or affective neuroscience.

1.1 Emotions and Emotional Development

According to Scherer’s component process model (2005), an emotion is defined as a specific response to an external or internal stimulus, which is associated with five interrelated processes in body and brain. These processes comprise a cognitive evaluation of the stimulus, bodily sensations, action tendencies, a facial or vocal expression and the subjective experience of the mental state, called feeling. Thus, Scherer’s approach integrates cognition, neurophysiology and motivation as well as motor expression and subjective feeling in one model. The five components can function independently, however, it is only during an emotional episode that all of them synchronize. Thereby, the feeling component plays a particularly important role. Its main function is to integrate and centrally represent the current status of the five processes involved in an emotion, enabling the individual to express and communicate the experienced state to others (Scherer, 2009). This central role in maintaining the integrity of an emotion probably makes the feeling component most vulnerable to disturbances in terms of affective symptoms, which are present in most psychiatric disorders.

In his theory of core affect, Russell (2003) claims that each emotion can be distinctively categorized on the basis of valence and arousal – from pleasure to displeasure, from excitement to drowsiness. Joy and fear, for example, are two considerably different
emotions with regard to valence, whereas their arousal potential might be similar. Fear and sadness, in turn, are comparably unpleasant experiences, but they differ on the arousal dimension: sadness usually has a rather paralyzing effect whereas fear elicits increased alertness and makes you ready to take flight or fight.

Most parts of the human emotion system develop throughout childhood and adolescence. Only a small set of abilities, such as facial emotion expression, is thought as the “basic configuration” of the emotion system and thus develops independently of social influences (Ekman, 1993; Izard & Malatesta, 1987). However, previous investigations have shown that the development of emotional abilities is predominantly mediated by close relationships between the child and its primary caregiver (Thompson, 2008). From a theoretical perspective, these relationships are best described in terms of Bowlby’s construct of attachment (Bowlby, 1958). Attachment between child and caregiver begins to develop a few weeks after birth, but remains vulnerable to adverse experiences or parental psychopathology throughout childhood (Schechter & Wilhelm, 2009). Secure attachment requires a sensitive, comforting and responsive caregiver and allows for the development of a “secure base” enabling the infant to explore the environment and to try new modes of behavior (Bowlby, 1973). Secure relationships between child and caregiver are also characterized by a climate of protection, reciprocity, participation and guided learning (Grusec & Davidov, 2010). In addition, adequate emotional expressiveness, parental sensitivity and consistent reactivity have a favorable influence on the child’s social and emotional development (Allen, 2011; Boyum & Parke, 1995). Neurobiological research has shown that a secure attachment relationship promotes the development of the emotion regulating limbic system, comprising brain structures such as hippocampus and amygdala (Schore, 2001).

1.2 The Influence of Early Life Stress

These sensitive developmental processes as described above can easily be disturbed by adverse environmental factors. Among these factors is early life stress, defined as “the exposure to multiple events during childhood that exceeds the child’s coping resources and leads to prolonged phases of stress” (Pechtel & Pizzagalli, 2010). Such events comprise experiences of emotional and physical abuse or neglect, sexual abuse or assault, witnessing crime or violence, as well as parental separation. To fulfill the definition of abuse or neglect, the intention to harm the victimized individual is not necessarily needed (Glaser, 2005). Although short sequences of stress and the resulting
bodily activation are crucial to our survival, prolonged exposure to early life stress has a considerable impact on an individual’s health. Early life stress is related to an increased risk of premature mortality (Brown et al., 2009) and physical illness (Weckerle, 2011). It also affects emotional functioning (Cohen, 2006b; Schore, 2001), personality (McFarlane et al., 2005) and brain development (Coplan et al., 2010; Kaufman et al., 2000). The association between early stress exposure and adult mental health seems mainly biological in nature, with negative social environments becoming “embedded as changes in neural structure [...] and, ultimately, in behaviors that lead to mental illness” (Tottenham & Sheridan, 2010). On a neural level, the relevance of limbic structures in the investigation of ELS-related effects is clearly indicated by a large human and non-human animal literature. Hippocampus and amygdala, for example, are central structures within limbic emotion processing circuits and show strong connections with the activity of the hypothalamic pituitary adrenocortical (HPA) axis, which mediates neuroendocrine stress responses in humans. In addition, functional imaging studies have revealed altered activation patterns in limbic structures to be associated with early life stress (Pechtel & Pizzagalli, 2010; Teicher et al., 2003; Taylor et al., 2006). On a behavioral level, early childhood adversities significantly increase incidence rates of affective disorders such as depression (Heim & Binder, 2012) and can affect the development of emotional abilities (Freyberger, 1977; Lumley, Neely & Burger, 2007). A child growing up in a cold, distant and emotionally negligent atmosphere might have difficulties developing emotional abilities such as self-awareness and introspection to the same extent as a child growing up in a warm, protective and emotionally supportive home (Thompson, 2008). This form of emotional maltreatment can impede a secure attachment between caregiver and care recipient (Bekker, Bachrach & Croon, 2007; Grusec, 2011) and might result in the development of altered emotional abilities (Frewen et al., 2008, Montebanocci et al., 2004).

1.3 One possible outcome: Alexithymia

One prevalent case of altered emotional abilities in the emotional-experiential and emotional-expressive domain is alexithymia. Alexithymia is a multi-facet personality trait associated with difficulties identifying, decoding, experiencing and communicating one’s own emotional state and emotional aspects of social interaction processes. It is also associated with increased individual and interpersonal distress (Humphreys, Wood & Parker, 2009). On a neural level, alexithymia has been related to altered functioning
of structures important for emotion processing, such as insula (Reker et al., 2010; Silani et al., 2008), amygdala (Kugel et al., 2008), parahippocampal gyrus (Reker et al., 2010), and anterior cingulate cortex (Berthoz et al., 2002; Heinzel et al., 2010; Mériau et al., 2006). With regard to etiological factors, there are two theoretical positions, which, at first sight, seem conflicting: one approach considers alexithymia a stable personality trait (Zackheim, 2007), the other one regards alexithymia as an individual’s dysfunctional reaction to traumatic experiences (Gündel, Ceballos-Baumann & von Rad, 2002). Followers of the first approach usually refer to studies reporting long-term stability of alexithymia as measured by test-retest correlations in a five-year longitudinal design (for example Salminen et al., 2006; $r = .69$). At this point, however, a differentiation between absolute and relative stability becomes crucial for conclusions about alexithymia being a stable “trait” variable (Lumley, Neely & Burger, 2007). Longitudinal studies only allow for conclusions about relative stability, implicating that alexithymia scores remain stable within a certain ranking order, but may change in their absolute value. Consequently, alexithymic tendencies might show individual variations, clearing the way for the second theoretical approach that considers alexithymia a dysfunctional adaptation to stress. Following a more developmental approach, it has been suggested that alexithymia is related to the experience early life stress and can be considered a maladaptive coping behavior to growing up in a physical and emotional unsafe environment (Montebarocci et al., 2004). This approach has previously been tested in clinical study populations, in which alexithymia is a prominent symptom. In these studies, associations between alexithymia and early life stress are reported for patients groups with major depression (Honkalampi et al., 2004; Wingenfeld et al., 2011), substance dependence (Evren et al., 2009), post-traumatic stress disorder (Zahradnik et al., 2009), borderline personality disorder (Zlotnik, Jill & Zimmermann, 2001) or mixed psychiatric disorders (Weber et al., 2008). Studies on alexithymia and early life stress in the absence of psychological disorders, however, have hardly been conducted yet.

In addition to its potential relationship with early life stress, alexithymia is associated with depression in both healthy individuals (Hintikka et al., 2001) and clinical populations, such as those with alcohol dependence (Pinard et al., 1996) or eating disorders (Eizaguirre et al., 2004). However, there are still controversial discussions about the actual role of alexithymia in the etiology of major depression. Some authors think of alexithymia as a risk factor for psychiatric disorders in general (Taylor, Bagby
& Parker, 1997; Zackheim, 2007) and depression in particular (Kojima et al., 2007). As another recent study suggests, “depressive symptoms may act as a mediator between alexithymia and psychiatric morbidity” (Honkalampi et al., 2010). However, others bring forward the argument that the shared variance of alexithymia and depression seems mainly to be due to one alexithymic facet (“difficulty in identifying feelings”; Luminet, 2010). Therefore, the close association between alexithymia and depression reported in previous studies might rather be the result of an overlap on the phenomenological level.

1.4 Another possible outcome: Major Depression

Another case of disturbed emotional abilities, which is related to adversities in early life, is major depression. Major depression is a psychiatric disorder characterized by discrete, recurrent episodes of low mood with a number of affective symptoms such as anhedonia, the loss of interest in pleasant activities, feelings of helplessness and worthlessness, impaired psychomotor activity, disturbed sleep, reduced appetite and libido, as well as low motivation and anergia (Fitzgerald et al., 2008). Thus, a depressed individual undergoes considerable disturbances on the emotional-experiential and the emotional-expressive domain. As estimated by the World Health Organization (WHO), major depression will become one of the main causes of premature death and disability by the year 2020, significantly increasing the burden for health care system and society (Murray & Lopez, 1996). On a neural level, major depression has been linked to increased limbic activity and decreased prefrontal activity in response to emotional information processing (Fitzgerald et al., 2008). The anterior cingulate cortex, and its pre- and subgenual portions in particular, seem to play a key role in the development of major depressive disorders and a depressed patient’s response to pharmacological treatment (Pizzagalli et al., 2001; Seminowicz et al., 2004). As far as potential risk factors are concerned, a large number of studies have identified a variety of variables contributing to the development of major depression. These variables comprise genetic dispositions (Sullivan, Neale & Kendler, 2000), intrapersonal factors such as neuroticism and trait anxiety (Kendler, Karkowski & Prescott, 1999) or specific thought patterns (Beck, 1963), as well as the experience of early life stress (Heim & Binder, 2012). Comprehensive etiological models, so-called “vulnerability-stress models”, have been formulated to integrate these factors and emphasize their interdependent influence on the development of major depression (Brakemeier, Normann & Berger, 2008).
Consequently, investigating their neural basis is necessary to provide critical insight into the development, the course and the nature of the disorder. Exploring neural correlates of emotional-experiential processes, their modulation by intrapersonal and environmental factors, as well as their potential as a risk and vulnerability marker might be of particular value, given the considerable impact of depression on experiencing emotions.

1.5 Aims of the Dissertation Project

The main goal of the present dissertation project was to investigate the influence of early life stress on emotional abilities. Because close relationships to primary caregivers seem to be crucial for the development of the human emotion system, the project focuses on affective functioning on a behavioral, functional and structural level. The goal was to explore the influence of early life stress under different “basic emotional configurations” (e.g. high and low levels of alexithymia; a history of major depression) to gain some insight into individual processes of adaptation to early experiences of stress. To investigate emotional brain functioning in a valid psychological setting, we designed an experiment using musical stimuli to induce emotional experiences and measured their neural correlates via functional magnetic resonance imaging (fMRI). So far, a lot of attention has been drawn to experimental designs targeting emotion recognition or purely visual emotion processing, whereas the neural basis of music-induced emotional processes has hardly been addressed (Chapter 3 will address the power of music to induce strong emotions in greater detail). Moreover, studies on neural correlates of emotional experiences are scarce, particularly in populations with emotional disturbances, which is surprising given the impact of alexithymia and depression on experiencing emotions. Based on these considerations, the present dissertation project addresses the following questions:

How does early life stress relate to emotional abilities in the absence of psychiatric disorders? In the first study, the relationship between early life stress and alexithymia was investigated in a healthy adult population. Alexithymia was chosen as one potential form of emotional-experiential disturbance on a subclinical level, bearing in mind that early life stress might play an important role in the development of alexithymic features. Emotional-experiential abilities were additionally assessed on a behavioral level (see Chapter 2).
How can emotional experiences and their neural and behavioral correlates be investigated? The second study was designed to develop a task for a functional magnetic resonance imaging (fMRI) experiment, capable of inducing emotions in the participants. The task was supposed to exceed the emotion-inducing potential of a classical, purely visual experimental design, allowing for an assessment of emotional experiences and its neural and behavioral correlates in both healthy and psychiatric study populations (see Chapter 3).

How does early life stress modulate emotional brain responses as a function of alexithymia? In the third study, the newly developed fMRI task was applied to investigate the neural basis of pleasant and unpleasant emotional experiences as a function of early life stress and alexithymia in a healthy population (see Chapter 5). The aim was to find additional evidence for the special role of early life stress in the context of alexithymia (as indicated by Chapter 2). Furthermore, the study helped to evaluate the emotion-inducing potential of the fMRI task, which had previously been demonstrated on a behavioral level in Chapter 3.

And how does early life stress influence the brain on a structural level in individuals with high and low levels of emotional functioning? In Chapter 6, we investigated the volume of the two most frequently described brain regions affected by early life stress, hippocampus and amygdala, and explored how volume differences were affected by early stress exposure as a function of alexithymia. The findings reported in this chapter were particularly interesting with regard to the foregoing investigation of functional brain differences in the exact same sample.

Finally, how does early life stress modulate emotional brain responses in other populations with altered emotional functioning? The final study transferred the approved music-based fMRI approach to a clinical study population with likely disturbances in the emotional-experiential domain. The effects of early life stress and additional cognitive-interpersonal variables on neural correlates of emotional experiences were investigated in euthymic individuals with and without a history of major depression. The aim was to complement previous findings on the vulnerability-stress model of depression by identifying neural markers for depression and their modulation by environmental factors (see Chapter 7).
Chapter 2

The Role of Early Emotional Neglect in Alexithymia

This chapter was published as

Accessible online: http://dx.doi.org/10.1037/a0027314
Chapter 3

Development of a task to assess Neural and Behavioral Correlates of Emotional Experiences

Note: The fMRI task used to induce pleasant and unpleasant emotional experiences as presented in Chapters 5 and 7 was developed and tested in a behavioral study in advance, which will be described on the following pages. In this pre-study, we included a larger set of emotional stimuli and implemented a more detailed rating procedure than in the final fMRI task. The aims of the pre-study were (1) to select a homogeneous set of equally arousing stimuli with the best possible distance on the valence dimension and (2) to test whether the stimulus material evoked the intended emotional states in healthy participants. The pre-study is briefly referred to in both fMRI manuscripts, but has not been submitted as an independent publication.

3.1 Introduction

Music is closely connected to emotions. Music can modulate one’s current emotional state and is commonly applied to enhance the spectator’s emotional involvement in film material such as movies or commercials. From a psychotherapeutic perspective, music has recently become an established part in the treatment of psychological disorders such as depression (Maratos, Crawford & Procter, 2011) or autism spectrum disorders (Kaplan & Steele, 2005). In the field of neuroscience, Blood and colleagues (1999) were the first to discover that music elicits neural responses in emotion related regions in the human brain. Since then, a number of studies have been conducted to investigate the underlying mechanisms of the emotional power of music and found core emotional structures such as hippocampus, insula, anterior cingulate cortex and amygdala to be involved in music processing (Juslin & Västfjäll, 2008; Koelsch et al., 2006; Koelsch, 2010). In their review article on emotional responses to music, Juslin and Västfjäll (2008) suggest six psychological mechanisms that can be regarded as complementary ways of musical emotion induction: (1) a musical stimulus leads to the involvement of the brain stem, (2) it evokes a process of evaluative conditioning, (3) it activates
relevant emotional representations that lead to emotional contagion in the listener, (4) it is related to visual imagery, (5) it involves episodic memory processes and (6) activates musical expectancies in the listener. Koelsch (2010) considers musically induced emotions “real […] and biologically comparable to everyday emotions”. A detailed summary of arguments why music-evoked emotions are more than just mood states or aesthetic experiences and comprise both motivational aspects and goal relevance can be found in Jüslin & Västfjäll (2008).

Despite a number of convincing findings, the majority of neuroimaging studies in psychiatric or community-dwelling populations still use purely visual stimulus material such as pictures of facial affect (Ekman, 1993) or the IAPS collection (“International Affective Pictures System”; Bradley & Lang, 2007) to investigate neural correlates of emotional processes. A recent study dared a cross-modal comparison and impressively showed that the emotional potential of a visual stimulus can greatly be enhanced by auditory emotional stimuli such as classical music (Baumgartner, Esslen & Jäncke, 2006a). Purely visual stimuli evoked a “more cognitive mode of emotion perception”, reflected by an activation increase in the right dorsolateral prefrontal cortex, whereas audiovisual stimuli were associated with increased activations in wide parts of the emotion network, such as amygdala, hippocampus, parahippocampus, insula, striatum, medial ventral frontal cortex, cerebellum, and fusiform gyrus. Because our first fMRI study (see Chapter 5) was supposed to capture neural correlates of the emotional experiences in individuals having difficulties identifying emotions (i.e. high levels of alexithymia), we needed to develop a task, which induces strong emotions and thus exceeds the emotional power of a purely visual face recognition task.

On the basis of Baumgartner’s cross-modal comparison study (2006a), our aim was to develop a task, which induces pleasant and unpleasant emotional experiences in the participants, using a visual, an auditory, and an audiovisual condition, with congruent visual and auditory stimuli being presented simultaneously. Because emotional reactions to musical stimuli had not been investigated in clinical or subclinical study populations until then, a purely auditory task would have been too experimental, so we decided to investigate emotional reactions to all three modalities. By means of the behavioral pre-study, we planned (1) to select a homogeneous set of equally arousing stimuli with the best possible distance on the valence dimension and (2) to test whether the stimuli evoked the intended emotional states in the participants. We also tested which stimulus modality (visual, auditory, or audiovisual) evoked the strongest
emotional responses in which stimulus valence category (pleasant, unpleasant, or neutral). Because alexithymia, depression and anxiety are important intrapersonal variables possibly influencing emotional responses to pleasant or unpleasant stimuli, we assessed these variables via questionnaire to be able to exclude participants with clinically relevant scores (alexithymia/ depression) and to explore their influence on emotional responses.

3.2 Material and Methods

3.2.1 Participants

Thirty healthy right-handed German native volunteers with an age range between 19 and 50 years were investigated regarding behavioral responses to pleasant and unpleasant emotional stimuli as well as alexithymia, depression and anxiety. None of them participated in the following fMRI studies as described in Chapters 5 and 7.

3.2.2 Procedure

Participants were recruited via a newsletter announcing empirical studies at Freie Universität Berlin, which provided an opportunity to register without obligation. The announcement offered a study on “Music and Emotion”, looking for healthy volunteers between 18 and 50 years without any history of psychological or medical disorders. Registered participants received our telephone call, were informed about the study procedure and, if interested, made an appointment for participation. Having arrived at our lab, all volunteers initially gave written informed consent and then filled out questionnaires measuring alexithymia, depression and anxiety (see Measures). Thereafter, participants sat down in front of the computer, put on headphones and completed several test trials to get used to the task. After an individually determined number of test trials had been completed, the actual experiment started. The whole session including questionnaires and the emotion induction task lasted 1.5 hours. Participants were reimbursed with 10 Euros.

3.2.3 Measures

Assessment of Alexithymia. Alexithymia was assessed using the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994). The scale shows good psychometric qualities that have been investigated in healthy samples (Cronbach’s α > .80; Bagby et
al., 1994). The TAS-20 includes three cognition-oriented subscales (difficulty describing feelings, difficulty identifying feelings and externally oriented thinking) with high scores indicating high levels of alexithymia.

**Assessment of Depression.** We used the 21-item Beck Depression Inventory (BDI; Beck et al., 1961) to control for the current degree of depression. The BDI shows a good validity in differentiating between depressed and nondepressed subjects (Richter et al., 1998). The cutoff point to exclude subjects with a clinically relevant depressive episode was 12 (Rush et al., 2006; Beck et al., 1988). The questionnaire has been validated for use in German clinical and non-clinical samples (Kühner et al., 2007).

**Assessment of Anxiety.** We used the 40-item State and Trait Anxiety Inventory (STAI; Spielberger, Gorsuch & Lushene, 1970) to assess anxiety. The questionnaire consists of two separate scales, one assessing the participants’ current degree of anxiety (“state”) and the other measuring habitual anxiety (“trait”). The items comprise short descriptions of emotional states (e.g. “I am happy” or “I get in a state of tension or turmoil over my recent concerns and interests”). Participants rate the degree to which each item reflects their current or habitual anxiety on a 1 to 4 scale, from “not at all” to “very much”. The STAI shows satisfactory psychometric qualities (Cronbach’s α > .90 for both subscales; Laux et al., 1981) and is recommended to use in both diagnostics and research.

### 3.2.4 Behavioral Emotion Induction Task

**Stimulus Material.** We used music and human emotional faces to induce pleasant and unpleasant emotional experiences; neutral stimuli were used as a control condition. For visual stimulation we used pictures of facial affect of the recently developed database “FACES” (Ebner et al., 2010), including naturalistic emotional faces of young, middle-aged and older women and men that correspond well to the age distribution of our sample. Previous studies report an own-age bias in face recognition (Anastasi & Rhodes, 2006), and face recognition, in turn, was shown to be essential for emotional contagion through others’ facial expressions (Hatfield et al., 2009). The chosen faces expressed joy (pleasant condition), fear (unpleasant condition) or showed a neutral expression (control condition). For auditory stimulation we used music from different epochs and musical genres to induce pleasant (e.g. classical music, jazz, Irish dances) and unpleasant (music taken from horror movies) emotional experiences. Sequences of
random tones were used as neutral control stimuli, carefully matched with each pleasant/unpleasant piece of music with regard to mean pitch, pitch variation, spectral complexity, instrumentation, and tempo (beats per minute), because previous studies report an influence of these parameters on emotional responses (Khalfa et al., 2008). The analysis of these parameters was completed using “Essentia”, an in-house library for extracting audio and music features from audio files (http://mtg.upf.edu/technologies/essentia).

**Task Design.** We used a block design with the three conditions “pleasant”, “unpleasant” and “neutral” (see Figure 3.2.4). One trial consisted of 30 seconds of stimulus presentation (one stimulus refers to one piece of music, or a sequence of three face pictures presented for ten seconds each, or one piece of music running simultaneously with a sequence of three face pictures) followed by eight ratings (three seconds each), with a two- and a four-seconds pause before and after the rating period. During these pauses, participants looked at a white fixation cross on a grey screen. Participants rated their current emotional experience evoked by the stimuli with respect to pleasantness, arousal, joy, fear, anger, surprise, disgust and sadness on nine-point scales ranging from “very strong” (=9) to “not at all” (=1). Ratings were given via button-press on a computer keyboard. The dimensions “pleasantness” and “arousal” were chosen according to Russell’s model of core affect (Russell, 2003). Joy and fear directly corresponded to the emotions induced by the stimuli. The remaining four basic emotions (according to Ekman, 1993) anger, surprise, disgust and sadness were added as rating options, so that ambiguous emotional reactions to the stimuli could be captured.

![Figure 3.2.4. Behavioral emotion induction task with eight rating options.](image-url)
3.2.5 Data Analysis

Behavioral Data Analysis. To examine which modality (visual, auditory, or audio-visual) evoked the strongest emotional responses in which valence category (pleasant, unpleasant, or neutral) paired t-tests were performed. Alexithymia, depression and anxiety were normally distributed in the sample (Kolomogorov-Smirnoff-Test, all tested variables p> .05). Thus, analyses with TAS-20, BDI and STAI scores were calculated using Pearson’s correlation coefficient. In all analyses, a $p$ value < 0.05 was considered as statistically significant. If necessary, Bonferroni corrections were applied to counteract the problem of multiple comparisons.

Stimulus Selection. For each stimulus, we calculated its deviation from the ideal valence rating. For example, an unpleasant stimulus should evoke feelings of unpleasantness, reflected in valence ratings close to 1. A pleasant stimulus, however, should be attended by pleasant feelings reflected in valence ratings close to 9. Neutral stimuli are expected to evoke neither pleasant nor unpleasant emotional states, reflected by a valence rating close to 5. All stimuli were then ordered by deviation, so that stimuli with a deviation > 3 from the ideal valence score could be excluded. In a second step, pleasant stimuli with a deviation > 5 from the ideal “joy” score and unpleasant stimuli with a deviation > 5 from the ideal “fear” score were excluded. We also excluded those stimuli evoking emotions other than joy or fear, reflected by ratings > 2 on any other emotional dimension (i. e. anger, surprise, disgust or sadness). In a final step, pleasant and unpleasant stimuli were matched with regard to their arousal potential indicated by the ratings, so that the task for the following fMRI studies only included stimuli of distinctly positive, negative and neutral valence with a similar potential to evoke arousal.

3.3 Results

3.3.1 Descriptive Statistics

The sample included 30 healthy participants, 15 of them were females. The mean age was 28.8 years ($SD=8.4$) with no age differences between males and females. All participants showed low levels of alexithymia (TAS-20: $M=37.9$, $SD=9.5$), depression (BDI: $M=6.9$, $SD=4.3$) and anxiety (STAI state: $M=39.1$, $SD=9.2$; STAI trait: $M=39.8$, $SD=10.6$). There were no gender differences with regard to these variables.
3.3.2 Effects of Stimulus Valence

Note: Effects of stimulus valence and modality were calculated for those stimuli that survived the selection procedure described above. This was necessary to evaluate the emotion inducing character of the paradigm that was supposed to be applied in the following fMRI studies.

Averaged across all modalities, pleasant stimuli were experienced as more pleasant ($M=6.5$, $SD=.91$) and evoked stronger feelings of joy ($M=5.0$, $SD=1.6$) and less fear ($M=1.2$, $SD=.31$) than unpleasant (pleasantness: $M=3.6$, $SD=.91$; joy: $M=1.2$, $SD=.31$; fear: $M=3.0$, $SD=1.5$) or neutral stimuli (pleasantness: $M=4.0$, $SD=.79$; joy: $M=1.9$, $SD=1.0$; fear: $M=1.7$, $SD=.70$) (all tests $p<.001$). Unpleasant stimuli were experienced as more unpleasant and evoked stronger fear responses than pleasant and neutral stimuli ($p<.001$). There were no arousal differences between pleasant ($M=4.6$, $SD=1.3$) and unpleasant ($M=4.7$, $SD=1.1$) stimuli, however, both were experienced more arousing than neutral stimuli ($M=3.5$, $SD=1.3$). Effects of valence are visualized in Figure 3.3.2:

![Figure 3.3.2](image)

Figure 3.3.2. Effects of stimulus valence on self-rated emotional experiences.

3.3.3 Effects of Stimulus Modality

In the pleasant condition (see Figure 3.3.3), visual stimuli were experienced less pleasant ($M=6.3$, $SD=1.2$) and less arousing ($M=3.3$, $SD=1.5$) than auditory stimuli (pleasantness: $M=6.7$, $SD=1.1$; arousal: $M=3.8$, $SD=1.4$) ($p<.05$), while there were no significant differences when comparing visual with audiovisual or auditory with audiovisual stimuli. With regard to their joy evoking potential, audiovisual stimuli were associated with stronger joy responses ($M=5.3$, $SD=1.7$) than purely visual stimuli.
while there were no differences when compared to purely auditory stimuli. In the unpleasant condition (see Figure 3.3.3), there were no significant differences across modalities with regard to experienced unpleasantness, while visual stimuli were experienced as less arousing (M=4.1, SD=1.4) and less fear evoking (M=2.6, SD=1.4) than audiovisual stimuli (arousal: M=4.7, SD=1.5; fear: M=3.3, SD=1.7) (all tests p< .001). Neutral control stimuli did not elicit any differences in emotional responses as a function of modality except for arousal: visual stimuli (M=3.3, SD=1.1) were experienced less arousing than auditory (M=3.9, SD=1.3) or audiovisual stimuli (M=3.9, SD=1.2) (all tests p< .001).

![Figure 3.3.3. Effects of stimulus modality in the pleasant and unpleasant condition.](image)

### 3.3.4 Effects of Alexithymia, Depression and Anxiety on Emotional Responses

Bivariate correlation analyses revealed that emotional responses to both pleasant and unpleasant stimuli were modulated by alexithymia and anxiety. Alexithymia and trait anxiety were associated with a less pleasant response to neutral faces (alexithymia: r=-.41, trait anxiety: r=-.43; p<.05). Experienced arousal to pleasant music was modulated by alexithymia (r=.40; p<.05) and experienced joy to pleasant faces was negatively associated with state anxiety (r=-.40; p<.05). Moreover, alexithymia was positively related to experiences of fear in response to pleasant (r=.38; p<.05) and neutral r=.46; p<.05) faces, and trait anxiety modulated the fear response to neutral faces as well (r= .44; p< .05). There were no significant associations between depression and emotional responses to pleasant or unpleasant stimuli.
3.4 Discussion

The present study was conducted (1) to select a homogeneous set of equally arousing stimuli with the best possible distance on the valence dimension and (2) to test whether the chosen stimuli, presented in different modalities, evoked the intended emotional states in the participants. Furthermore, the effects of individual levels of alexithymia, depression and anxiety on emotional responses to pleasant and unpleasant stimuli were explored.

First of all, our data suggest that the selected stimuli are clearly able to induce the intended emotional experiences in healthy participants. Pleasant stimuli were experienced more pleasant and joyful, unpleasant stimuli evoked responses of unpleasantness and fear, and the responses to neutral control stimuli appeared in between. Since there were no significant differences between pleasant and unpleasant stimuli with regard to experienced arousal, we met our first claim to select a set of equally arousing stimuli with a reasonable distance on the valence dimension. Our results also show that the development of neutral control stimuli worked well for all three modalities, reflected in an average valence rating of 4.0 on a scale from 1 to 9 (with 4.2 for visual, 3.9 for auditory and 3.9 for audiovisual stimuli).

With regard to stimulus modality, our data show that audiovisual stimuli evoke stronger emotional responses than purely visual stimuli in the unpleasant condition. Baumgartner and colleagues (2006b) describe this phenomenon as emotional “on-off-switch” effect, referring to the well-known situation when spectators of horror films switch off the sound of their television “to reduce their current emotional experience to a tolerable level” (p. 151). Multisensory integration processes may contribute to the enhanced emotional experiences evoked by audiovisual stimuli as compared to purely visual stimuli (Baumgartner et al., 2006a and 2006b). However, this cannot explain why purely auditory stimuli evoked stronger responses than visual stimuli in the pleasant (and neutral) condition. One plausible explanation for the arousal difference between visual and auditory stimuli could be the difference in stimulus complexity, as indicated by a recent study investigating event-related potentials in response to IAPS pictures with different degrees of complexity (Bradley et al., 2007). In addition, pictures provide a concrete, so-called “real-world content” (Eldar et al., 2007), whereas music might leave more room for individual interpretations and therefore activates emotion-generating processes of visual imagery and episodic memory (Barrett et al., 2010; Jüslin
& Västfjäll, 2008). Some of our cross-modal comparisons did not reveal any differences though. Unpleasant pictures of faces, for example, were not experienced less unpleasant than music or the combination of both. All in all, our data suggest only a slight trend towards superiority of audiovisual stimuli with regard to emotional enhancement, however, this was not even true for all facets of emotional experience (valence, arousal, joy and fear) in equal measure. As a consequence, we decided to include all three modalities in the final fMRI design.

In addition to the cross-conditional and cross-modal comparisons described above, the influence of alexithymia, depression and anxiety on emotional responses was explored. Alexithymia was significantly associated with a less pleasant response to neutral faces, increased arousal to pleasant music and higher experiences of fear in response to pleasant faces. These responses may reflect a subtle hint towards the difficulties high alexithymic individuals show in experiencing and identifying emotions. However, one needs to keep in mind that all participants showed very low scores of alexithymia (mean score: 38), so the spectrum of emotional responses to our stimuli might look different in high alexithymic populations. In addition, individual depression scores as measured by BDI did not modulate emotional responses. Here, a similar problem applies, with BDI scores being generally low in the sample (mean score: 7; BDI scores can range from 0 to 63; participants with a score > 12/19/28 are considered mildly/moderately/severely depressed). Trait anxiety modulated emotional responses to neutral faces: it was positively associated with reduced experiences of pleasantness and stronger fear responses, however, no modulation of responses to unpleasant, fear inducing stimuli were found. As previously reported for the perception of fear inducing visual stimuli (Cooper, Rowe & Penton-Voak, 2008), trait anxiety does not seem to influence the perception of fear in auditory and audiovisual stimuli either – at least in individuals with generally low levels of trait anxiety. To conclude, the associations of alexithymia, depression and anxiety with emotional responses to pleasant and unpleasant stimuli turned out to be rather weak. This might be due to generally low scores with little variation within the present sample, reducing the probability to detect meaningful correlations.

To conclude, the present study showed that the chosen stimuli have the potential to form a powerful emotion inducing fMRI task, which goes beyond classical mono-modal approaches and which can strike a new path of emotion assessment in affective neuroscience.
Chapter 4

Introduction to Neuroimaging Methods

Note: The following two pages will provide a brief overview of the two main neuroimaging methods applied in the present dissertation project. The first method, magnetic resonance imaging (MRI), is used to map anatomical structures of the brain and forms the basis for the second method called functional magnetic resonance imaging (fMRI), which is applied to measure functional brain activity in response to a stimulus. Both techniques allow for a non-invasive investigation of brain structure and function. Some authors consider the underlying physical mechanisms “the most important imaging advance since the introduction of X-rays by Conrad Röntgen in 1895” (Logothetis, 2008).

4.1 Magnetic Resonance Imaging (MRI)

For Magnetic Resonance Imaging (MRI), the nuclei of hydrogen atoms are essential. These nuclei called protons can be found in any biological system such as the human body and show particular magnetic properties. As all elementary particles, they have an immanent rotation, the so-called “spin”. Therefore they behave like a little magnet and are aligned randomly, if no external magnetic field is present. However, if an external and homogeneous magnetic field occurs, they align either parallel or anti-parallel along the field and deliver energy to their environment. As a consequence, a minimal imbalance between parallel and anti-parallel aligned spins occurs. Within an external magnetic field, protons react with a compensating movement (“precession”) in a particular frequency (“Larmor frequency”) occurring directly proportional to the strength of the magnetic field. Using short impulses (so-called HF-impulses) with exactly the same frequency, the spins are deflected and raised to a high-energy state. As soon as the HF-impulse stops, the spins return to their original state and thereby release energy, which can be recorded and displayed as an image. The time protons need to return to a low-energy state (“spin relaxation”) depends on the sort of tissue and, in the case of the human brain, is different in gray matter as compared to white matter areas. As a consequence of different durations of spin relaxation, different MR-signals can be
obtained from different brain structures, displayed in form of a contrast image. Longitudinal relaxation times (T1) produce so-called T1-weighted images of anatomical structures, whereas transverse relaxation times (T2) produce so-called T2-weighted images, which can display functional changes in the human brain. These functional changes occur in brain regions as a result of an increase in oxygenation, which, for example, can be provoked by a neural response to emotional stimuli. Blood oxygenation level dependent (BOLD) contrasts can then be used to investigate emotional brain responses to joy inducing music and therefore are the most important component of functional MRI, which is described in the following section.

4.2 Functional Magnetic Resonance Imaging (fMRI)

The basic physiological principle of functional imaging of the brain is based on the close link between neuronal activity and energy metabolism, as first described by neurophysiologist Charles Sherrington and his colleague Charles Roy in 1890. When an individual is confronted with emotional stimuli, for example with a joyful peace of music, brain areas involved in emotional processing are activated and thus show an increased metabolic activity. More precisely, activated brain areas need oxygen and glucose, which leads to a local increase in blood flow. This mechanism is described as hemodynamic response function (HRF). At this point, functional magnetic resonance imaging takes advantage of the different magnetic properties of oxygenated or deoxygenated blood. Changes in the concentration of deoxygenated blood are visible as changes in the magnetic field, which are measureable as signal increases. This signal increase starts two seconds after stimulus onset, has its peak about four to six seconds later and is followed by a signal decrease back to baseline or even below, which is known as “undershoot” and can last up to thirty seconds. This characteristic course of the HRF needs to be taken into account when designing an fMRI experiment.

An important limitation is that fMRI provides only an indirect measure of neuronal activity. Although Logothetis and colleagues (2001) have shown that there is a link between neuronal activity and the BOLD contrast, one has to keep in mind that fMRI does not measure the activity itself, but activity-related changes in the regional blood flow provoked by a number of physiological processes (Ogawa et al., 1992). This association between local neural activity and subsequent blood flow alterations is called neurovascular coupling.
Chapter 5

How Emotional Abilities modulate the Influence of Early Life Stress on Hippocampal Functioning

Abstract. Early life stress (ELS) is known to have considerable influence on brain development and affective functioning. Previous studies in clinical populations have shown that hippocampus and amygdala, two central structures of limbic emotion processing circuits, are predominantly affected by early stress exposure. Given the inconsistent findings on ELS-related effects in healthy populations and the associations of ELS and affective functioning, the question arises whether there are additional emotion-relevant variables that need to be considered to better understand the effects of ELS. We therefore used FSL-FIRST, a method to automatically segment subcortical structures on T1-weighted magnetic resonance images, to investigate the volume of hippocampus and amygdala in 25 high alexithymic (h-ALEX) and 25 low alexithymic (l-ALEX) individuals, which were matched with regard to ELS, but significantly differed in their degree of emotional functioning. Alexithymia was assessed using the Toronto Alexithymia Scale and Bermond-Vorst Alexithymia Questionnaire. ELS was assessed by Childhood Trauma Questionnaire (CTQ) and Early Trauma Inventory. Our data showed that ELS was negatively associated with right hippocampus volume in h-ALEX individuals, while there was no such association in the l-ALEX group. Furthermore, ELS was positively associated with left amygdala volume in l-ALEX individuals. The present study emphasizes a considerable influence of intrapersonal factors on the nature of neural alterations related to the experience of ELS. Longitudinal study designs are necessary to pursue the question of how emotional abilities modulate individual adaptations to early stress exposure.

1Adapted version of a manuscript in preparation for submission
6.1 Introduction

In Western countries, the experience of early life stress (ELS) is a common phenomenon. About 30 to 40% of the adult population report experiences of emotional or physical maltreatment during childhood (Scher et al., 2004). Previous research revealed that ELS significantly increases incidence rates of affective disorders and can have an impact on the development of emotional abilities (Heim & Binder, 2012). The association between early stress exposure and adult mental health seems mainly biological in nature, with negative social environments becoming “embedded as changes in neural structure […] and, ultimately, in behaviors that lead to mental illness” (Tottenham & Sheridan, 2010). On a neural level, the relevance of hippocampus and amygdala in the investigation of ELS-related effects is clearly indicated by a large human and non-human animal literature. Being two central structures within limbic emotion processing circuits, amygdala and hippocampus seem to be particularly influenced by ELS (Heim & Binder, 2012; Pechtel & Pizzagalli, 2010; Teicher et al., 2003; Taylor et al., 2006). Furthermore, both regions are important for emotional functioning and show strong connections with the activity of the hypothalamic pituitary adrenocortical (HPA) axis, which mediates neuroendocrine stress responses in humans.

Both increased (Tottenham et al., 2010) and decreased (Driessen et al., 2000; Schmahl et al., 2003) amygdala volumes have previously been reported as neural markers following ELS. Also, associations of reduced hippocampal volumes and ELS are a common finding in clinical populations (Kronmüller et al., 2008; MacQueen & Frodl, 2010; Woon & Hedges, 2008). As indicated by neurobiological models, a hippocampal volume decrease might result from early exposure to elevated levels of the stress-related corticotropin releasing hormone (CRH), which can lead to a degeneration of hippocampal neurons (Brunson et al., 2001) or can even have a direct neurotoxic effect on them (Chen et al., 2012; Zhao et al., 2007). When the effects of ELS on limbic structures are investigated in the absence of psychiatric disorders, however, results are less clear. A number of studies show ELS-related hippocampal volume reductions in healthy populations (e.g. Dannlowski et al., 2012; for a recent review see Woon, Sood & Hedges, 2010), whereas others did not reveal this finding (e.g. Cohen et al., 2006a). Given the impact of ELS on affective functioning (Cohen, 2006b; Pechtel & Pizzagalli, 2010; Schore, 2001), the question arises whether there are additional emotion-relevant variables that need to be considered to better understand the effects of ELS on hippocampus and amygdala volume in healthy individuals.
In this regard, the consideration of alexithymia as a variable potentially modulating ELS-related effects could be promising. Alexithymia, defined as the difficulty identifying, decoding and communicating one’s own emotional state (Franz et al., 2008), has been described as one potential outcome of ELS on the behavioral level (Freyberger, 1977; Frewen et al., 2008; Lumley et al., 2007). Its association with ELS has been demonstrated in a number of clinical studies (e.g. Weber et al., 2008; Wingenfeld et al., 2011) and also in a very recent investigation of healthy individuals (see Chapter 3). On the neural level, alexithymia has been linked to reduced limbic responses to emotional stimuli (e.g. in the amygdala, Kugel et al., 2008; for a recent review see Moriguchi & Komaki, 2013; and also Chapter 5). Although a significant association of ELS and alexithymia has already been demonstrated on the behavioral level, studies that investigate the effects of ELS on structural aspects of the brain and, at the same time, account for this association do not exist to the best of our knowledge.

Therefore, the aim of the present study was to investigate the effects of ELS on gray matter volumes of hippocampus and amygdala, the two most frequently described brain regions affected by early stress exposure. To account for different degrees of individual emotional abilities, we tested ELS-related effects in a high alexithymic (h-ALEX) and a low alexithymic (l-ALEX) sample, which were matched with regard to ELS exposure.

6.2 Materials and Methods

6.2.1 Participants

Fifty healthy German native volunteers with an age range between 22 and 55 were investigated regarding ELS and alexithymia. Individual hippocampus and amygdala gray matter volumes were measured via magnetic resonance imaging (MRI).

6.2.2 Procedure

The process of sample recruitment is described in detail elsewhere (Chapters 2 and 5). Twenty-five high (h-ALEX) and 25 low (l-ALEX) alexithymic individuals from a healthy community-dwelling sample took part in the study. To investigate the specific effects of early life stress as a function of alexithymia, the two groups were matched regarding their experiences of ELS as measured via questionnaire and interview (see Measures). Therefore we were able to test how ELS affects hippocampus and amygdala volumes in the presence and absence of alexithymia.
At a previous step of recruitment, psychiatric interviews (M.I.N.I.; Sheehan et al., 1998) had been conducted to exclude participants with any current or lifetime psychiatric disorder. Depression and Trait Anxiety were additionally assessed on the day of MRI recording (see Measures). Participants were given information regarding the course of the study and written informed consent was obtained from them. They were reimbursed for participation (10 € per hour). The study protocol was approved by the local ethics committee and carried out in accordance with the declaration of Helsinki.

6.2.3 Measures

Assessment of Early Life Stress. Early childhood adversities were assessed in retrospect using the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) with 28 items assigned to the following five subscales: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. On the basis of CTQ total scores, we matched h-ALEX and l-ALEX participants regarding their history of ELS. Individual CTQ scores were reassessed by a 45 minutes face-to-face interview (Early Trauma Interview; Bremner et al., 2000), which shows good convergent validity with the CTQ ($r = .72$; Wingenfeld et al., 2010).

Assessment of Alexithymia. Alexithymia was assessed using the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994) and the more detailed 40-item Bermond-Vorst Alexithymia Questionnaire (BVAQ; Vorst & Bermond, 2001). The TAS-20 includes three cognition-oriented subscales (difficulty describing feelings, difficulty identifying feelings and externally oriented thinking). The BVAQ consists of three cognitive and two affective subscales assessing the individual capacity of identifying, verbalizing and analyzing feelings as well as the capacity of emotionalizing and fantasizing. On both TAS-20 and BVAQ, high scores indicate high levels of alexithymia.

Assessment of Depressive Symptoms. We used the 21-item Beck Depression Inventory (BDI; Beck et al., 1961) to assess the current degree of depression. The BDI shows a good validity in differentiating between depressed and non-depressed subjects (Richter et al., 1998). The cutoff point to exclude subjects with a clinically relevant depressive episode was 12 (Rush et al., 2006; Beck et al., 1988).

Assessment of Trait Anxiety. We used the 20-item trait version of the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch & Lushene, 1970) to measure habitual
anxiety. The items comprise short descriptions of emotional states (e.g. “I am happy” or “I get in a state of tension or turmoil over my recent concerns and interests”). Participants rate the degree to which each item reflects their habitual anxiety on a 1 to 4 scale, from “not at all” to “very much”. The STAI is recommended to use in both diagnostics and research (Laux et al., 1981).

6.2.4 Magnetic Resonance Imaging (MRI)

Whole-brain structural scans were acquired at the Dahlem Institute for Neuroimaging of Emotion at Freie Universität Berlin using a 3D MP-RAGE sequence on a 3T Siemens Magnetom TimTrio whole body scanner (Siemens Medical Systems, Erlangen, Germany) using a 12-channel head coil. For each subject, 176 sagittal partitions with an image matrix of 256 × 256 and an isotropic spatial resolution of 1 mm³ were acquired. Total scan time was about 6 minutes, other image acquisition parameters were TR 1900 ms, TI 900 ms, TR of the gradient-echo kernel 7.5 ms, TE 2.52 ms, flip angle 9°, and bandwidth 170 Hz / vx,

6.2.5 Data Analysis

MRI Data Processing and Analysis. Volumes of 15 subcortical structures (Thalamus, Nucleus caudatus, Putamen, Pallidum, Hippocampus, Amygdala, Nucleus accumbens in left and right hemispheres as well as the Brain-Stem/ 4th Ventricle) were obtained using FSL-FIRST (Webster, 2012). There are two steps, firstly an affine transformation to standard space, and secondly the segmentation of the subcortical structures. The affine transformation was carried out in two steps: A first stage with a registration to a whole brain template, the second stage used an MNI152 sub-cortical mask to exclude voxels outside the sub-cortical regions. The transformation was visually checked for all participants. The segmentation fits models of deformable meshes of the subcortical structures, incorporating prior information about the shape and intensities, to the structural image. This was followed by a boundary correction, classifying whether each boundary voxel should remain part of the segmentation or not. Segmentation results (volumes of the subcortical structures) were read into SPSS 19.0 (IBM SPSS Inc., Chicago, IL, USA). Given our a priori hypotheses, only hippocampal and amygdala volumes were considered. Analyses of variance were performed to assess main effects of ELS as well as interactions of ELS and alexithymia. Partial correlation analyses were
used to investigate the association of ELS and gray matter volume within the h-ALEX and l-ALEX group, controlling for age, depression and trait anxiety.

**Behavioral Data Analysis.** Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, Illinois). In all analyses, a $p$ value < 0.05 was considered as statistically significant. If necessary, Bonferroni corrections were applied to counteract the problem of multiple comparisons. Since CTQ scores were normally distributed within the h-ALEX and l-ALEX group (Kolomogorov-Smirnoff-Test, $p > .05$), Pearson’s correlation coefficient was used to assess associations between ELS and gray matter volume within each group.

### 6.3 Results

#### 6.3.1 Descriptive Statistics

The mean age in the sample of 50 healthy volunteers was 34.1 years ($SD=9.9$). In the high alexithymic (h-ALEX, $N=25$) group, participants (12 female, 13 male) had a TAS-20 total score above 60, in the low alexithymic group (l-ALEX; $N=25$), participants (12 female, 13 male) had a TAS-20 total score below 45. Since the two groups were matched regarding ELS, there were no group differences in terms of CTQ or any of its five subscales. There were also no differences between h- and l-ALEX participants with regard to age, years of education, depression and trait anxiety (see Table 6.3.1). Furthermore, there were no gender differences in either group on all reported measures. BDI and trait anxiety scores did not differ between individuals with and without a history of ELS in neither of the groups.

#### 6.3.2 Results of Volumetric Analyses

Neither the volume of hippocampus nor that of the amygdala differed significantly between participants with high and low degrees of ELS exposure. However, if alexithymia was considered in combination with ELS, there was a significant interaction of ELS and alexithymia ($F(3,48)=4.88$, $p<.05$) for the right hippocampus: Only within the h-ALEX group, its volume was smaller in individuals with a history of ELS ($M=4826.73$, $SD=685.40$) as compared to those without such a history ($M=5354.57$, $SD=424.72$). The interaction of ELS and alexithymia in the left amygdala approached statistical significance ($F(3,48)=3.13$, $p=.077$). Therefore, we calculated an univariate analysis of variance within both groups separately. Within the l-ALEX
group, there was a significant main effect of ELS in the left amygdala \((F(2,24)=5.38; \ p< .05)\) with ELS-exposed individuals showing a bigger volume \((M=2057.67, \ SD=188.39)\) than unexposed individuals \((M=1900.85, \ SD=165.71)\). No such effects were found within the h-ALEX group.

<table>
<thead>
<tr>
<th>Measure</th>
<th>h-ALEX (N=25)</th>
<th>l-ALEX (N=25)</th>
<th>(t)</th>
<th>(Df)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.0 10.4</td>
<td>32.7 9.4</td>
<td>1.2</td>
<td>48</td>
<td>.238</td>
</tr>
<tr>
<td>Years of Education</td>
<td>12.7 1.2</td>
<td>12.5 1.4</td>
<td>.36</td>
<td>48</td>
<td>.718</td>
</tr>
<tr>
<td>TAS-20 total score</td>
<td>66.0 6.5</td>
<td>37.6 4.6</td>
<td>18.1</td>
<td>48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BVAQ total score</td>
<td>131.9 12.9</td>
<td>84.8 15.0</td>
<td>11.8</td>
<td>48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CTQ total score</td>
<td>41.0 14.6</td>
<td>40.2 15.8</td>
<td>.19</td>
<td>48</td>
<td>.845</td>
</tr>
<tr>
<td>CTQ emotional neglect</td>
<td>12.5 5.6</td>
<td>10.9 5.3</td>
<td>1.0</td>
<td>48</td>
<td>.302</td>
</tr>
<tr>
<td>CTQ emotional abuse</td>
<td>9.6 4.7</td>
<td>10.0 5.6</td>
<td>-.32</td>
<td>48</td>
<td>.751</td>
</tr>
<tr>
<td>CTQ physical neglect</td>
<td>7.5 3.8</td>
<td>6.1 2.0</td>
<td>1.6</td>
<td>48</td>
<td>.120</td>
</tr>
<tr>
<td>CTQ physical abuse</td>
<td>6.1 2.1</td>
<td>6.7 2.2</td>
<td>-.96</td>
<td>48</td>
<td>.342</td>
</tr>
<tr>
<td>CTQ sexual abuse</td>
<td>5.4 1.3</td>
<td>6.4 4.3</td>
<td>-1.1</td>
<td>48</td>
<td>.259</td>
</tr>
<tr>
<td>BDI</td>
<td>7.3 4.8</td>
<td>3.9 3.3</td>
<td>2.9</td>
<td>48</td>
<td>.006</td>
</tr>
<tr>
<td>STAI trait</td>
<td>39.0 8.6</td>
<td>33.7 7.1</td>
<td>2.5</td>
<td>48</td>
<td>.020</td>
</tr>
</tbody>
</table>

Table 6.3.1. Test of group differences regarding age, years of education, alexithymia, early life stress, depression and trait anxiety \((N=50)\). h-ALEX = high alexithymic; l-ALEX = low alexithymic; \(M\) = mean score; \(SD\) = standard deviation; TAS-20 = Toronto Alexithymia Scale; BVAQ = Bermond-Vorst Alexithymia Questionnaire; CTQ = Childhood Trauma Questionnaire; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory. Bonferroni adjusted alpha levels of .004 per test (.05/12).

Bivariate correlation analysis confirmed these patterns: there was a negative association of right hippocampus volume and CTQ total score in the h-ALEX group \((r=-.68, \ p< .001; \) see Figure 6.3.2\), but not in l-ALEX individuals \((p=.220)\). When controlling for age, depression and trait anxiety, the correlation coefficient decreased \((r=-.41)\), but remained significant \((p< .05)\). Bivariate correlation analysis also revealed a positive association of left amygdala volume and CTQ total score in the l-ALEX group \((r=.42, \ p< .05; \) see Figure 6.3.2\), but not in h-ALEX individuals \((p=.741)\). When controlling for age, depression and trait anxiety, the correlation coefficient even increased \((r=.45, \ p< .05)\).
Figure 6.3.2. The influence of ELS on hippocampus and amygdala volume in individuals with high and low degrees of alexithymia. The correlation of CTQ and right hippocampus gray matter volume in h-ALEX individuals (right figure) remains significant ($p<.05$) after removing the subject with the highest CTQ score.

6.4 Discussion

The aim of the present study was to investigate the effects of early stress exposure on the volume of hippocampus and amygdala in a carefully recruited sample of 50 healthy community-dwelling individuals. This is the first study to consider individual emotional abilities as a variable potentially modulating ELS-related effects on structural characteristics of limbic emotion processing circuits. There was a significant interaction of ELS and alexithymia in the right hippocampus as well as a main effect of ELS in the left amygdala within the l-ALEX group. Interestingly, ELS was negatively associated with right hippocampus gray matter volume in individuals with altered emotional abilities (i.e. high degrees of alexithymia), whereas in individuals with regular emotional abilities (i.e. low degrees of alexithymia) ELS was positively associated with left amygdala gray matter volume. Age, depression and trait anxiety did not significantly influence these associations.

As revealed by post-hoc tests, the right hippocampus was smaller in h-ALEX participants with a history of ELS compared to those without, while no such association was found in the absence of alexithymia. As described above, previous studies of predominantly clinical populations indicated that early stress exposure can affect hippocampal development (Kitayama et al., 2005; Kronmüller et al., 2008; Woon, Sood & Hedges, 2010), suggesting an initially regular hippocampus with subsequent...
abnormal volumetric development after trauma exposure (Woon & Hedges, 2008). Furthermore, the mechanisms of stress-related chronic CRH exposure on hippocampal microarchitecture and cell number are well described in the literature (e.g. Chen et al., 2012; Zhao et al., 2007). Less consistent results, however, are reported by studies investigating ELS-related effects in healthy study populations. As our data show, one possible reason for these inconsistent results might be that previous studies disregarded the influence of individual emotional functioning. We found that ELS is associated with reduced hippocampal volume in healthy individuals as a function of alexithymia – that is only in the presence of alexithymia. We were also able to show that in the absence of alexithymia, the experience of ELS is related to an increased amygdala volume in healthy participants. Thus, the individual degree of emotional functioning seems to have a significant influence on the nature of neural alterations induced by the experience of ELS.

Developmental models suggest that early attachment relationships establish the basis for emotional functioning, i.e. emotional awareness or the ability to express emotions, during childhood. This basis can be disturbed by a child’s exposure to experiences of abuse or neglect, facilitating the development of emotional disturbances such as alexithymia. Following this line of argument, reduced hippocampal volumes in h-ALEX individuals with a history of ELS could be interpreted as the result of accumulating effects of early stress exposure and low degrees of emotional functioning, since no such effects were found in the absence of alexithymia. As shown in a number of human and non-human animal studies, the hippocampus is a slowly developing brain structure with prolonged phases of neuronal proliferation during childhood into adulthood (Gogtay et al., 2006; Tottenham & Sheridan, 2010). Therefore, it shows an increased susceptibility to ELS but, at the same time, there might also be a longer time frame for protective action. As Yang and colleagues (2007) reported, alterations in the hippocampus are more likely to reverse under enriched environmental conditions. This might explain why we did not find any association of hippocampal volume and ELS in the l-ALEX group characterized by a high degree of emotional functioning, implicating the presence of some kind of intrapersonal or environmental protective factors in these individuals. However, although h-ALEX participants had been exposed to severe stressful events and even showed a neural correlate of early stress exposure, none of them developed post-traumatic stress disorder (PTSD) or any other psychiatric disorder. It is possible that, despite their persisting “hippocampal stress signature”, these individuals might
have been protected from reacting with a post-traumatic stress response as well – by alexithymia. As described above, alexithymia is related to reduced limbic responses to emotional stimuli (Moriguchi & Komaki, 2013). Thereby, alexithymia might have altered the processing of adverse events during childhood and youth, with difficulties experiencing emotions and attaching low importance to one’s own emotions acting as a kind of “coping strategy”. As shown in our fMRI study reported in Chapter 5, hippocampal responses to pleasant emotional stimuli were positively correlated with individual CTQ scores in h-ALEX individuals. An increased hippocampal reactivity to pleasant stimuli despite decreased gray matter volumes in the same region could provide a first indication of alexithymia serving as a kind of coping strategy in very specific individuals. However, the question remains whether alexithymia should rather be considered a “maladaptive” coping strategy, given that in h-ALEX individuals ELS-related hippocampus gray matter volume reductions seem to persist into adulthood, whereas l-ALEX individuals exposed to similar levels of ELS showed unaltered (maybe restored?) hippocampus volumes. Longitudinal study designs would be necessary to pursue the question of how emotional abilities modulate individual adaptations to early stress exposure.

In participants with high degrees of emotional functioning (i.e. low levels of alexithymia), our data show that the experience of ELS is associated with an increased left amygdala volume, even after controlling for influences of age, depression and trait anxiety, while the hippocampus remained unaffected. The amygdala is involved in rapid processing of emotional information and is important for learning about safety of an individual’s environment (Davis & Whalen, 2001). It appears to be more reactive in early life than in adulthood (Tottenham & Sheridan, 2010). Previous studies have shown that an exposure to circulating glucocorticoids can lead to long-term changes in structure and function of the amygdala. Studies using functional imaging methods consistently report an increased amygdala responsiveness to negative emotional stimuli associated with early stress exposure (e.g. Dannlowski et al., 2012; White et al., 2012; Shin et al., 2006), indicating that ELS can change an individual’s threshold for reacting to emotional events. On a structural level, both decreased (Driessen et al., 2000; Schmahl et al., 2003) and increased (Metha et al., 2009; Tottenham et al., 2010) amygdala volumes have been reported following ELS, with animal studies also pointing to an amygdala volume increase related to ELS (Vyas et al., 2002).
As previous research indicates, ELS-related changes in the amygdala begin rapidly after stress exposure and, once established, appear resistant to ameliorative environmental influences (Tottenham et al., 2010). This might explain the present finding of an amygdala volume increase in h-ALEX individuals with a history of ELS despite their high degree of emotional functioning. However, if ELS-related changes in amygdala volume seem to persist into adulthood independent from environmental conditions, they should have been present in the h-ALEX group as well. In a post-hoc analysis, although there was no main effect of alexithymia, we found that individual alexithymia scores were negatively associated with left amygdala gray matter volume ($r = -.26, p < .05$; controlling for age, depression and trait anxiety). Thus, there might have been slight alexithymia-related effects on left amygdala gray matter volume masking antecedent ELS-related amygdala volume increases. This interpretation is in line with a recent study by Ihme and colleagues (2013) reporting reduced left amygdala gray matter volume in healthy individuals with high degrees of alexithymia.

When interpreting the findings of the present study, the following limitations must be acknowledged. The volumetric measures of hippocampus and amygdala showed their associations with ELS to the right (hippocampus) and left (amygdala) hemisphere. Conclusions with regard to laterality should be handled with care, because some effects might just have narrowly missed statistical significance, which does not mean that they can be disregarded with respect to an individual’s emotional functioning. The interaction of ELS and alexithymia we found in the hippocampus, for example, was also detectable in the left hemisphere, but did not reach statistical significance ($p = .078$). It is possible that more severe experiences of ELS are necessary to affect the hippocampus bilaterally. This question might be interesting to pursue in future studies.

Moreover, the use of structured interviews would have been beneficial to assess emotional functioning more reliably, however, there was no validated German version of the Toronto Structured Interview for Alexithymia (TSIA; Grabe et al., 2009) available at the time of data acquisition. However, we did not solely rely on the TAS-20 but added the BVAQ, a more detailed, conceptually broader and widely used questionnaire in many studies on alexithymia. In the assessment of ELS, a semi-structured face-to-face interview was used to validate participants’ individual CTQ scores. Subjects were explicitly asked for examples of observable behavior to explain their experience of a negligent or abusive environment. In case of lacking consistency or missing examples, subjects would have been excluded from participation.
When assessing ELS, the problem of recall biases and the nature of reconstructive memory (Hyman & Loftus, 1998) has to be solved. It is usually approached by including medical records in the process of data collection or by interviewing family members. In the present sample, participants predominantly reported emotional traumata. However, these experiences mostly lack visible bodily injury, so medical records from childhood would have been of limited use. In addition, many participants were not in regular contact with their families. Thus, family interviews would have been difficult to arrange and probably emotionally draining for our participants.

To conclude, this is the first study to show that individual emotional abilities modulate the effects of early life stress on structural characteristics of limbic emotion processing circuits. Depending on the presence of alexithymia, exposure to ELS had differential effects on hippocampus and amygdala volume. ELS was negatively associated with right hippocampus volume in high alexithymic individuals and had a positive association with left amygdala volume in low alexithymic emotionally high functioning individuals. The study emphasizes the considerable influence of intrapersonal factors on the nature of neural alterations related to the experience of ELS.

6.5 Acknowledgements

The authors thank the team of the Dahlem Institute for Neuroimaging of Emotion for their technical support.
Chapter 7

Music in Depression:
Neural Correlates of Emotional Experiences in Remitted Depression¹

¹This chapter was published as
Accessible online: http://dx.doi.org/10.5498/wjp.v3.i2.8
8.1 Summary of Empirical Studies and Further Thoughts

The main goal of the present dissertation project was to investigate how early stress exposure modulates emotional abilities as well as function and structure of emotion processing circuits in the brain. To capture individual degrees of emotional ability, we investigated healthy individuals with high and low levels of alexithymia as well as participants with and without a history of major depression. The goal was to explore the influence of early life stress under different “basic emotional configurations” to gain some insight into individual processes of adaptation to early experiences of stress, such as emotional and physical abuse or neglect. In short, the “neural signature” of early life stress was investigated as a function of emotional abilities. To investigate emotional brain functioning as validly as possible, we designed an experiment using musical stimuli to induce strong emotional experiences and measured their neural correlates via fMRI. Furthermore, the volumes of emotion-relevant brain areas were measured via MRI to explore the effects of early life stress on a structural level.

One of the main results of the present empirical investigations is that early life stress is associated with altered emotional abilities (i.e. high degrees of alexithymia) in healthy individuals and that this association is also represented on the neural level, arising in increased hippocampal reactivity in response to pleasant audiovisual stimuli. The study showed, for the first time in the absence of psychiatric disorders, that the effects of early life stress on emotion related hippocampal functioning are highly individual and need to be investigated in due consideration of trait variables that potentially modulate emotional functioning, such as alexithymia. Questioning the traditional conceptualization of alexithymia as a risk factor for mental and physical health, we discussed whether alexithymic tendencies, such as not attaching great significance to emotions, can develop in adaptation to early childhood adversities, serving as a protective factor in individual cases. A closer look at the brain on a structural level revealed that early life stress was negatively associated with hippocampus gray matter volume, but only in the presence of alexithymia. Participants with low degrees of alexithymia showed an ELS-
related amygdala volume increase as described by previous studies, however, their hippocampus volume was not affected by ELS. Given that the hippocampus is a slowly developing brain structure and that ELS-related volumetric alterations have been shown to be reversible under enriched environmental conditions, our finding could also be interpreted as the result of accumulating effects of early stress exposure and low degrees of emotional functioning. Nevertheless, the interpretation of alexithymia as a potentially protective factor should, in our opinion, not be rejected completely. One has to keep in mind that, although h-ALEX participants had been exposed to severe stressful events and even showed a neural correlate of early stress exposure, none of them developed post-traumatic stress disorder (PTSD) or any other psychiatric disorder. It is possible that, despite the persisting “hippocampal stress signature”, these individuals might have been protected from reacting with a post-traumatic stress response as well – by alexithymia. Longitudinal study designs are strongly needed to pursue the question of how high and low degrees of emotional ability can modulate individual adaptations to early stress exposure.

Another merit of this dissertation project is the discovery of a neural marker for depression vulnerability, namely reduced pregenual anterior cingulate cortex (ACC) reactivity in response to audiovisual emotional stimuli, which has been identified in individuals with a history of major depression. We also found that a substantial part of variance of pregenual ACC activity was explained by early life stress, which leads us back to the initial question how environmental factors shape neural representations of emotional processes and thus an individual’s “emotional world”. Regarding the role of alexithymia in the etiology of major depression, our study showed that alexithymia might be a variable relevant within depressive episodes, but not a vulnerability marker. We therefore suggest that the close association between alexithymia and depression reported in previous studies might rather result from an overlap on the phenomenological level. This line of argumentation also strengthens the notion that alexithymia should not be considered a risk factor per se.

Early stress exposure, as demonstrated by the present investigations (see Figure 8.1), remains a considerable factor with regard to brain development, affective functioning and, in the broader sense, to mental health. Thus, the need for prevention programs is clearly indicated. According to a recent review on childhood maltreatment prevention, a number of programs have been established to counteract the problem of child neglect and abuse, however, the programs mostly lack systematic empirical examination (Mac-
Millan et al., 2009). Apart from the need to investigate short- and long-term effects of child maltreatment prevention, the present project emphasizes the importance of programs targeting the development of emotional abilities in children and young adults exposed to ELS. Assessing individuals such as the l-ALEX group with a history of ELS (see Chapters 5 and 6) regarding emotional abilities and coping behavior might shed some light into the development of resilience and health supporting behaviors on multiple levels.

![Diagram of Emotional and Neurological Responses](image)

**Figure 8.1. Summary of main findings.**

Finally, the present dissertation project has designed and validated a new paradigm for the assessment of emotional experiences via fMRI. The results of the empirical investigation of this paradigm show that music modulates emotional experiences on a neural and behavioral level in different populations characterized by disturbances on the emotional-experiential and -expressive domain. The emerging publications in peer-reviewed journals and project-related talks on international conferences (see Appendix) underpinned the significant role of music in emotion research. Furthermore, the results of the present dissertation project bring up the idea to apply music to promote emotional abilities within psychotherapeutic interventions and, as a future outlook, to investigate the effectiveness of music-based therapy on a neural level.
8.2 From music-induced Emotions to music-based Interventions

Besides new findings on how early environmental factors modulate neural correlates of emotional experiences under different “basic emotional configurations”, the present dissertation project demonstrates the good applicability of music in emotion research. In the fMRI studies as described in Chapters 5 and 7, music was able to activate central structures of the emotion network, such as hippocampus, parahippocampal gyrus, anterior cingulate cortex, insula or temporal pole. Moving from research into practice, the question arises whether the emotional power of music could be used to full capacity in therapeutic settings to promote individual emotional abilities. In recent years, music has eventually been integrated in the treatment of psychological disorders such as depression (Maratos, Crawford & Procter, 2011) or autism (Kaplan & Steele, 2005). In music therapy, a variety of methods are applied to use music “as a medium for communication and emotional expression” (Fachner, Gold & Erkkilä, 2012) to improve or restore an individual's emotional abilities and, finally, her or his mental health. Music therapy can include receptive and/ or active parts. The receptive part is thought to directly influence physical or emotional processes by means of movement, meditation or relaxation (Maratos et al., 2009). The active part makes use of music production in terms of composition or improvisation in an individual or group setting (Bruscia, 1987). The overall therapeutic process is based on “the mutual construction of meaning of emerging thoughts, images, emotional content and expressive qualities that often originate from the musical experience and are then conceptualized and further processed in the verbal domain” (Erkkilä et al., 2011). According to Hillecke and colleagues (2005), the effectiveness of music therapeutic interventions can be traced back to the modulation of attention, emotion, cognition, behavior and communication processes. In the case of receptive music therapy, listening to music seems to be related to social cognition, that is “processes of mental state attribution” or “mentalizing” (Koelsch, 2009), driven by an individual’s need to decode the intentions, desires, and beliefs of the person who performs or even composed the piece of music. As Steinbeis and Koelsch (2009) impressively showed via functional magnetic resonance imaging, listening to man-made music (“composer condition”) evoked stronger activation of the so-called mentalizing network than music that was supposed to be generated by a computer. This finding might pave the way for music-based trainings to increase empathetic skills. In particular, music could be applied to promote emotional empathy, i.e. an individual’s ability to actually feel with another person – in opposition to the
ability to recognize others’ emotional states from nonverbal cues, which is considered cognitive empathy. Previous studies revealed that individuals with high levels of alexithymia show low levels of empathy and a reduced activation of the mentalizing network consisting of dorso- and ventromedial prefrontal cortex, temporo-parietal junction and posterior cingulate cortex (Bird et al., 2010; Moriguchi et al., 2006; Silani et al., 2008). However, skills of emotion recognition seem to be unaffected (Kessler et al., 2006; Montebarocci et al., 2011). Thus, individuals with high levels of alexithymia might benefit from a receptive music-based intervention targeting emotional empathy skills. But also active elements of music therapy could be beneficial for high alexithymic individuals to improve emotional-expressive skills. Music can be a medium to express diffuse emotional states, enabling the individual to communicate with his or her environment without the need to find the correct words for feelings. Making music might operate on a protosymbolic level, preparing the individual to verbalize emotions (Erkkilä et al., 2011). Thus, non-verbal emotional expression through music might enable high alexithymic individuals to share their feelings and, in turn, to establish a cognitive link between their internal state, the musical expression and a concrete verbalization.

Similar mechanisms might apply to patients with major depression. Depressed individuals who report feelings of diffuse tension or who are unable to articulate their emotions can benefit from active techniques of music therapy. The experience of being able to express emotions through music or to actively change states of low mood could help a depressed person to re-establish his or her internal locus of control, because emotions become tangible and eventually controllable. Moreover, the use of music in depression therapy adds the important aspect of behavioral activation (Kanter et al., 2010) to the beneficial mechanisms mentioned above, which has previously been shown to be effective in reducing depressive symptoms (Mazzucchelli, Kane & Rees, 2009). Receptive music therapy, in turn, might also be useful in the treatment of depression by energizing the body, inducing states of relaxation or blocking painful thoughts (Maratos et al., 2009).

Although music-based interventions seem a promising tool in the treatment of emotional disturbances, empirical examinations of music therapy are rare. Only a small number of research groups tested music therapy and found that music is capable to reduce depression symptom severity as measured by questionnaires and clinical interviews (Brandes et al., 2010; Erkkilä et al., 2008; Erkkilä et al., 2011). Interestingly,
nothing is known about the effects of music on the depressed brain, whereas the effectiveness of cognitive-behavioral therapy (Dichter, Felder & Smoski, 2010) or antidepressant medication (for example Arnone et al., 2012) in the treatment of depression has repeatedly been demonstrated on the neural level. As far as the “healthy brain” is concerned, a number of studies, including Chapters 5 and 7 of this dissertation, have shown that music is able to modulate (para-)limbic reactivity in core emotion processing circuits such as insula, anterior cingulate cortex, amygdala and hippocampus. Together with previous research (e.g. Blood & Zatorre, 2001; Blood et al., 1999; Koelsch et al., 2006), the present findings indicate that music therapy might be effective in the treatment of various kinds of behavioral disturbances, although randomized controlled trials are still needed to reveal psychological factors and mechanisms of change associated with music-based interventions.
References


Lebenslauf\textsuperscript{1}

\textsuperscript{1}Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.
Selbständigkeitserklärung


Berlin, den 02. Mai 2013

________________________________________
Sabine Aust