The association of three anxiety dimensions in children and adolescents: their influence on the brain and malleability by a prevention program

Der Zusammenhang dreier Angstdimensionen bei Kindern und Jugendlichen: ihr Einfluss auf das Gehirn und ihre Veränderbarkeit durch ein Präventionsprogramm

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I hereby confirm that my thesis entitled „The association of three anxiety dimensions in children and adolescents: their influence on the brain and malleability by a prevention program" is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

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Abstract

Anxiety disorders are the most prevalent group of neuropsychiatric disorders and go along with high personal suffering. They often arise during childhood and show a progression across the life span, thus making this age a specific vulnerable period during development. Still most research about these disorders is done in adults. In light of this, it seems of utmost importance to identify predictive factors of anxiety disorders in children and adolescents. Temperament or personality traits have been proclaimed as risk markers for the development of subsequent anxiety disorders, but their exact interplay is not clear. In this dissertation an effort is made to contribute to the understanding of how risk markers of early temperamental traits, in this case Trait Anxiety, Anxiety Sensitivity and Separation Anxiety are interplaying. While Trait Anxiety is regarded as a more general tendency to react anxiously to threatening situations or stimuli (Unnewehr, Joormann, Schneider, & Margraf, 1992), Anxiety Sensitivity is the tendency to react with fear to one's own anxious sensations (Allan et al., 2014; S. Reiss, Peterson, Gursky, & McNally, 1986), and Separation Anxiety is referring to the extent to which the child is avoiding certain situations because of the fear of being separated from primary care givers (In-Albon & Schneider, 2011). In addition, it will be addressed how these measurements are associated with negative life events, as well as brain functioning and if they are malleable by a prevention program in children and adolescents. In study 1 the aim was to extend the knowledge about the interrelations of this anxiety dimensions and negative life events. Results indicated positive correlations of all three anxiety traits as well as with negative life events. Thus, a close connection of all three anxiety measures as well as with negative life events could be indicated. The closest association was found between Anxiety Sensitivity and Trait Anxiety and between Separation Anxiety and Anxiety Sensitivity. Furthermore, negative life events functioned as mediator between Anxiety Sensitivity and Trait Anxiety, indicating that a part of the association was explained by negative life events. In study 2 we extended the findings from study 1 with neurobiological parameters and examined the influence of anxiety traits on emotional brain activation by administering the "emotional face matching task". This task activated bilateral prefrontal regions as well as both hippocampi and the right amygdala. Further analyses indicated dimension-specific brain activations: Trait Anxiety was associated with a hyperactivation of the left inferior frontal gyrus (IFG) and Separation Anxiety with a lower activation bilaterally in the IFG and the right middle frontal gyrus (MFG). Furthermore, the association between Separation Anxiety and Anxiety Sensitivity was moderated by bi-

hemispheric Separation-Anxiety-related IFG activation. Thus, we could identify distinct brain activation patterns for the anxiety dimensions (Trait Anxiety and Separation Anxiety) and their associations (Separation Anxiety and Anxiety Sensitivity). The aim of study 3 was to probe the selective malleability of the anxiety dimensions via a prevention program in an at-risk population. We could identify a reduction of all three anxiety traits from pre- to post-prevention-assessment and that this effect was significant in Anxiety Sensitivity and Trait Anxiety scores. Furthermore, we found that pre-intervention Separation Anxiety and Anxiety Sensitivity post-intervention were associated. In addition, pre-interventive scores were correlated with the intervention-induced change within the measure (i.e., the higher the score before the intervention the higher the prevention-induced change) and pre-intervention Anxiety Sensitivity correlated with the change in Separation Anxiety scores. All relations, seemed to be direct, as mediation/moderation analyses with negative life events did not reveal any significant effect. These results are very promising, because research about anxiety prevention in children and adolescents is still rare and our results are indicating that cognitive-behavioural-therapy based prevention is gilding significant results in an indicated sample even when samples sizes are small like in our study.

In sum the present findings hint towards distinct mechanisms underlying the three different anxiety dimensions on a phenomenological and neurobiological level, though they are highly overlapping (Higa-McMillan, Francis, Rith-Najarian, & Chorpita, 2016; Taylor, 1998). Furthermore, the closest associations were found between Anxiety Sensitivity and Trait Anxiety, as well as between Separation Anxiety and Anxiety Sensitivity. Specifically, we were able to find a neuronal manifestation of the association between Separation Anxiety and Anxiety Sensitivity (Separation Anxiety-specific IFG activation) and a predictive potential on prevention influence. The results of these studies lead to a better understanding of the etiology of anxiety disorders and the interplay between different anxiety-related temperamental traits and could lead to further valuable knowledge about the intervention as well as further prevention strategies.

Zusammenfassung

Angststörungen sind die am häufigsten auftretende Gruppe neuropsychiatrischer Erkrankungen und führen in vielen Fällen zu großem Leid. Sie beginnen häufig in der Kindheit und Spontanremissionen sind selten, im Gegenteil - die Erkrankungen verschlimmern sich häufig und führen zu weiteren psychischen Erkrankungen. Dabei stellt die Kindheit eine Lebensphase mit besonderer Vulnerabilität für die Entwicklung von Angsterkrankungen dar. Trotzdem werden die meisten Studien zu Angststörungen weiterhin mit Erwachsenen durchgeführt. Vor diesem Hintergrund scheint es von größter Bedeutung, prädiktive Faktoren für Angststörungen bei Kindern und Jugendlichen zu identifizieren. Temperament- oder Persönlichkeitsmerkmale werden als Risikomarker für Angststörungen gesehen. Dabei ist das genaue Zusammenspiel dieser Risikomarker im Kindes- und Jugendalter nicht klar. Diese Dissertation leistet dabei einen Beitrag zum Verständnis des Zusammenspiels der Risikomarker Trait-Angst, Angstsensitivität und Trennungsangst. Während Trait-Angst als eine eher allgemeinere Tendenz angesehen wird, ängstlich auf bedrohliche Situationen oder Reize zu reagieren (Unnewehr et al., 1992), ist Angstsensitivität die Tendenz, mit Angst auf die eigenen potentiell angst-assoziierten Empfindungen zu reagieren (Allan et al., 2014; S. Reiss et al., 1986). Trennungsangst bezieht sich auf das Ausmaß, in dem das Kind bestimmt Situationen vermeidet, weil es befürchtet von Primärbezugspersonen getrennt zu werden (In-Albon & Schneider, 2011). Darüber hinaus befasst sich diese Dissertation damit, wie diese drei Angstmaße mit negativen Lebensereignissen und Gehirnaktivierung zusammenhängen und evaluiert deren Veränderbarkeit durch ein indiziertes Präventionsprogram. Zu diesem Zweck wurden drei Studien durchgeführt. In Studie 1 war das Ziel, das Wissen, um die Wechselbeziehungen dieser Angstmaße und negativer Lebensereignisse zu erweitern. Die Ergebnisse zeigten enge Zusammenhänge zwischen den drei Angstmaßen und ebenso mit der Anzahl negativer Lebensereignissen. Darüber hinaus fungierten negative Lebensereignisse als Mediator zwischen Angstsensitivität und Trait-Angst, was darauf hinweist, dass ein Teil des Zusammenhangs dieser beiden Angstmaße durch negative Lebensereignisse erklärt wird. In Studie 2 erweiterten wir die Ergebnisse aus Studie 1 um ein neurobiologisches Maß und untersuchten den Einfluss der Angstmaße auf Hirnaktivierung während emotionaler Verarbeitung mittels der Durchführung des „emotional face matching task“. Die Analyse zeigte eine Aktivierung während der Aufgabe in bilateralen präfrontalen Regionen sowie beiden Hippocampi und der rechten Amygdala. Angstspezifische Aktivierungen zeigten eine Trait-Angst-spezifische Hyperaktivierung im linken gyrus frontalis inferior (IFG) und eine Trennungsangst-spezifische Hypoaktivierung in beiden IFG und dem rechten gyrus frontalis

medius. Darüber hinaus wurde der Zusammenhang zwischen Trennungsangst und Angstsensitivität durch bi-hemisphärische Trennungsangst-spezifische IFG Aktivierung moderiert. Wir konnten also Hirnregionen identifizieren, die spezifisch mit den Angstmaßen assoziiert waren (Trait-Angst und Trennungsangst) und auch deren Verbindung moderierten (Trennungsangst und Angstsensitivität). Ziel der Studie 3 war es, die Veränderbarkeit der Angstmaße anhand eines Präventionsprogramms in einer Risikopopulation zu untersuchen. Wir konnten eine Verringerung aller drei Angstmaße durch die Prävention feststellen und dieser Effekt war für Angstsensitivität und Trait-Angst statistisch signifikant. Darüber hinaus konnten wir zeigen, dass die Trennungsangst vor der Prävention signifikant mit der Angstsensitivität nach der Prävention korrelierte. Zusätzlich sagte das Ausmaß der Angstmaße vor der Prävention die durch die Intervention induzierten Veränderung innerhalb eines Maßes signifikant voraus (Je höher die Werte vor der Intervention, desto höher die präventionsinduzierte Änderung), zudem vermochte Angstsensitivität vor der Intervention Änderung der Trennungsangstwerte zu prognostizierten. Alle gefunden Zusammenhänge schienen darüber hinaus direkt zu sein, da Mediations- / Moderationsanalysen mit negativen Lebensereignissen keinen signifikanten Effekt zeigten. Diese Ergebnisse sind sehr vielversprechend, da es nur wenig Forschung zur Angstprävention bei Kindern und Jugendlichen gibt und unsere Ergebnisse darauf hinweisen das Präventionsprogramme, welche auf Kognitiv-verhaltenstherapeutischen Elementen beruhen in einer indizierten Population gute Effekte erzielen können, selbst wenn es sich, wie in unserem Fall, um eine kleine Stichprobengröße handelt.

Zusammenfassend deuten die vorliegenden Ergebnisse auf unterschiedliche Mechanismen hin, die den drei verschiedenen Angstmaßen auf phänomenologischer und neurobiologischer Ebene zugrunde liegen. Darüber hinaus wurden enge Assoziationen zwischen Angstsensitivität und Trait-Angst sowie Trennungsangst und Angstsensitivität gefunden. Insbesondere konnten wir eine neuronale Manifestation des Zusammenhangs zwischen Trennungsangst und Angstsensitivität (Trennungangstspezifische IFG-Aktivierung) und ein Vorhersagepotential für den Einfluss der Prävention finden. Die Resultate der beschriebenen Studien tragen zu einem besseren Verständnis der Ätiologie von Angststörungen und dem Zusammenspiel verschiedener angstspezifischer Temperamentmerkmale bei, und können zu weiteren wertvollen Erkenntnissen über Interventions- sowie Präventionsstrategien führen.

1. General Introduction

Anxiety disorders are a group of psychiatric disorders, characterized by excessive and persistent worry or fear (American Psychiatric Association, 2013; World Health Organization, 2004a, 2014). They are the most prevalent group of neuropsychiatric disorders (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Wittchen et al., 2011) and the seventh most common cause lived with a disability worldwide (Vos et al., 2012), with more than 61.5 Million persons affected in the European Union and a 12-month prevalence of 14% (Kessler et al., 2012; Wittchen et al., 2011). Consequently, anxiety disorders are among the most chronic disorders and go along with high socioeconomic implications and health care costs (Wittchen et al., 2011). The disorder group is rather heterogenous with regard to the worry or fear experienced by patients, consisting of several distinct disorders such as for example generalized anxiety disorder (GAD), panic disorder (PD) and separation anxiety disorder (SAD) (American Psychiatric Association, 2013; World Health Organization, 2004a, 2014).

Even though epidemiological research suggests that half of all mental disorders that are present in adulthood show their onset before 14 years of age and mental disorders are very prevalent in childhood and adolescence (Kessler et al., 2007; Kessler et al., 2005), the main research focus today rests on research done in adult samples. Similarly, anxiety disorders often arise during childhood, with a median onset of 11 years of age (Bandelow & Michaelis, 2015; Kessler et al., 2005). In addition, disease onsets of subtypes vary across the life span: whereas SAD is most frequently diagnosed in early childhood (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005), the specific onset of GAD and PD lies in young adulthood (Beesdo et al., 2009; Beesdo, Pine, Lieb, & Wittchen, 2010; Kessler et al., 2005). Anxiety disorders show a progression across the life span and have a high comorbidity with other mental disorders (American Psychiatric Association, 2013; Langley, Bergman, McCracken, & Piacentini, 2004; World Health Organization, 2004a, 2014). Additionally, they are considered as a risk factor for the development of other mental disorders, such as for example mood disorders (Beesdo et al., 2009; Beesdo-Baum et al., 2015; Cole, Peeke, Martin, Truglio, & Seroczynski, 1998; Essau, 2003; Keller et al., 1992; Kessler et al., 2005). Furthermore, anxiety disorders have a negative influence on several other life factors such as well-being of child and family (Erath, Flanagan, & Bierman, 2007; Hudson & Rapee, 2002), academic performance (Mendlowicz & Stein, 2000; Van Ameringen, Mancini, & Farvolden, 2003), and overall child development (Erath et al., 2007; Langley et al., 2004; Mendlowicz & Stein, 2000; Van Ameringen et al., 2003). In light of this, it seems of utmost importance to identify and evaluate potential risk factors of the development of anxiety disorders in children and adolescents (Donovan & Spence, 2000).

Candidates are to be found among those factors involved in the development and maintenance of this disorder group, which according to the current state of research is depicting itself in terms of a diathesis-stress model (A. Bernstein, Leen-Feldner, E. W., Kotov, R., Schmidt, N. B., & Zvolensky, M. J., 2006; Lesch et al., 1996; Reinelt et al., 2013; Zuckerman, 1999). Following this model, psychiatric diseases arise through a complex interaction between biological (e. g. neuronal functioning, genetics), psychological (e. g. early temperament) and environmental factors (e. g. negative life events (negLE)) during development (Beesdo-Baum et al., 2015; Chambers, Power, & Durham, 2004; Domschke, 2014; Donovan & Spence, 2000; Monk, 2008; Zinbarg & Barlow, 1996). A high vulnerability is for example comprising of certain temperamental factors and/or certain neuronal functioning in combination with environmental factors such as a higher number of negative life events (A. Bernstein, Leen-Feldner, E. W., Kotov, R., Schmidt, N. B., & Zvolensky, M. J., 2006; Domschke, 2014; Zinbarg & Barlow, 1996; Zuckerman, 1999).

The experience of fear or anxiety is not regarded as pathological, but rather as part of natural human development, which can be observed in all healthy individuals (Craske, 1997; Gullone, 2000; Muris & Field, 2011). During development, the anxiety inducing content is changing according to the cognitive developmental stage of the child (Beesdo-Baum et al., 2015; Muris & Field, 2011). Developmental appropriate and typical anxieties for different age groups are for example separation of caregivers (toddlers, 0 - 2 years), animals or darkness (preschool, 3 - 6 years), academic achievement or death (middle childhood 7/8 – 12 years) and social situations (adolescents, 13 - 18 years) (Schneider & Seehagen, 2014). Anxiety disorders are developing and diagnosed, if the content, the duration and persistence of the anxiety is not age or development appropriate and the child has a certain degree of impairment due to the anxiety (American Psychiatric Association, 2013; Beesdo-Baum et al., 2015; World Health Organization, 2004a, 2014). Among the most common anxiety disorders during childhood and adolescents are GAD and SAD (Schneider & Seehagen, 2014), PD in comparison, is only rarely diagnosed in childhood (Battaglia, Ogliari, D'Amato, & Kinkead, 2014; Battaglia et al., 2009; Hannesdottir, Sigurjonsdottir, Njardvik, & Ollendick, 2018; Roberson-Nay, Eaves, Hettema, Kendler, & Silberg, 2012). GAD is characterized by the presence of excessive fear and worry (American Psychiatric Association, 2013; World Health Organization, 2004a, 2014). The child or adolescent is struggling to control the worry and presents accompanying symptoms such as fatigue, muscle tension, restlessness or sleep disturbance (American Psychiatric Association, 2013; Schneider & Seehagen, 2014; World Health Organization, 2004a, 2014). While the disorder progresses the focus of worrying might change accordingly to the cognitive

developmental stage (American Psychiatric Association, 2013; Beesdo et al., 2009; Songco, Hudson, & Fox, 2020; World Health Organization, 2004a, 2014). Lifetime prevalence for GAD is about 9 % and in adolescents about 1% (American Psychiatric Association, 2013; Kessler et al., 2005; Tottenham & Galvan, 2016; Wittchen et al., 2011; World Health Organization, 2004a). The peak onset is around the age of 30 years, but the onset age has a spread over a large age range (American Psychiatric Association, 2013; Beesdo et al., 2009; Kessler et al., 2005). PD on the other hand is characterized by the experience of panic attacks, which are unexpected intense feelings of fear (World Health Organization, 2004a, 2014). The whole duration of a panic attack takes minutes and individuals are experiencing a range of sensations such as trembling, chest pain, sweating and fear of dying (World Health Organization, 2004a, 2014). For the diagnosis of PD, the panic attack has to be followed by a time of concern about a further panic attack and a maladaptive change of behavior (American Psychiatric Association, 2013). The overall 12-month prevalence of PD is around 3% (American Psychiatric Association, 2013). While panic attacks might occur in children the prevalence of PD is low before the age of 14 years and shows an increase during adolescence (American Psychiatric Association, 2013). Finally, SAD is characterized by anxiety concerning the separation of primary caregivers that is not age-appropriate (American Psychiatric Association, 2013; World Health Organization, 2014). This fear is accompanied by excessive worry about the physical safety of caregivers (such as death or illness) or the own safety (such as being kidnapped or becoming ill) resulting in a separation from the primary caregiver (American Psychiatric Association, 2013; Schiele, Gottschalk, & Domschke, 2020; World Health Organization, 2004a). Often children refuse to go to sleep alone (American Psychiatric Association, 2013). Nightmares involving the theme of separation or physical symptoms (such as head- or stomachaches) when confronted with a separation are common (American Psychiatric Association, 2013; Werner-Seidler, Perry, Calear, Newby, & Christensen, 2017; World Health Organization, 2004a). SAD is the most prevalent anxiety disorder in children younger than 12 years (American Psychiatric Association, 2013), with a prevalence of roughly 4% in children between 6 and 12 years and its prevalence decrease from childhood to adolescence (Beesdo et al., 2009; World Health Organization, 2004a). Interestingly, there seems to be a close connection between the development of SAD and the later development of PD (Battaglia et al., 2014; Hannesdottir et al., 2018; Kossowsky et al., 2013): the diagnosis of SAD in childhood is a strong predictor for PD in adulthood (Milrod et al., 2014) and PD and SAD share a genetic diathesis (Roberson-Nay et al., 2012). Furthermore, children of parents suffering from PD are more likely to develop SAD (for review see e.g. (Milrod et al., 2014). Reciprocally, PD patients report a significantly

increased number of separation life events as compared to healthy controls (Klauke, Deckert, Reif, Pauli, & Domschke, 2010).

1.1 Anxiety measures in association with anxiety disorders

Psychological factors, such as early temperament or personality traits have been identified as subclinical risk markers for subsequent psychopathology and especially for different anxiety disorders (Beesdo-Baum et al., 2015; Bienvenu et al., 2009; Chambers et al., 2004; Schmidt et al., 2010; Schmidt, Zvolensky, & Maner, 2006). In this dissertation, the early temperamental traits of Trait Anxiety, Anxiety Sensitivity and Separation Anxiety are of special interest, because, to clarify how these risk markers are contributing to the development of anxiety disorders in children and adolescents could contribute to a better understanding and evaluation of the etiology, diagnosis, treatment and ultimately preventive programs (Chorpita & Lilienfeld, 1999; Noel & Francis, 2011).

1.1.1 Trait Anxiety

The concept of Trait Anxiety is based on the "State-Trait Anxiety Model" developed by Spielberg (Spielberg, 1972) and is defined as a latent personality trait that describes the intraindividual and global tendency to react and interpret situations as threatening or fear inducing (Chambers et al., 2004; Spielberg, 1972; Unnewehr et al., 1992). In children, it is measured with the State-Trait Anxiety Inventory for children (STAIC) (Unnewehr et al., 1992). High Trait Anxiety has been associated with anxiety disorders (Mundy et al., 2015), identified as a predictor for the onset of anxiety disorders (Mundy et al., 2015; Schmidt et al., 2006) and the STAIC in particular has been used to differentiate individuals with anxiety disorders from subjects with other psychopathologies (Seligman, Ollendick, Langley, & Baldacci, 2004). For example, Hensley and Varela indicated that Trait Anxiety predicted GAD and Post Traumatic Stress Disorder in children that experienced negative/ traumatic life events (Hensley & Varela, 2008).

Trait Anxiety is a global measure for anxiety and can be applied in a variety of settings (Melfsen & Walitza, 2010; Unnewehr et al., 1992). It can be assessed with the German version of the "State-Trait Anxiety Inventory" *STAIK* (Melfsen & Walitza, 2010; Unnewehr et al., 1992). The STAIK covers the quantification of State as well as Trait Anxiety, therefore, to assess Trait Anxiety only the trait self-report questionnaire was used in the following studies (*Trait scale of the State-Trait Anxiety Inventory for Children* (STAIK-T)). The appropriate age for application of the STAIK has been set from 8 to 16 years (Melfsen & Walitza, 2010). The STAIK-T comprises of 20 statements on a three-point Likert scale (1) "almost never", (2)

"sometimes" and (3) "often", resulting in a total sum score between 20 and 60, with higher scores reflecting higher levels of Trait Anxiety (Unnewehr et al., 1992).

1.1.2 Anxiety Sensitivity

A second construct that has been identified as predisposing factor for anxiety disorder is "Anxiety Sensitivity" (Sandin, Sanchez-Arribas, Chorot, & Valiente, 2015; Schmidt et al., 2010). It is considered a relatively stable personality trait (Allan et al., 2014; Hovenkamp-Hermelink et al., 2019; Schmidt et al., 2010), that is unique from other constructs such as Trait Anxiety (Rapee & Medoro, 1994; Taylor, Koch, & Crockett, 1991) and provides incremental validity in predicting anxiety disorders and symptoms (Allan et al., 2014; Noel & Francis, 2011; Rapee & Medoro, 1994; Taylor, Koch, Woody, & McLean, 1996). Anxiety Sensitivity covers the personality construct of fear of anxiety-related sensations (Evans, 2017; S. Reiss, & McNally, R. J., 1985; Taylor, 1995). These sensations are believed to have harmful bodily, psychological and social consequences and go beyond the pure bodily sensations during anxiety states (Evans, 2017; S. Reiss, & McNally, R. J., 1985; Taylor, 1995). Individuals with a high Anxiety Sensitivity may experience fear of feeling tremulous or close to fainting or might experience fear of an accelerated heart rate because this could lead to humiliation or indicate an approaching heart attack (Eley, Stirling, Ehlers, Gregory, & Clark, 2004; Noel & Francis, 2011; Olatunji & Wolitzky-Taylor, 2009). The construct is an individual trait that is supposed to be influenced by factors such as genetics (Waszczuk, Zavos, & Eley, 2013; Zavos, Rijsdijk, Gregory, & Eley, 2010) and learning experiences (Schneider, Adornetto, In-Albon, Federer, & Hensdiek, 2009; Silverman, Fleisig, Rabian, & Peterson, 1991; Zavos et al., 2010). Most researchers have argued that Anxiety Sensitivity can be measured from middle childhood (Silverman et al., 1991; Silverman, Ginsburg, & Goedhart, 1999). In adults and early adolescents the construct of Anxiety Sensitivity has been related to the onset of anxiety disorders, in terms of serving as a predictor for the incidence (Schmidt et al., 2010) and maintenance (Schmidt et al., 2006) as well as symptom severity (Hannesdottir et al., 2018; Sandin et al., 2015). Thereby Anxiety Sensitivity functions as a continuum that is experienced by everyone to some degree. However high Anxiety Sensitivity is thought to amplify fearful reactions and thereby placing people at risk to develop anxiety, especially panic symptoms (Cox, 1999; Eley et al., 2004; Olatunji & Wolitzky-Taylor, 2009; Shipherd, Beck, & Ohtake, 2001). Adolescents with an elevated level of Anxiety Sensitivity show increased rates of PD and panic symptoms (Allan et al., 2014; Calamari et al., 2001; Schmidt et al., 2006; Weems, Hayward, Killen, & Taylor, 2002), even compared to patients with mood disorders or other forms of anxiety disorders (Noel & Francis, 2011; Olatunji & Wolitzky-Taylor, 2009). Anxiety

Sensitivity has been identified as a predictor for the severity of PD in adults (Sandin et al., 2015) and for the first onset of PD as well as of panic symptoms one year later in adolescence (Allan et al., 2014; Schmidt, Lerew, & Jackson, 1999; Schmidt et al., 2006). While Anxiety Sensitivity shows a strong relation to some anxiety disorders in adults (such as PD, specific and social phobia) it still seems to operate as a general risk and incremental factor of anxiety disorders in general (Allan et al., 2014; Naragon-Gainey, 2010; Waszczuk et al., 2013). An elevated level of Anxiety Sensitivity has been associated with general anxiety symptoms and is able to predict anxiety over depression (Joiner et al., 2002).

Similarly, to findings among adult samples, children and adolescence diagnosed with an anxiety disorder show elevated levels of Anxiety Sensitivity compared to children not meeting diagnostic criteria for an anxiety disorder (Joiner et al., 2002; Noel & Francis, 2011). Schmidt and colleagues (2010) reported that Anxiety Sensitivity predicted the development of anxiety symptoms one year later in adolescence when controlling for baseline anxiety (Schmidt et al., 2010) and predicted PD even after controlling for Trait Anxiety (Schmidt et al., 1999). While the relationship between Anxiety Sensitivity and anxiety disorders in adult and adolescent samples seems to be very consistent, there is controversy however, as to whether children between the age of 6-11 years can experience Anxiety Sensitivity (Noel & Francis, 2011). This debate stems from the fact that during this age, children are in the cognitive developmental stage of concrete operations, which is attributed with a strong overall cognitive maturation that is not yet completed (Bibace & Walsh, 1980; Piaget, 1952). This developmental stage corresponds to an increasing ability to consider physical symptoms in relation to anxiety and is thought to start at the age of 7 (Muris, Vermeer, & Horselenberg, 2008; Noel & Francis, 2011; Waszczuk et al., 2013). A meta-analysis by Noel and Francis (2011) could indicate that indeed there is a relationship between Anxiety Sensitivity and anxiety symptoms in childhood, but this relationship is not as pronounced as in adolescents and adults, which is in accordance with the not yet fully developed ability to associate bodily sensations with future consequences (Noel & Francis, 2011).

Anxiety Sensitivity in children is measured with the Children's Anxiety Sensitivity Index (CASI), a self- report questionnaire that was developed by Silverman and colleagues (Silverman et al., 1991). It is based on the "Anxiety Sensitivity Index" (ASI) questionnaire for adults and was transferred into an appropriate language for children and adolescents between the age of 6 and 17 (S. Reiss et al., 1986; Silverman et al., 1991; Silverman et al., 1999). The CASI consists of 18 items, while the first 16 items show identical correspondence to the ASI, two further items were added to the children version (Schneider, Adornetto, et al., 2009;

Schneider & Hensdiek, 1994). CASI item 17 parallels item 1 (not wanting others to know own feelings) and item 18 parallels item 14 (fear of body sensations) (Silverman et al., 1999). Example items are “it scares me when my heart beats fast” and “it scares me when I feel nervous” (Schneider, Adornetto, et al., 2009; Schneider & Hensdiek, 1994). The German version of the CASI that was used in this work is a translation by Schneider and Hensdiek of the 18 item English version by Silverman (Adornetto et al., 2008; Schneider & Hensdiek, 1994). The CASI is a self-report scale where children respond to each item on a three-point Likert scale (1) “none”, (2) “some” and (3) “a lot”, resulting in a sum score between 18 and 54, with higher scores reflecting higher levels of Anxiety Sensitivity (Silverman et al., 1991; Silverman et al., 1999).

1.1.3 Separation Anxiety

Separation Anxiety is measured with the German Separation Anxiety Inventory (TAI: Trennungsangst-Inventar (In-Albon & Schneider, 2011), consisting of two parts: a self-report (TAI-K: Trennungsangst-Inventar Kind) and external assessment questionnaire for parents (TAI-E: Trennungsangst-Inventar Eltern) (In-Albon & Schneider, 2011). The TAI measures the extent to which the child is avoiding certain situations because of the fear of being separated from primary care givers (In-Albon & Schneider, 2011). For the diagnosis of separation anxiety, via DSM-V and ICD-10 it is not absolutely essential that the child is avoiding fear inducing situations, but the avoidance of these situations is inborn to the group of anxiety disorders and is often part of the clinical picture (American Psychiatric Association, 2013; World Health Organization, 2014). In this aspect the TAI is thus depicting an important aspect of Separation Anxiety. The TAI consists of 12 items with the opportunity to answer to questions on a five-point Likert scale (0) “never”, (1) “seldom”, (2) “half of the time”, (3) “usually” and (4) “always”, resulting in a sum score between 0 and 48, with higher scores reflecting higher levels of Separation Anxiety (In-Albon & Schneider, 2011). In this work the TAI-K, thus the children questionnaire, was used and is referred to as TAI in the following chapters. To our knowledge, research with the TAI as a quantitative measure of anxiety symptomatology has been limited and most application is done in clinical settings, where the therapeutic treatment effect has been assessed with the TAI (In-Albon & Knappe, 2019; Schneider et al., 2011; Schneider et al., 2013; Schneider & Margraf, 2009).

1.2 Negative Life events in association with anxiety

Despite the established link between personality traits and anxiety disorders in children and adolescents, not all fearful or anxious children develop an anxiety disorder later in life (Cabral & Patel, 2020; Muris & Field, 2011). Following the diathesis-stress model of

psychopathology, it is presumed that a certain vulnerability factor, in this case a personality trait renders a child more prone to develop a psychopathology, but only under certain circumstances (Belsky & Pluess, 2009; Zuckerman, 1999). That is for example being exposed to a certain stressor, such as when children and adolescents have experienced negLE (Cabral & Patel, 2020). In this case the temperamental make-up of a child interacts with negLE in the onset of an anxiety disorder (Cabral & Patel, 2020; Zuckerman, 1999). Adverse life events and stress have an impact on behavior as well as physiology and mental health (Cohen, Janicki-Deverts, & Miller, 2007). NegLE are considered to play a major role and are treated as the main environmental risk factor in the development of anxiety disorders (Allen, Rapee, & Sandberg, 2008; Chorpita & Barlow, 1998; Klauke et al., 2010). Research indicates that children suffering from an anxiety disorder experience more negLE than healthy control children (Boer et al., 2002; Eley & Stevenson, 2000). Fernandes and Osorio indicated in a systematic review that people that have experienced a form of emotional trauma such as physical abuse or emotional neglect have a 1.9 to 3.6 times higher risk of developing an anxiety disorder compared to those how did not experience such an event (Fernandes & Osorio, 2015). The impact of negLE seems to be "dose-dependent" (Bremner et al., 1992; Copeland, Keeler, Angold, & Costello, 2007; Ganzel, Kim, Gilmore, Tottenham, & Temple, 2013), with trauma exposure posing a risk factor for the development of psychiatric disorders in healthy individuals (Battaglia et al., 2014; Bremner et al., 1992). In healthy adolescents and adults, research indicates that severe adverse life events are associated with the current level of anxiety (Ganzel et al., 2013). In this context higher levels of Trait Anxiety have been reported in patients with a history of abuse during childhood (Handa, Nukina, Hosoi, & Kubo, 2008). In adolescents and young adults, a study was able to demonstrate the association between life events and childhood maltreatment with increases in Anxiety Sensitivity (McLaughlin & Hatzenbuehler, 2009; Scher & Stein, 2003).

To assess negLE, The German *Zürcher Life-Event List (ZLEL*) (Steinhausen & Winkler-Metzke, 2001) was used in this dissertation. It consists of 36 items, including events in different settings such as school, family, peers and potential traumatic events, e.g. accidents and losses (Steinhausen & Winkler-Metzke, 2001). Questions can be answered with "yes" or "no". Additionally, if a participant answers "yes" the retrospective subjective stress will be assessed on a 5-point Likert scale from -2 to +2 as well (Steinhausen & Winkler-Metzke, 2001). Items rated with -1 or -2 are rated as negative life events and we counted these to receive the total scores (Steinhausen & Winkler-Metzke, 2001).

1.3 Neural underpinnings of emotional processing in anxiety

Since the brain is the physical manifestation and "primary mediator between life stress and bio-behavioral outcomes " (Ganzel, Morris, & Wethington, 2010) and alterations in brain function lead to changes in behavior, brain functioning is extensively studied in psychiatric disorders (Monk, 2008). Of special interest in this research domain is the processing of emotional stimuli, since many psychiatric disorders show aberrancies in the "detection of, response to and interpretation of emotion" (Monk, 2008) and it is assumed that the development of these disorders is related to the disturbance in emotion processing (Monk, 2008). Research concerned with the brain network implicated in emotion regulation, involving a fronto-limbic circuitry, indicates that this network is disrupted and/or shows alterations in anxiety disorders (Birbaumer et al., 1998; Monk et al., 2006; Monk, Telzer, et al., 2008; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; K. M. Thomas et al., 2001). Most research in this field is done in adult samples, and it is therefore of utmost importance to understand the neural underpinning of emotional processing and to relate disturbances and aberrancies to anxiety during childhood and adolescence to understand the development of this psychopathology (Monk, 2008; Monk, Klein, et al., 2008). It is not possible to transfer results from adult populations to children's samples, because regions recruited during a task in adults may not correspond to the regions involved during childhood and/or adolescence (Swartz & Monk, 2014). This is due to the fact, that the human brain continues to mature up until young adulthood (Giedd & Rapoport, 2010; Lau, Hilbert, & Gregory, 2013). This maturation process is comprising of a variety of aspects, such as age specific increases and decreases in white matter and grey matter, that are linear or u-shaped (Giedd & Rapoport, 2010; Lau et al., 2013). It is assumed that this process is increasing the efficiency of the system (Durston et al., 2006).

Probably the most commonly used stimuli in emotional processing research are human faces with emotional expressions (Davidson & Slagter, 2000; Monk, 2008). This is because humans are social creatures, whose lives are highly dependent on the ability to understand, interpret and recognize emotional expressions on the faces of their social group (Fusar-Poli et al., 2009). The competence to recognize faces is an early developing cognitive ability in infants, underlining the importance of this cognitive ability (Grossmann & Johnson, 2007). The subsequent competence to recognize facial expressions permits the individual to detect emotional states in others and to choose an appropriate form of social interaction (Fusar-Poli et al., 2009; Grossmann & Johnson, 2007). There are some emotional facial expressions, the so-called basic emotions: surprise, happiness, anger, fear, disgust and sadness (Adolphs, 2002; Celeghin, Diano, Bagnis, Viola, & Tamietto, 2017). These can be most reliably recognized by humans

across cultures and age groups (Adolphs, 2002; Celeghin et al., 2017). The processing of emotional stimuli such as faces can roughly be divided into three cognitive steps: 1) Perceptual processing of the stimuli and the recognition of the emotional information, thus a combination of visual input and memory retrieval; 2) Change of the affective mental state as a response to the stimulus, thus generating an emotional reaction as a response and 3) Regulation of the emotional state or response (Adolphs, 2002; Grossmann & Johnson, 2007; Leppanen, 2006; Phillips, Drevets, Rauch, & Lane, 2003; Sladky et al., 2012).

Distinct neural substrates of emotional processing have been defined (Monk, 2008). It comprises of a fronto-limbic network, which consists the amygdala, ventral striatum and the ventral prefrontal cortex (with the ventrolateral prefrontal, orbitofrontal and anterior cingulate cortex) (Monk, 2008). Specific regions are involved during different processes: the fusiform gyrus and the occipitotemporal cortex during the perceptual processing of the emotional stimulus; the amygdala, anterior insula, orbitofrontal cortex and ventral striatum during the recognition of the emotion and the generation of an emotional reaction as a response; and the anterior cingulate cortex and prefrontal cortex during the regulation of the emotional response to the stimulus (Adolphs, 2002; Leppanen, 2006; Phillips et al., 2003).

Among these structures, the amygdala has been identified as a key brain structure during the processing of emotional stimuli (Monk, 2008; Phelps & LeDoux, 2005). The amygdala comprises of several nuclei in the anterior temporal lobe (Phelps & LeDoux, 2005) and has been consistently identified of being highly involved in the mediation of emotional behavior, as a core gateway for emotional processing, identification and evaluation of emotional stimuli (Phan, Wager, Taylor, & Liberzon, 2002; Phelps & LeDoux, 2005). Research, primarily done in rats, but also in other mammals, could identify the central role of the amygdala in the identification of threat (Amaral & Price, 1984; Davis, 1992; LeDoux, 1992), but also its important role in social behavior (Jonason & Enloe, 1971; LeDoux, 1992). Individuals with lesions in this brain area display changes in social behavior as well as problems in the recognition of emotion (Zola-Morgan, Squire, Alvarez-Royo, & Clower, 1991). Thus, the amygdala is treated as a general key node that is involved in the detection of salient information in the environment that may impact the overall well-being of an individual (Phan et al., 2004).

The amygdala has anatomical and functional connections to regions within the prefrontal cortex (PFC) that are involved in the generation and regulation of an emotional reaction as a response to a stimulus (Barbas, 2000; Bechara, Damasio, & Damasio, 2000; Rule, Shimamura, & Knight, 2002). The PFC can further be subdivided into the orbitofrontal cortex, the ventromedial and ventrolateral prefrontal cortex as well as anterior cingulate cortex (Monk,

2008; Swartz & Monk, 2014). Thereby these regions can be associated with different cognitive functions (Monk, 2008; Phillips, Ladouceur, & Drevets, 2008; Swartz & Monk, 2014). While the medial regions of the ventral prefrontal cortex seem to be involved in automatic processing the more lateral regions are involved in more voluntary processes (Phillips et al., 2008; Swartz & Monk, 2014). Specifically, the ventrolateral prefrontal cortex (vlPFC), the lower portion of the prefrontal cortex, and to a lesser extent and possibly mediated by the vlPFC, the dorsolateral prefrontal cortex (dlPFC), seem to be involved in the amplification of emotional signals from limbic structures (Kalin, Shelton, Davidson, & Kelley, 2001; Monk, 2008; Phillips et al., 2008). These regions thereby exhibit an inhibitory control over the amygdala (Monk, 2008; Phillips et al., 2003; Phillips et al., 2008; Swartz & Monk, 2014), while the amygdala is relating information regarding the emotional significance (Phillips et al., 2003; Phillips et al., 2008; Swartz & Monk, 2014).

For neuroimaging studies targeting psychiatric disorders, it is of great interest to differentiate, whether the functional changes found are preceding the onset of anxiety disorders and or whether they are caused by the disorder itself (Christensen, Van Ameringen, & Hall, 2015). To answer this question, it is crucial to do neuroimaging research in healthy children and adolescents. Furthermore, research in this age group is especially important, because the transition from childhood to adolescence and adolescence itself is considered a critical time point to develop an anxiety disorder (Deardorff et al., 2007; Ferri, Bress, Eaton, & Proudfit, 2014). In a neuro-developmental framework, this phenomenon is explained by research that is indicating that during adolescence the prefrontal cortex is following a protracted developmental time course, compared to other structures, such as the amygdala (Casey et al., 1995; Giedd et al., 1996; Gogtay et al., 2004; Swartz & Monk, 2014). During this time the amygdala might be under-regulated by prefrontal cortex regions, thus creating an risk period for the development of emotional disturbances, but also for a sensitive period for environmental influences (Swartz & Monk, 2014).

1.4 Malleability and prevention of anxiety disorders

There are several psychotherapeutic intervention programs to treat different anxiety disorders effectively in children and adolescents (James, James, Cowdrey, Soler, & Choke, 2013; Waddell, Hua, Garland, Peters, & McEwan, 2007). However, research suggests that only roughly 20-30% of diseased children receive treatment (Essau, 2005; Keller et al., 1992; Waddell et al., 2007), furthermore many children fail to respond to or terminate treatment prematurely (P. M. Barrett, Dadds, & Rapee, 1996; Donovan & Spence, 2000; Kendall, 1994; Wang et al., 2017; Wittchen et al., 2011). The failure to respond to treatment is seen by different

research groups in a tardy application of therapy, when disorder symptoms are already heavily manifested and on their way to comorbid illness (Donovan & Spence, 2000; Essau, 2005; Wittchen et al., 2011). In the same vein these groups are critical of the oftentimes-adapted strategy in healthcare settings to care primarily for those individuals with the most severe symptoms (Kessler et al., 2003; Wittchen et al., 2011). A more promising approach, with a high impact could be seen in early detection (Cabral & Patel, 2020; Kessler et al., 2012) and prevention. In that context, anxiety disorders seem a highly promising target (Wittchen et al., 2011). With regard to the high prevalence, the early onset, low response rates to psychotherapeutic treatment, subsequent high healthcare costs and suffering of patients, there is the implication to identify and evaluate risk and predictive factors (Cabral & Patel, 2020; Donovan & Spence, 2000). These factors could then be used to identify children and adolescents at risk and to implement preventive programs in childhood, to ultimately reduce the incidence of the disease group and make elements of psychotherapy available to a broad audience (Cabral & Patel, 2020). On this note the World Health Organization (WHO) takes this approach in its Comprehensive Mental Action Plan 2013-2020 emphasizing the utmost importance of developing preventive procedures to tackle mental disorders (World Health Organization, 2013). Thereby preventive interventions can be categorized differently. A popular classification of prevention strategies is based on the target population and distinguishes between three different categories (Cabral & Patel, 2020; Perrez, 1992): 1) Universal prevention: Population as a whole, who have not been identified as risk population (Cabral & Patel, 2020); 2) Selective prevention: Population at a higher risk for the development of disorder as indicated by risk markers (Cabral & Patel, 2020); 3) Indicated prevention: Population with high risk, who have been identified with symptoms foreshadowing disease or markers indicating predisposition for disorder, but do not meet diagnostic criteria (Cabral & Patel, 2020).

There are currently few evaluated preventive interventions available addressing childhood anxiety (Cabral & Patel, 2020; Dadds et al., 1999; Neil & Christensen, 2009). The best-examined programs are used for example in the Netherlands, the UK and Australia (P. Barrett, Farrell, Dadds, & Boulter, 2005; Kosters, Chinapaw, Zwaanswijk, van der Wal, & Koot, 2015) where they are applied in a variety of settings, such as schools or hospitals. The program recommended by the WHO is the “FRIENDS” program developed by Prof. Dr. Paula Barrett (World Health Organization, 2004b). It is addressing children at different ages and is designed to meet the different developmental needs of pre-school children (Fun FRIENDS, 4 - 7 years), primary school children (FRIENDS for Life, 7 - 11 years) and youth (My FRIENDS Youth, 12

- 15 years) (P. M. Barrett, 2010; P. M. Barrett, 2017; Friends-Resilience, 2019; World Health Organization, 2004b). It is a manualized group-based intervention, which has a resilience promotion framework and uses among others, elements of the cognitive-behavioral therapy (CBT), as well as elements of the mindfulness stress reduction approach (P. M. Barrett, 2010; P. M. Barrett, 2017; Friends-Resilience, 2019). The goal of the program is to promote emotional resilience (P. M. Barrett, 2017; Friends-Resilience, 2019), which is defined as the ability to adapt and recover from stress, adverse life events and in the face of extreme risk with positive outcomes (Atkinson, Martin, & Rankin, 2009; Goldstein & Brooks, 2005). The FRIENDS program has a firm theoretical background, and is integrating research about the development and maintenance of anxiety into the skills and techniques that are taught (P. M. Barrett, 2010; P. M. Barrett, 2017). In the program children are trained in small groups to identify symptoms of anxiety, recognize and deal with bodily clues, as well as "unhelpful" thoughts (cognitive restructuring), create structured and graded exposure to feared stimuli, learn and apply relaxation techniques and problem solving strategies as well as strengthen their social skills and broaden their social network (P. M. Barrett, 2010; P. M. Barrett, 2017). It assists children at their developmental level and incorporates the child's value and social system as well as environment into an individualized and multisystem teaching approach, involving children, families, teachers and schools in the prevention process (P. M. Barrett, 2017; Iizuka, Barrett, & Morris, 2013). There is a multitude of literature examining the effectiveness of the FRIENDS for life program as a therapeutic and preventive intervention, either as an indicated or a universal intervention for the reduction of anxiety symptoms (P. M. Barrett, 2010; P. M. Barrett, 2017; P. M. Barrett, Farrell, Ollendick, & Dadds, 2006; Goldstein & Brooks, 2005; Iizuka et al., 2013).

1.5 Objectives and Organization of the Thesis

This dissertation is concerned with the influence and interaction of Trait Anxiety, Anxiety Sensitivity and Separation Anxiety in healthy children and adolescents (studies 1 and 2) and a subclinical sample of highly anxious children (study 3). An additional interest of this thesis is to assess if negative life events and brain activation are functioning as mediators or moderators of these connections in a healthy population (study 1 and 2). Furthermore, the selective malleability of these parameters via a preventive program is probed in a high-risk sample of children and adolescence (study 3) (for a schematic depiction of the three studies, see **figure 1**)

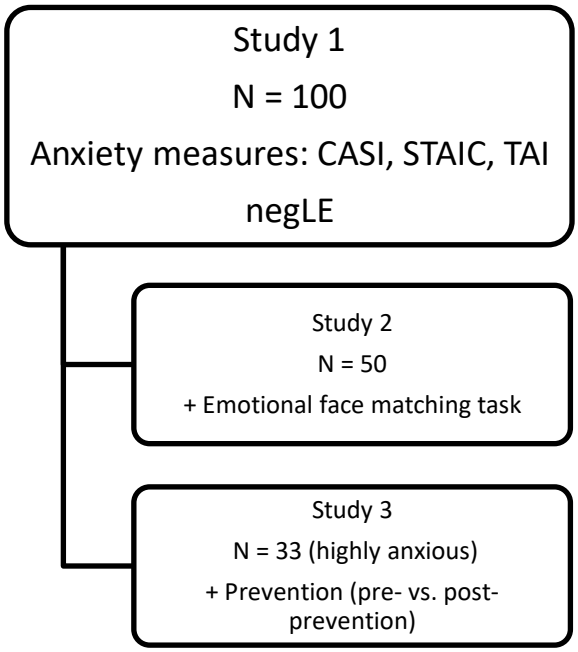

Figure 1: Connection and addition of the three studies

In this first chapter, the theoretical context of anxiety disorders and anxiety measures, their neuronal underpinning and results from prevention programs have been reported. Additionally, a brief summary and update about the state of research has been provided and the general aims, and hypotheses of the thesis have been given. The second chapter is providing information about study 1. Here the aim was to evaluate the interaction and connection of the three anxiety measures (State Anxiety, Anxiety Sensitivity and Separation Anxiety). In the third chapter, study 2 will be described, here anxiety-specific brain activation patterns in association with the anxiety measures were analyzed and in the fourth chapter study 3, concerned with the effect of a selective preventive program is presented. Finally, in the fifth chapter, findings are summarized and discussed.

To evaluate the assumptions and hypothesis (1) non-parametric correlation coefficients, (2) multiple regressions and (3) mediation- and moderation analyses were used. Furthermore, the sample in studies 2 and 3 were subsamples of study 1 (overlap between samples 2 and 3: n = 4).

1.6 Aims and Hypotheses

The superordinate aim of the present dissertation was to aid in a better understanding of the interaction of subclinical risk markers, in this case Trait Anxiety, Anxiety Sensitivity and Separation Anxiety as well as negative life events in children and adolescents. The precise aims were:

1) further the understanding of the exact interaction between STAIC, CASI and TAI and their association, in combination with negLE, in a healthy developing population.
2) examine the influence of these anxious phenotypes on neural processing during an emotional face matching task and clarify the influence of brain activation on the found associations between anxiety measures.
3) probe the ability of a prevention program to target these anxiety measures in a high-risk population.

Three studies were conducted to evaluate and analyse the hypotheses, each study answered specific questions contributing to the superordinate aims listed above (for a summary see **figure 2**).

In the first experiment the anxiety measures were assessed in a sample of healthy children and adolescence.

1.1 We assumed high positive correlations between STAIC, CASI and TAI, based on the reported correlations between CASI and STAIC in adolescents (Chorpita, Albano, & Barlow, 1996) and the close association between SAD (as represented by TAI) and PD (as represented by CASI) in clinical samples (Battaglia et al., 2014). We assumed that these associations could be established on a dimensional level in our healthy sample of children and adolescents, as well.
1.2 A close association between all anxiety measures and negLE was assumed, meaning that anxiety scores should be positively correlated with negLE. This hypothesis was based on the assumption that negLE play a role in the development of anxiety disorders and patients with anxiety disorders report higher negLE (Allen et al., 2008). Furthermore, an association between higher negLE and Trait Anxiety (Handa et al., 2008) in patients and Anxiety Sensitivity in adolescents (McLaughlin & Hatzenbuehler, 2009) has been reported.
1.3 After testing hypothesis 1.1 and 1.2 and establishing associations between anxiety measures as well as between anxiety measures and negLE, we assumed that negLE would explain additional variance in the association between anxiety traits. We used this approach as a means of model generation for the following (explorative) analyses and tested for all possible models.
1.4 Also explorative in nature, we assumed that if negLE explained additional variance in anxiety measures, they function as moderators or mediators in those models. Since we established the specific association in hypothesis 1.3 we assumed that negLE only function as mediator or moderator in those models that revealed significance in step 1.3.

In the second experiment the effect of anxiety measures on the neural activation during emotional processing was ascertained in healthy and normally developing children and adolescents using fMRI in an "emotional face matching paradigm" (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002).

2.1 Following on results in a variety of samples, we assumed that the "emotional face matching task" should elicit a response in a fronto-limbic network consisting of the amygdala, ventral striatum and the ventral prefrontal cortex as indicated by different research groups as key components of emotional processing (Hariri et al., 2002; Monk, 2008).

Further assumptions were that higher anxiety scores elicited anxiety specific responses in limbic and frontal regions, similar to results from under-aged anxiety patient samples.

2.2 We assumed higher limbic (i. e. amygdala) activation to be associated with higher anxiety scores, since research indicates that adolescents with anxiety disorders, show heightened amygdala response to emotional faces (McClure et al., 2007; K. M. Thomas et al., 2001; van den Bulk et al., 2014) and amygdala activation has been implicated in a variety of anxiety disorders and is not anxiety disorder specific.

2.3 Additionally, a higher frontal activation with higher STAIC scores, was assumed, specifically in the vlPFC, since as greater vlPFC activation has been found in youth with GAD compared to controls (Monk et al., 2006).

2.4 Regarding CASI and TAI we assumed a positive association with higher vlPFC and/or dlPFC activation as well, since it is broadly accepted that the vlPFC and dlPFC are involved in downregulation of signals from limbic structures (Kalin et al., 2001; Monk, 2008) and emotional procession is disturbed in anxiety disorder.

2.5 Finally, we probed if these anxiety specific activation patterns and negLE functioned as moderators or mediators between the connection of anxiety measures in the models found via hypothesis 1.3.

In study three the selective preventive program "FRIENDS for Life" was conducted in a sample of highly anxious children and adolescents. Specific hypotheses were:

3.1 Significant reductions of all anxiety measures from pre- to post- assessment was assumed, since the "Friends for LIFE" program has been implicated in the effective reduction of anxiety symptoms (Briesch, Sanetti, & Briesch, 2010).

3.2 We further assumed that negLE would function as moderator of the connection between pre- and post- anxiety measures, with the group of individuals with higher negLE experienced, being associated with lower improvement by the prevention program. This analysis is based on

studies indicating an effect of life events on therapy outcomes in some internalizing psychiatric disorders (Birmaher et al., 2000; Blackshaw, Evans, & Cooper, 2018; Valdez, Mills, Barrueco, Leis, & Riley, 2011).

3.3 We further tested if changes in one anxiety dimension had an influence in other dimensions. This analysis was explorative in nature and was in close association to the results found from hypothesis 1.3. Thus, we tested for a predictive effect of one anxiety dimension to another according to our models established there.

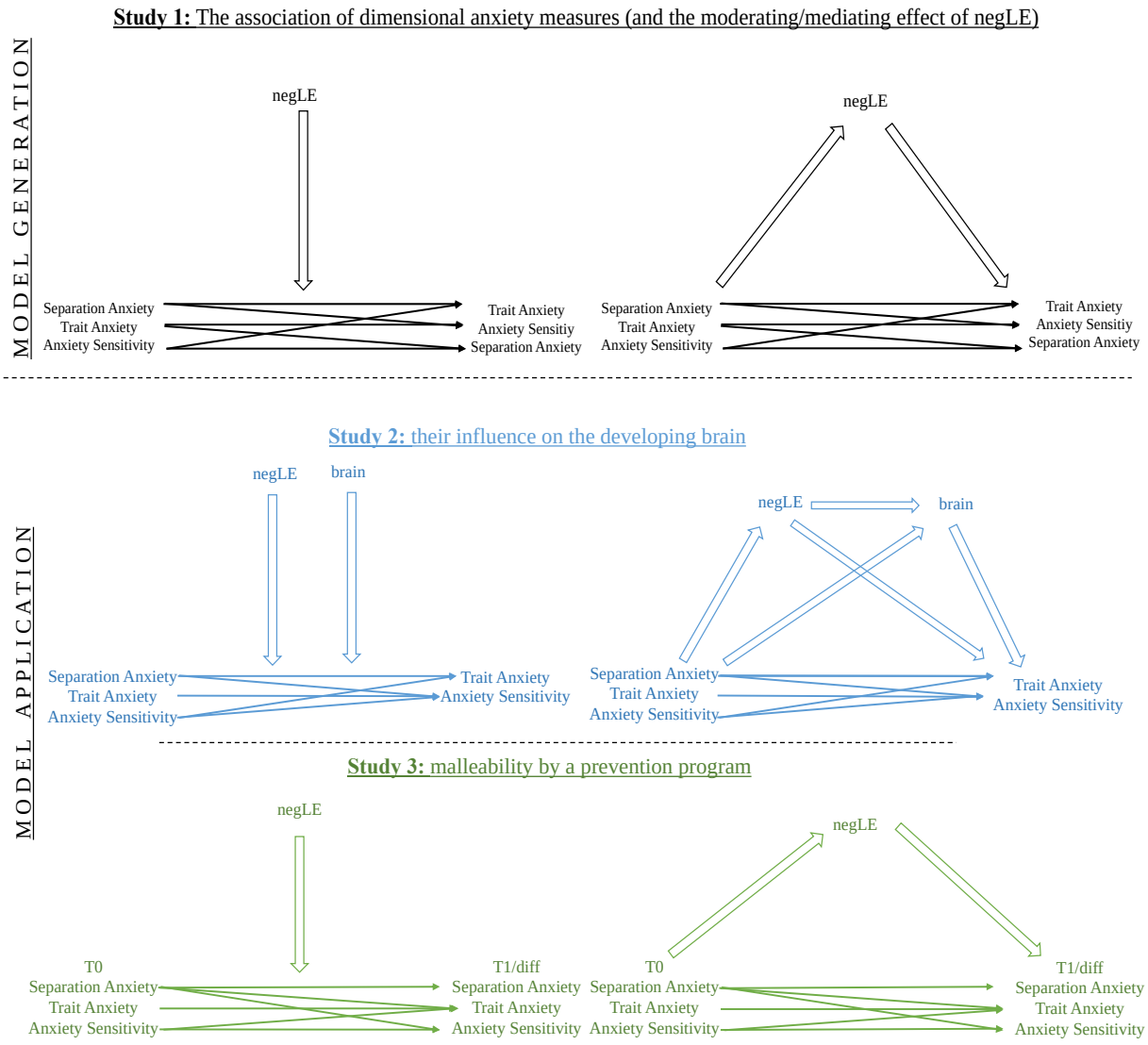

Figure 2: Models tested in this dissertation, sorted by study. While study 1 is used as model generating element, study 2 and 3 are used for testing.

2. Study 1: The interaction of Trait Anxiety, Anxiety Sensitivity, Separation Anxiety in a sample of healthy children and adolescents

2.1 Introduction: *Association of anxiety measures*

The anxiety measures of Trait Anxiety, Anxiety Sensitivity and, to a lesser extend Separation Anxiety, are widely used measurements that assess different aspects or "forms" of anxiety. The interaction between these measures has not been extensively studied in children and adolescents, despite their wide application in clinical as well as research settings (Muris, Schmidt, Merckelbach, & Schouten, 2001). A study in children and adolescents with anxiety disorders indicated that CASI and STAIC were highly correlated and that CASI predicted STAIC above physiological worry, but only in the adolescent age group (Chorpita et al., 1996). A different group of researchers replicated these results, but could not find a difference in age groups (Weems, Hammond-Laurence, Silverman, & Ginsburg, 1998). Furthermore a group of researchers from the Netherlands showed that CASI and STAIC were highly correlated in a group of healthy Dutch adolescents (age 13 - 16) (Muris et al., 2001). Thus, CASI and STAIC are thought to represent closely connected constructs (Muris et al., 2001). In adults, some research groups indicated that Trait Anxiety and Anxiety Sensitivity are close connected but different constructs (Taylor, 1995) and others have claimed that Anxiety Sensitivity might be a "subfactor" of Trait Anxiety (S. O. Lilienfeld, Jacob, & Turner, 1989; S. O. Lilienfeld, Turner, S. M., Jacob, R. G., 1993). Regarding the relationship between Anxiety Sensitivity and Separation Anxiety, the majority of evidence stems from clinical population to date (Silove et al., 2015). That is, SAD and PD are thought to represent a developmental trajectory (Battaglia et al., 2014) and SAD is handled as a specific risk factor for the development of PD later in life (Hannesdottir et al., 2018). If these associations can be found in a healthy group of children and adolescents and on a dimensional level (correlations with traits in contrast to group comparisons patients vs. controls) is of interest in this thesis. To our knowledge no study has examined the relationship between Separation Anxiety and Trait Anxiety to date. From the conceptual proximity of the constructs, it can be assumed that they are connected since they measure different "forms" of anxiety, that should be associated, but to our knowledge no study has looked into this association, yet.

In this study, we addressed the relation between the three anxiety measures. Since negLE are treated as a developmental risk factor for anxiety disorders (Allen et al., 2008; Chorpita & Barlow, 1998) and life events have been associated with increases in Anxiety Sensitivity (McLaughlin & Hatzenbuehler, 2009; Scher & Stein, 2003) we further tested if negLE were

associated with the three anxiety measures we assessed. Furthermore, we tested, via multiple regression, mediation and moderation models, if negLE functioned as a causal association between measures or if the association between measures was dependable on the "dose" of negLE with mediation and moderation models.

2.2 Material and Methods

2.2.1 Sample

A total of 100 children and adolescents (females: 52; mean age = 11.2, SD = 1.9 between 8 and 15 years) were recruited within the greater Würzburg area (Germany) as part of the Collaborative Research Center SFB-TRR-58 funded by the German Research Foundation (DFG). (For descriptive characteristics of the sample see **table A 1**). We obtained the approval from education authorities to address school principals to inform them about our research and to hand in flyers and information material to the students. We informed schools and parents, by handing out flyers and information leaflets of the study. Volunteers were screened for exclusion criteria by means of a telephone interview, acquiring information about exclusion as well as inclusion criteria. Inclusion criteria were: Caucasian descent, average intelligence (IQ < 85), ascertained by the German Culture Fair Intelligence Test 2 (Weiss, 2006) and fluency in German. Exclusion criteria were lifetime or current as well as family history of psychiatric or neurological disorders and intake of psychoactive medication. On the day of the investigation, the participants as well as their parents/legal guardians underwent a clinical diagnostic interview, the German version of the Diagnostic Interview for Mental Disorders for Children and Adolescents to confirm the absence of a psychiatric diagnosis *Kinder-DIPS;* (Schneider, Unnewehr, & Margraf, 2009). Participants underwent an intensive clinical and neuropsychological assessment comprising of the trait version of the STAIC (Unnewehr et al., 1992), CASI (Schneider & Hensdiek, 1994), TAI (In-Albon & Schneider, 2011) and the ZLEL (Steinhausen & Winkler-Metzke, 2001).

Normal physical development was assessed using the Tanner stages (Marshall & Tanner, 1969, 1970) and questioning parents and children about pubertal (i.e., menarche, pubic hair growth or voice change) and developmental landmarks. Participants as well as their parents/legal guardians gave written informed consent for the participation in the experiments prior to testing. The participants received a financial compensation for the participation (€50). All procedures of the study were in accordance with the Declaration of Helsinki in its latest version and the medical ethics committee of the University of Würzburg (139/15; 239/15).

2.2.2 Statistical Analyses

Data were analyzed using SPSS version 26 (SPSS Inc, Chicago, Illinois, USA). Variance, standard deviation, mean, skewness and kurtosis were calculated for all data. All results are reported with correction for multiple testing by the procedure of Benjamini and Hochberg (1995). Furthermore, *a priori* sex differences were calculated. Because homogeneity of variance could be assumed, but several variables were not normally distributed within the groups, differences between sexes were calculated with Mann-Whitney-U-test (Field, 2013).

Correlation coefficients were analyzed for the intercorrelation of all three anxiety measures and negLE. Since several variables were significantly non normal distributed, the association between STAIC, CASI, TAI, and negLE were explored using Spearman's correlation coefficient (Field, 2013).

The assumptions for multiple regression as well as mediation and moderation were tested. Here the Kolmogorov-Smirnov test gilded significant results. After exclusion of two outliers the hypothesis of normal distribution of residuals was met for most residuals, for the models with the dependent variable TAI, residuals were normally distributed with a natural logarithmic transformation plus addition of a constant (+1). (For all details of statistical assumption testing please see **tables A2 - A6**). The multiple regression models were analyzed using a stepwise inclusion of independent variables. Concerning the regression models, 6 models were evaluated with all three anxiety measures as independent and dependent variable and with negLE as second predictor variable. To answer the causal condition and causal process behind the found connection, 3 mediation and moderation analyses with the moderator/mediator negLE were performed, based on significant result from multiple regression models. Moderation models answer the question when and under which conditions the observed effect occurred, while mediation models answer the question as to how or why this effect occurs. The mediation and moderation analyses were explored using PROCESS software by Hayes for SPSS (A. Hayes, 2017; A. F. Hayes, 2012).

2.3 Results Anxiety Phenotypes

In the sample the average age was 11.23 (SD = 1.89; 54 females) and the mean developmental stage was 1.85 (SD = 1.87) as expected in this age group. The average IQ was 109.23 (SD = 15.76) and anxiety measures STAIC, CASI, TAI and negLE had a mean and standard deviation as follows: (M_{STAIC} = 30.26, SD = 7.08; M_{CASI} = 26.36, SD = 5.49; M_{TAI} = 6.67, SD = 7.76; M_{negLE} = 6.88, SD = 5.90) (for further details of the sample characteristics see **table A1**). The results of the Mann-Whitney-U-test yielded no significant difference between

male and female subjects, after correction for multiple testing (see **table A4**). Furthermore, there were no significant correlations with age (see **table 1**).

Correlation analyses revealed significant positive correlations between all three anxiety measures, with the highest correlation between STAIC and CASI (r_s = .72, p < .03). CASI as well as STAIC were significantly positive correlated with TAI ($r_{s\ CASI}$ = .44; p < .03; $r_{s\ STAIC}$ = .33; p < .03) and with negLE ($r_{s\ STAIC}$ = .40, p < .03; $r_{s\ CASI}$ = .35, p < .03) (for details see **table 1**).

Table 1: Spearman's correlation coefficient of anxiety measures and negative life events

Variable	Age	STAIC	CASI	TAI	negLE
Age	1	.02	.05	-.10	.05
STAIC		1	.72*	.33*	.40*
CASI			1	.44*	.35*
TAI				1	.11
negLE					1

Note: STAIC: Trait scale of the State/Trait Inventory for Children, CASI: Children's' Anxiety Sensitivity Index, TAI: Child questionnaire of the German Trennungsangst Inventory; negLE: Negative life events of the German Zürcher Life-Event List. For the total sample (n = 100) a correction was performed resulting in a corrected p threshold of q* = .03 (*p < q* (Benjamini & Hochberg, 1995)), * = q.

A multiple linear regression was calculated to predict STAIC based on CASI and negLE. A significant regression equation was found (F2,92) = 83.25, p < .00), with R^2 = 0.64. In this case CASI accounted for 63% of the variation in STAIC scores and negLE for only 1% in variation. This means, that an increase of CASI scores by 1, will result in an increase of STAIC scores by 0.92, while an increase of negLE by 1, will result in an increase of 0.16 in STAIC scores. When STAIC was predicted based on TAI scores and negLE, a significant regression equation was found (F2,92) = 19.24, p < .00) with R^2 = 0.23. Both TAI and negLE were significant predictors. In this case TAI accounted for 15% of the variation and negLE for 8% in variation in STAIC scores. An increase of TAI scores by 1, will result in an increase of STAIC scores by 0.26, while an increase of negLE by 1, will result in an increase of 0.34 in STAIC scores. When CASI was predicted, by TAI and negLE both were significant predictors (R^2 = 0.34), with the significant regression equation (F2,92) = 32.95, p < .00). TAI scores explained 27 % in variation of CASI scores and negLE 8 %, an increase in TAI scores by 1 will result in an increase of CASI scores by 0.32 and an increase of negLE by 1, will result in an increase of CASI scores by 0.24 (all significant regression models can be found in **table 2**). No model with TAI as dependent or STAIC as independent variable was significant in combination with negLE (please see **tables A7** and **A8**).

Table 2: Significant regression models of study 1

CASI and negLE on the dependent variable **STAIC**						TAI and negLE on the dependent variable **STAIC**						TAI and negLE on the dependent variable **CASI**					
	R^2	**b**	**SE B**	**Beta**	**p**		**R^2**	**b**	**SE B**	**Beta**	**p**		**R^2**	**b**	**SE B**	**Beta**	**p**
Step 1						**Step 1**						**Step 1**					
Constant	0.63	4.26	2.11		.05	Constant	0.15	27.34	0.79		.00*	Constant	0.27	23.79	0.60		.00*
CASI		0.98	0.08	.79	.00*	TAI		0.31	0.08	.38	.00*	TAI		0.35	0.06	.52	.00*
Step 2						**Step 2**						**Step 2**					
Constant	0.64	4.65	2.07		.03*	Constant	0.23	22.53	0.96		.00*	Constant	0.34	22.52	0.74		.00*
CASI		0.92	0.08	.74	.00*	TAI		0.26	0.08	.32	.00*	TAI		0.32	0.06	.47	.00*
negLE		0.16	0.08	.14	.03*	negLE		0.34	0.11	.30	.00*	negLE		0.24	0.09	.26	.01*

Regression models for the corrected sample (N = 98). A correction was performed resulting in a corrected p threshold of q* = .04 (*p < q* (Benjamin and Hochberg, 1995)); * = q.

Furthermore, 3 mediation and moderation analyses were performed, respectively and one of the mediation models reached significance. Here negLE significantly partially mediated the association between CASI and STAIC. The indirect effect was computed for each of 5000 bootstrapped samples and the 95 % confidence interval ranged from .00 to .14 and accounted for 6% of the total effect (see **table 3**. For all others see **tables A9** and **A10**).

Table 3: Mediation model of the effect of CASI on STAIC by negLE

	Coefficient (b)	**SE B**	**p**	**BC bootstrap 95% CI[a]**	
				Lower	Upper
Total effect of CASI on **STAIC**	0.93	0.09	.00*	0.75	1.12
Model R^2	.64		.00*		
F	101.58				
Direct effect of CASI on STAIC	0.92	0.08	.00*	0.76	1.08
Effect of CASI on negLE	0.36	0.11	.00*	0.14	0.57
Effect of negLE on STAIC	0.16	0.08	.03*	0.02	0.31
Indirect effect of CASI on STAIC through negLE	0.06	0.04		0.00*	0.14*

Significant partial mediation of the effect of CASI on STAIC via negLE, with a = 5000 bootstraps; * = sig.

2.4 Discussion

Study 1 investigated the association of STAIC, CASI and TAI and negLE in healthy children and adolescents. In line with our hypothesis, CASI and STAIC were highly correlated, while the correlation coefficient of STAIC and TAI as well as TAI and CASI were lower. Thus, based on the explained variance, our results showed, that STAIC and CASI were closer related, than TAI and STAIC and likewise TAI and CASI were more closely related than TAI and STAIC. This highlights that the three anxiety measures are assessing very close concepts, but that specifically STAIC and CASI are closely associated and TAI and CASI share a special connection. This is in line with results indicating, that STAIC and CASI are close related constructs (Muris et al., 2001; Olatunji & Wolitzky-Taylor, 2009) and is further in line with results from clinical populations that are proclaiming a SAD-PD-trajectory (Battaglia et al., 2014; Hannesdottir et al., 2018). Furthermore, in accordance with our assumption CASI and STAIC were positively correlated with negLE experienced, indicating that higher anxiety scores were associated with more negLE reported. This is mirroring results from psychotherapy

research, where stressful life events are seen as contribution to the development of psychiatric disorders (Allen et al., 2008; Chorpita & Barlow, 1998). Interestingly in our sample a similar association was found, highlighting a dimensional association even in typically developing children and adolescents.

To further assess the connection between the anxiety measures, regression and mediation as well as moderation analyses were performed. CASI as well as TAI in combination with negLE did significantly predict STAIC scores. Thus, CASI and TAI, in combination with negLE were contributing to an overall higher STAIC. CASI had a substantial connection, but the influence of negLE was small. On the other hand, TAI only had a small influence on STAIC, but the influence of negLE was more pronounced. These results seem to underline the implication for the STAIC as a global anxiety measurement, that is assessing the overall anxiety in a more general manner as indicated by some research groups (Muris et al., 2001; Olatunji & Wolitzky-Taylor, 2009; Taylor, 1995; Taylor & Cox, 1998). The results were further specified by a mediation model, where negLE functioned as a mediator between CASI and STAIC scores, indicating that at least a part of the connection of CASI and STAIC is explained by the amount of negLE experienced. In this example higher STAIC scores were occurring because children reported higher CASI scores and did experience higher negLE. In this case a partial mediation occurred, were the direct connection between CASI and STAIC was still significant and only a small part of the connection was explained by negLE. This is in close connection to the diathesis-stress-model of anxiety disorders (Belsky & Pluess, 2009; Zuckerman, 1999), where a certain vulnerability, in this case CASI and negLE are contributing to a certain phenotype, in this case Trait Anxiety.

Regarding the relation between TAI and CASI a regression model reached significance: In this model, TAI in combination with negLE significantly predicted CASI. Here negLE accounted for 8% in variability in CASI, while 27 % were explained by TAI. This is a further implication for the close connection between SAD in childhood and PD in adults (Battaglia et al., 2014; Hannesdottir et al., 2018; Silove et al., 2015). Our results seem to mimic this connection in our healthy sample.

In sum, we identified two major connections, the close relation between Trait Anxiety and Anxiety Sensitivity as well as the Anxiety Sensitivity and Separation Anxiety, both interrelated by negLE.

3. Study 2: The influences of Trait Anxiety, Anxiety Sensitivity, Separation Anxiety on emotional faces processing in a healthy population of children and adolescents

3.1. Introduction*: Neural underpinnings of emotional processing in anxiety*

It is widely accepted that patients with an anxiety disorder display heightened amygdala activation compared to healthy individuals when confronted with emotional faces or threatening situations (Birbaumer et al., 1998; Phan, Fitzgerald, Nathan, & Tancer, 2006; Shin et al., 2005; Stein et al., 2002). In adolescents with anxiety disorders, research indicates a heightened amygdala response to fearful as well as angry faces (McClure et al., 2007; K. M. Thomas et al., 2001; van den Bulk et al., 2014). This activation pattern seems to be dependent on symptom severity, as self- reported anxiety levels correlated with the amygdala activation in adolescents with anxiety disorders (K. M. Thomas et al., 2001; van den Bulk et al., 2014). This association could also been found in healthy anxiety prone students (high Trait Anxiety and high Anxiety Sensitivity) (Stein, Simmons, Feinstein, & Paulus, 2007) and children "at risk" (parents with social anxiety disorder diagnosis) (Christensen et al., 2015). Here subjects at high risk or anxiety prone subjects showed a significantly greater bilateral amygdala activation to emotional faces, than individuals scoring low in these measurements (Christensen et al., 2015; Stein et al., 2007).

Additionally, research suggests that frontal activation, especially activation of the vlPFC, is altered in individuals with anxiety disorders (Swartz & Monk, 2014). In adults the findings suggest a mechanism for anxiety disorder comprising of two stages (Lau et al., 2013): While the initial response to emotional stimuli, i.e. the limbic or amygdala response is too strong, the following modulation of the response (comprising of the prefrontal cortex response) is too weak (Lau et al., 2013; Li et al., 2020). However, this picture seems not to be clear cut in children and adolescents (Pine, Guyer, & Leibenluft, 2008). For example, greater vlPFC activation has been found in response to angry faces in youth with GAD compared to controls (Monk et al., 2006), but there was a negative association within the GAD group with symptom severity. Furthermore, children and adolescents with GAD showed a weaker amygdala and vlPFC connectivity (Monk, Telzer, et al., 2008) and a higher activation in ventral PFC regions as well as ACC regions compared to controls (McClure et al., 2007).

These results indicate that vlPFC activation might be modulating activity in limbic structures, such as the amygdala and might thus be indirectly related to symptom severity (Monk, 2008). In addition, children at a high risk for developing anxiety disorders, as assessed by parent anxiety (Christensen et al., 2015) or inhibited temperament (Clauss, Benningfield, Rao, & Blackford, 2016), showed heightened activation in other regions relevant for processing

and regulation of emotions such as the right MFG (dlPFC), hippocampus and ACC (Christensen et al., 2015). Furthermore, in addition to the altered activation of these regions in anxiety individuals, there also seems to be a reduced connectivity between these regions (Christensen et al., 2015; Clauss et al., 2016).

Based on the observation that temperamental factors predispose for anxiety disorders (Chambers et al., 2004; Schmidt et al., 2010) and that emotional face processing is disturbed in individuals with anxiety disorders (McClure et al., 2007; Phan et al., 2006; Swartz & Monk, 2014) association between these factors are highly interesting. We assessed whether fronto-limbic activation during emotional processing could be defined as a biomarker in dependence of our outcome variables (STAIC, CASI, TAI) and if we could find a neuronal manifestation of the association between the anxiety measures, we found in study 1.

3.2 Material and Methods

3.2.1 Sample

A total of 50 typically developing children and adolescents between the age of 8 and 15 years (19 females; mean age = 11.3, SD = 1.6) participated in the study. Two children cancelled the experiment during scanning procedures. Thus, a total of 48 children (18 females; mean age = 11.4, SD = 1.5, between 8 and 15 years) were included in the study. Descriptive characteristics are given in the **table A 11**. All participants were a subsample of the in study 1 described sample, thus recruitment was the same as described earlier. Participants as well as their parents/legal guardian gave written informed consent for the participation in the experiment prior to testing. The participants received a financial compensation (€50) for the participation and an experienced radiologist reviewed all anatomical scans to rule out abnormal neurological development or abnormality. All procedures of this study were in accordance with the Declaration of Helsinki in its latest version and the medical ethics committee of the University of Würzburg (139/15; 239/15). A part of the data presented here has been published under a different research question in a research article in *European Child and Adolescent Psychiatry* (Kneer et al., 2020).

3.2.2 Task

We administered the "emotional face matching task" by Hariri and colleagues (Hariri et al., 2002). Participants were asked to match a target stimulus presented in the upper row of the screen (i.e., an emotional face or a geometric shape) with one of two stimuli presented in the lower row of the screen (for an exemplary stimulus see **figure 3**).

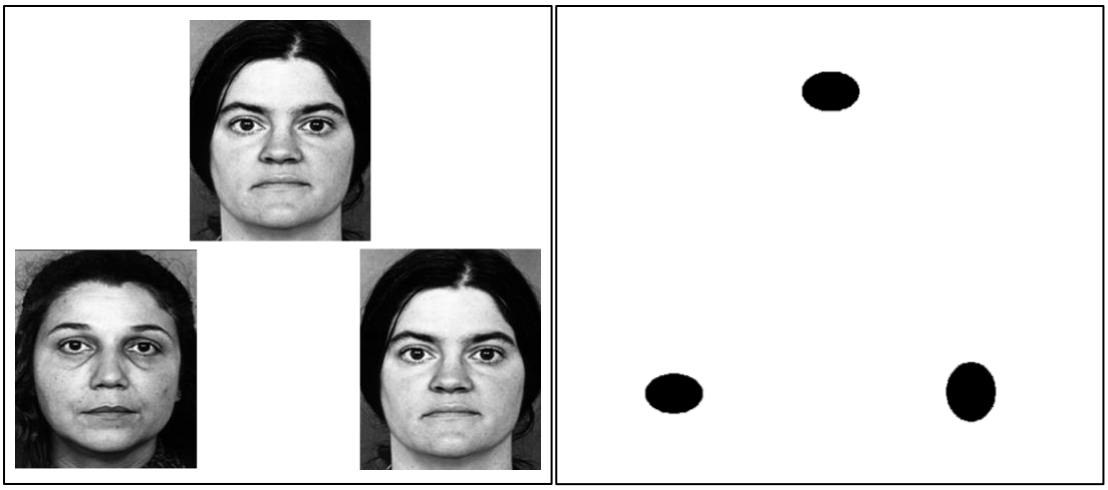

Figure 3: Representation of the emotional face matching paradigm; example for a face matching condition (left) and shape matching condition (right)

Participants indicated which shape or form in the lower row was the same as the one presented at the upper by pressing a button with their index finger, either with the right or the left hand, depending on the location of their answer (right or left stimulus in the lower row). This task was presented as a block design with five shape matching blocks interleaved by four emotional face matching blocks. Each block started with an introduction (2s) announcing the condition (shape vs. face) and blocks consisted of six trials respectively, with a trial duration of 2.9s. Trials started with a 400ms stimulus presentation, followed by a response time of 2.5s and inter-trial intervals varied between 1.5s and 5.5s. In total, the task consisted of 9 blocks with inter-block intervals and lasted 6.2min. Participants completed a training prior to scanning, to insure the understanding of the instructions. Shape blocks lasted for 24s and face blocks for 18s, and consisted of six trials respectively, represented for 2s each.

3.2.3 MRI data acquisition

Scanning was performed on a 3 Tesla TIM Trio Scanner (Siemens, Erlangen, Germany), equipped with a 12-channel head coil. Whole-brain T2*-weighted Blood-Oxygen-Level-Dependent (BOLD) images were recorded with a gradient echo-planar imaging (EPI) sequence (repetition time (TR) = 2000ms, echo time (TE) = 30ms, 33 slices, 3mm thickness, field of view (FoV) = 192mm, flip angle 90°, 187 volumes). Anatomical images were obtained, using isotropic high-resolution T1-weighted 3D structural MR images (sMRI) (magnetization prepared rapid gradient echo (MPRAGE): 176 sagittal slices, TR = 2300ms, TE = 2.95ms, FoV = 270mm, flip angle 9°, slice thickness 1.20mm).

3.2.4 MRI data processing

MRI Data processing was performed using the Statistical Parametric Mapping Software Package (SPM12, Wellcome Department of Imaging Neuroscience, London, UK, Wellcome

Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). All functional images were realigned to the first functional volume and unwarped. Images were spatially normalization into a standard stereotactic space (Montreal Neurological Institute, MNI), resampled to isotropic 2x2x2 mm^3 voxel size and smoothed with a Gaussian kernel of 8mm FWHM (full width at half maximum). Statistical analysis on the individual first level was based on the general linear model (GLM) approach. Experimental conditions within the model specification were defined as "faces" and "shapes". For each condition, block onset times were determined when instruction was presented on the screen. Next to the experimental conditions, "realignment parameters" (six regressors containing movement in three spatial and three rotational axes) were specified as nuisance regressors. To identify brain activation associated with emotional face matching, the contrast of interest was defined as "face > shapes" on single subject level, to identify brain activation associated with emotional face matching.

3.2.5 Statistical analyses

3.2.5.1 Behavioral Data and Anxiety Phenotypes

Data were analyzed using SPSS version 26 (SPSS Inc, Chicago, Illinois, USA). The described workflow from study 1 for correlation analyses and *a priori* sex differences was followed (for details of assumption testing please see **tables A 12 - A 15** and **A17**).

3.2.5.2 fMRI Data

A one sample t-test was performed using the contrast image "faces>shapes" to assess the activated brain network during emotional face matching. Furthermore, to identify the distinct influence of STAIC, CASI and TAI, multiple regression analyses were performed. In this case STAIC, CASI, TAI were defined as independent factors.

After the identification of regions involved during emotional processing and dimension-specific activation, contrast estimates were extracted from the local maxima (see 3.4.2), mediation and moderation analyses were performed to reveal the interaction between brain activation and STAIC and CASI and TAI. As independent and dependent factor we defined anxiety measures as described in the workflow from study 1. However, in addition to negLE as mediator/moderator variable, anxiety specific activation scores entered analyses, thus in all of these models mediating and/or moderating variables were negLE and frontal brain activation (i.e., anxiety specific contrast estimates of significantly activated clusters).

Across all fMRI analyses region of interest (ROI)-based analyses were performed focusing on brain regions in the fronto-limbic network associated with emotional processing [using masks of the AAL atlas (Automated Anatomical labeling, Tzourio-Mazoyer et al., 2002), Frontal_Mid_L/R, Front_Mid_orb_L/R, Front_Inf_oper_L/R, Front_Inf_otri_L/R,

Front_Inf_orb_L/R, Front_Med_orb_L/R, Hippocampus_L/R and Amygdala_L/R as implemented in the Wake Forest University PICKATLAS toolbox (http://www.fmri.wfubmc.edu)]. All results were reported when they passed the $p < 0.05$ threshold corrected for multiple comparisons on voxel level using FDR (Benjamini & Hochberg, 1995).

3.3 Results

3.3.1 Behavioral Data and Anxiety Phenotypes

In the sample the average age was 11.42 (SD = 1.55) and the mean developmental stage was 2.13 (SD = 0.88). The average IQ was 110.45 (SD = 13.89). Anxiety measures and negLE showed mean and standard deviations as follows (M_{STAIC} = 28.08, SD = 6.36; M_{CASI} = 24.72, SD = 5.15; M_{TAI} = 6.21, SD = 8.41, M_{negLE} = 6.09, SD = 5.69). Behavioral measures had means and standard deviations as follows ($M_{accuracy\_overall}$ = 95.62, SD = 7.17; $M_{accuracy\_faceMatch}$ = 98.37, SD = 2.84; $M_{Reactiontime\_overall}$ = 1211.79, SD = 360.13, $M_{reaction\_faceMatch}$ = 1297.86, SD = 360.13) (For further sample description see **table A 10**).

The results of the Mann-Whitney-U-test test yielded no significant difference between male and female subjects on behavioral or anxiety measures (see **table A 13**). For the behavioral data age was significantly negatively correlated with overall reaction time (r_s = -.45, $p_{corr} < .05$). There were no further significant correlations with age. Anxiety measures did not influence any behavioral parameters.

Correlation analyses revealed a significant positive correlation between all three anxiety measures. With a high intercorrelation between STAIC and CASI (r_s = .60, $p_{corr} < .05$). Both measures were significantly positive correlated with TAI ($r_{s\ CASI}$ = .47, $p_{corr} < .05$; $r_{s\ STAIC}$ = .45, $p_{corr} < .05$). There were no significant correlations between anxiety measures and negLE. (Further correlation coefficients can be found in **table A16**).

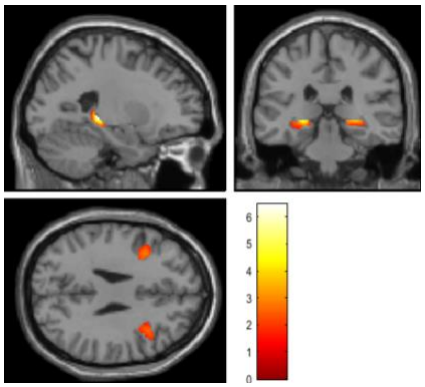

Figure 4: Clusters illustrating statistical maps of significant during emotional face processing

Result were corrected for multiple testing using FDR on voxel level (Benjamini & Hochberg, 1995).

3.3.2 fMRI Data

The one-sample t-test for the contrast "faces > shapes" yielded significant results in the right and left hippocampus (HC, left: x = -24, y = -32, z = -2, $T_{(1,47)}$ = 6.2; right: x = 26; y = -30; z = -4; $T_{(1,47)}$ = 3.9), two cluster in the prefrontal cortex (left inferior frontal gyrus (IFG) pars orbitals; x = -34, y = 32, z = -8, $T_{(1,47)}$ = 3.6; right IFG pars triangularis x = 38, y = 16, z = 24; $T_{(1,47)}$

= 3.3) as well as in the right amygdala (x = 32, y = 4, z = -20; $T_{(1,47)}$ = 3.1) (results are depicted in **figure 4** and **table 4**).

3.3.2.1 Regions varying in function of anxiety measures

Multiple regression analyses revealed a positive correlation between STAIC and activation in the left IFG, pars triangularis (x = -38, y = 10, z = 22; $T_{(1,43)}$ = 3.3). Multiple regression analyses revealed no significant correlation with CASI scores and for the TAI negative correlations with a region in the left IFG, pars triangularis (x = - 36, y = 24, z = 14; $T_{(1,43)}$ = 3.2), the right MFG (x = 40, y = 36, z = 22; $T_{(1,43)}$ = 3.3) and the right IFG (x = 40, y = 36, z = 22; $T_{(1,43)}$ = 3.3) were found (results can be found in **table 4**). Furthermore, the respective activation in the lIFG, pars triangularis was dimension specific to STAIC and TAI as can be seen in **Figure 5**.

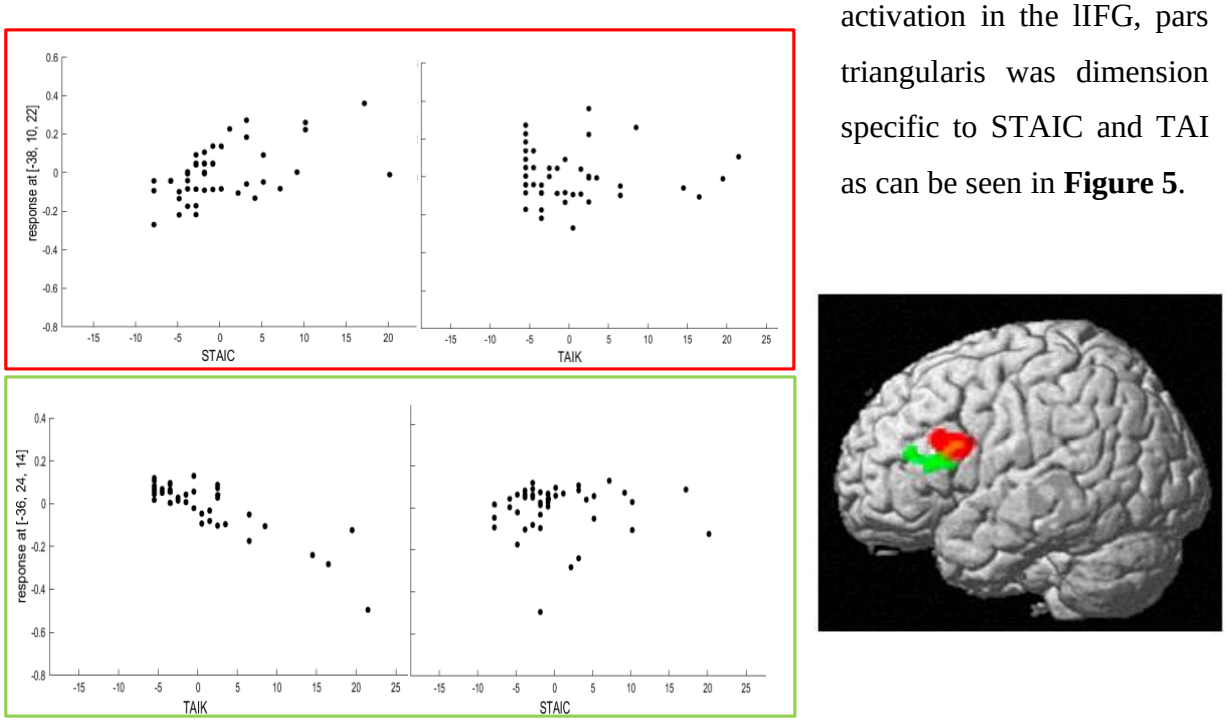

Figure 5: TAI and STAIC specific lIFG activation

Above left: Scatterplots indicating correlation of STAIC scores and activation in the lIFG (x = -38, y = 10, z = 22 and no correlation with TAI; Below left: Scatterplots indicating correlation of TAI scores and activation in the left lIFG (x = - 36, y = 24, z = 14). On the right, cluster illustrating the regions associated with STAIC (red) and TAI (green) in the lIFG; Abbreviation: TAIK: Children questionnaire of the German Trennungsangstinventar

Table 4: fMRI results

Contrast	X	Y	Z	T	regions
faces > shapes	-24	-32	-2	6.2	lHC
	26	-30	-4	3.9	rHC
	-34	32	-8	3.6	lIFG, pars orbitalis
	38	16	24	3.3	rIFG, pars triangularis
	32	4	-20	3.1	right amygdala
Dimension-specific					
$STAIC^+$	-38	10	22	3.3	lIFG, pars triangularis
$CASI^-$					n.s.
TAI^-	- 36	24	14	3.2	lIFG, pars triangularis
	40	36	22	3.3	rMFG
	38	24	14	3.3	rIFG, pars triangularis

After identification of brain regions associated with anxiety measures, mediation and moderation analyses were performed to address the underlying mechanisms and to assess

whether brain activation and negLE served as potential mediator or moderator between anxiety measures. Contrast estimates of the four anxiety-specific activations were extracted and entered mediation/moderation analysis. In addition, negLE were defined as a second mediating/moderating variable in every model as well. In total 8 models were defined as mediation and moderation:

(1) X = CASI, Y = STAIC, W = negLE, Z = STAIC_lIFG
(2) X = TAI, Y = CASI, W = negLE, Z = TAI_rIFG,
(3) X = TAI, Y = CASI, W = negLE, Z = TAI_lIFG,
(4) X = TAI, Y = CASI, W = negLE, Z = TAI_rMFG,
(5) X = TAI, Y = STAIC, W = negLE, Z = TAI_rIFG,
(6) X = TAI, Y = STAIC, W = negLE, Z = TAI_lIFG,
(7) X = TAI, Y = STAIC, W = negLE, Z = TAI_rMFG,
(8) X = TAI, Y = STAIC, W = negLE, Z = STAIC_lIFG,

Out of the 8 moderation models with functional brain activation and negLE as moderator, 2 reached significance. In one model on the influence of TAI on CASI, we found that TAI significantly predicted CASI ($T = 2.8$, $p_{corr} < .05$), and this relation was positively moderated by both, negLE and TAI-specific left IFG activation ($F_{TAI*negLE} = 9.5$, $p_{corr} < .05$; $F_{TAI*TAI\text{-}lIFG} = 24.8$, $p_{corr} < .05$, $F_{both} = 16.9$, $p_{corr} < .05$). The moderation effect was significant in medium to high numbers of negLE and medium to high activation strength. In low numbers of negLE and low activation as well as with medium number of negLE and low brain activation, the moderation effect was not significant (see **table 5** and **figure 6**). A similar moderation effect was found for the right-hemispheric TAI-specific IFG activation (see **table A19** and **figure 6**), however, in this case the direct association between TAI and CASI was not significant. (For all other models see tables **A18- A25**).

Table 5: Moderation model with X = TAI, Y = CASI, W = negLE, Z = TAI_rIFG

Model Summary						
R	R^2	MSE	F	df1	df2	p
0.78	0.60	11.8	9.4	5	42	.000
Model						
	coeff	Se	t	p	LLCI	ULCI
constant	22.87	0.97	23.6	.000*	20.91	24.83
TAI	0.20	0.12	1.6	.116	-0.05	0.44
negLE	0.01	0.12	0.1	.921	-0.23	0.26
Int_1	0.04	0.01	3.0	.004*	0.01	0.06
TAI_rIFG	-5.99	3.58	-1.7	.102	-13.22	1.25
Int_2	1.47	0.33	4.4	.000*	0.80	2.14
Test(s) of highest order unconditional interaction(s):						
		R^2-chng	F	df1	df2	p
TAI*negLE	X*W	0.13	9.2	1	42	.004*
TAI*TAI_rIFG	X*Z	0.16	19.6	1	42	.000*
	BOTH	0.23	9.8	2	42	.000*
Note: * indicating significant q* = .012 (*p < q* (Benjamin and Hochberg, 1995).						

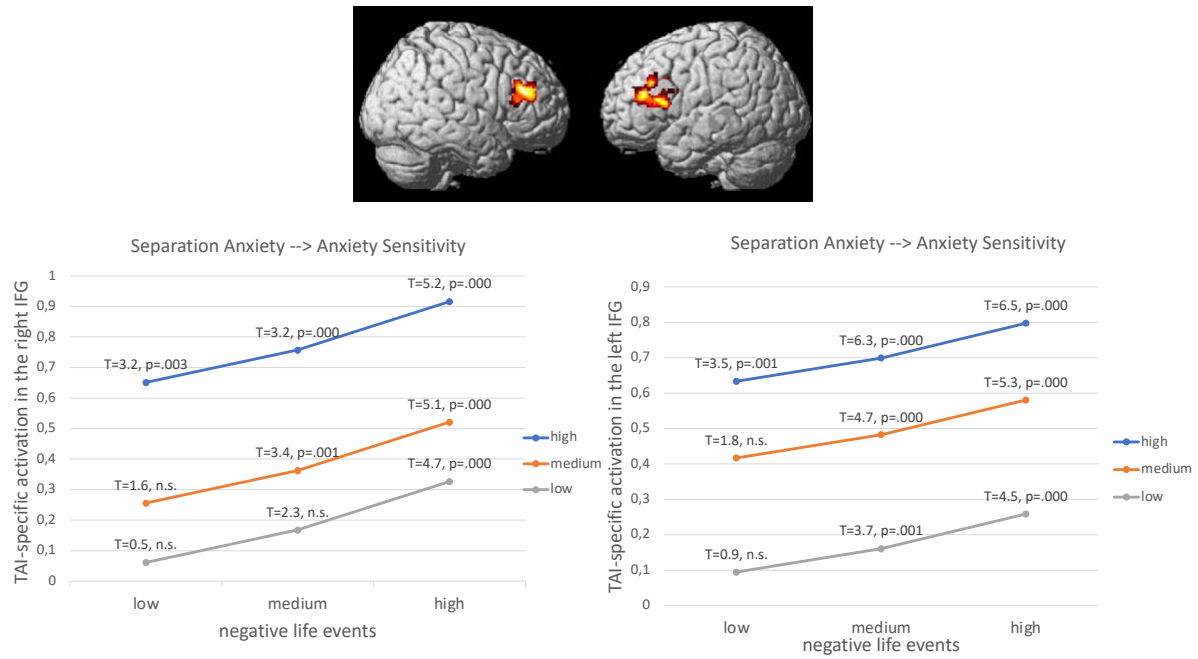

Figure 6: Significant moderation models on the influence of TAI on CASI by negLE and IFG activation

3.4 Discussion

Study 2 investigated the association of three anxiety measures in combination with brain functioning. The aim was to extend the findings from study 1 with a neurobiological measurement.

We assessed positive correlations of all three anxiety measures in this sample. NegLE were not associated with any anxiety dimensions. This was possibly the case, due to the subsample of children undergoing MRI measurements showing lower overall anxiety scores and the sample being substantially smaller than the one in study 1. Lower participation and anxiety scores might be due to the fact that participation in an MRI experiments is in itself a challenging situation, especially for children (Kada, Satinovic, Booth, & Miller, 2019). It can be assumed, that if MRI acquisition is not a medical emergency a higher portion of anxious individuals will not participate in that kind of experiment, since many children and adolescents need sedation to participate in a MRI procedure if it is a medical necessity (Netzke-Doyle, 2010). Thus, the participants should not be considered representative of a population as whole. A further explanation might be that the interplay between anxiety measures and negLE is only to be found within special groups. This could hint that negLE do play a role in the development of anxious phenotypes, but that their unique contribution to the interplay between phenotypes could be different in highly healthy in comparison to pathological groups. This speaks for a “dose-dependent” effect of negLE as found in anxiety disorder patients (Bremner et al., 1992; Copeland et al., 2007; Ganzel et al., 2013). Specifically, with a higher number of negLE

experienced, a more global burden of symptoms is experienced, and this might only show in those having experienced a certain number of events. If these results are due to sample size or pose a substantially different mechanism should be assessed in further research.

The association between brain functioning during the emotional face matching task and anxiety measures was assessed. The analysis of activation during the "Hariri Task" (Hariri et al., 2002) revealed that the task activated bilateral prefrontal regions in the vlPFC, namely the IFG as well as the HC bilaterally and the right amygdala. These results are in accordance with our expectations, that the "emotional face matching task" would elicit a response in fronto-limbic regions (Hariri et al., 2002). Specifically we found bilateral activation of regions in the vlPFC, which is involved in the amplification of emotional signals from limbic structures (Kalin et al., 2001; Monk, 2008) and activation of limbic structures, such as the amygdala as a key node of the emotion processing (Phan et al., 2004). Thus, the results found in adults could be replicated in our younger and healthy sample and seem to underline the implication of emotional processing as a process, where the vlPFC exhibits an inhibitory control over the amygdala, while the amygdala is relating information regarding the emotional significance (Swartz & Monk, 2014). Interestingly only the right amygdala was significantly activated during task performance, indicating a right lateralized use of limbic regions in our healthy underage sample. This is in line with a recently published study, where the right amygdala has been indicated as a neural correlate of "normal empathy" in a fMRI experience in boys (age 8-16 years) (von Polier et al., 2020). In this experiment healthy boys in comparison with boys with a conduct disorder showed higher right amygdala activation in response to emotional faces and higher empathic abilities were correlated with higher right amygdala activation (von Polier et al., 2020). Thus, we interpret the found right amygdala activation along those lines.

In a further step the effect of the three anxiety measures was assessed. In accordance with our hypothesis, STAIC was positive associated with a region in the lIFG. Thus, higher STAIC scores were associated with higher activation in vlPFC, mirroring results from a study done in GAD patients, were a greater vlPFC activation has been found in youth with GAD compared to controls (Monk et al., 2006). This might indicate a modulatory frontal activation of limbic structures, that Monk (2008) has interpreted as an indirectly measure of symptom severity (Monk, 2008). In the aforementioned study greater activation within the vlPFC was associated with a decrease in symptom severity, which the authors interpreted as compensatory response (Monk et al., 2006; Monk, Telzer, et al., 2008). Since the sample in the study were individuals with a GAD diagnosis and our sample was healthy, there might be a mechanism at play, where healthy highly anxious and "low" anxious anxiety patients use a compensatory frontal control,

comprising of a higher vlPFC activation. We could not find any CASI-specific fronto-limbic regions. This might be the case because of the high intercorrelation of CASI and STAIC and we corrected for STAIC in multiple regressions, thereby reducing variance. For TAI we could find three frontal regions that were negatively correlated with TAI scores, thus higher TAI scores were associated with a decreased activation in these areas. Thus, this frontal regions in the vlPFC and right MFG seem to be uniquely involved in the anxiety of separation from a primary caregiver. These results seem to indicate a dysfunctional top-down control in these specific frontal regions that are associated with Separation Anxiety. Nonetheless we hypothesized that we would find a positive association of TAI with these regions. However, the picture about frontal hyper- or hypoactivation in anxiety is not clear, since results from imaging studies have also found that patients with anxiety disorders or high anxiety measures in children and adults show decreased activation in PFC regions (Etkin & Schatzberg, 2011; Ionescu, Niciu, Mathews, Richards, & Zarate, 2013; Klumpp et al., 2018; Toazza et al., 2016; Waugh, Hamilton, Chen, Joormann, & Gotlib, 2012; Yin et al., 2017). Mirroring our results, a meta-analysis found reduced volume in the left IFG in different anxiety patients (Shang et al., 2014), which hints that these regions might be involved in the development of several anxiety symptoms. Similarly, previous research suggested that anxious individuals (GAD, SAD and social anxiety disorder) show reduced left amygdala-MFG connectivity compared to the healthy group during processing of fearful faces (Kujawa et al., 2016). Lower frontal activation could be due to ongoing maturation (Fair et al., 2009) or could be seen as the result of a dysfunctional top-down control because of higher anxiety severity, even in this healthy sample. In line with this result the specific hypoactivation of the right IFG has been implicated in a study with adult PD, where a stronger activation of the right IFG has been shown in healthy adults compared to patients, in an alerting network (Neufang et al., 2019). These are very interesting results, because this might indicate that the activation in the right IFG is specifically disrupted in PD/individuals with high Separation Anxiety as indicated by a hypoactivation. This in turn can be interpreted as a flawed top-down-control mechanism and can already be assessed in children and adolescences.

Furthermore, along those lines, from moderation analyses we learned that especially TAI and CASI were related, and that this relation was moderation by negLE as well as brain activation bilaterally in the IFG. This moderation was significant as soon as subjects had experienced medium to high number of negLE and activated the regions to a medium to high strength.

The left IFG was indicated in two of the three anxiety measures and thus seems to be of special interest for different anxiety types. These results are in line with results from a different study in pediatric anxiety disorder patients (among them patients with SAD, social phobia and GAD) (Strawn et al., 2015). Here individuals with an anxiety disorder exhibited less gray matter volume in a lIFG (Strawn et al., 2015).

Interestingly no specific amygdala activation was found for any anxiety measure. The amygdala is presented as the key node brain center for emotional processing and specifically pathological mechanisms are found to be at play in anxiety disorders (Phan et al., 2004; Phelps & LeDoux, 2005). Our results could stem from the fact the sample is comprised of a healthy population and there was no hyperactivity of limbic regions due to normal maturation. On the other hand there are studies showing mixed results for the amygdala activation in combination with anxiety measures, with some studies finding associations (Phan et al., 2006) while others did not (Killgore & Yurgelun-Todd, 2005; Monk et al., 2006; Pezawas et al., 2005). Furthermore, during adolescents, the sensitivity to social cues, such as faces is rapidly increasing and coinciding with changes in neural structures (Durand, Gallay, Seigneuric, Robichon, & Baudouin, 2007; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; L. A. Thomas, De Bellis, Graham, & LaBar, 2007). Research has indicated that during puberty amygdala activation to faces is amplified (Moore et al., 2012). Furthermore the amygdala might be a region in the brain that is directly influenced by hormonal changes, since it contains oestrogen and androgen receptors (Ferri et al., 2014) and the administration of sex hormones has been connected to increased amygdala reactivity to emotional faces (Bos, van Honk, Ramsey, Stein, & Hermans, 2013). Since most of our participants were not in puberty or only at an early stage, our results might be due to this young age group.

4. Study 3: Selective malleability of Trait Anxiety, Anxiety Sensitivity and Separation Anxiety via a preventive program in a group of children at high risk for the development of an anxiety disorder

4.1 Introduction: "FRIENDS for LIFE" as a prevention program for anxiety

The effectiveness of the "FRIENDS" program as a universal prevention program has been assessed in different studies (P. M. Barrett, 2017; Iizuka et al., 2013). The first study to evaluate the effectiveness of the program as a universal program to "prevent anxiety symptoms" was conducted by Barrett and Turner (2001). In this study the "FRIENDS" program was implemented in the standard classroom curriculum and either applied by trained teachers or psychologists, while the control group received no intervention, but the standard curriculum (P. Barrett & Turner, 2001). After prevention there was a significant reduction in anxiety symptoms in the two intervention groups compared to the control group (P. Barrett & Turner, 2001). These results gave initial evidence for the effectiveness of the "FRIENDS" program in reducing anxiety symptoms (P. Barrett & Turner, 2001). Research groups have since replicated and expanded results about the effectiveness of the program (G. A. Bernstein, Layne, Egan, & Tennison, 2005; Dadds, Spence, Holland, Barrett, & Laurens, 1997; Essau, Conradt, Sasagawa, & Ollendick, 2012; Iizuka et al., 2013). The effects of "FRIENDS" as a universal intervention have been replicated in e.g. Germany (Essau et al., 2012), South Africa (Mostert & Loxton, 2008), the United Kingdom (Stallard et al., 2005) and the Netherlands (Kosters et al., 2015).

The first study that looked at the effects of "FRIENDS" as an indicated school-based prevention of anxiety symptoms was conducted in 1997 (Dadds et al., 1997). 128 children were randomly assigned to either the program or a monitoring control group. Children receiving the program showed lower rates of anxiety disorders at follow-up and 6-months follow-up, compared to the monitoring control group. In the control group 54 % of children who showed some features of but did not meet all diagnostic criteria for an anxiety disorder at baseline showed a diagnosis of an anxiety disorder at 6-month follow up assessment, while this was true for 16 % of children who received the program. The results of this study indicate that the program is successful in reducing the prevalence of a full-blown anxiety disorder as well as preventing the manifestation of a disorder in children at risk (Dadds et al., 1997). These results were replicated in independent samples from different research groups, e.g. in the Netherlands (Kosters et al., 2015), Portugal (Pereira, Marques, Russo, Barros, & Barrett, 2014) and Scotland (Liddle & Macmillan, 2010).

The effectiveness of the "FRIENDS for LIFE" program as an indicated or universal prevention program has been assessed in a variety of studies, depicting a general positive effect

on anxiety markers (P. M. Barrett, 2017; Briesch et al., 2010). A review from 2010 (Briesch et al., 2010) which evaluated effectiveness revealed higher levels of efficacy for the indicated than for the universal intervention, while both groups yielded positive results (Briesch et al., 2010).

Concerning anxiety markers, it could be indicated that the application of CBT is reducing Anxiety Sensitivity in adult anxiety patients (Asnaani, Tyler, McCann, Brown, & Zang, 2020; Smits, Berry, Tart, & Powers, 2008). This suggests, together with results from a genetic twin-study in children and adolescents by Waszczuk and colleagues, that Anxiety Sensitivity not only is a developmental risk factor of anxiety disorders (Waszczuk et al., 2013) but also a CBT-based, target for prevention (Gardenswartz & Craske, 2001). Since the CASI scores of children and early adolescents (Schmidt et al., 2010) as well as adults (Sandin et al., 2015) predicts onset of anxiety disorders and is treated as a risk marker (Sandin et al., 2015; Schmidt et al., 2010), we used the CASI to select individuals at risk for developing an anxiety disorder. We then tested the selective effect of an indicated prevention program on CASI, STAIC as well as TAI scores in a high-risk sample of healthy subjects from age 8 to twelve. We furthermore tested for cross-over effects between anxiety measures, assessing if the models assessed in study 1 held predictive power. We applied the latest version of the FRIENDS for LIFE program for the first time in Germany in a shortened version (P. M. Barrett, 2017), in a group of children with a high CASI score and postulated a reduction in all of these three anxiety measures form pre- to post assessment.

4.2 Materials and Methods

4.2.1 Sample

For the recruitment of highly anxious individuals, we obtained the approval from education authorities to address school principals to inform them about our research and to hand out flyers and information material. We contacted 31 schools and were allowed to hand out approximately 5000 flyers and information leaflets of the study aim. 496 Volunteers contacted us, 142 via e-mail and 354 via telephone. Of those 279 were in the right age range (8-12) and did not indicate any exclusion criteria within first contact and were thus screened for exclusion criteria by means of a telephone interview (KK). We acquired information about exclusion as well as inclusion criteria (inclusion and exclusion criteria were as described above, since participant were a subsample of study 1). Afterwards we send out 112 consent forms to participants. Of those 25 participants declined participation, resulting in a sample of 87 highly anxious participant. After the first study inclusions and the randomization to control and prevention group it became clear that drop-out rates and no-shows on the second appointment, due to randomization into the control group were very high (8 out of 10). Due to this we had to

adjust the randomization process. Participants were offered a place in the prevention group and we started the recruitment of a matched control group. Still, we had 7 no-shows on the control group at the second appointment, even though we called the families in advance and send out reminder E-mails the previous day. Unfortunately, 23 participants (7 prevention group; 16 control group) cancelled participation later on, due to not being able to find the time, either due to extracurricular activities, the school workload, illness, or were not reachable anymore, even though we adjusted the application of the prevention to school holidays only and to a minimum group size of 2 and control group appointments were flexible in timing (for details of recruitment process see **figure 7**). Thus, recruitment resulted in a total of 33 typically developing children between the age of 8 and 12 years (females = 26; mean age = 10.7; SD = 1.3) with a high risk for developing an anxiety disorder as defined and ascertained by the CASI (CASI > 24) in the prevention group and 8 participants (females = 5, mean age = 10.8; SD = 1.3) in the control group of the study.

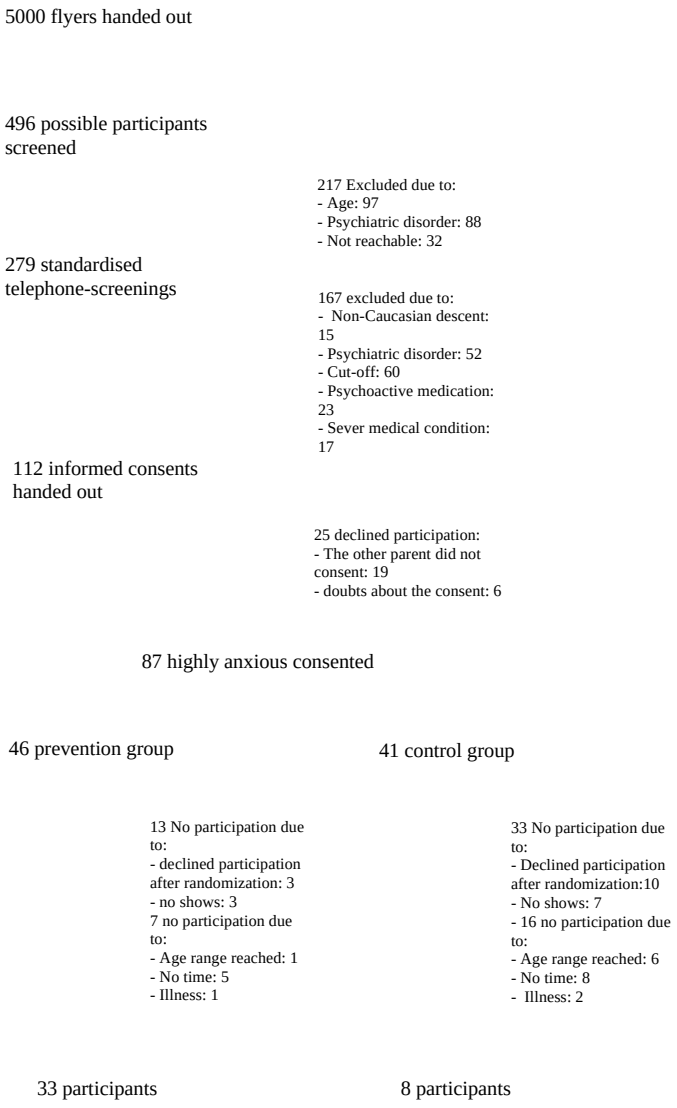

Figure 7: Flow-chart of the process of recruitment of study 3

On the first day of the investigation in both groups, the participants as well as their parents/legal guardians underwent a clinical diagnostic interview, the German version of the Diagnostic Interview for Mental Disorders for Children and Adolescents by a trained clinical psychologist (KK) to confirm the absence of a psychiatric diagnosis *Kinder-DIPS;* (Schneider, Unnewehr, et al., 2009). The outcome measures (ascertained by self-administered questionnaires) were assessed on the first training day prior to the FRIENDS session. Post

assessment was done directly after the last session. In the control group the second appointment was scheduled exactly two weeks after the first day of investigation. The participants underwent an intensive clinical and neuropsychological assessment as described in study 1 (prior as well as post prevention). The participants received a financial compensation of €50 at T0 and T1 for the participation. All procedures of the study were in accordance with the Declaration of Helsinki in its latest version and the medical ethics committee of the University of Würzburg (139/15).

4.2.2 FRIENDS for LIFE Program

All children in the prevention group participated in the "FRIENDS for LIFE" program (P. M. Barrett, 2017). Prior to the implementation of the program, we translated the program into German (SN, KK) with permission of the author. In our case the program consisted of five appointments with a duration of approximately 2.5 - 3.0 hours each, over the course of two weeks. The program was administered by the same trained clinical psychologist (KK) and an assistant. Group size varied from three to five participants. Due to extracurricular activity and school workload, groups could only be administered during school holidays. All children participated in all five sessions. The "FRIENDS for LIFE" program is a manualized group-based prevention (P. M. Barrett, 2017). We administered five sessions by combining two sessions each. Every session had a clear structure: First there was a short introduction of the topic, followed by a warm-up practice with a gratitude or happiness experience and a mindfulness mediation and homework at the end.

Session 1 consisted of an introduction to the program and presented the word "FRIENDS" as acronym for the different skills that are taught during the following sessions. In this session the letter F for Feeling was presented: understanding own feelings and feelings of others, understanding that there is a choice about what to do with feelings and that all living beings do experience feelings, having the courage to apologize, caring for the safety and well-being of others. Furthermore, the topic of talking about feelings and understanding body language and how it helps to communicate feelings are taught. Session 2: In this session the letter "R" ("relaxation") was presented. This topic consists of learning body clues and relaxation techniques, how to recognize body signs during worry, recognizing situations that make one feel worried, activities that can help to calm down and feeling confident and relaxed. In session 3 the topic was "Learning to pay careful attention to our 5 senses", thus mindfulness practices. Another topic was how to change dysfunctional into functional thoughts and restructure unhelpful thoughts and being able to decide what to do with feelings and present functional behavior. This was presenting the third step "I" = "I can do it, I can try my best". Furthermore,

the concept of values and role models is discussed and implemented. Session 4: Functional problem-solving skills were discussed in this session using "Coping step plans" and functional solution finding plans. Session 5: In this session the last letters are discussed. In this using the FRIENDS skills should be used to help ourselves and others. Topics are: "Now reward yourself", "do not forget to practice", "smile", "stay calm" and "talk to your support networks". The skill taught during the program are reviewed and transferred to life values. A plan how to apply the taught expertise in the future is made.

4.2.3 Statistical Analyses

Data were analyzed using SPSS version 26 (SPSS Inc, Chicago, Illinois, USA). Due to sample size of the control group, we reduced statistical analysis to the prevention group only. The described workflow from study 1 for correlation analyses and *a priori* sex differences was followed. The score difference between pre- and post-prevention scores for STAIC and CASI (STAIC_diff and CASI_diff) were normally distributed, but the differences for TAI scores (TAI_diff) were not normal distributed. Because of this the analysis for STAIC_diff and CASI_diff was calculated with the dependent t-test and the TAI_diff was analyzed with the Wilcoxon signed-rank test. (For all assumption testing please see **tables A28 – A32**). To evaluate the effect further correlation analyses with pre-and post-prevention data as well as difference scores were performed. Furthermore, to evaluate a possible mechanisms mediation and moderation models, for the pre- and post-prevention data within the same measure as well as between measures (as established in study 1) and difference scores, in combination with negLE were performed (A. Hayes, 2017).

4.3 Results

4.3.1 Anxiety Phenotypes

In the sample the average age was 10.67 (SD = 1.34) and the mean developmental stage was 1.58 (SD = 0.11) as expected in this age group. The average IQ was 110.33 (SD = 16.63). Anxiety measures and negLE had mean and standard deviations as follows (M_{STAIC} = 32.42, SD = 5.49; M_{CASI} = 27.94, SD = 3.86; M_{TAI} = 7.42, SD = 8.43; M_{negLE} = 6.48) (further sample characteristic and control group characteristics can be found in **tables A26** and **A27**). The results of the Mann-Whitney-U-test yielded no significant difference between male and female subjects, after correction for multiple testing (for the results please see **table A 30**). There was no age effect on anxiety measures. In this small sample, anxiety measures showed only correlations with a trend to significance after correction of multiple comparison. Furthermore, anxiety measures were not correlated with negLE (see **table 6**).

Table 6: Spearman's correlation coefficient anxiety measures, negative life events and post prevention anxiety measures

Variable	Age	STAIC_T0	CASI_T0	TAI_T0	negLE	STAIC_T1	CASI_T1	TAI_T1
Age	1	-.07	.11	-.30	.21	.25	.36	-.20
STAIC_T0		1	.39 p =.024	.12	.38	.31	.21	.05
CASI_T0			1	.40 p = .021	.32	.27	.58*	-.08
TAI_T0				1	.15	.21	.45*	.58*
negLE					1	.39 p = .027	.21	-.03
STAIC_T1						1	.33	.39
CASI_T1							1	.07
TAI_T1								1

For the total sample (n = 33) a correction was performed resulting in a corrected p threshold of q* = .009 (*p < q* (Benjamin and Hochberg, 1995)); * = q; _T0 = pre-intervention anxiety measures, _T1 = post-intervention anxiety measures.

4.3.2 Results of the prevention effect

In accordance with our hypothesis the effects of the prevention revealed a reduction of all anxiety parameters, which was statistically significant in CASI and STAIC (CASI: *t(32)* = 3.9, p = .000; STAIC: *t(32)* = 2.9, p = .007, TAI: T = 1.6, p = .11) (see **table 7** and **figure 8**).

Table 7: Paired sample t-test and Wilcoxon signed-rank test

STAIC_T0 - STAIC_T1	CASI_T0 - CASI_T1	TAI_T0 - TAI_T1
t(32) = 2.87, p = .007*	*t*(32) = 3.93, p = .000*	T = 1.63 p = .11

For the total sample (n = 33) a correction was performed resulting in a corrected p threshold or q* = .03 (*p < q* (Benjamin and Hochberg, 1995)). * = q; _T0 = pre-intervention anxiety measures, _T1 = post-intervention anxiety measures.

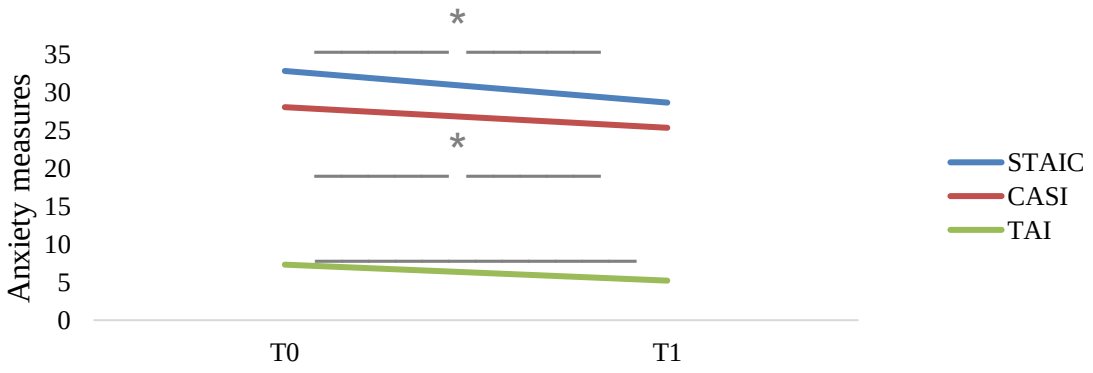

Figure 8: Effect of the prevention program

Graphic display of the prevention effect from T0 (pre-intervention) to T1 (post-intervention) in anxiety measures. Significant reduction of STAIC and CASI scores from T0 to T1 displayed with an *.

STAIC prior to prevention was not correlated with post prevention data (**table 6**). CASI and TAI prior to the prevention were significantly positive correlated with their post prevention values (r_{CASIs} = .58, p < .009) (r_{TAIs} = .58, p < .009). Furthermore, TAI scores prior to prevention were significantly correlated with CASI scores post prevention (r_s = .45, p < .009) (please see **table 6**). Further moderation and mediation models with pre-and post-data were performed. When CASI scores after prevention were predicted based on CASI scores prior to prevention, a significant regression equation was found (F1,31) = 18.69, p < .00) with R^2 = 0.38, but negLE did not predict CASI scores post prevention. When TAI scores post intervention were predicted by TAI scores prior to the prevention program, a significant regression equation was found (F1,31) = 3.67, p < .00) with R^2 = 0.26, but again negLE did not predict TAI scores post intervention. Thus, negLE did not influence the prevention effect or were able to predict post prevention data. Furthermore, negLE could not be identified as mediator or moderator variable between pre-and post-prevention scores in any of our tested models (for further details please see **tables A33** and **A 36**).

Table 8: Correlation of anxiety measures prior to prevention and intervention induced changes

Variable	STAIC_diff	CASI_diff	TAI_diff
Age	-.33	-.28	-.14
STAIC_T0	.49*,	.14	.37 p = .039
CASI_T0	.01	.46*	.49*
TAI_T0	-.15	-.01	.59*,
negLE_T0	-.05	-.03	.15

For the total sample (n = 33) a correction was performed resulting in a corrected p threshold of q* = .009 (*p < q* (Benjamin and Hochberg, 1995)); * = q, Abbreviation: _diff = intervention induced changes.

When correlating anxiety markers at preintervention with intervention-induced changes (i.e., diff-scores), we found that pre-scores in all anxiety measures were correlated with the changes within the same measures (see **table 8**). In addition, the pre-intervention CASI score was correlated with the changes in TAI, supporting the close interrelation between Anxiety Sensitivity and Separation Anxiety. Like in pre-post-intervention analyses, neither relation between pre-intervention score and intervention-induced changes were mediated/moderated by negLE, hinting towards a direct relation (see **tables A37** and **A 38**).

4.4 Discussion

Study 3 investigated the effect of an indicated prevention program on the three anxiety measures in a subsample of study 1 of highly anxious children. Its aim was to extend the findings from study 1 and 2 and probe the malleability of these markers via an indicated prevention program.

Surprisingly, anxiety measures prior to prevention were only correlated on an uncorrected level, i.e., showing a trend to significance. Even though our analysis is lacking power, due to our sample size, given the high effect size of the association between CASI and STAIC in study 1 and 2, power should have been sufficient to detect this association ((as assessed by G*Power (Faul, Erdfelder, Lang, & Buchner, 2007): post-hoc calculated power of 0.89, with an effect size of p = 0.5, alpha-error probability = .05 and n = 33). Additionally, in this sample, we focussed on highly anxious participants, and results might indicate a different pathological mechanism being at play in healthy populations in comparison to highly vulnerable i.e., subclinical samples. A mechanism where different anxiety measures are individually pronounced and no longer that tightly related, when subjects are highly anxious, but healthy, could be conceived. Future research on a bigger samples size should answer this interesting new research question.

In accordance with our expectations, a main result of study 3 is that the effect of the prevention program could be quantified by a reduction of all three anxiety traits from pre to post prevention assessment. These results are in line with results from studies and meta-analyses reporting a small, but significant effect of universal as well as indicated prevention programs (Feiss et al., 2019; Hugh-Jones, Beckett, Tumelty, & Mallikarjun, 2020). That the effect was only trend wise significant in TAI scores might be due to the already low TAI scores in our sample and the very specific nature of the TAI questionnaire which is assessing avoidance of separation situations. Furthermore, the prevention program is specifically addressing symptoms of Trait Anxiety and Anxiety Sensitivity, such as for example bodily and cognitive symptoms of anxiety and not specific avoidance symptoms of separation anxiety. Thus, it is plausible that we saw significant effects in CASI and STAIC scores.

Overall the significant reduction of CASI and STAIC scores are very promising results, indicating that the cost effective and economic method of CBT-based indicated prevention is gilding significant results in an indicated sample even when samples sizes are small (assessed by G*Power (Faul et al., 2007) revealing a post-hoc power of 0.88 with a medium effect size of f = .025, alpha error probability = .05, n = 33, number of groups = 1, number of measurements = 2 and a correlation among repeated measures of 0.6). This is in accordance with our hypothesis and is to our knowledge the first study using CASI and STAIC to evaluate the effectiveness of an indicated prevention with the newest and time efficient form of the FRIENDS for Life program. Further research should assess if the STAIC and the CASI can be efficiently used in bigger groups and different study designs and if the effects are still present in comparison with a control group.

In comparison to STAIC scores, CASI and TAI scores pre- and post-prevention were correlated - indicating a certain stability for these two anxiety traits. We found that pre-intervention scores were significantly correlated with the intervention-induced change within the anxiety measure. Furthermore, the pre-intervention CASI scores, were significantly positively correlated with the change in TAI and the pre-intervention TAI scores were correlated with post CASI scores. This is supporting the assumption that these two anxiety measures are linked, change in the same direction and hold a predicative power over the other. Surprisingly STAIC scores pre and post intervention were not correlated, even though STAIC scores are supposed to be relatively robust over time (Unnewehr et al., 1992). On the one hand this could drive home the point that we had different mechanisms at play in this highly anxious sample, with STAIC not being as stable in this specific sample. On the other hand, the results could indicate that the effect of the prevention program had the most effect on STAIC scores, resulting in no association between pre- and post-intervention data.

However, we did not find any predictive effect of negLE data on post intervention anxiety scores. In an explorative analysis we followed up on the question whether negLE would influence the prevention effect in any way. Accordingly, negLE did not mediate or moderate the connection. A reason for that might be the young age of the participants of this study (i.e., 8-12 years) in general and in our sample with the modal of negLE of 6.7, in particular.

Overall prevention results are very promising, because even though prevention of anxiety disorders is a pressing matter at hand, research about prevention in children and adolescents is still scarce. Studies using CBT-based prevention programs are very heterogeneous, when it comes to the program application (e.g., school based, indicated, selective), program adherence, age group, outcome measures and participations (Feiss et al., 2019). Furthermore apart from the FRIENDS program there are other CBT-based prevention programs that have been used to reduce anxiety symptoms effectively (e.g. Penn resiliency program (Cutuli, Chaplin, Gillham, Reivich, & Seligman, 2006), Cool little Kids (Lyneham, Abbott, Wignall, & Rapee, 2003; Macquarie University), Coping and Promoting Strength (Ginsburg, Drake, Tein, Teetsel, & Riddle, 2015) (Feiss et al., 2019; Hugh-Jones et al., 2020; Werner-Seidler et al., 2017). Still results from meta-analyses are heterogeneous when it comes to the efficiency and effectiveness of malleability of anxiety symptoms, and it will thus be of special interest what elements of CBT interventions are effective under what conditions in a impactful reduction of anxiety symptoms.

5. General Discussion

In this present work, the influence of several anxiety measures, namely Trait Anxiety, Anxiety Sensitivity and Separation Anxiety, their interaction and their connection with negative life events was examined in children and adolescents. Fronto-limbic activation during emotional face processing as well as malleability via a prevention program was assessed.

5.1 Key Findings

Overall, we could assess close connections of all three anxiety measures, as well as specific associations between measures. This indicated that all three questionnaires were assessing distinct constructs, that nonetheless were closely connected. Specifically, we learned that the closest connections could be assessed between STAIC and CASI, as well as between TAI and CASI.

5.1.1 The relation between STAIC and CASI

Studies predominantly done in adults give rise to an ongoing discussion as to what the connection of Trait Anxiety and Anxiety Sensitivity is like (S. O. Lilienfeld, Turner, S. M., Jacob, R. G., 1993; L. A. McWilliams & Cox, 2001; Taylor, 1995). For example, some research is indicating that Anxiety Sensitivity and Trait Anxiety are distinct constructs (Taylor, 1995) but could also be organized hierarchically with Anxiety Sensitivity operating as a lower order trait of Trait Anxiety (S. O. Lilienfeld, Turner, S. M., Jacob, R. G., 1993). In our studies, we established a close connection of both measures (study 1), as indicated by a high correlation coefficient, but at the same time both measures made specific contributions to different analyses. Both measures were positively correlated with negLE indicating that the association between life events and anxiety (Allen et al., 2008; Cabral & Patel, 2020) can be found on a subclinical level. Our model suggested further, that CASI and negLE were predicting STAIC significantly and that these association were partially mediated by negLE. This is mirroring the diathesis-stress-model of anxiety disorders (Belsky & Pluess, 2009; Cabral & Patel, 2020; Zuckerman, 1999) in a healthy sample: CASI and negLE were contributing to a certain phenotype, in this case STAIC and a part of the causal association was explained by negLE. However, this causal association was very small, indicating that negLE was having a small, but stable effect on the relationship (see **figure 9** for the model association).

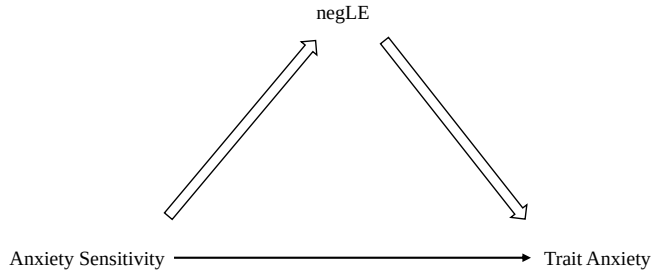

Figure 9: Significant model between Anxiety Sensitivity and Trait Anxiety

Furthermore, in study 2, in contrast to the association between TAI and CASI, we did not find a manifestation of the relationship between CASI and STAIC on the neural level. We found a STAIC-specific increase in the left IFG, indicating a modulatory frontal activation of limbic structures, that has been interpreted as an indirect measure of symptom severity (Monk, 2008). However, moderation/mediation analyses including STAIC and CASI did not show a significant role of brain activation. Furthermore, STAIC and CASI scores were malleable by the preventive intervention (study 3) and scores reduced significantly from pre- to post-assessment which was speaking for the strong effect of the prevention program. However, in contrast to the TAI-CASI association we found no cross-over effects of the preventive intervention between measures (neither CASI_T0*STAIC_diff/T1 nor CASI_diff*STAIC_diff).

5.1.2 The interplay between CASI and TAI

We were able to reveal multiple aspects of the relationship between CASI and TAI, i.e., as correlational effect (study 1), on a neuronal level (study 2), and by the predictive potential of the preventive response of CASI on TAI (study 3). We were able to assess a close connection of both measures by a high correlation coefficient and the additional variance explained of TAI on CASI by negLE. These results seem to mimic the connection between SAD in childhood and PD in adults (Battaglia et al., 2014; Hannesdottir et al., 2018) in our healthy sample, thereby indicating that the association might be found on a continuum from subclinical to clinical level and from an early age on.

Furthermore, we could establish a manifestation of this association on the neuronal level. We found moderating effects bilaterally by TAI specific IFG (study 2 and see **figure 10**). Our models suggested that the interplay between TAI and CASI was dependent on negLE and the activation of the IFG. The association was significantly more pronounced when the IFG was medium to strongly activated and when negLE were medium and high. In line with this result the specific hypoactivation of the right IFG results has been reported in a study with adult PD patients, in an alerting network (Neufang et al., 2019). This indicates that the activation in the right IFG is specifically disrupted in PD/individuals with high Separation Anxiety. This is indicated by a hypoactivation which can be interpreted as a flawed top-down-control mechanism which can

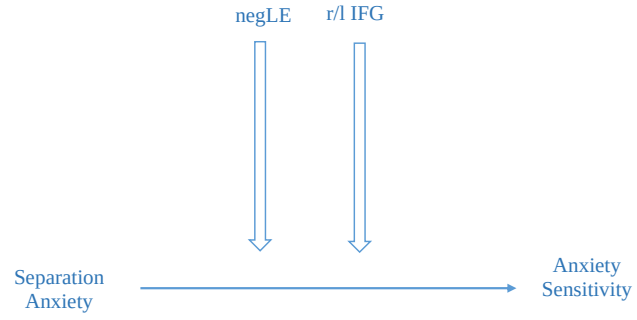

Figure 10: Significant model between Separation Anxiety and Anxiety Sensitivity with brain functioning

already be assessed in healthy children and adolescences. Our results thus gave further evidence for this developmental trajectory and furthermore an indication of a neuronal manifestation of this association. Lastly, in close connection to findings from a prevention study done in adults, where changes in Anxiety Sensitivity scores were correlated with changes in Separation Anxiety scores (Schiele et al., 2021), we found, that even though the reduction from pre- to post-assessment was not significant in TAI scores, pre-intervention CASI score correlated with the changes in TAI scores. Likewise, preintervention TAI scores were correlated with CASI scores post intervention. Thus, CASI scores held a predictive potential for the prevention response in TAI and vice versa (see **figure 11**). These results gave further indication for the manifestation of a PD-SAD trajectory and indicated that TAI scores might indirectly improve by reducing CASI scores.

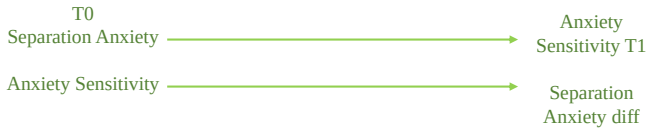

Figure 11: Significant model of the predicted effect of Separation Anxiety and Anxiety Sensitivity

5.2 Conclusion and Limitations

There are a number of limitations to the present studies that should be considered and are limiting the results. We want to point out, that while we made interferences between the assessed anxiety measures and anxiety disorders, some research has implicated controversial results concerning this relationship and that these measures might be relevant in other psychopathologies as well. In that line, some research has indicated that the association between Anxiety Sensitivity and PD is not that clear, since in one study in undergraduates Anxiety Sensitivity was connected with PD, but not after controlling for Trait Anxiety (Plehn, 2002) and another study indicated that Anxiety Sensitivity might play a role in mood disorders (L. McWilliams, Becker, Margraf, Clara, & Vriends, 2006; Naragon-Gainey, 2010; Taylor et al., 1996). Likewise, a meta-analysis found evidence that the Trait Anxiety was strongly related to anxiety disorders (i.e., can distinguish between individuals with and without an anxiety disorder, (Seligman et al., 2004)). The picture, however, was mixed when it comes to distinguish between anxiety and other psychiatric disorders: Trait Anxiety could distinguish anxiety disorders and externalizing disorders, but not between affective and anxiety disorders (Bados, Gomez-Benito, & Balaguer, 2010; Seligman et al., 2004). Since anxiety disorders and affective disorders have a high comorbidity and Trait Anxiety and Anxiety Sensitivity are highly correlated, we interpreted these results along those lines and not as controversial to our result.

Furthermore, it is necessary to mention that phenotypes were characterized via self-report questionnaires, which pose a certain limiting factor to the internal consistency via socially

desirable answers (Logan, Claar, & Scharff, 2008). This is the case even though research with questionnaire data has indicated that children are able to report on their mood and that these might be more reliable data than parent report (Fonseca, 2001; Michael & Merrell, 1998) or teacher reports (Kosters et al., 2015). In that line it is noteworthy that a range of phenotypical data, such as parenting style (Cabral & Patel, 2020; Watt, Stewart, & Cox, 1998), parent anxiety (Drake, 2008) and attachment to parents (Breinholst, Tolstrup, & Esbjorn, 2019) could indicate further influential factors via vulnerability or mediation/moderation of symptom severity. In that vein a relatively new concept of parents sensitivity to their child's Anxiety Sensitivity could be an interesting concept and lead to future research questions (Wissemann, Gorday, & Meyer, 2018). Furthermore, we did not assess positive life events, even though evidence suggests that a positive environment can increase resilience and thus reduce incidence of mental disorder (Rutten et al., 2013; Schiele et al., 2020). Especially in research about prevention programs this could lead to future research questions, since many programs follow a resilience-based framework and thus positive life events could have an influence on outcome variables, possibly via moderation effects.

As mentioned, we assessed negLE with a self-assessed questionnaire. To our knowledge the literature about the influence of life events is very diverse, with research groups assessing chronic life adversities, traumatic experience, or life experiences as such (Blackshaw et al., 2018; Cabral & Patel, 2020). Furthermore, the differentiation of these concepts seems oftentimes blurry and very different neurobiological and social consequences should therefore be at play. Here we assessed life events and their subjective interpretation; thus, results cannot be generalized onto groups having experienced traumatic life events. Furthermore, we did not assess "chronic stress", which has been implicated in the development of mental disorders, especially during development and adolescents and can alter brain function (Tottenham & Galvan, 2016). In a similar note, we did not assess, when events took place. Some research has implicated that life events do have very different impact depending on the age there are occurring (Kendler et al., 2011; Monk, 2008; Waszczuk et al., 2013), for example administration of selective-serotonin-inhibitors in mice can lead to a more or less anxiety related behaviour depending on the age and duration of administration (Ansorge, Morelli, & Gingrich, 2008; Troelsen, Nielsen, & Mirza, 2005). Similarly, future research will have to assess stressful life events prior to birth, since preclinical studies are suggesting that stressful life events might be transmitted through epigenetic information onto offspring (Schiele et al., 2020). Furthermore, it is noteworthy that a part of the found connection between negLE and anxiety traits could be due to a memory bias. Since research groups found a memory bias

between low and high trait anxious individuals, where high anxious individuals did recall more threatening situations than non-threatening situations (Reidy & Richards, 1997) and individuals with low Trait Anxiety thought about non worrying items far less than about worry items, while there was no difference in the high anxious group (Reidy, 2004).

Some sample characteristics could pose a limiting factor for our results, as well. Firstly, because the age range in our samples is quite large for a developing population (at least in sample 1 and 2) studies with a closer age range could be used to further pinpoint developmental critical age ranges for the associations found. Secondly, the incidence and prevalence of anxiety disorders as well as reported anxiety measures seems to be a different between male and female subjects (Stewart, Taylor, & Baker, 1997; Zolog, Bonillo, Ballabriga, & Canals, 2011). A priori we could not find sex differences between phenotypes, nonetheless anxiety disorders have a higher prevalence in women (World Health Organization, 2004a). The fact, that we did not found these differences, could be due to our sample mostly comprising children before puberty, because puberty poses a vulnerability for the development of psychopathology (Deardorff et al., 2007; Ferri et al., 2014; Kessler et al., 2005). This is due to rapid changes in hormone levels, shifts in motivation, physical development and changes in the social system during puberty, a rapid increase of psychiatric disorders is seen in this age group (Deardorff et al., 2007; Ferri et al., 2014). For example, in one longitudinal population based study, increase in female depression symptoms was seen and this has been implicated in the transition to Tanner stage III, which is entirely explained by sexual hormones (Copeland, Angold, Shanahan, & Costello, 2014). Similarly in a longitudinal study in children at risk for anxiety disorder development, females and males showed similar rates of anxiety symptoms in childhood, but greater symptoms in adulthood (Bosquet & Egeland, 2006). Another factor why we might not have found sex differences is that our sample comprises of healthy children and adolescents. Nonetheless, some studies have indicated no sex difference of STAI (Trait Anxiety in adults) or ASI (Anxiety Sensitivity in adults) scores in PD patients (Foot & Koszycki, 2004). Thus, to evaluate this aspect further longitudinal data with a closer age range and stratified for sex in a well characterized sample are needed, to further clarify and specify age effects as well as pinpoint the critical age range for the development of the disorder group further. Our results indicate however, that there might not be a detectable difference of anxiety measures in mostly pre-pubertal healthy samples.

For our neuroimaging data, we focused on a fronto-limbic network, but if other brain regions are specifically involved for certain phenotypes we did not assess. Furthermore, there are many neurobiological markers that were not assessed in this work and were beyond the

scope of the presented studies. With this in mind, hormonal status, (epi)genetic, or neuronal functional in other regions or during other tasks could pose potential targets to be included in the research concerned with the prevention of anxiety disorders (Barendse et al., 2018; Schiele et al., 2020). Furthermore, even though the "Hariri task" is a well-established and widely used task (Preckel et al., 2019), there are some problems with the task itself. For example, since emotional expressions are compared to shapes the two conditions differ in more than one category, namely in emotional valence and social content (Preckel et al., 2019), making it difficult to attribute results to one category. Furthermore, it is important to note that we used face stimuli from adult samples. Using facial expressions from children might change the results further, since initial evidence from adolescent samples indicate that emotional faces from a peer-group might elicit a different neuronal response than stimuli from adults (Ferri et al., 2014; Marusak, Carre, & Thomason, 2013).

Even though the effect of the preventive program was evaluated via a pre-post design, further longitudinal data over a longer time period with a bigger well characterized sample size and a matched control group should further evaluate the effect. In this aspect cross sectional and longitudinal data could ultimately be used to improve personalised treatment.

5.3 Outlook and Clinical Implications

Research in children and adolescents with and about anxiety disorders and adjunct mechanism is still scares in comparison with studies done in adults. This is especially remarkable, since the prevalence of anxiety disorder is high during childhood and adolescents (Kessler et al., 2007) and it is a critical time point for the development of psychopathology (Kessler et al., 2012). One might suspect that ethical and logistic factors to implement studies in this age group might be some of the reasons why there is still such a knowledge gap. In the same vein especially in MRI studies and studies with a higher personal investment, such as with the prevention program where participants and thus families have to commit for a lot of appointments, drop-out rates might be high an initial willingness to participate might be low. Nonetheless, further research is needed to evaluate and replicate the findings presented here. Especially research in clinical, developmental and bigger samples are needed, during the critical developmental time period related to the onset of anxiety disorders. Furthermore, the markers for the three different phenotype-groups that were probed here and should be evaluated in larger samples in a preventive and clinical interventional setting over a longitudinal design with a control group. Especially childhood from 8 to 12, as studied in sample 3 seems to be crucial period, in that aspect, since this age seems to be a sensitive period in the development of anxiety disorders because of changes in brain structures (Gee et al., 2013; Gogtay et al., 2004), cognitive

abilities (Ofen, 2012; Ofen, Chai, Schuil, Whitfield-Gabrieli, & Gabrieli, 2012) and environment (Gee et al., 2013; Gogtay et al., 2004; Ofen, 2012; Ofen et al., 2012).

We found that the three temperamental factors are in close connection and could distinguish neurobiological markers for STAIC and TAI. CASI and STAIC were found to be malleable with a cost effective and short preventive intervention. This are very promising results in the light of the still scares research done in children and adolescents. To reduce the incidence and prevalence of anxiety disorders it will be of utmost importance to use these effective screening tools to identify individuals at risk and to apply effective strategies to reduce the symptomatology. In that line our results imply that STAIC and CASI can be seen as such screening tools. However, the association between TAI and CASI can be seen as a most promising transdiagnostic target for prevention on a developmental trajectory. In an approach of personalized medicine, we hopefully will be able to apply these findings in indicated individuals and evaluate the effectiveness even on a neurobiological level in the future. This will ultimately reduce incidence and prevalence of anxiety disorders in the future and thus help to improve the lives of children and their families.

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7. Glossary

Abbreviations	*Definition*
AAL	Automated Anatomical labeling
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactive Disorder
ASI	Anxiety Sensitivity Index in adults
BOLD	Blood-Oxygen-Level-Dependent
CASI	Children anxiety sensitivity index
CASI_diff	Children anxiety sensitivity index difference score between pre- and post- prevention
CASI_T0	Children anxiety sensitivity index prior prevention
CASI_T1	Children anxiety sensitivity index post prevention
CBT	Cognitive Behavioural Therapy
DFG	German Research Foundation
DIPS	Diagnostic Inventory of Psychiatric disorders
dlPFC	dorsolateral Pre-Frontal Cortex
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Version 5
ECNP	European College of Neuropsychopharmacology
EPI	Echo-Planar Imaging
FDR	False-Discovery Rate
fMRI	functional Magnetic Resonance Imaging
FoV	Field of View
FWHM	Full Width at Half Maximum
GLM	General Linear Model
GAD	Generalized Anxiety Disorder
HC	Hippocampus
ICD-10	International statistical Classification of Disease and related health problems Version 10
IQ	Average Intelligence
IFG	Inferior Frontal Gyrus
lIFG	left Inferior Frontal Gyrus
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MOG	Medial Orbital Gyrus
MRI	Magnetic Resonance Imaging
MPRAGE	Magnetization Prepared Rapid Gradient Echo
negLE	negative Life Events
PD	Panic Disorder
PFC	Pre-Frontal Cortex
rIFG	right Inferior Frontal Gyrus

rMGF	right Middle Frontal Gyrus
ROI	Region of Interest
SAD	Separation anxiety disorder
SFB	Collaborative Research Centre
sMRI	structural Magnetic Resonance Imaging
SPM	Statistical Parametric Mapping Software Package
STAI	Trait Anxiety in adults
STAIC	State-Trait-Anxiety Inventory for Children
STAIK	German State-Trait Anxiety Inventory for Children
STAIK-T	German Trait scale of the State-Trait Anxiety Inventory for Children
STAIC_diff	State-Trait-Anxiety Inventory for Children difference score between pre- and post-prevention
STAIC_T0	State-Trait Anxiety Inventory for Children prior prevention
STAIC_T1	State-Trait Anxiety Inventory for Children post prevention
TAI	Separation Anxiety Inventory
TAI-E	German Separation Anxiety Inventory Parents questionnaire
TAI-K	German Separation Anxiety Inventory Children questionnaire
TAI_diff	Separation Anxiety Inventory difference score between pre- and post-prevention
TAI_T0	Separation Anxiety Inventory prior prevention
TAI_T1	Separation Anxiety Inventory post prevention
TE	Echo Time
TR	Repetition Time
vlPFC	ventrolateral Pre-Frontal Cortex
WASAD	World Association for Stress Related and Anxiety Disorders
WHO	World Health Organization
ZEP	Centre for Mental Health
ZLEL	Zürcher Life Events List

8. Appendix

8.1 Tables

Table A 1: Sample description study 1

Variable	Population	Mean	SD	Variance	Kurtosis	Skewness
Age	All	11.23	1.89	3.58	1.43 (0.48)	0.89 (0.24)
	male	11.62	2.20	4.85	0.53 (0.69)	0.82 (0.35)
	female	10.89	1.52	2.31	1.23 (0.64)	0.36 (0.33)
Tanner	All	1.85	0.83	0.69	1.77 (0.52)	1.08 (0.26)
	male	1.87	0.99	0.98	1.79 (0.75)	1.33 (0.38)
	female	1.83	0.68	0.49	-0.75 (0.69)	0.22 (0.35)
CFT	All	109.23	15.76	248.34	-0.91 (0.50)	0.22 (0.25)
	male	108.13	15.69	246.16	-0.51 (0.73)	0.42 (0.37)
	female	110.09	15.92	253.28	0.39 (0.66)	0.07 (0.33)
STAIC	All	30.26	7.08	50.05	0.60 (0.48)	0.95 (0.24)
	male	28.95	7.03	49.38	-0.20 (0.70)	0.92 (0.36)
	female	31.45	7.06	49.79	1.26 (0.64)	1.08 (0.33)
CASI	All	26.36	5.49	30.13	3.97 (0.48)	1.46 (0.24)
	male	25.25	4.64	21.49	-0.69 (0.70)	0.50 (0.36)
	female	27.23	6.01	36.14	4.64 (0.64)	1.76 (0.33)
TAI	All	6.67	7.76	60.15	0.91 (0.51)	1.33 (0.26)
	male	6.53	7.72	59.61	2.17 (0.75)	1.62 (0.38)
	female	6.21	7.32	53.62	0.17 (0.67)	1.17 (0.34)
negLE	All	6.88	5.90	34.86	1.65 (0.49)	1.42 (0.25)
	male	6.25	5.45	29.72	3.17 (0.70)	1.76 (0.36)
	female	7.55	6.25	39.02	6.25 (0.33)	1.18 (0.64)

Descriptive characterization of total sample (N = 100) with variance, distribution and means, as well as stratified for sex.

Table A 2: Levens' test for the test of normal variance between groups (male/female) in study 1

Age	STAIC	CASI	TAI	negLE
F = 3.46	F = 0.17	F = 0.41	F = 0.01	F = 1.38
p = .07	*p* = .68	*p* = .53	*p* = .93	*p* = .24

Normality of variance within sex groups for the total sample (N = 100); Homogeneity of variance can be assumed for all variables. A correction was performed resulting in a corrected p threshold or q* = .01 (*p < q* (Benjamin and Hochberg (1995)).

Table A 3: Kolmogorov-Smirnov test of the normal distribution within groups (male/female) in study 1

Age		STAIC		CASI		TAI		negLE	
male	female	male	female	Male	female	male	female	male	female
D = 0.14	D = 0.11	D = 0.21	D = 0.11	D = 0.14	D = 0.15	D = 0.20	D = 0.20	D = 0.18	D = 0.16
p = .03*	*p* = .20	*p* = .00*	*p* = .15	*p* = .03*	*p* = .00*	*p* = .00*	*p* = .00*	*p* = .00*	*p* = .00*

Test for the normal distribution within sex groups for the total sample of (N = 100). A correction was performed resulting in a corrected p threshold or q* = .04 (*p < q* (Benjamin and Hochberg (1995)); * = q.

Table A 4: Mann-Whitney-U-test for group differences between males and females study 1

	All	male	female	Statistics
N	100	46	54	
Age	11.2 (1.9)	11.6 (2.2)	10.9 (1.5)	*U = 1037, z = -1.4, p = .16*
STAIC	30.3 (7.1)	28.8 (7.0)	31.5 (6.9)	*U = 897, z =-2.2, p = .03*
CASI	26.3 (5.5)	25.2 (4.6)	27.2 (6.1)	*U = 979, z = -1.7, p = .10*
TAI	6.7 (7.7)	6.7 (7.7)	6.5 (7.8)	*U = 861, z = -.45, p = .66*
negLE	6.9 (5.9)	6.3 (5.5)	7.4 (6.3)	*U = 1061, z = -.76, p = .45*

Sex differences within the sample assessed for the total sample (N = 100). A correction was performed resulting in a corrected p threshold or q* = .01 (*p < q* (Benjamin and Hochberg (1995)).

Table A 5: Kolmogorov-Smirnov test for the normal distribution study 1

Age	STAIC	CASI	TAI	negLE
D = 0.13	D = 0.13	D = 0.11	D = 0.20	D = 0.16
p = .00*	*p* = .01*	*p* = .00*	*p* = .00*	*p* = .00*

Test for the normal distribution for the total sample of (N = 100). A correction was performed resulting in a corrected p threshold or q* = .05 (*p < q* (Benjamin and Hochberg (1995)); * = q.

Table A 6: Kolmogorov-Smirnov-test of regression residuals study 1

Z standardized Regression residuals	CnegS	TnegS	SnegC	TnegC	SnegT	CnegT	logSnegT	logCnegT
	D = 0.09 *p* = .05	D = 0.09 *p* = .16	D = 0.08 *p* = .10	D = 0.09 *p* = .19	D = 0.19 *p* = .00*	D = 0.14 *p* = .00*	D = 0.10 *p* = .05	D = 0.06 *p* = .20

Test of normality of the residuals for the corrected sample of (N = 98). A correction was performed resulting in a corrected p threshold or q* = .006 (*p < q* (Benjamin and Hochberg (1995)). * = q; Abbreviation C = CASI, S = STAIC, T = TAI, neg = Negative life events, log = natural logarithm.

Table A 7: Regression models in study 1

STAIC and negLE on the dependent variable CASI						STAIC and negLE on the dependent variable TAI					
	R*2	**b**	**SE B**	**Beta**	**p**		**R*2**	**b**	**SE B**	**Beta**	**p**
Step 1						**Step 1**					
Constant	0.63	7.15	1.59		.00*	Constant	0.15	-7.51	3.75		.05
STAIC		0.64	0.05	.79	.00*	STAIC		0.47	0.12	.38	.00*
Step 2						**Step 2**					
Constant	0.64	7.22	1.60		.03	Constant	0.15	-7.19	3.80		.00*
STAIC		0.63	0.06	.78	.00*	STAIC		0.43	0.14	.36	.00*
negLE		0.02	0.06	.02	.73	negLE		0.10	0.15	.07	.53

Regression models for the corrected sample (N = 98). A correction was performed resulting in a corrected p threshold of q* = .04 (*p < q* (Benjamin and Hochberg, 1995)); * = q.

Table A 8: Regression models with logarithm data in study 1

logSTAIC and lognegLE on the dependent variable logTAI						logCASI and lognegLE on the dependent variable logTAI					
	R*2	**b**	**SE B**	**Beta**	**p**		**R*2**	**b**	**SE B**	**Beta**	**p**
Step 1						**Step 1**					
Constant	0.15	-5.00	2.02		.02*	Constant	0.24	-8.57	1.07		.00*
logSTAIC		1.91	0.60	.33	.00*	logCASI		3.09	0.61	.49	.00*
Step 2						**Step 2**					
Constant	0.15	-4.97	2.08		.02*	Constant	0.24	-8.62	2.00		.00*
logSTAIC		1.88	0.64	.32	.00*	logCASI		3.11	0.64	.50	.00*
lognegLE		0.03	0.17	.01	.86	lognegLE		-0.02	0.15	-.01	.90

Regression models for the corrected sample (N = 98). A correction was performed resulting in a corrected p threshold of q* = .04 (*p < q* (Benjamin and Hochberg, 1995)); * = q.

Table A 9: Moderation models with negLE as moderator in study 1

Effect of CASI on STAIC (R^{*2} = .65)							Effect of TAI on STAIC (R^{*2} = .26)							Effect of TAI on CASI (R^{*2} = .35)						
					95% CI							**95% CI**								**95% CI**
	b	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**
Constant	5.99	3.45	1.74	.09	-0.87	12.85		26.65	1.18	22.58	.00*	24.30	29.00		23.14	0.92	25.39	.00*	21.31	24.97
M	-0.12	0.35	-0.34	.73	-0.81	0.57		0.15	0.16	0.90	.37	-0.18	0.48		0.13	0.13	1.05	.30	-0.12	0.39
CASI	0.83	0.13	6.46	.00*	0.57	1.08	**TAI**	0.13	0.11	1.16	.25	-0.10	0.360	**TAI**	0.24	0.09	2.77	.01*	0.07	0.42
CASI* negLE	0.01	0.01	0.82	.41	-0.02	0.03	**TAI* negLE**	0.02	0.01	1.61	.11	-0.01	0.04	**TAI* negLE**	0.01	0.01	1.62	.25	-0.02	0.03

Moderation models for the corrected sample of (N= 98). A correction was performed resulting in a corrected p threshold of q* = .05 (*p < q* (Benjamin and Hochberg, 1995)); * = q.

Table A 10: Mediation with negLE as mediator in study 1

Effect TAI on STAIC by negLE						Effect of TAI on CASI					
				95% CI						**95% CI**	
	b	**SE B**	**p**	**LL**	**UL**		**b**	**SE B**	**p**	**LL**	**UL**
Total effect	0.36	0.08	.00*	0.20	0.53	**Total effect**	0.34	0.06	.00*	0.22	0.46
Model R^2	.27		.00*			**Model R^2**	.32		.07		
F	15.69					**F**	20.70				
Direct effect	0.26	0.08	.00*	0.10	0.43	**Direct effect**	0.32	0.06	.00*	0.19	0.44
Indirect effect	0.05	0.04		-0.02	0.15	**Indirect effect**	0.04	0.04		-0.01	0.12

Mediation models for the corrected samples of (N= 98); * = sig.

Table A 11: Sample description study 2

Variable	**Population**	**Mean**	**SD**	**Variance**	**kurtosis**	**skewness**
Age	All	11.42	1.55	2.39	0.23 (0.67)	0.07 (0.34)
	male	11.69	1.62	2.64	0.33 (0.83)	0.13 (0.43)
	female	10.97	1.33	1.76	-0.15 (1.04)	-0.65 (0.54)
Tanner	All	2.13	0.88	0.78	1.50 (0.69)	0.94 (0.35)
	male	2.11	1.03	1.06	1.16 (0.86)	1.08 (0.44)
	female	2.11	0.62	0.38	-0.10 (1.04)	1.08 (0.44)
CFT	All	110.45	13.89	193.05	-.033 (0.69)	0.33(0.35)
	male	109.39	15.24	232.25	-0.25 (0.86)	0.56 (0.44)
	female	112.08	11.73	137.48	-0.29 (1.04)	-0.13 (0.54)
STAIC	All	28.08	6.36	40.42	2.03 (0.67)	1.47 (0.34)
	male	28.10	6.60	43.54	0.89 (0.83)	1.21 (0.43)
	female	28.06	6.12	37.47	6.21 (1.04)	2.19 (0.54)
CASI	All	24.72	5.15	26.55	4.01 (0.68)	1.70 (0.35)
	male	24.45	4.57	20.90	-0.45 (0.85)	0.70 (0.43)
	female	25.17	6.09	37.09	6.34 (0.85)	2.38 (0.43)
TAI	All	6.21	8.41	70.69	3.18 (0.68)	1.93 (0.35)
	male	6.03	7.68	58.96	5.13 (0.85)	2.17 (0.43)
	female	6.50	9.70	94.03	2.18 (1.04)	1.78 (0.54)
negLE	All	6.09	5.69	32.34	2.71 (0.68)	1.75 (0.35)
	male	5.45	4.61	21.26	3.75 (0.85)	1.72 (0.43)
	female	7.11	7.12	50.69	1.20 (1.04)	1.51 (0.54)

Accuracy [overall, %correct]	All	95.62	7.17	14.34	22.06 (0.69)	-4.24 (0.35)
	male	96.02	4.56	20.76	3.43 (0.87)	-1.83 (0.45)
	female	94.76	10.11	102.16	15.38 (1.04)	-3.81 (0.54)
Accuracy [faceMatch, %correct]	All	98.37	2.84	8.08	0.92 (0.69)	-1.51 (0.35)
	male	98.15	2.91	8.46	0.46 (0.87)	-1.31 (0.45)
	female	91.67	2.85	8.17	2.44(1.04)	-1.91 (0.54)
Reaction time [overall, ms]	All	1211.79	360.13	129691.97	3.47 (0.69)	-1.57 (0.35)
	male	1260.45	260.78	68007.93	-0.17 (0.87)	-0.49 (0.45)
	female	1146.74	319.49	102080.72	6.77 (1.04)	-2.18 (0.54)
Reaction time [faceMatch, ms]	All	1297.86	360.13	129691.97	3.47 (0.69)	-1.57 (0.35)
	male	1376	289.80	83981.85	0.12 (0.87)	-0.67 (0.45)
	female	1246.06	346.55	120099.79	6.26 (1.04)	-2.10 (0.54)

Descriptive characterization of total sample of (N = 48); with variance, distribution and means, as well as stratified for sex.

Table A 12: Levens' test for the test of normal variance between groups (male/female) in study 2

Age	STAIC	CASI	TAI	negLE
F = 0.22	F = 0.50	F = 0.13	F = 1.02	F = 2.27
p = .64	*p* = .48	*p* = .72	*p* = .32	*p* = .14

Normality of variance within sex groups for the total sample (N = 48); Homogeneity of variance can be assumed for all variables. Homogeneity of variance can be assumed for all variables. A correction was performed resulting in a corrected p threshold or q* = .01 (*p < q* (Benjamin and Hochberg (1995)).

Table A 13: Kolmogorov-Smirnov test of the normal distribution within groups (male/female) in study 2

Age		STAIC		CASI		TAI		negLE	
male	female	male	female	male	female	male	female	male	female
D = 0.10	D = 0.14	D = 0.23	D = 0.20	D = 0.18	D = 0.25	D = 0.23	D = 0.28	D = 0.21	D = 0.28
p = .20	*p* = .20	*p* = .00	*p* = .05	*p* = .02*	*p* = .00*	*p* = .00*	*p* = .00*	*p* = .00*	*p* = .00*

Test for the normal distribution within sex groups for the total sample of (N = 48). A correction was performed resulting in a corrected p threshold or q* = .04 (*p < q* (Benjamin and Hochberg (1995)); * = q.

Table A 14: Mann-Whitney-U-test for group differences between males and females in study 2

	All	male	female	Statistics
N	48	30	18	
Age (SD)	11.4 (1.5)	11.7 (1.6)	11.0 (1.3)	*U=202, z= -1.3, p = .20*
Tanner	2.1 (0.9)	2.1 (1.0)	2.2 (0.6)	*U=209, z= -.86, p = .40*
IQ	110 (13.9)	109.4 (15.2)	112.1 (11.7)	*U=215, z= -.85, p = .41*
Phenotypes/Life events				
STAIC	28.1 (6.4)	28.1 (6.6)	28.1 (6.1)	*U=260, z= -.03, p = .98*
CASI	24.7 (5.2)	24.5 (4.6)	25.2 (6.1)	*U=250, z= -.25, p = .81*
TAI	6.0 (7.3)	6.1 (7.0)	5.8 (8.1)	*U=226, z= -.77, p = .45*
negLE	6.1 (5.7)	5.5 (4.6)	7.1 (7.1)	*U=240, z= -.46, p = .65*
Behavioural performance				
Accuracy [overall, %correct]	95.1(7.2)	96.2 (4.5)	94.8 (10.1)	*U= 240, z= -.10, p = .93*
Accuracy [faceMatch, %correct]	98.4 (2.8)	98.2 (2.9)	98.6 (2.9)	*U= 219, z= -.70, p = .51*
Reaction time [overall, ms]	1211.8 (285.3)	1253.6 (258.5)	1146.7 (319.5)	*U= 192, z= -1.2, p = .25*
Reaction time [faceMatch, ms]	1297.8 (360.1)	1331.2 (371.0)	1246.1 (346.6)	*U= 183, z= -1.4, p = .17*

Sex differences within the sample assessed for the total sample (N = 48). A correction was performed resulting in a corrected p threshold or q* = .005 (*p < q* (Benjamin and Hochberg (1995)).

Table A 15: Kolmogorov-Smirnov test for the normal distribution in study 2

Age	STAIC	CASI	TAI	negLE
D = .09	D = .21	D = .21	D = .23	D = .23
p = .20	*p* = .00*	*p* = .00*	*p* = .00*	*p* = .00*

Test for the normal distribution for the total sample of (N = 48). A correction was performed resulting in a corrected p threshold or q* = .04 (*p < q* (Benjamin and Hochberg (1995)). * = q

Table A 16: Spearman's correlation coefficient of anxiety measures, negative life events and age

	Age	STAIC	CASI	TAI	negLE	$acc_{overall}$	acc_{face+}	$rt_{overall}$*	rt_{face+}
Age	1	-.22	-.20	.05	-.34	.39	.12	-.45*	-.35
STAIC		1	.60*	.40*	.19	-.08	-.05	.27	.15
CASI			1	.40*	.27	.25	.20	.25	.20
TAI				1	.23	.09	-.06	-.05	.01
negLE					1	-.05	.04	.37	.34

For the total sample (n = 48) a correction was performed resulting in a corrected p threshold or q* = .03 (*p < q* (Benjamin and Hochberg, 1995)); * = q; Abbreviation: Acc = accuracy; rt = reaction times *face = face match condition.

Table A 17: Kolmogorov-Smirnov test of the Z standardised regression residuals of study 2

Cneg_SlIFG_S	TnegS_TrIFG_C	TnegS_TlIFG_C	TnegS_TrMFG_C	TnegS_SlIFG_S	TnegC_TrIFG_S	TnegC_TlIFG_S	TnegC_TrMFG_S
D = 0.08	D = 0.11	D = 0.07	D = 0.09	D = 0.08	D = 0.08	D = 0.05	D = 0.12
p = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .09

Test of normality of the residuals for the total sample of (N = 33), a correction was performed resulting in a corrected p threshold or q* = .006 (*p < q* (Benjamin and Hochberg, 1995)). Abbreviation: C = CASI, S = STAIC, T = TAI, neg = Negative life events, SlIFG = STAIC specific lIFG activation, TrIFG = TAI specific rIFG activation, TlIFG = TAI specific left IFG activation, TrMFG = TAI specific rMFG activation,

Table A 18: Moderation model with X = CASI, Y = STAIC, W = negLE, Z = STAIC_lIFG

Model Summary						
R	R^2	MSE	F	df1	df2	p
0.90	0.80	8.08	32.05	5	42	.000*
Model						
	coeff	Se	t	p	LLCI	ULCI
constant	6.29	3.62	1.7	.090	-1.03	13.61
CASI	0.85	0.15	5.7	.000*	0.55	1.15
negLE	-0.19	0.33	-0.6	.570	-0.84	0.47
Int_1	0.01	0.01	0.6	.530	-0.02	0.03
STAIC_lIFG	-4.57	8.76	-0.5	.605	-22.27	13.14
Int_2	0.37	0.35	1.1	.295	-0.34	1.09
Test(s) of highest order unconditional interaction(s):						
		R^2-chng	F	df1	df2	p
CASI*negLE	X*W	0.002	0.4	1	42	.530
CASI*STAIC_lIFG	X*Z	0.006	1.1	1	42	.296
	BOTH	0.010	1.0	2	42	.374

Note. ** indicating significant q* = .012 (*p < q* (Benjamin and Hochberg, 1995)*
Abbreviation: STAIC_lIFG = STAIC specific left IFG activation

Table A 19: Moderation models of the effect of TAI on CASI by brain activation

Moderation model with X = TAI, Y = CASI, W = negLE, Z = TAI_lIFG							Moderation model with X = TAI, Y = CASI, W = negLE, Z = TAI_rMFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.81	0.66	10.16	10.16	5	42	.000*	0.78	0.61	11.62	12.44	5	42	.000*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	22.19	0.84	26.3	.000*	20.48	23.89	constant	21.87	1.04	21.0	.000*	19.76	23.97
TAI	3.34	0.12	2.8	.007*	0.10	0.57	TAI	0.52	0.15	2.4	.002*	0.21	0.83
negLE	0.05	0.13	0.4	.705	-0.22	0.31	negLE	0.02	0.14	0.1	.904	-0.26	0.30
Int_1	0.02	0.01	3.08	.004*	0.01	0.04	Int_1	0.02	0.01	2.5	.018	0.00	0.04
TAI_lIFG	-0.48	1.56	-0.31	.758	-3.63	2.66	TAI_rMFG	-1.43	2.22	-0.7	.522	-5.91	3.05
Int_2	1.04	0.21	5.0	.000*	0.62	1.50	Int_2	0.88	0.22	3.9	.000*	0.43	1.33
Test(s) of highest order unconditional interaction(s):							Test(s) of highest order unconditional interaction(s):						
		R^2-chng	F	df1	df2	p			R^2-chng	F	df1	df2	p
TAI*negLE	X*W	0.05	9.5	1	42	.004*	TAI*negLE	X*W	0.06	6.07	1	42	.018
TAI*TAI_lIFG	X*Z	0.15	24.8	1	42	.000*	TAI*TAI_rMFG	X*Z	0.15	15.45	1	42	.000*
	BOTH	0.21	16.9	2	42	.000*		BOTH	0.22	11.37	2	42	.000*

Note. ** indicating significant q* = .012 (*p < q* (Benjamin and Hochberg, 1995), ** = q; Abbreviation: TAI_lIFG = TAI specific left IFG activation, TAI_rMFG = TAI specific right MFG activation

Table A 20: Moderation models of the effect of TAI on STAIC by brain (1)

Moderation model with X = TAI, Y = STAIC, W = negLE, Z = STAIC_lIFG							Moderation model with X = TAI, Y = STAIC, W = negLE, Z = TAI_rIFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.76	0.57	17.34	10.66	5	42	.000*	0.56	0.43	22.99	6.08	5	42	.000*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	25.22	1.20	21.1	.000*	22.81	27.64	constant	25.49	1.40	18.2	.000*	22.66	28.32
TAI	0.19	0.14	1.4	.185	-0.09	0.47	TAI	0.26	0.17	1.5	.132	-0.08	0.60
negLE	0.01	0.17	0.5	.962	-0.34	0.35	negLE	0.01	0.19	0.1	.945	-0.38	0.41
Int_1	0.03	0.01	2.4	.021	0.00	0.05	Int_1	0.03	0.01	2.3	.025	0.00	0.06
STAIC_lIFG	3.72	2.61	1.4	.163	-1.56	9.00	TAI_rIFG	-2.28	5.36	-0.4	.672	-13.11	8.55
Int_2	0.89	0.30	3.0	.006*	0.28	1.51	Int_2	1.27	0.51	2.5	.017	0.24	2.20
Test(s) of highest order unconditional interaction(s):							Test(s) of highest order unconditional interaction(s):						
		R^2-chng	F	df1	df2	p			R^2-chng	F	df1	df2	p
TAI*negLE	X*W	0.06	5.7	1	42	.021	TAI*negLE	X*W	0.08	5.43	1	42	.025
TAI*STAIC_lIFG	X*Z	0.09	8.6	1	42	.006*	TAI*TAI_rIFG	X*Z	0.09	6.16	1	42	.017
	BOTH	0.15	7.0	2	42	.002*		BOTH	0.13	4.62	2	42	.016

Note. ** indicating significant q* = .012 (*p < q* (Benjamin and Hochberg, 1995), ** = q; Abbreviation: STAIC_lIFG = STAIC specific left IFG activation, TAI_rIFG = TAI specific right IFG activation

Table A 21: Moderation models of the effect of TAI on STAIC by brain (2)

Moderation model with X = TAI, Y = STAIC, W = negLE, Z = TAI_lIFG							Moderation model with X = TAI, Y = STAIC, W = negLE, Z = TAI_rMFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.72	0.52	19.43	8.66	5	42	.000*	0.67	0.45	22.19	6.6	5	42	.000*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	24.80	1.28	19.4	.000*	22.21	27.39	constant	25.08	1.44	17.5	.000*	22.17	27.97
TAI	0.40	0.16	2.5	.017	0.08	0.73	TAI	0.54	0.21	2.6	.015	0.11	0.97
negLE	0.06	0.18	0.3	.747	-0.30	0.42	negLE	-0.01	0.20	-0.1	.946	-0.41	0.38
Int_1	0.02	0.01	1.5	.130	-0.01	0.04	Int_1	0.02	0.01	1.72	.094	-0.00	0.05
TAI_lIFG	2.56	3.29	0.78	.440	-4.08	9.21	TAI_rMFG	1.50	3.07	0.5	.628	-4.70	7.70
Int_2	0.94	0.34	2.8	.009*	0.25	1.62	Int_2	0.74	0.31	2.4	.022	0.11	1.36
Test(s) of highest order unconditional interaction(s):							Test(s) of highest order unconditional interaction(s):						
		R^2-chng	F	df1	df2	p			R^2-chng	F	df1	df2	p
TAI*negLE	X*W	0.03	2.3	1	42	.130	TAI*negLE	X*W	0.04	2.95	1	42	.094
TAI*TAI_lIFG	X*Z	0.09	7.6	1	42	.009*	TAI*TAI_rMFG	X*Z	0.08	5.73	1	42	.022
	BOTH	0.12	5.2	2	42	.010*		BOTH	0.13	4.60	2	42	.016

Note. ** indicating significant q* = .012 (*p < q* (Benjamin and Hochberg, 1995)*, * = q; Abbreviation: TAI_lIFG = TAI specific left IFG activation, TAI_rMFG = TAI specific right MFG activation

Table A 22: Mediation models with brain activation and negLE as mediators (1)

Mediation model with X = CASI, Y = STAIC, M1 = negLE, M2 = STAIC_lIFG							Mediation model with X = TAI, Y = CASI, M1 = negLE, M2 = TAI_rIFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.50	0.25	25.30	14.7	3	44	.000*	0.61	0.38	17.64	8.45	3	42	.000*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	3.19	2.20	1.5	.154	-1.25	7.62	constant	21.11	1.00	20.9	.000*	19.09	23.15
CASI/Direct effect	0.98	0.10	10.3	.000*	0.79	1.18	TAI/Direct effect	0.31	0.11	2.8	.009	0.08	0.54
negLE	-0.00	0.09	-0.1	.965	-0.18	0.17	negLE	0.32	0.12	2.8	.008	0.09	0.56
STAIC_lIFG	4.52	1.41	3.2	.003*	1.66	7.37	TAI_rIFG	1.96	3.79	0.5	.609	-5.70	9.62
Indirect effect of predictors on STAIC through							Indirect effect of predictor on CASI through						
CASI*negLE	-0.00	0.04			-0.10	0.09	TAI*negLE	0.10	0.08			-0.02	0.25
CASI*STAIC_lIFG	0.03	0.04			-0.06	0.11	TAI*TAI_rIFG	-0.03	0.06			-0.14	0.25
CASI*negLE* STAIC_lIFG	-0.00	0.03			-0.07	0.05	TAI*negLE* TAI_rIFG	0.00	0.06			-0.02	0.02

Note. * = q; Abbreviation: STAIC_lIFG = STAIC specific left IFG activation, TAI_rIFG = TAI specific right IFG activation.

Table A 23: Mediation models of the effect of TAI on CASI with brain activation and negLE as mediators

Mediation model with X = TAI, Y = CASI, M1 = negLE, M2 = TAI_lIFG							Mediation model with X = TAI, Y = CASI, M1 = negLE, M2 = TAI_rMFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.67	0.45	15.65	11.3	3	42	.000*	0.62	0.39	17.36	8.8	3	42	.000*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	20.89	0.91	22.8	.000*	19.04	22.73	constant	21.41	1.00	22.4	.000*	19.48	23.34
TAI/Direct effect	0.36	0.10	3.6	.000*	0.16	0.56	TAI/Direct effect	0.34	0.11	3.0	.005*	0.11	0.56
negLE	0.32	0.11	2.8	.007*	0.09	0.53	negLE	0.30	0.12	2.5	.016*	0.06	0.54
TAI_lIFG	5.67	2.39	2.4	.022*	0.85	10.48	TAI_rMFG	2.26	2.34	1.0	.339	-2.46	6.99
Indirect effect of predictors on CASI through							Indirect effect of predictor on CASI						
TAI*negLE	0.10	0.07			-0.02	0.23	TAI*negLE	0.09	0.07			-0.10	0.24
TAI*TAI_lIFG	-0.08	0.05			-0.18	0.00	TAI*TAI_rMFG	-0.05	0.05			-0.16	0.04
TAI*negLE* TAI_lIFG	0.01	0.02			-0.02	0.04	TAI*negLE* TAI_rMFG	0.01	0.01			-0.02	0.03

Note. * = q; Abbreviation: TAI_lIFG = TAI specific left IFG activation, TAI_rMFG = TAI specific right MFG activation.

Table A 24: Mediation models of the effect of TAI on STAIC with brain activation and negLE as mediators (1)

Mediation model with X = TAI, Y = STAIC, M1 = negLE, M2 = STAIC_lIFG							Mediation model with X = TAI, Y = STAIC, M1 = negLE, M2 = TAI_rIFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.65	0.42	22.32	10.2	3	42	.000*	0.55	0.30	26.94	6.0	3	42	.002*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	23.61	1.09	21.6	.000*	21.41	25.82	constant	23.87	1.24	19.2	.000*	21.36	26.38
TAI/Direct effect	0.39	0.11	3.4	.002*	0.16	0.62	TAI/Direct effect	0.38	0.14	2.7	.011*	0.09	0.65
negLE	0.27	0.13	2.0	.049*	0.02	0.53	negLE	0.30	0.15	2.1	.043*	0.01	0.59
STAIC_lIFG	7.51	2.39	3.1	.003*	2.68	12.35	TAI_rIFG	4.52	4.69	1.0	.341	-4.95	13.99
Indirect effect of predictors on STAIC through							Indirect effect of predictor on STAIC through						
TAI*negLE	0.08	0.07			-0.02	0.24	TAI*negLE	0.09	0.08			-0.02	0.26
TAI*STAIC_lIFG	-0.08	0.06			-0.20	0.02	TAI*TAI_rIFG	-0.06	0.07			-0.22	0.07
TAI*negLE* STAIC_lIFG	0.01	0.03			-0.03	0.07	TAI*negLE* TAI_rIFG	0.00	0.01			-0.03	0.03

Note. * = q; Abbreviation: STAIC_lIFG = STAIC specific left IFG activation, TAI_rIFG = TAI specific right IFG activation.

Table A 25: Mediation models of the effect of TAI on STAIC with brain activation and negLE as mediators (2)

Mediation model with X = TAI, Y = STAIC, M1 = negLE, M2 = TAI_lIFG							Mediation model with X = TAI, Y = STAIC, M1 = negLE, M2 = TAI_rMFG						
Model Summary													
R	R^2	MSE	F	df1	df2	p	R	R^2	MSE	F	df1	df2	p
0.63	0.40	23.26	9.2	3	42	.000*	0.57	0.33	25.99	6.8	3	42	.001*
Model							Model						
	coeff	Se	t	p	LLCI	ULCI		coeff	Se	t	p	LLCI	ULCI
constant	23.68	1.12	21.3	.000*	21.43	25.93	constant	24.51	1.17	21.0	.000*	22.15	26.87
TAI/Direct effect	0.42	0.12	3.5	.001*	0.18	0.66	TAI/Direct effect	0.41	0.14	3.0	.004*	0.14	0.69
negLE	0.29	0.14	2.1	.039*	0.02	0.56	negLE	0.26	0.15	1.8	.009*	-0.04	0.55
TAI_lIFG	8.10	2.91	2.8	.008*	2.22	13.97	TAI_rMFG	4.54	2.86	1.6	.120	-1.24	10.32
Indirect effect of predictors on STAIC through							Indirect effect of predictor on STAIC through						
TAI*negLE	0.19	0.07			-0.02	0.25	TAI*negLE	0.08	0.07			-0.02	0.25
TAI*TAI_lIFG	-0.11	0.07			-0.26	0.00	TAI*TAI_rMFG	-0.10	0.07			-0.24	0.00
TAI*negLE* TAI_lIFG	0.01	0.02			-0.04	0.06	TAI*negLE* TAI_rMFG	0.02	0.02			-0.01	0.05

Note. * = q; Abbreviation: TAI_lIFG = TAI specific left IFG activation, TAI_rMFG = TAI specific right MFG activation.

Table A 26: Sample description study 3 prevention group

Variable	Population	Mean	SD	Variance	Kurtosis	Skewness
Age	All	10.67	1.34	1.80	-0.92 (0.80)	-0.46 (0.41)
	male	10.11	1.50	2.25	-0.64 (1.59)	0.09(0.79)
	female	10.82	1.29	1.66	-0.76 (0.89)	-0.60 (0.47)
Tanner	All	1.58	0.11	0.38	-0.52 (0.80)	0.56 (0.41)
	male	1.29	0.49	0.49	-0.84 (1.59)	1.23 (0.79)
	female	1.65	0.63	0.40	-0.55 (0.89)	0.41 (0.46)
CFT	All	110.33	16.63	276.42	0.34 (0.80)	0.32 (0.41)
	male	106.43	11.83	139.95	1.38 (1.59)	-1.22 (0.79)
	female	111.65	17.10	291.44	-0.17 (0.89)	0.54 (0.46)
STAIC_T0	All	32.42	5.49	30.13	1.45 (0.80)	0.84 (0.41)
	male	29.57	6.68	44.62	1.05 (0.79)	1.20 (1.59)
	female	33.27	5.04	25.41	2.35 (0.89)	1.27 (0.46)
CASI_T0	All	27.94	3.86	14.87	1.29 (0.80)	0.92 (0.41)
	male	27.00	3.51	12.33	0.64 (1.59)	0.45 (0.79)
	female	28.19	3.97	15.76	1.38 (0.89)	0.98 (0.46)
TAI_T0	All	7.42	8.43	71.00	0.31 (0.80)	1.13 (0.41)
	male	9.71	10.55	111.24	-0.34 (1.59)	0.90 (0.79)
	female	5.73	6.81	46.37	0.37 (0.89)	1.19 (0.46)
negLE	All	6.48	5.31	28.20	5.93 (0.80)	1.00 (0.41)
	male	4.14	4.10	16.81	-0.57 (1.59)	0.83 (0.79)
	female	7.42	5.47	29.93	0.17 (0.89)	0.81 (0.46)
STAIC_T1	All	29.09	5.56	30.90	-0.64 (0.80)	0.68 (0.41)
	male	28.00	5.91	35.00	-1.44 (1.59)	0.69 (0.79)
	female	29.38	5.54	30.73	-0.47 (0.89)	0.75 (0.46)
CASI_T1	All	25.60	3.99	15.94	0.81 (80)	0.63 (0.41)
	male	23.14	2.97	8.81	-0.18 (1.59)	-0.84 (0.79)
	female	26.23	4.03	16.19	0.52 (0.89)	0.65 (0.46)
TAI_T1	All	5.35	6.35	40.37	3.29 (0.82)	1.67 (0.42)
	male	7.14	6.47	41.81	-1.97 (1.59)	0.08 (0.79)
	female	4.83	6.36	40.49	2.20 (0.47)	5.86 (0.92)

Descriptive characterization of total sample of (N = 33); with variance, distribution and means, as well as stratified for sex; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 27: Sample description study 3 control group

Variable	Population	Mean	SD	Variance	Kurtosis	Skewness
Age	All	10.81	1.25	1.55	-2.58 (2.00)	-0.43 (0.91)
	male	10.50	0.33	0.22	-----	-----
	female	10.34	0.86	2.20	-----	1.51 (1.23)
Tanner	All	1.38	0.74	0.55	3.21 (1.48)	1.95 (0.75)
	male	1.33	0.33	0.58	-----	1.73 (1.23)
	female	1.40	0.40	0.80	5.00 (2.00)	2.24 (0.91)
CFT	All	116.71	13.16	173.24	-1.85 (1.59)	-0.07 (0.79)
	male	113.67	9.56	274.33	--------	0.45 (1.23)
	female	119.0	6.07	147.33	-5.93 (2.62)	0.00 (1.01)
STAIC_T0	All	31.37	5.29	27.98	-0.38 (1.48)	0.03 (0.75)
	male	30.00	2.64	21.00	--------	-0.94 (1.23)
	female	32.20	2.69	36.20	-0.04 (2.00)	-0.19 (0.91)
CASI_T0	All	26.63	4.24	17.98	-1.32 (1.48)	0.33 (0.75)
	male	27.00	1.53	7.00	-------	1.45 (1.23)
	female	26.40	2.36	27.80	-2.56 (2.00)	0.50 (0.91)
TAI_T0	All	6.29	7.14	50.91	-1.53 (1.59)	0.61 (0.79)
	male	0.00	0.00	0.00	---	-----
	female	8.80	3.12	48.70	-1.79 (2.00)	-0.12 (0.91)
negLE	All	4.00	3.27	10.67	0.72 (1.59)	1.09 (0.79)
	male	5.33	2.60	20.33	------	0.33 (1.23)
	female	3.00	1.08	4.67	1.50 (2.62)	1.19 (1.01)
STAIC_T1	All	28.86	6.53	48.14	-0.90 (1.59)	0.47 (0.79)
	male	25.33	2.73	22.33	----	-1.39 (1.22)
	female	31.50	3.86	59.67	-4.41 (2.62)	-0.17 (1.01)
CASI_T1	All	24.43	3.51	12.29	1.14 (1.58)	0.47(0.79)
	male	24.00	1.73	9.00	------	0.00 (1.22)
	female	24.75	2.14	18.25	2.92 (2.62)	1.73 (1.01)
TAI_T1	All	6.00	6.53	42.67	-0.49 (1.59)	0.83 (0.79)
	male	0.33	0.33	0.33	-----	1.73 (1.22)
	female	10.25	2.69	28.92	-1.71 (2.62)	0.57 (1.01)

Descriptive characterization of total sample of (N = 8); with variance, distribution and means, as well as stratified for sex; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 28: Levens` test of normal variance between groups (male/female) in study 3 (prevention group)

Age	STAIC_T0	CASI_T0	TAI_T0	negLE	STAIC_T1	CASI_T1	TAI_T1
F = 0.12 *p* = .73	F = 0.54 *p* = .47	F = 0.64 *p* = .84	F = 3.85 *p* = .06	F = 1.17 *p* = .29	F = 0.13 *p* = .72	F = 0.45 *p* = .51	F = 0.46 *p* = .50

Normality of variance within sex groups for the total sample (N = 33); Homogeneity of variance can be assumed for all variables.A correction was performed resulting in a corrected p threshold or q* = .006 (*p < q* (Benjamin and Hochberg (1995)). Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 29: Kolmogorov-Smirnov test of the normal distribution within groups (male/female) in study 3 (prevention group)

Age		STAIC_T0		CASI_T0		TAI_T0		negLE		STAIC_T1		CASI_T1		TAI_T1	
male	female	male	female	male	female	male	female	male	female	male	female	male	female	male	female
D = 0.13 *p* = .20	D = 0.16 *p* = .10	D = 0.18 *p* = .20	D = 0.13 *p* = .20	D = 0.14 *p* = .20	D = 0.14 *p* = .00*	D = 0.24 *p* = .20	D = 0.22 *p* = .00*	D = 0.21 *p* = .20	D = 0.16 *p* = .10	D = 0.20 *p* = .20	D = 0.17 *p* = .05	D = 0.19 *p* = .20	D = 0.14 *p* = .20	D = 0.26 *p* = .18	D = 0.22 *p* = .00*

Test for the normal distribution within sex groups for the total sample of (N = 33) A correction was performed resulting in a corrected p threshold or q* = .009 (*p < q* (Benjamin and Hochberg (1995)). * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 30: Mann-Whitney-U-test for group differences between males and females in study 3

	All	male	female	Statistics
N	33	7	26	
Age (SD)	10.7 (1.3)	10.1 (1.5)	10.8 (1.3)	*U= 62.5, z= -1.3, p = .21*
Tanner	1.6 (0.6)	1.3 (0.5)	1.7 (0.6)	*U= 62.5, z= -1.4, p = .16*
IQ	110 (16.6)	104.7 (13.6)	111.8 (17.3)	*U= 78.5, z= -0.6, p = .59*
Phenotypes/Life events				
STAIC_T0	32.4 (5.5)	29.6 (6.7)	33.2 (5.0)	*U= 55, z= -1.6, p = .11*
STAIC_T1	29.1 (5.6)	28.0 (5.9)	29.4 (4.0)	*U= 72, z= -0.84, p = .40*
CASI_T0	28.0 (3.9)	27.0 (3.5)	28.2 (4.0)	*U= 74.5, z= -0.73, p = .46*
CASI_T1	25.6(4.0)	23.1(3.0)	26.2 (4.0)	*U= 49.0, z= -1.9, p = .06*
TAI_T0	7.4 (8.4)	11.6 (10.1)	6.3 (7.8)	*U= 72.0, z= -0.85, p = .39*
TAI_ T1	5.4 (5.7)	7.14 (6.5)	5.0 (5.5)	*U= 61.0, z= -1.1, p = .27*
negLE	6.5 (5.3)	4.1 (4.1)	7.1 (5.5)	*U= 55.5, z= -1.6, p = .12*

Sex differences within the sample assessed for the total sample (N = 33). A correction was performed resulting in a corrected p threshold or q* = .005 (*p < q* (Benjamin and Hochberg (1995)). A correction was performed resulting in a corrected p threshold or q* = .009 (*p < q* (Benjamin and Hochberg (1995)); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 31 Kolmogorov-Smirnov test for the correlation of study 3

Age	STAIC_T0	CASI_T0	TAI_T0	negLE	STAIC_T1	CASI_T1	TAI_T1	STAIC_diff	CASI_diff	TAI_diff
D = 0.14	D = 0.11	D = 0.15	D = 0.23	D = 0.17	D = 0.16	D = 0.13	D = 0.20	D = 0.15	D = 0.15	D = 0.15
p = .13	*p* = .20	*p* = .06	*p* = .00*	*p* = .02	*p* = .20	*p* = .05	*p* = .00*	*p* = .14	*p* = .10	*p* = .24

Test of normality of the residuals for the total sample of (N = 33). A correction was performed resulting in a corrected p threshold or q* = .009 (*p < q* (Benjamin and Hochberg (1995)). * = q A correction was performed resulting in a corrected p threshold or q* = .009 (*p < q* (Benjamin and Hochberg (1995)); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data, _diff = Intervention induced change.

Table A 32: Kolmogorov-Smirnov test of the Z standardised regression residuals of study 3

SnegS	CnegC	TnegT	TnegC	CnegS	TnegS	SnegSdiff	CnegCdiff	TnegTdiff
D = 0.11	D = 0.08	D = 0.15	D = 0.12	D = 0.12	D = 0.11	D = 0.12	D = 0.09	D = 0.15
p = .20	*p* = .20	*p* = .06	*p* = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .20	*p* = .07

Test of normality of the residuals for the total sample of (N = 33). A correction was performed resulting in a corrected p threshold or q* = .009 (*p < q* (Benjamin and Hochberg (1995)). Abbreviation C = CASI, S = STAIC, T = TAI, neg = Negative life events, diff = intervention induced change.

Table A 33: Mediation with negLE as mediator in study 3

Effect of CASI_T0 on STAIC_T1						Effect TAI_T0 on CASI_T1						Effect of TAI_T0 on STAIC_T1					
				95% CI						95% CI						95% CI	
	b	SE B	p	LL	UL		b	SE B	p	LL	UL		b	SE B	p	LL	UL
Total effect	0.38	0.25	.14	-0.13	0.88	**Total effect**	0.20	0.09	.03	0.02	0.37	**Total effect**	0.13	0.13	.31	-0.12	0.39
Model R^2	0.13		.13			**Model R^2**	0.15		.09			**Model R^2**	0.10		.22		
F	2.17					**F**	2.68					**F**	1.59				
Direct effect	0.35	0.25	.16	-0.15	0.86	**Direct effect**	0.19	0.09	.03*	0.02	0.37	**Direct effect**	0.12	0.12	.33	-0.13	0.38
Indirect effect	0.02	0.12		-0.14	0.34	**Indirect effect**	0.00	0.02		-0.03	0.05	**Indirect effect**	0.01	0.05		-0.06	0.14

Mediation models for the samples of (N= 33). * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 34: Moderation with negLE as moderator in study 3

Effect of CASI_T0 on STAIC_T1 *(R^{*2} = .19)*							Effect of TAI_T0 on CASI_T1 *(R^{*2} = .17)*							Effect of TAI_T0 on STAIC_T1 *(R^{*2} = .13)*						
					95% CI							95% CI						95% CI	
	b	SE B	t	p	LL	UL		b	SE B	t	p	LL	UL		b	SE B	t	p	LL	UL
Constant	8.53	9.22	0.93	.36	-10.34	27.39	**Constant**	23.45	1.42	16.56	.00*	20.55	26.34	**Constant**	25.35	2.01	12.63	.00*	21.45	29.46
M	2.60	1.62	1.61	.12	-0.71	5.92	**M**	-0.01	0.02	-0.67	.51	-0.05	0.03	**M**	0.50	0.28	1.79	.08	-0.07	1.07
CASI_T0	0.67	0.33	2.06	.05	0.01	1.34	**TAI_T0**	0.26	0.13	2.00	.06	-0.01	0.53	**TAI_T0**	0.28	0.19	1.50	.14	-0.10	0.66
CASI_T0* negLE	-0.08	0.06	-1.50	.16	-0.20	0.03	**TAI_T0* negLE**	-0.01	0.02	-0.67	.51	-0.05	0.03	**TAI_T0* negLE**	-0.03	0.03	-1.13	.27	-0.09	0.03

Moderation models for the corrected sample of (N = 33). A correction was performed resulting in a corrected p threshold or q* = .008 (*p < q* (Benjamin and Hochberg (1995)). * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 35: Mediation with negLE as mediator of pre on post data in study 3

Effect of STAIC_T0 on STAIC_T1						Effect CASI_T0 on CASI_T1						Effect of TAI_T0 on TAI_T1					
				95% CI						95% CI						95% CI	
	b	SE B	p	LL	UL		b	SE B	p	LL	UL		b	SE B	p	LL	UL
Total effect	0.26	0.18	.15	-0.10	0.05	**Total effect**	0.64	0.15	.00	0.35	0.94	**Total effect**	0.41	0.13	.00	0.15	0.68
Model R^2	0.07		.16			**Model R^2**	0.38		.00			**Model R^2**	0.30		.03		
F	2.17					**F**	18.69					**F**	3.67				
Direct effect	0.29	0.18	.11	-0.07	0.66	**Direct effect**	0.63	0.15	.00	0.33	0.94	**Direct effect**	0.44	0.14	.01	0.14	0.73
Indirect effect	0.04	0.07		-0.07	0.23	**Indirect effect**	0.00	0.04		-0.04	0.10	**Indirect effect**	-0.02	0.05		-0.14	0.05

Mediation models for the samples of (N= 33); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 36: Moderation with negLE as moderator of pre on post data in study 3

Effect of STAIC_T0 on STAIC_T1 *(R^{*2} = .27)*							Effect of CASI_T0 on CASI_T1 *(R^{*2} = .38)*							Effect of TAI_T0 on TAI_T1 *(R^{*2} = .31)*						
					95% CI							**95% CI**						**95% CI**	
	b	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**
Constant	7.03	9.93	0.71	.49	-13.28	27.34	**Constant**	6.22	5.76	1.08	.29	-5.59	18.04	**Constant**	6.22	5.76	1.08	.29	-5.59	18.04
M	2.35	0.33	2.06	.05	0.01	1.34	**M**	0.42	1.01	0.41	.68	-1.66	2.49	**M**	0.42	1.01	0.41	.68	-1.66	2.49
STAIC_T0	0.67	0.33	2.06	.05	0.01	1.34	**CASI_T0**	0.68	0.21	3.34	.00*	0.27	1.10	**TAI_T0**	0.68	0.21	3.34	.00*	0.27	1.10
STAIC_T0* negLE	-0.07	0.04	-1.66	.11	-0.15	0.02	**CASI_T0* negLE**	-0.01	0.04	-0.38	.71	-0.09	0.06	**TAI_T0* negLE**	-0.01	0.04	-0.38	.71	-0.09	0.06

Moderation models for the corrected sample of (N = 33). A correction was performed resulting in a corrected p threshold or q* = .008 (*p < q* (Benjamin and Hochberg (1995)); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 37: Moderation with negLE as moderator on intervention induced changes in study 3

Effect of STAIC_T0 on STAIC_diff *(R^{*2} = .45)*							Effect of CASI_T0 on CASI_diff (R^{*2} = .17)							Effect of TAI_T0 on TAI_diff (R^{*2} = .56)						
					95% CI							**95% CI**						**95% CI**	
	b	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**		**b**	**SE B**	**t**	**p**	**LL**	**UL**
Constant	-6.38	9.78	-0.65	.51	-26.39	13.63	**Constant**	-6.22	5.78	-1.08	.29	-18.04	5.59	**Constant**	-3.19	2.01	-1.59	.12	-7.32	0.93
M	-2.40	1.27	-1.89	.07	-5.00	0.20	**M**	-0.42	1.02	-0.41	.68	-2.49	1.66	**M**	0.50	0.28	1.79	.08	-0.07	1.07
STAIC_T0	0.31	0.32	0.95	.35	-0.35	0.96	**CASI_T0**	0.32	0.21	1.54	.13	-0.10	0.74	**TAI_T0**	0.70	0.17	3.96	.00*	0.34	1.06
STAIC_T0* negLE	0.07	0.04	1.74	.09	-0.01	0.16	**CASI_T0* negLE**	0.01	0.04	0.38	.71	-0.05	0.08	**TAI_T0* negLE**	-0.00	0.03	-0.09	.93	-0.06	0.05

Moderation models for the corrected sample of (N = 33). A correction was performed resulting in a corrected p threshold or q* = .004 (*p < q* (Benjamin and Hochberg (1995)); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

Table A 38: Mediation with negLE as mediator of pre on post data on intervention induced changes in study 3

Effect of STAIC_T0 on STAIC_diff						Effect CASI_T0 on CASI_diff						Effect of TAI_T0 on TAI_diff					
				95% CI						**95% CI**						**95% CI**	
	b	**SE B**	**p**	**LL**	**UL**		**b**	**SE B**	**p**	**LL**	**UL**		**b**	**SE B**	**p**	**LL**	**UL**
Total effect	0.63	0.16	.00*	0.30	0.97	**Total effect**	0.35	0.14	.02	0.06	0.63	**Total effect**	0.63	0.11	.00*	0.40	0.86
Model R^2	0.33		.00*			**Model R^2**	0.16		.06			**Model R^2**	0.51		.00*		
F	7.98					**F**	3.02					**F**	15.76				
Direct effect	0.67	0.17	.00*	0.33	1.01	**Direct effect**	0.35	0.14	.02	0.06	0.64	**Direct effect**	0.63	0.11	.00*	0.40	0.86
Indirect effect	-0.04	0.06		-0.19	0.34	**Indirect effect**	-0.00	0.03		-0.08	0.05	**Indirect effect**	-0.02	0.03		-0.04	0.07

Mediation models for the samples of (N= 33); * = q; Abbreviation: _T0 = pre intervention data, _T1 = post intervention data.

8.2 Informed consents

8.2.1 Study 239/15

8.2.1.1 Parents/Legal guardians

Universitätsklinikum Würzburg

Klinik und Poliklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie
Direktor: Prof. Dr. med. Marcel Romanos

Klinik und Poliklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie · Füchsleinstr. 15 · 97080 Würzburg

Studienaufklärung
für Eltern/Sorgeberechtigte von minderjährigen Proband

Therapie-induzierte Veränderungen von Hirnaktivierung während der Verarbeitung emotionaler Reize bei Kindern

Liebe Eltern, liebe Sorgeberechtige,

vielen Dank für Ihr Interesse an unserer Untersuchung. Als Entscheidungshilfe möchten wir Ihnen auf den folgenden Seiten ausführliche Informationen über unsere Studie geben. Wir haben die Informationen bewusst ausführlich gestaltet, damit Sie sich ein umfassendes Bild von unserer Untersuchung machen können. Bitte lesen Sie die folgenden Informationen sorgfältig durch, bevor Sie sich mit Ihrem Kind für eine Teilnahme an unserer Studie entscheiden. Wenn Sie und Ihr Kind teilnehmen möchten, füllen Sie bitte die Einverständniserklärung aus und unterschreiben Sie diese.

Anliegen der funktionellen Magnetresonanztomographie - Studie

Angsterkrankungen zählen zu den häufigsten psychischen Erkrankungen überhaupt- in Europa sind über 60 Millionen Menschen davon bestroffen. Angsterkrankungen entstehen bereits im Kindesalter und können die Patienten trotz guter Therapien sehr belasten. Obwohl Angststörungen die häufigsten psychischen Störungen im Kindes- und Jugendalter sind, liegen noch immer zu wenige wissenschaftlich gesicherte Erkenntnisse dazu vor. Es ist das Ziel unserer Studie, Angsterkrankungen im Kindes- und Jugendalter besser verstehen und behandeln zu können.

Diese funktionelle Magnetresonanztomographie (fMRT) – Studie ist an eine multizentrische Therapiestudie angegliedert. Diese Therapiestudie ist Teil des Forschungsnetzwerks zu Angststörungen und wird durch das Bundesministerium für Bildung und Forschung (BMBF) finanziell gefördert. Im Rahmen dieser Therapiestudie werden an vier Universitäten - Bochum, Dresden, Marburg und Würzburg - 400 Kinder mit Angststörungen mit kognitiver Verhaltenstherapie behandelt. Die Zusammenarbeit der vier Universitäten wird es uns erlauben, eine große Zahl von Kindern mit Angststörungen zu behandeln und damit aussagekräftige Ergebnisse zu erhalten.

Zur Untersuchung von therapie-abhängigen Veränderungen dient unter anderem diese fMRT-Studie, in die folgenden zwei Fragestellungen untersucht werden: *(1)* Verarbeiten Kinder mit Angststörungen emotionale Reize anders als Gleichaltrige ohne Angsterkrankungen? Und, wenn ja, zeigen sich diese in auch in der Arbeitsweise des Gehirns? Hierzu möchten wir gerne Ihr Kind als sogenannten Kontrollprobanden (Kind ohne

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Angsterkrankung) untersuchen und die Ergebnisse mit denen von Kindern mit Angsterkrankungen vor ihrer Therapie vergleichen.

(2) Lassen sich Therapieerfolge auf Ebene der Verarbeitungsweise des Gehirns messen? Und, wenn ja, sind die Veränderungen als eine Normalisierung zu verstehen? Zu der Bearbeitung dieser Fragestellung werden Kinder mit Angststörungen unmittelbar vor und nach der Therapie untersucht, sowie nach 6 Monaten. Hierfür würden wir Ihr Kind als Kontrollproband ebenfalls gerne nach 6 Monaten erneut untersuchen um Veränderungen, die aufgrund einer normalen Entwicklung wie bei Ihrem Kind von Veränderungen durch die Therapie bei den Kindern mit Angsterkrankungen vergleichen zu können.

In dieser Studie fokussieren wir uns auf die Verarbeitung emotionaler Reize in Form von Gesichtern mit unterschiedlichen Gefühlsausdrücken. Bei der Verarbeitung derartiger Bilder sind vor allem zwei Gedankenbereiche aktiv-die Wahrnehmung von Gefühlen, die oft mit einer Gefühlsübertragung einher geht, d.h. als Betrachter eines lachenden Gesichts muss ich ebenfalls lächeln. Auf der anderen Seite sind rationale Kontrollmechanismen aktiv, die die Gefühle in einem, für mein eigenes Wohl, angemessenen Rahmen halten.

Diese beiden Gedankenbereiche sind mit ganz bestimmten Gehirnstrukturen verbunden- die Amygdala ist bei der Verarbeitung von Gefühlen aktiv, der präfrontale Kortex bei der Regulierung der Gefühle. Diese beide Strukturen inkl. ihrer Hilfsstrukturen untersuchen wir in Kindern mit und ohne Angsterkrankungen sowie vor und nach der Therapie sowie nach 6 Monaten. Die fMRT-Untersuchuchungen sollen zeitnah zu den Laboruntersuchungen durchgeführt werden.

Wie läuft die Magnetresonanztomographie -Untersuchung ab?

Während der Untersuchung liegt Ihr Kind ca. 25 Minuten in dem MR-Tomographen. In einem ersten Teil führt Ihr Kind eine Computeraufgabe zur Erkennung von Gefühlsausdrücken in Gesichtern durch. Die Aufgabe wird Ihrem Kind vor der Untersuchung außerhalb des Tomographen an einem Computer erklärt. Um die Aufgabe im Tomographen sehen zu können, wird eine Art Fernglas an der MR-Spule befestigt, in welches die Aufgabe projiziert wird. Um Antworten geben zu können, bekommt Ihr Kind eine Art Tastatur mit zwei Knöpfen in die Hand. Diese Aufgabe dauert. 5 min.

In einem zweiten Teil soll Ihr Kind 6 Minuten lang ruhig in dem MR-Tomographen liegen, ohne an etwas Bestimmtes zu denken. In einem letzten Teil werden einige anatomische Aufnahmen gemacht. Während dieser Messungen, darf sich Ihr Kind einen Film aussuchen, den es dann über das Fernglas anschauen darf.

Auf Ihren Wunsch bzw. dem Ihres Kindes ist es möglich, dass eine Person, entweder ein Familienmitglied oder eine Person des Studienpersonals Ihr Kind in den MRT-Raum während der Messung begleitet. Diese Person steht für die Dauer der Messung außerhalb des MR-Gerätes und hält die Hand Ihres Kindes.

Die reine Messzeit der Untersuchung dauert 25 Minuten, inkl. der Einführung in die Untersuchung und den MR-Tomographen sollten etwa 1 Stunde eingeplant werden. Es ist Ihnen bzw. Ihrem Kind möglich, die Untersuchung zu jeder Zeit ohne Angabe von Gründen abzubrechen.

Welche Risiken sind mit der Magnetresonanztomographie -Untersuchung verbunden?

Die Untersuchungsmethode MRT ist als Routineuntersuchung etabliert. Vor Beginn der Untersuchung erklären wir Ihrem Kind genau den Ablauf und es hat ausreichend Gelegenheit, sich mit dem Gerät vertraut zu machen. Dann wird Ihr Kind auf einer speziellen Liege mit dem Kopf voran in das MRT-Gerät gefahren. Dabei handelt es sich um ein röhrenförmiges Gebilde, in dem es auf dem Rücken liegen wird. Über eine Sprechanlage und ein Mikrophon steht Ihr Kind mit uns in ständiger Verbindung. Während der Zeit in der Röhre, die im Normalfall ca. 25 Minuten dauert, werden Bilder von dem Gehirn Ihres Kindes aufgenommen. Weil dabei ein lautes Klopfen und Lärm im Gerät entsteht, geben wir Ihrem Kind als Hörschutz Ohrstöpsel sowie einen Forschungskopfhörer. Da Ihr Kind sich während dieser Untersuchung so wenig wie möglich bewegen soll, bieten wir ihm an, einen Film aus unserer Filmauswahl anzuschauen.

Da die Röhre sehr wenig Raum bietet, kann es vorkommen, dass bei manchen Probanden durch die Enge Platzangst entsteht. Sollte dies bei Ihrem Kind der Fall sein, kann das der Untersuchungsleiter erkennen, da er sich in unmittelbarer Sichtweite aufhält. Außerdem ist es Ihrem Kind zu jedem Zeitpunkt möglich, mit dem Untersucher über die Sprechanlage in Kontakt zu treten und die Untersuchung gegebenenfalls abzubrechen.

Diese Untersuchungen sind nicht invasiv und beeinträchtigen Ihr Kind nach heutigem Kenntnisstand nicht. Um an der Studie teilnehmen zu können, müssen bestimmte Voraussetzungen gegeben sein. Füllen Sie deshalb bitte den beigelegten Fragebogen sorgfältig aus (s. u.).

Erfolgt eine Rückmeldung über die Ergebnisse der Datenerhebung?

Die Datenerhebung erfolgt für rein wissenschaftliche Zwecke ohne einen unmittelbaren Nutzen für die Teilnehmer. Individuelle Untersuchungsergebnisse werden im Regelfall nicht rückgemeldet (außer im Falle von Zufallsbefunden, s. o.).

Kann ich meine bzw. mein Kind seine Einwilligung widerrufen?

Sie können bzw. Ihr Kind kann jederzeit, ohne Angabe von Gründen und ohne Nachteile für Sie oder Ihrem Kind von der Studienteilnahme zurücktreten. In diesem Fall werden bereits gewonnene Informationen gelöscht.

Es bestehen keine ethischen Bedenken von Seiten der Ethikkommission der Medizinischen Fakultät der Universität Würzburg gegen die Durchführung der Studie. Die Verantwortung während der gesamten Studie trägt Dr. Susanne Neufang (Klinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, Universitätsklinikum Würzburg, Füchsleinstraße 15, 97080 Würzburg).

Kontaktperson:

Name: _____

Telefon: _____

Email: _____

Datenschutz

Für uns gilt die ärztliche Schweigepflicht; alle Informationen, die wir von Ihnen und Ihrem Kind erhalten, unterliegen dem Datenschutz. Das bedeutet, dass die erhobenen MRT-Daten in pseudonymisierter Form - also ohne Nennung des Namens Ihres Kindes – für einen Zeitraum von 10 Jahre verwahrt werden. Die Daten werden dabei auf externen Festplatten elektronisch unter Verschluss gelagert. Im Fall eines Studienabbruchs oder Widerrufs Ihrerseits werden die Daten Ihres Kindes umgehend gelöscht.
Weiterhin bedeutet es, dass der Zugriff auf alle Daten ausschließlich autorisierten Personen vorbehalten ist, die direkt mit der Untersuchung im Zusammenhang stehen (Studienleitung, Studienärzte, Forschungsassistenten). Es erfolgt keine Weitergabe an Dritte. Die erhobenen Daten dienen rein wissenschaftlichen Zwecken und werden ohne Bezug auf konkrete Personen ausgewertet. Die Ergebnisse werden im Rahmen von wissenschaftlichen Konferenzen und Fachzeitschriften veröffentlicht.

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MRT-Fragebogen

Hohe Magnetfelder bewirken, dass metallische Implantate oder Fremdkörper im Körper wandern können, was zu Komplikationen führen kann. Das hohe Magnetfeld des Tomographen bewirkt weiterhin, dass elektronisch aktive Implantate (z.B. Herzschrittmacher) nicht mehr ordnungsgemäß funktionieren, deshalb dürfen Herzschrittmacher-Träger an dieser Studie nicht teilnehmen. Sollte Ihr Kind Schrittmacherträger sein, oder sich Metallteile im Körper Ihres Kindes befinden, informieren Sie bitte das Untersuchungspersonal darüber.

Bei festen Zahnspangen bzw. Retainern kann es in seltenen Fällen zu Wärmeentwicklung kommen. In diesem Fall wird Ihr Kind dazu instruiert, die Messung abzubrechen.

Metallteile, die Ihr Kind mit sich führt, sind eine potentielle Gefahr für Ihr Kind und Andere. Elektronische Datenträger und Geräte (z.B. Kredit- und Scheckkarten, Mobiltelefone, Uhren, Hörgeräte) können im Magnetfeld unbrauchbar werden. Bitte nehmen Sie Schlüssel, Geldbeutel, Mobiltelefone und dergleichen Ihres Kindes vor der Untersuchung an sich.

BITTE ALLE FRAGEN BEANTWORTEN	Ja	Nein
Trägt Ihr Kind ein aktives Implantat? (z.B. Herzschrittmacher, Neurostimulator, Medikamentenpumpe) **Ist Ihr Kind schon einmal operiert worden?** (gegebenenfalls wann und wie häufig)		
Befinden sich metallische oder elektronische Teile am oder im Körper Ihres Kindes? (z.B. Splitter, Prothesen, Metallplatten, Klammern, Zahnspangen, Spirale, Piercing)		
Ist Ihr Kind tätowiert?		
Hat oder hatte Ihr Kind mit Metallverarbeitung zu tun? **Leidet Ihr Kind unter Angst vor engen Räumen oder Platzangst?**		
Hatte Ihr Kind schon einmal epileptische Anfälle? (wenn ja, wann und wie häufig)		
Nimmt Ihr Kind momentan Medikamente? (wenn ja, bitte auflisten mit Dosierung)		
Wie ist das aktuelle Gewicht Ihres Kindes?		**kg**
Wie ist die aktuelle Größe Ihres Kindes?		**cm**

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Einwilligungserklärung für Eltern/Sorgeberechtigte von minderjährigen Probanden

Therapie-induzierte Veränderungen von Hirnaktivierung während der Verarbeitung emotionaler Reize bei Kindern

Die vorgesehene Untersuchung einschließlich der Risiken, sowie die Studieninformation und die Einverständniserklärung wurden mir durch Herrn / Frau _____ zu meiner Zufriedenheit erklärt. Alle meine Fragen wurden so umfassend beantwortet, dass ich gut darüber informiert bin, warum diese Untersuchung durchgeführt wird und wie die Studie aufgebaut ist.

Ich habe die Studieninformation gelesen und verstanden, Ich konnte die schriftliche Probandeninformation behalten und eine Kopie der schriftlichen Einverständniserklärung erhalten. Ich hatte genügend Zeit, um eine Entscheidung zu treffen, und bin einverstanden, dass mein Kind an der Studie teilnimmt, d,h, an der Durchführung einer Messung im Magnetresonanztomographen.

Ich erkläre mich freiwillig mit der Datenerhebung einverstanden. Über mögliche Risiken wurde ich aufgeklärt. Ich weiß, dass es mir nicht möglich ist, Informationen über die Untersuchungsergebnisse meines Kindes zu erhalten. Die Teilnahme meines Kindes ist freiwillig. Wenn es die Teilnahme ablehnt oder widerruft, wird dies keine negativen Konsequenzen mit sich bringen. Namen und Daten werden streng vertraulich behandelt und ausgewertet, ohne den Namen meines Kindes zu nennen.
Ich erkläre mich darüber hinaus damit einverstanden, dass die aus der Datenerhebung gewonnenen Informationen gemäß geltender Datenschutzbestimmungen verschlüsselt (d.h., in unpersönlicher Form ohne Namens- oder Initialennennung) aufgezeichnet, in Computern gespeichert und ausgewertet werden. Ich bin auch damit einverstanden, dass die Ergebnisse der Studie in Gruppen zusammengefasst wissenschaftlich veröffentlicht werden.

Es ist mir oder meinem Kind jederzeit möglich, die Einwilligung zur Teilnahme ohne Angabe von Gründen zurückzuziehen. Hieraus werden meinem Kind keinerlei Nachteile entstehen. Die bis dahin gewonnenen Daten werden gelöscht..

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Über Zufallsbefunde mit möglichem Krankheitswert möchte ich informiert werden.

Ja	Nein
☐	☐

Name des teilnehmenden Kindes: .....

Name und Unterschrift der Sorgeberechtigten:

1) ....
Name Datum Unterschrift

2) ....
Name Datum Unterschrift

Name und Unterschrift des aufklärenden Studienarztes:

....
Name Datum Unterschrift

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Studienaufklärung für minderjährige Probanden

Therapie-induzierte Veränderungen von Hirnaktivierung während der Verarbeitung emotionaler Reize bei Kindern

Liebe Studienteilnehmerin, lieber Studienteilnehmer,

Vielen Dank, dass Du Dich für unsere Studie interessierst! In diesem Brief beschreiben wir Dir, worum es bei unserer Studie geht. Bitte lies Dir alles genau durch und sprich mit Deinen Eltern darüber. Danach sollst Du entscheiden, ob Du bei unserer Studie mitmachen möchtest.

Was ist der Grund für unsere Untersuchung?

Wie Du bestimmt aus Deiner Klasse oder Deinem Freundeskreis weißt, gibt es Kinder, die ein bisschen ängstlicher sind als andere oder sich nicht so viel trauen wie andere. Dies kann sogar so stark ausgeprägt sein, dass man sie als krank bezeichnen kann. Dann haben diese Kinder eine sogenannte Angsterkrankung. Obwohl viele Kinder starke Ängste haben, wissen wir erst wenig über diese Krankheiten. Wir möchten mit dieser Untersuchung Angsterkrankungen von Kindern besser verstehen. Dafür untersuchen wir Kinder mit Angsterkrankungen und Kinder ohne Angst, und dabei könntest Du uns helfen.

Mit dem, was wir von Dir und den anderen teilnehmenden Kindern erfahren, können wir dann wiederum anderen Kindern helfen, ihre Angst zu überwinden. Mit dieser Untersuchung wollen wir also zum einen mehr über Angsterkrankungen bei Kindern herausfinden und zeitgleich Kindern mit starken Ängsten helfen, so dass es ihnen wieder besser geht.

Warum die fMRT-Studie?

Die funktionelle Magnetresonanztomographie- (fMRT) ist eine Methode, mit der man die Arbeitsweise eines Gehims untersuchen kann. In dieser Studie wäre dies zum Beispiel, wie Dein Gehim auf Gesichter mit ganz verschiedenen Gefühlsausdrücken (lachen, ängstlich drein schauen, weinen) reagiert.

In dieser Untersuchung geht es um zwei Fragen- *(1)* Verarbeiten Gehirne von Kindern mit Angst Gefühlsausdrücke in Gesichtern anders als Gehirne von Kindern ohne Angst? Um diese Frage zu beantworten möchten wir Dich gerne mittels fMRT untersuchen und die Ergebnisse von Kindern mit Angsterkrankungen, die ebenfalls bei der Untersuchung mitmachen, vergleichen.

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(2) Die Kinder mit Angsterkrankungen, die an dieser Studie teilnehmen, machen eine Therapie im Rahmen der gleichen Studie. Um zu schauen, ob sich das, was die Kinder in der Therapie gelernt haben, auch in der Arbeitsweise ihrer Gehirne zeigt, untersuchen wir diese Kinder nach einem halben Jahr noch einmal. Hierfür würden wir Dich als gesundes Kind ebenfalls gerne nach 6 Monaten erneut untersuchen. Dann können wir vergleichen, wie gesunde Kinder wie Du sich im Vergleich zu Kindern mit Angsterkrankungen in diesem Zeitraum entwickelt haben.

Wie geht eine fMRT-Untersuchung?

Während der Untersuchung liegst Du ca. 25 Minuten in dem MR-Tomographen. Das ist eine große Röhre, in die Du auf mit einer Liege hingefahren wirst. Über Deinem Kopf setzen wir noch eine Art Helm auf, der die Bilder von Deinem Gehirn aufnimmt.

In einem ersten Teil machst Du eine Computeraufgabe, in der Du ein Bild von einem Gesicht mit einem bestimmten Gesichtsausdruck mit zwei anderen vergleichen sollst. Wie die Aufgabe genau geht, wird Dir vor der Untersuchung an einem Computer gezeigt. Damit Du die Computeraufgabe in der Röhre auch sehen kannst, wird eine Art Fernglas an dem Helm festgemacht. Wenn Du da hineinschaust, siehst Du die Aufgabe. Um Antworten geben zu können, bekommst außerdem eine Art Tastatur mit zwei Knöpfen in die Hand- Du sollst dann auf die Taste drücken, auf welcher der gleiche Gesichtsausdruck zu sehen ist (rechte Seite auf dem Bildschirm- rechter Antwortknopf, linke Seite auf dem Bildschirm- linker Antwortknopf). Diese Aufgabe dauert 5 min.

In einem zweiten Teil sollst Du 6 Minuten lang einfach nur ruhig liegen bleiben, ohne an etwas Bestimmtes zu denken.

In einem letzten Teil werden noch einige anatomische Aufnahmen gemacht. Für diese Messungen darfst Du Dir einen Film aussuchen, den Du dann über das Fernglas anschauen kannst.

Auf Deinen Wunsch hin ist möglich, dass entweder Deine Mutter, Dein Vater oder eine Person des Studienpersonals während der Messung bei Dir in dem Untersuchungsraum bleibt. Diese Person steht außerhalb der Röhre und kann Deine Hand halten.

Die reine Messzeit der Untersuchung dauert 25 Minuten, insgesamt dauert der Termin etwa 1 Stunde (Röhre anschauen, Computeraufgabe kennen lernen und so weiter).

Du darfst die Untersuchung zu jeder Zeit ohne Angabe von Gründen abzubrechen.

Ist die fMRT-Untersuchung gefährlich?

Die Art der Untersuchung wird in einem Krankenhaus routinemäßig, d.h. täglich an vielen Personen eingesetzt. Vor Beginn kannst Du Dir in Ruhe die Röhre anschauen und Fragen zu der Untersuchung stellen. Während der Untersuchung spricht der Untersucher über eine Sprechanlage mit Dir und er kann Dich auch hören, wenn Du einfach in den Raum hinein sprichst. Falls Du aus der Röhre heraus möchtest, kannst Du das direkt sagen, oder aber uns dies über das Drücken des sogenannten Notfallballs mitteilen. Der Notfallball ist ein Gummiball, den wir Dir an Deinem Hosenbund festmachen. Wenn Du ihn drückst, erscheint ein lauter Ton und die Messung wird unterbrochen. Weil das Geräusch des Gerätes während der Messung sehr laut werden kann, bekommst Du

Ohrstöpsel und spezielle Forschungskopfhörer, die das Geräusch auf eine Lautstärke herunter regeln können, die man gut aushalten kann.

Kann ich mit der Studie wieder aufhören?

Du kannst jederzeit, ohne Angabe von Gründen und ohne negative Konsequenzen von der Studienteilnahme zurücktreten. In diesem Fall werden bereits gemessenen Daten gelöscht.

MRT-Fragebogen

Hohe Magnetfelder bewirken, dass metallische Implantate oder Fremdkörper im Körper wandern können, was zu Komplikationen führen kann. Das hohe Magnetfeld des Tomographen bewirkt weiterhin, dass elektronisch aktive Implantate (z.B. Herzschrittmacher) nicht mehr ordnungsgemäß funktionieren, deshalb dürfen Herzschrittmacher-Träger an dieser Studie nicht teilnehmen.

Solltest Du Schrittmacherträger sein, oder sich Metallteile in Deinem Körper befinden, informiere bitte das Untersuchungspersonal darüber.

Bei festen Zahnspangen bzw. Retainern kann es in seltenen Fällen zu Wärmeentwicklung kommen. In diesem Fall wirst Du dazu instruiert, die Messung abzubrechen. Metallteile, die Du mit Dir führst, sind eine potentielle Gefahr für Dich und andere. Elektronische Datenträger und Geräte (z.B. Kredit- und Scheckkarten, Mobiltelefone, Uhren, Hörgeräte) können im Magnetfeld unbrauchbar werden. Bitte lege daher Schlüssel, Geldbeutel, Mobiltelefone und dergleichen vor der Untersuchung ab.

BITTE ALLE FRAGEN BEANTWORTEN	Ja	Nein
Trägst Du ein aktives Implantat? (z.B. Herzschrittmacher, Neurostimulator, Medikamentenpumpe)		
Bist Du schon einmal operiert worden? (gegebenenfalls wann und wie häufig) **Befinden sich metallische oder elektronische Teile an oder in Deinem Körper?** (z.B. Splitter, Prothesen, Metallplatten, Klammern, Zahnspangen, Spirale, Piercing)		
Bist Du tätowiert?		
Hast oder hattest Du mit Metallverarbeitung zu tun?		
Leidest Du unter Angst vor engen Räumen oder Platzangst?		
Hattest Du schon einmal epileptische Anfälle? (wenn ja, wann und wie häufig) **Nimmst Du momentan Medikamente?** (wenn ja, bitte auflisten mit Dosierung)		
Wie ist Dein aktuelles Gewicht? **Wie ist Deine aktuelle Größe?**		**kg** **cm**

8.2.2 Study 139/15

8.2.2.1 Parents/Legal Guardians

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Ärztliche Direktorin der Klinik für Psychiatrie und Psychotherapie, Universitätsklinikum Freiburg

Name des/der Proband/in: _____

Geburtsdatum: _____

STUDIENINFORMATION
FÜR ELTERN/SORGEBERECHTIGTE VON MINDERJÄHRIGEN STUDIENTEILNEHMERN

Prävention von Trennungsangst und Panikstörung – Angstsensitivität, (epi)genetische, physiologische und neurale Parameter als modulierbare Risikomarker

Sehr geehrte Eltern, sehr geehrte Sorgeberechtigte,

wie wir bereits mit Ihnen besprochen haben, möchten wir Sie bitten, dass Ihr Kind an einer wissenschaftlichen Studie zur Untersuchung der Entstehung von Angst und Angsterkrankungen teilnimmt.

Angsterkrankungen zählen zu den häufigsten psychischen Erkrankungen überhaupt – in Europa sind über 60 Millionen Menschen davon betroffen. Angsterkrankungen entstehen bereits im Kindesalter und können die Patienten trotz guter Therapien sehr belasten. Um das Auftreten von Angsterkrankungen

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von vornherein zu verhindern, sind präventive Maßnahmen zur Vorbeugung („Prävention") notwendig. Diese präventiven Maßnahmen für Angst, die u.a. auf einen besseren Umgang mit Körpersymptomen von Angst und Stress zielen, sind v.a. aus den Niederlanden, Australien und den USA bekannt und für Kinder in Deutschland im Rahmen des FRIENDS Programms (siehe weiter unten) gut etabliert. Zur Verbesserung der Prävention von Angsterkrankungen ist es wichtig, verlässliche psychologische und biologische Risikomarker zu identifizieren, die eine noch wirksamere Prävention von Angsterkrankungen ermöglichen.

Eine erhöhte Angstsensitivität bei gesunden Menschen, d.h. eine erhöhte Wachsamkeit gegenüber körpereigenen Empfindungen, wurde als ein solcher Risikofaktor sowohl für die Trennungsangststörung bei Kindern als auch für die Panikstörung bei Erwachsenen beschrieben. Weiterhin wissen wir, dass neben Umwelteinflüssen wie z.B. Trennungserlebnissen auch genetische (erbliche) Faktoren eine Rolle bei der Entstehung von Angsterkrankungen spielen. Seit kurzem ist zudem bekannt, dass biochemische Prozesse an der Erbsubstanz (DNA) - wie z.B. die DNA Methylierung - die Funktionsweise der Gene entscheidend beeinflussen. Diese sogenannten „epigenetischen" Mechanismen sind im Gegensatz zur genetischen Ausstattung veränderlich und können auch auf Umwelteinflüsse reagieren.

In der hier geplanten Studie soll daher bei gesunden Kindern die Beeinflussbarkeit der Angstsensitivität durch eine präventive Maßnahme, das sogenannte FRIENDS for Life Programm, untersucht werden. Der Hälfte der Kinder mit einer relativ hohen Angstsensitivität wird im Zufallsprinzip ein 4-5 wöchiges strukturiertes Programm angeboten, das über einen besseren Umgang mit Stress und körperlichen Symptomen von Stress in verschiedenen Studien eine Verringerung des Risikos für spätere Angsterkrankungen bewirkt hat. Die andere Hälfte der Kinder mit einer relativ hohen Angstsensitivität nimmt nicht an der präventiven Maßnahme teil (Kontrollbedingung). Zusätzlich werden sowohl vor der präventiven Maßnahme als auch zu verschiedenen Zeitpunkten danach einige der oben beschriebenen Risikofaktoren für Angsterkrankungen, d.h. (epi)genetische Marker und Lebensereignisse untersucht.

Diese Informationen über psychologische/biologische Risikomarker können dazu beitragen, dass in Zukunft noch gezieltere präventive Programme entwickelt werden können und damit die individuell wie gesundheitsökonomisch sehr belastenden Angsterkrankungen zunehmend bereits vor ihrer Entstehung verhindert werden.

Was beinhaltet die Teilnahme an der Untersuchung?

Diese wissenschaftliche Untersuchung beinhaltet verschiedene Untersuchungseinheiten, die zu vier Zeitpunkten (*T1-4*) durchgeführt werden.

Zu Beginn (*T0*) wird eine Eingangsuntersuchung durchgeführt. Diese beinhaltet drei Untersuchungseinheiten, in denen wir Sie und Ihr Kind gerne um folgende Informationen bitten würden:

- *Neuropsychologische Untersuchungseinheit (U1)*: Hier werden mit Ihrem Kind Fragebögen zur Ausprägung von Ängstlichkeit sowie zu in der letzten Zeit erlebten Lebensereignissen ausgefüllt und

ein strukturiertes klinisches Interview zur Erfassung der Symptome psychischer Erkrankungen durchgeführt.

- *Genetische/epigenetische Untersuchungseinheit (U2)*: Diese umfasst die Entnahme von ca. 20 ml (ca. 2 Esslöffeln entsprechend) Blut.
- *Untersuchungseinheit Bildgebung (U3)*:

Hier soll bei ängstlicheren Kindern vor (*T0*) und nach der Prävention (*T1*) in der Kernspintomographie (MRT, „Röhre“) die Verarbeitung sogenannter emotionaler Reize im Gehirn untersucht werden. Dazu wird Ihr Kind verschiedene Gesichter mit unterschiedlichen Gefühlsausdrücken sehen.
Diese drei Untersuchungseinheiten erfolgen an einem Termin und dauern insgesamt etwa 3-4 Stunden.

Danach schließt sich für eine zufällig ausgewählte („randomisierte“) Subgruppe von Kindern mit relativ hoher Angstsensitivität ein *4-5-wöchiges präventives Programm*, das sogenannte FREUNDE-Programm („FRIENDS for Life“; siehe im Detail unten) an.

Nachuntersuchung (T2-T3): Im Anschluss an das präventive Programm möchten wir mittels einer erneuten Datenerhebung untersuchen, ob sich genetische Muster, die Gehirntätigkeit und/oder der Umgang Ihres Kindes mit Ängstlichkeit in Abhängigkeit des präventiven Programms verändert haben. Dieser Termin wird erneut 3 Stunden dauern. Um den präventiven Nutzen des Programms besser beurteilen zu können, würden wir Sie und Ihr Kind, gerne nach 6 und 12 Monaten zu zwei weiteren Nachsorge-Terminen einladen (*T2&T3*) (Dauer: ca. 1,5 Stunden).

Insgesamt sollen 200 Kinder im Alter von 8-11 Jahren untersucht werden, die präventive Intervention erhalten 50 Kinder, 50 weitere Kinder werden in der Wartebedingung untersucht. Jede(r) Proband(in) wird eine Aufwandsentschädigung von jeweils € 50,- pro Untersuchung zu den Zeitpunkten T0 und T1 bzw. € 25.- zu den Zeitpunkten T2 und T3 erhalten.

Wie läuft die Magnetresonanztomographie-Untersuchung ab?

Mittels der Magnetresonanztomographie (MRT) ist es möglich, Bilder vom Gehirn aufzunehmen, Diese Bilder können hochaufgelöste Bilder der Hirnanatomie sein, so dass man sich den Aufbau des Gehirns genau anschauen kann, Man kann sich aber auch das Gehirn anschauen, während es ‚arbeitet', wie zum Beispiel, wenn der Proband oder Patient, der in dem MR-Tomographen liegt, eine Aufgabe macht.

Während der Untersuchung liegt Ihr Kind ca. 25 Minuten in dem MR-Tomographen. In einem ersten Teil führt Ihr Kind eine Computeraufgabe zur Erkennung von Gefühlsausdrücken in Gesichtern durch. Die Aufgabe wird Ihrem Kind vor der Untersuchung außerhalb des Tomographen an einem Computer erklärt. Um die Aufgabe im Tomographen sehen zu können, wird eine Art Fernglas an der MR-Spule befestigt, in welcher die Aufgabe zu sehen sein wird. Um Antworten geben zu können, bekommt Ihr Kind zwei Antwortknöpfe in die Hand. Diese Aufgabe dauert. 5 Minuten. Nach der Aufgabe werden noch verschiedene Aufnahmen von dem Aufbau des Gehirns durchgeführt.

Während dieser kann Ihr Kind sich einen Film aussuchen, den wir ihm über das Fernglas vorspielen. Die reine Messzeit der Untersuchung dauert 25 Minuten, inkl. der Einführung in die Untersuchung und den MR-Tomographen sollte etwa 1 Stunde eingeplant werden. Es ist Ihnen bzw. Ihrem Kind möglich, die Untersuchung zu jeder Zeit ohne Angabe von Gründen abzubrechen.

Welche Risiken sind mit der MRT -Untersuchung verbunden?

Die Untersuchungsmethode MRT ist als Routineuntersuchung etabliert. Vor Beginn der Untersuchung erklären wir Ihrem Kind genau den Ablauf und es hat ausreichend Gelegenheit, sich mit dem Gerät vertraut zu machen. Dann wird Ihr Kind auf einer speziellen Liege mit dem Kopf voran in das MRT-Gerät gefahren. Dabei handelt es sich um ein röhrenförmiges Gebilde, in dem es auf dem Rücken liegen wird. Über eine Sprechanlage und ein Mikrophon steht Ihr Kind mit uns in ständiger Verbindung. Während der Zeit in der Röhre, die im Normalfall ca. 25 Minuten dauert, werden Bilder von dem Gehirn Ihres Kindes aufgenommen. Weil dabei ein lautes Klopfen und Lärm im Gerät entsteht, geben wir Ihrem Kind als Hörschutz Ohrstöpsel sowie einen Kopfhörer mit aktiver Geräuschunterdrückung. Da Ihr Kind sich während dieser Untersuchung so wenig wie möglich bewegen soll, bieten wir ihm an, einen Film aus unserer Filmauswahl anzuschauen.

Da die Röhre sehr wenig Raum bietet, kann es vorkommen, dass bei manchen Probanden durch die Enge Platzangst entsteht. Sollte dies bei Ihrem Kind der Fall sein, kann das der Untersuchungsleiter erkennen, da er sich in unmittelbarer Sichtweite aufhält. Außerdem ist es Ihrem Kind zu jedem Zeitpunkt möglich, mit dem Untersucher über die Sprechanlage in Kontakt zu treten und die Untersuchung gegebenenfalls abzubrechen.

Diese Untersuchungen sind nicht invasiv, stellen also keinen Eingriff in den Körper Ihres Kindes dar, und beeinträchtigen Ihr Kind nach heutigem Kenntnisstand nicht. Um an der Studie teilnehmen zu können, müssen bestimmte Voraussetzungen gegeben sein. Füllen Sie deshalb bitte den beigelegten Fragebogen sorgfältig aus (s. u.).

Welche Risiken sind mit der Blutentnahme verbunden?

Die Blutentnahme erfolgt unter sterilen, also keimfreien Bedingungen und entspricht bzgl. der Menge des entnommenen Bluts einer Routineuntersuchung durch den Kinderarzt. Die Blutentnahme erfolgt durch medizinisch qualifiziertes Personal (Ärzte oder anderes medizinisches Personal). Die Risiken der Blutentnahme sind identisch mit denen einer Routineblutabnahme: örtliche (lokale) Infektion („bakterielle Entzündung, Vereiterung“), das versehentliche Treffen („Fehlpunktion“) einer Schlagader oder eine Nervenschädigung. Diese Risiken sind bei sachgemäßer Durchführung jedoch extrem selten. Etwas häufiger jedoch kann es zu einem harmlosen, aber unter Umständen schmerzhaften „blauen Fleck“ (Hämatom) kommen.

Was genau beinhaltet das präventive Programm?

Das FREUNDE-Trainingsprogramm zur Prävention von Angst und Depression ist für Kinder von 8 bis 11 Jahren entwickelt worden mit dem Ziel soziale und emotionale Fähigkeiten zu stärken,

Belastbarkeit und Widerstandsfähigkeit zu fördern sowie über Atemübungen einen besseren Umgang mit körpereigenen Empfindungen zu erlernen und damit insgesamt das Risiko für Angsterkrankungen zu vermindern. Das FREUNDE-Programm ist von der Weltgesundheitsorganisation (WHO) als wirksames Präventionsprogramm anerkannt. Es umfasst 5 Sitzungen: Sitzung 1 beinhaltet „psychoedukative" Aspekte, d.h. Aufklärung über das Wesen und die Entstehungsmechanismen von Ängstlichkeit, in Sitzung 2 werden Entspannungs- und Atemtechniken eingeführt, die in den folgenden Sitzungen regelmäßig geübt werden. Sitzungen 3 bis 5 besprechen der Reihe nach die Themen F: Fühlst Du Dich von Sorgen geplagt?, R: Relax und lass es Dir gut gehen, E: Eigene hilfreiche Gedanken und Selbstgespräche nutzen, U: Untersuche, was Du tun kannst; N: Nach guter Arbeit kannst Du Dich belohnen; D: Das Üben nicht vergessen; E: Entspannt und ruhig bleiben.

Was sind die Vorteile für mein Kind und mich, wenn er/sie an dieser Studie teilnimmt?

Diese Untersuchung wird keinen direkten Nutzen für Sie und Ihr Kind haben, da die Studie der Wissenschaft dient und Sie keine individuellen Ergebnisse erhalten werden. Im Rahmen einer randomisierten Zuteilung erhalten N=60 der Kinder mit einer relativ hohen Angstsensitivität im Rahmen der Studie ein präventives Programm. Denjenigen Kindern mit einer relativ hohen Angstsensitivität, die im Rahmen der Studie zufällig der Kontrollbedingung (=kein Präventionstraining) zugeteilt werden, wird im weiteren Verlauf die Teilnahme am Präventionsprogramm außerhalb der aktuellen Studie angeboten werden. Durch Ihre Bereitschaft, an dieser Studie teilzunehmen, leisten Sie einen wichtigen Beitrag zu einem besseren Verständnis psychischer Funktionen und Erkrankungen. Auch wenn wir nicht davon ausgehen können, dass die Ergebnisse in absehbarer Zeit zur Entwicklung von neuen Therapien führen, erhoffen wir uns über die Aufklärung der Entstehungswege psychischer Erkrankungen Fortschritte in der Prävention und Therapie.

Werden die Daten meines Kindes vertraulich behandelt?

Alle Untersucher unterliegen der Schweigepflicht. Alle Informationen, die wir von Ihnen bzw. Ihrem Kind bekommen, werden streng vertraulich behandelt. Alle persönlichen Daten wie z.B. Name und Adresse werden streng getrennt von den Fragebögen, den Interviewdaten sowie den Ergebnissen der (epi)genetischen Tests für die Dauer von mindestens 10 Jahren bzw. bis zum Widerruf Ihres Einverständnisses bzw. dem Ihres Kindes aufbewahrt. Es werden alle technischen und organisatorischen Maßnahmen getroffen, damit keine Unbefugten an Informationen zur Person Ihres Kindes gelangen können (z.B. Passwort-gesichertes Computerlaufwerk; abschließbare Datenschränke). Zugang zu den Daten Ihres Kindes haben lediglich die verantwortlichen Wissenschaftler. Alle medizinischen Informationen werden vor der Verwendung für wissenschaftliche Analysen entsprechend den geltenden Datenschutzgesetzen pseudonymisiert. Dies bedeutet, dass die Fragebögen, die Aufzeichnungen aus dem Interview, die Blutprobe und die (epi)genetischen Testergebnisse mit einem speziellen Zahlencode versehen werden, wenn sie zur Analyse geschickt werden. Persönliche Daten werden den Wissenschaftlern, die die

wissenschaftlichen Analysen ausführen, nicht offen gelegt. Ein direkter Rückgriff auf die Person Ihres Kindes ist somit ausgeschlossen. Bei der Erhebung, Speicherung und Analyse der Daten bzw. Proben sowie beim Austausch von Daten bzw. Proben mit kooperierenden Forschergruppen ist der Datenschutz entsprechend den geltenden Datenschutzgesetzen bzw. allen einschlägigen rechtlichen Anforderungen zum Datenschutz auf jeden Fall gewährleistet. Veröffentlicht werden die Daten in jedem Fall in anonymer Form als Sammeldatensatz. Bei einem Widerruf der Einverständniserklärung werden alle Proben und Daten (soweit nicht bereits veröffentlicht) vernichtet.

Zusammenarbeit mit anderen Forschungsgruppen

In der heutigen Forschung ist eine enge Zusammenarbeit mit anderen wissenschaftlichen Arbeitsgruppen von großer Bedeutung. Dies bedeutet, dass hierfür sowohl Biomaterialien als auch Informationen über klinische Daten zwischen den einzelnen Arbeitsgruppen ausgetauscht werden müssen. Die Weitergabe von Daten geschieht immer gemäß den gesetzlichen Datenschutzrichtlinien und unter Wahrung der Pseudonymisierung, d.h., dass diesen anderen Wissenschaftlern der Name Ihres Kindes, Geburtsdatum oder Ähnliches nicht bekannt sind.

An wen kann ich mich bei Fragen wenden?

Bei Rückfragen stehen Ihnen die verantwortlichen Studienleiter oder der aufklärende Arzt/Wissenschaftler gerne zur Verfügung.

Kontaktdaten der Studienleitung:

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Wir möchten Sie darauf hinweisen, dass Ihnen nach Art. 15 und Art. 16 der EU-Datenschutzgrundverordnung (EU-DSGVO) ein Auskunfts- und Berichtigungsrecht sowie ein Recht auf Löschung (Art. 17), Einschränkung der Verarbeitung (Art. 18) und Widerspruch gegen die Verarbeitung (Art. 21) zusteht. Im Falle eines Widerrufs können Sie grundsätzlich entscheiden, ob Ihre Daten und Proben gelöscht bzw. vernichtet werden sollen oder ob sie in anonymisierter Form für weitere Forschungsvorhaben verwendet werden dürfen. Die Rechtmäßigkeit der Verarbeitungen bis zum Zeitpunkt des Widerrufes bleibt davon unberührt. Möchten Sie eines dieser Rechte in Anspruch nehmen, wenden Sie sich bitte an die Studienleitung (s.o.). Bei Anliegen zur Datenverarbeitung und zur Einhaltung der datenschutzrechtlichen Anforderungen können Sie sich an den Datenschutzbeauftragten des Universitätsklinikums Würzburg wenden (Datenschutzbeauftragter des Universitätsklinikums Würzburg, Josef-Schneider-Straße 2, 97080 Würzburg, Telephon: 0931/201-55485, Email: datenschutz@ukw.de).

Außerdem haben Sie das Recht, Beschwerde bei der/den Datenschutz-Aufsichtsbehörde/n einzulegen, wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt. Dies ergibt sich aus Art. 77 DSGVO. Datenschutzrechtliche Beschwerden können an den Bayerischen Landesbeauftragte für den Datenschutz (BayLfD) gerichtet werden (Postfach 22 12 19, 80502 München, Telephon: 089/212672-0, Email: poststelle@datenschutzbayern.de). Die Beschwerde bei der Aufsichtsbehörde kann formlos erfolgen.

Verantwortliche Stelle für die Datenverarbeitung:

Universitätsklinikum Würzburg, Anstalt des öffentlichen Rechts, Josef-Schneider-Straße 2, 97080 Würzburg, Deutschland, Tel.: 0931 201 0

Wenn Sie bereit sind, dass Ihr Kind an dieser wissenschaftlichen Untersuchung teilnimmt, bitten wir Sie, uns Ihr Einverständnis schriftlich zu erklären. Auch wenn Sie unterschrieben haben, können Sie oder Ihr Kind natürlich jederzeit, ohne Angabe von Gründen und ohne Nachteile für Ihr Kind, Ihr Einverständnis rückgängig machen.

MRT-Fragebogen

Hohe Magnetfelder bewirken, dass metallische Implantate oder Fremdkörper im Körper wandern können, was zu Komplikationen führen kann. Das hohe Magnetfeld des Tomographen bewirkt weiterhin, dass elektronisch aktive Implantate (z.B. Herzschrittmacher) nicht mehr ordnungsgemäß funktionieren, deshalb dürfen Herzschrittmacher-Träger an dieser Studie nicht teilnehmen. Sollte Ihr Kind Schrittmacherträger sein, oder sich Metallteile im Körper Ihres Kindes befinden, informieren Sie bitte das Untersuchungspersonal darüber.

Bei festen Zahnspangen bzw. Retainern kann es in seltenen Fällen zu Wärmeentwicklung kommen. In diesem Fall wird Ihr Kind instruiert, die Messung abzubrechen.

Metallteile, die Ihr Kind mit sich führt, sind eine potentielle Gefahr für Ihr Kind und Andere. Elektronische Datenträger und Geräte (z.B. Kredit- und Scheckkarten, Mobiltelefone, Uhren, Hörgeräte) können im Magnetfeld unbrauchbar werden. Bitte nehmen Sie Schlüssel, Geldbeutel, Mobiltelefone und dergleichen Ihres Kindes vor der Untersuchung an sich.

BITTE ALLE FRAGEN BEANTWORTEN	Ja	Nein
Trägt Ihr Kind ein aktives Implantat? (z.B. Herzschrittmacher, Neurostimulator, Medikamentenpumpe)		
Ist Ihr Kind schon einmal operiert worden? (gegebenenfalls wann und wie häufig) **Befinden sich metallische oder elektronische Teile am oder im Körper Ihres Kindes?** (z.B. Splitter, Prothesen, Metallplatten, Klammern, Zahnspangen, Spirale, Piercing)		
Ist Ihr Kind tätowiert?		
Hat oder hatte Ihr Kind mit Metallverarbeitung zu tun?		
Leidet Ihr Kind unter Angst vor engen Räumen oder Platzangst?		
Hatte Ihr Kind schon einmal epileptische Anfälle? (wenn ja, wann und wie häufig) **Nimmt Ihr Kind momentan Medikamente?** (wenn ja, bitte auflisten mit Dosierung)		
Wie ist das aktuelle Gewicht Ihres Kindes?		**kg**
Wie ist die aktuelle Größe Ihres Kindes?		**cm**

Klinik und Poliklinik für Kinder- und Jugendpsychiatrie und Psychotherapie
Direktor: Prof. Dr. med. Marcel Romanos

EINWILLIGUNGSERKLÄRUNG

Prävention von Trennungsangst und Panikstörung – Angstsensitivität, (epi)genetische, physiologische und neurale Parameter als modulierbare Risikomarker

Name des/der Proband/in: _____

Geburtsdatum: _____

Ich bin über die geplante Untersuchung eingehend und ausreichend unterrichtet worden. Ich konnte Fragen stellen, die Informationen dazu habe ich inhaltlich verstanden. Ich habe keine weiteren Fragen, fühle mich ausreichend informiert und willige hiermit nach ausreichender Bedenkzeit freiwillig in die Untersuchung ein. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen und ohne Nachteile widerrufen kann. Ich weiß, dass die Untersuchung wissenschaftlichen Zwecken dient und die gewonnenen Daten eventuell für wissenschaftliche Veröffentlichungen verwendet werden. Ich stimme der Speicherung/Lagerung und Nutzung der Daten/Proben gemäß den geltenden Datenschutzbedingungen zu. Auch diese Einwilligung kann ich jederzeit widerrufen.

Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen und ohne Nachteile jederzeit mit Wirkung für die Zukunft widerrufen kann. Ich weiß, dass die Untersuchung wissenschaftlichen Zwecken dient, und bin einverstanden, dass die gewonnenen Daten für wissenschaftliche Veröffentlichungen und Forschung verwendet werden. Ich stimme der Speicherung/Lagerung und Nutzung der Daten/Proben gemäß den geltenden Datenschutzbedingungen zu. Auch diese Einwilligung kann ich jederzeit widerrufen.

Würzburg,_____ _____
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Würzburg,_____ _____
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Universitätsklinikum Würzburg

Klinik und Poliklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie
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Name des/der Proband/in: _____

Geburtsdatum: _____

STUDIENINFORMATION
FÜR MINDERJÄHRIGE STUDIENTEILNEHMER

Prävention von Trennungsangst und Panikstörung – Angstsensitivität, (epi)genetische, physiologische und neurale Parameter als modulierbare Risikomarker

Lieber Forschungshelfer, liebe Forschungshelferin,

wie wir bereits mit Dir und Deinen Eltern besprochen haben, möchten wir Dich bitten, an unserer wissenschaftlichen Studie zur Untersuchung der Entstehung von Angst und Angsterkrankungen teilzunehmen.

Wie Du bestimmt aus Deiner Klasse oder Deinem Freundeskreis weißt, gibt es Kinder, die ein bisschen ängstlicher sind als andere oder sich nicht so viel trauen wie andere. Dies kann sogar so

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stark ausgeprägt sein, dass man sie als krank bezeichnen kann. Dann haben diese Kinder eine sogenannte Angsterkrankung. Angsterkrankungen treten sogar so häufig auf, dass sich die Medizin viel mit diesen Krankheiten und deren Heilung beschäftigt. Bislang weiß man noch nicht genau, wie und warum Angsterkrankungen entstehen. Um dies besser zu verstehen und Programme zu entwickeln, die Kindern helfen mit Angst gut umzugehen und damit Angsterkrankungen gar nicht erst zu bekommen, führen wir diese Untersuchung durch.

Ziel der Untersuchung

In dieser wissenschaftlichen Untersuchung möchten wir anhand von zwei Untersuchungseinheiten Entstehungswege von Angst untersuchen, nämlich erbliche Faktoren und Deine Art und Weise mit Angst umzugehen. Außerdem wollen wir schauen, ob ein Training, das sogenannte FREUNDE-Programm verhindern kann, dass bei Kindern Angsterkrankungen ausbrechen.

Was beinhaltet die Teilnahme an der Untersuchung?

Zu Beginn würden wir gerne folgende Untersuchungen durchführen:

- *Interview und Fragebögen*: Hier füllen wir mit Dir Fragebögen zur Ausprägung Deiner Ängstlichkeit durch. Außerdem fragen wir Dich nach Ereignissen, die Du in der letzten Zeit erlebt hast.
- *Blutentnahme*: Hier nehmen wir Dir ein wenig Blut ab, etwa 20 ml, was ungefähr 2 Esslöffeln entspricht. Das ist in etwa die Menge, die Dein Kinderarzt bei einer normalen Untersuchung ebenfalls bei Dir abnimmt.
- *Funktionelle Magnetresonanztomographie* - Untersuchung: Die funktionelle Magnetresonanztomographie (fMRT) ist eine Methode, mit der man die Arbeitsweise eines Gehirns untersuchen kann. In dieser Studie wollen wir damit untersuchen, wie Dein Gehirn arbeitet, während es Gesichter mit ganz verschiedenen Gefühlsausdrücken (zum Beispiel: lachen, ängstlich drein schauen) sieht.

Diese Untersuchungen dauern insgesamt etwa 3-4 Stunden.

Danach wird manchen Kindern die Teilnahme an einem *4-5-wöchigen Programm*, dem sogenannten FREUNDE-Programm angeboten. In diesem Programm, welches Du mit 2-3 anderen Kindern gemeinsam durchführst, lernst Du einige Techniken mit Stress umzugehen und entspannt und ruhig zu bleiben. Im Anschluss daran würden wir Dich gerne noch einmal untersuchen, so, wie wir es an dem ersten Termin gemacht haben.

Um zu überprüfen, ob das Programm auch längerfristig helfen kann, würden wir Dich gerne nach 6 und 12 Monaten zu zwei weiteren Terminen einladen.

Für Deine Teilnahme bekommst Du jeweils € 50 für die ersten beiden Treffen mit fMRT-Untersuchung. Für die letzten beiden Termine bekommst Du noch einmal jeweils € 25.

Was kann bei der Blutentnahme passieren?

Wir führen die Blutentnahme unter sterilen, d.h. ganz sauberen Bedingungen durch. Nur Personen, die das schon oft bei Kindern gemacht haben und das wirklich gut können, werden diese Blutentnahme durchführen.

Was jedoch bei jeder Blutabnahme passieren kann, ist, dass kleine Entzündungen oder „blaue Flecke" an der Stelle, an der gepiekt wurde, entstehen. Diese sind harmlos, können aber etwas wehtun, so wie wenn Du Dich irgendwo angehauen hast. Es kann auch passieren, dass versehentlich daneben gestochen und die Ader nicht getroffen wird. Dies passiert jedoch extrem selten.

Wie geht eine fMRT-Untersuchung?

Während der Untersuchung liegst Du ca. 25 Minuten in dem MR-Tomographen. Das ist eine große Röhre, in die Du auf mit einer Liege hingefahren wirst. Über Deinem Kopf setzen wir noch eine Art Helm auf, der die Bilder von Deinem Gehim aufnimmt.

In einem ersten Teil machst Du eine Computeraufgabe, in der Du ein Bild von einem Gesicht mit einem bestimmten Gesichtsausdruck mit zwei anderen vergleichen sollst. Wie die Aufgabe genau geht, wird Dir vor der Untersuchung an einem Computer gezeigt. Damit Du die Computeraufgabe in der Röhre auch sehen kannst, wird eine Art Fernglas an dem Helm festgemacht. Wenn Du da hineinschaust, siehst Du die Aufgabe. Um Antworten geben zu können, bekommst außerdem eine Art Tastatur mit zwei Knöpfen in die Hand. Du sollst dann auf die Taste drücken, auf welcher der gleiche Gesichtsausdruck zu sehen ist (rechte Seite auf dem Bildschirm: rechter Antwortknopf, linke Seite auf dem Bildschirm: linker Antwortknopf). Diese Aufgabe dauert 5 Minuten. Nach der Aufgabe werden noch einige weitere Aufnahmen von Deinem Gehim gemacht. Für diese Messungen darfst Du Dir einen Film aussuchen, den Du dann über das Fernglas anschauen kannst. Die reine Messzeit der Untersuchung dauert 25 Minuten, insgesamt dauert der Termin etwa 1 Stunde (Röhre anschauen, Computeraufgabe kennen lernen und so weiter).

Du darfst die Untersuchung zu jeder Zeit ohne Angabe von Gründen abzubrechen.

Ist die fMRT-Untersuchung gefährlich?

Die Art der Untersuchung wird in einem Krankenhaus routinemäßig, d.h. täglich an vielen Personen eingesetzt. Vor Beginn kannst Du Dir in Ruhe die Röhre anschauen und Fragen zu der Untersuchung stellen. Während der Untersuchung spricht der Untersucher über eine Sprechanlage mit Dir und er kann Dich auch hören, wenn Du einfach in den Raum hinein sprichst. Falls Du aus der Röhre heraus möchtest, kannst Du das direkt sagen, oder aber uns dies über das Drücken des sogenannten Notfallballs mitteilen. Der Notfallball ist ein Gummiball, den wir Dir an Deinem Hosenbund festmachen. Wenn Du ihn drückst, gibt es einen lauten Ton und die Messung wird unterbrochen. Weil das Geräusch des Gerätes während der Messung sehr laut werden kann,

bekommst Du Ohrstöpsel und spezielle Forschungskopfhörer, die das Geräusch auf eine Lautstärke herunter regeln können, die man gut aushalten kann.

Was genau ist das FREUNDE-Programm?

Das FREUNDE-*Trainingsprogramm zur Vermeidung („Prävention") von Angst und Depression* ist speziell für Kinder in Deinem Alter entwickelt worden mit dem Ziel, Deine Belastbarkeit und Widerstandsfähigkeit zu fördern. Damit soll das Risiko, dass Du an einer Angsterkrankung erkrankst, verringert werden. Das FREUNDE-Programm umfasst 5 Treffen mit zwei bis drei anderen Kindern: In den Sitzung 1 wird mit Euch besprochen, was Angst und Stress ist, wie es zu Angst und Stress kommt und was man dagegen tun kann, in Sitzung 2 werden Euch Entspannungs- und Atemtechniken gezeigt. Sitzungen 3 bis 5 besprechen der Reihe nach die Themen F: Fühlst Du Dich von Sorgen geplagt?, R: Relax und lass es Dir gut gehen, E: Eigene hilfreiche Gedanken und Selbstgespräche nutzen, U: Untersuche, was Du tun kannst; N: Nach guter Arbeit kannst Du Dich belohnen; D: Das Üben nicht vergessen; E: Entspannt und ruhig bleiben.

Werden Meine Daten vertraulich behandelt?

Alle Untersucher, die an dieser Studie mitwirken, unterliegen der Schweigepflicht. Alle Informationen, die wir von Dir bekommen, werden streng vertraulich behandelt. Alle Deine persönlichen Daten wie z.B. Name und Adresse werden streng getrennt von Informationen, die wir im Rahmen dieser Untersuchung von Dir bekommen, aufbewahrt. Wir speichern die Informationen für die Dauer von mindestens 10 Jahren bzw. bis zu Deinem bzw. dem Widerruf des Einverständnisses Deiner Eltern.

Wir sorgen zudem dafür, dass keine Unbefugten an Informationen zu Deiner Person gelangen können (z.B. Passwort-gesichertes Computerlaufwerk; abschließbare Datenschränke). Zugang zu Deinen Daten haben lediglich die verantwortlichen Wissenschaftler. Außerdem werden Deine Daten statt mit Deinem Namen mit einem Code versehen, so dass niemand erkennen kann, dass es sich dabei um Deine Daten handelt. Wer hinter den Codes steht, wissen nur die verantwortlichen Studienleiter.

Zusammenarbeit mit anderen Forschungsgruppen

Wir arbeiten eng mit anderen Forschungsgruppen zusammen. Dies bedeutet auch, dass erhobene Daten zwischen den einzelnen Arbeitsgruppen ausgetauscht werden. Dieser Austausch geschieht jedoch immer unter Deinem Code, nie mit Deinem Namen, dies entspricht den gesetzlichen Datenschutzrichtlinien.

An wen kann ich mich bei Fragen wenden?

Bei Rückfragen stehen wir Dir und Deinen Eltern gerne zur Verfügung. Eine Kopie dieser Information wird Dir und Deiner Mutter / Deinem Vater ausgehändigt.

Datenschutz

Wir möchten Dich darauf hinweisen, dass Dir nach Art. 15 und Art. 16 der EU-Datenschutzgrundverordnung (EU-DSGVO) ein Auskunfts- und Berichtigungsrecht sowie ein Recht auf Löschung (Art. 17), Einschränkung der Verarbeitung (Art. 18) und Widerspruch gegen die Verarbeitung (Art. 21) zusteht. Im Falle eines Widerrufs kannst Du grundsätzlich entscheiden, ob Deine Daten und Proben gelöscht bzw. vernichtet werden sollen oder ob sie in anonymisierter Form für weitere Forschungsvorhaben verwendet werden dürfen. Die Rechtmäßigkeit der Verarbeitungen bis zum Zeitpunkt des Widerrufes bleibt davon unberührt, das heißt, dass die Daten, die vor Deinem Widerspruch gesammelt wurden, weiter für die Forschung verwendet werden dürfen. Möchtest Du eines dieser Rechte in Anspruch nehmen, wende Dich bitte mit deinen Eltern an die Studienleitung (s.o.). Bei Anliegen zur Datenverarbeitung und zur Einhaltung der datenschutzrechtlichen Anforderungen kannst Du Dich an den Datenschutzbeauftragten des Universitätsklinikums Würzburg wenden (Datenschutzbeauftragter des Universitätsklinikums Würzburg, Josef-Schneider-Straße 2, 97080 Würzburg, Telephon: 0931/201-55485, Email: datenschutz@ukw.de).

Außerdem hast Du das Recht, Beschwerde bei der/den Datenschutz-Aufsichtsbehörde/n einzulegen, wenn Du der Ansicht bist, dass die Verarbeitung der Dich betreffenden personenbezogenen Daten gegen die DSGVO verstößt. Dies ergibt sich aus Art. 77 DSGVO. Datenschutzrechtliche Beschwerden können an den Bayerischen Landesbeauftragte für den Datenschutz (BayLfD) gerichtet werden (Postfach 22 12 19, 80502 München, Telephon: 089/212672-0, Email: poststelle@datenschutzbayern.de). Die Beschwerde bei der Aufsichtsbehörde kann formlos erfolgen.

Verantwortliche Stelle für die Datenverarbeitung:

Universitätsklinikum Würzburg, Anstalt des öffentlichen Rechts, Josef-Schneider-Straße 2, 97080 Würzburg, Deutschland, Tel.: 0931 201 0

Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen und ohne Nachteile jederzeit mit Wirkung für die Zukunft widerrufen kann. Ich weiß, dass die Untersuchung wissenschaftlichen Zwecken dient, und bin einverstanden, dass die gewonnenen Daten für wissenschaftliche Veröffentlichungen und Forschung verwendet werden. Ich stimme der Speicherung/Lagerung und Nutzung der Daten/Proben gemäß den geltenden Datenschutzbedingungen zu. Auch diese Einwilligung kann ich jederzeit widerrufen.

MRT-FRAGEBOGEN

Hohe Magnetfelder bewirken, dass Metall im Körper wandern kann, was zu Komplikationen führen kann. Das hohe Magnetfeld des Tomographen bewirkt weiterhin, dass elektronisch aktive Implantate (z.B. Herzschrittmacher) nicht mehr ordnungsgemäß funktionieren, deshalb dürfen Herzschrittmacher-Träger an dieser Studie nicht teilnehmen. Solltest Du Schrittmacherträger sein, oder sich Metallteile wie z.B. Schrauben nach einem Knochenbruch in Deinem Körper befinden, informiere bitte das Untersuchungspersonal darüber.

Bei festen Zahnspangen bzw. Retainern kann es in seltenen Fällen zu Wärmeentwicklung kommen. In diesem Fall solltest Du die Messung abbrechen.

Lose Metallteile, die Du bei Dir hast, sind eine mögliche Gefahr für Dich und Andere. Elektronische Datenträger und Geräte (z.B. Kredit- und Scheckkarten, Mobiltelefone, Uhren, Hörgeräte) können im Magnetfeld unbrauchbar werden. Bitte lege Schlüssel, Geldbeutel, Mobiltelefone und dergleichen vor der Untersuchung ab.

BITTE ALLE FRAGEN BEANTWORTEN	Ja	Nein
Trägst Du ein aktives Implantat? (z.B. Herzschrittmacher, Neurostimulator, Medikamentenpumpe)		
Bist Du schon einmal operiert worden? (gegebenenfalls wann und wie häufig) **Befinden sich metallische oder elektronische Teile an oder in Deinem Körper?** (z.B. Splitter, Prothesen, Metallplatten, Klammern, Zahnspangen, Spirale, Piercing) **Bist Du tätowiert?**		
Hast oder hattest Du mit Metallverarbeitung zu tun?		
Leidest Du unter Angst vor engen Räumen oder Platzangst?		
Hattest Du schon einmal epileptische Anfälle? (wenn ja, wann und wie häufig)		
Nimmst Du momentan Medikamente? (wenn ja, bitte auflisten mit Dosierung)		
Wie ist Dein aktuelles Gewicht?	**kg**	
Wie ist Deine aktuelle Größe?	**cm**	

8.3 Questionnaires

8.3.1 STAIC

STAIC

Im folgenden Fragebogen findest Du eine Reihe von Feststellungen, die Mädchen und Jungen benutzen, um sich selbst zu beschreiben. Lies Dir jede Feststellung durch und entscheiden Sie, ob sie fast nie, oder manchmal oder oft auf Dich zutrifft. Kreuze dann bitte für jede Feststellung das entsprechende Kästchen an.

Es gibt keine richtigen oder falschen Antworten. Überlege bitte nicht zu lange und denke daran, diejenige Antwort auszuwählen, die am besten beschreibt, wie Du Dich im Allgemeinen fühlst.

1. Ich habe Angst, Fehler zu machen	☐ fast nie	☐ manchmal	☐ oft
2. Mir ist zum weinen zumute	☐ fast nie	☐ manchmal	☐ oft
3. Ich fühle mich unglücklich	☐ fast nie	☐ manchmal	☐ oft
4. Es fällt mir schwer, mich zu entscheiden	☐ fast nie	☐ manchmal	☐ oft
5. Es fällt mir schwer, meine Probleme anzupacken	☐ fast nie	☐ manchmal	☐ oft
6. Ich mache mir zuviel Sorgen	☐ fast nie	☐ manchmal	☐ oft
7. Zu Hause rege ich mich auf	☐ fast nie	☐ manchmal	☐ oft
8. Ich bin schüchtern	☐ fast nie	☐ manchmal	☐ oft
9. Ich bin beunruhigt	☐ fast nie	☐ manchmal	☐ oft
10. Unwichtige Gedanken gehen mir durch den Kopf und stören mich	☐ fast nie	☐ manchmal	☐ oft
11. Ich mache mir Sorgen über die Schule	☐ fast nie	☐ manchmal	☐ oft
12. Ich habe Schwierigkeiten zu entscheiden, was ich tun soll	☐ fast nie	☐ manchmal	☐ oft
13. Ich merke, dass mein Herz schneller schlägt	☐ fast nie	☐ manchmal	☐ oft
14. Ich fürchte mich heimlich	☐ fast nie	☐ manchmal	☐ oft
15. Ich mache mir Sorgen um meine Eltern	☐ fast nie	☐ manchmal	☐ oft
16. Ich bekomme feuchte Hände	☐ fast nie	☐ manchmal	☐ oft
17. Ich mache mir Sorgen über Dinge, die passieren könnten	☐ fast nie	☐ manchmal	☐ oft
18. Es fällt mir schwer, abends einzuschlafen	☐ fast nie	☐ manchmal	☐ oft
19. Ich habe ein komisches Gefühl im Magen	☐ fast nie	☐ manchmal	☐ oft
20. Ich grübele darüber nach, was andere Personen von mir denken	☐ fast nie	☐ manchmal	☐ oft

8.3.2 CASI

Auf dieser und auf der folgenden Seite findest du eine Reihe von Gefühlen und Gedanken, die Jungen und Mädchen haben können. Bitte lies diese Gefühle und Gedanken aufmerksam durch und mach ein Kreuz in das Kästchen, das auf Dich zutrifft. Dabei gibt es keine richtigen oder falschen Antworten, es geht nur darum, jeweils das Wort anzukreuzen, das Dich am besten beschreibt.

	gar nicht	manchmal	häufig
1. Ich möchte nicht, dass andere Menschen es merken, wenn ich mich ängstlich fühle.	θ	θ	θ
2. Wenn ich mich nicht auf meine Schulaufgaben konzentrieren kann, fürchte ich, dass ich verrückt werden könnte.	θ	θ	θ
3. Es macht mir Angst, wenn ich mich zittrig fühle.	θ	θ	θ
4. Es macht mir Angst, wenn ich mich so fühle, als ob ich in Ohnmacht falle.	θ	θ	θ
5. Es ist wichtig für mich, meine Gefühle unter Kontrolle zu haben.	θ	θ	θ
6. Es macht mir Angst, wenn mein Herz schnell schlägt.	θ	θ	θ
7. Es ist mir peinlich, wenn mein Magen knurrt (Geräusche macht).	θ	θ	θ
8. Es macht mir Angst, wenn ich mich so fühle, als ob ich mich übergeben muss.	θ	θ	θ
9. Wenn ich merke, dass mein H erz schnell schlägt, fürchte ich, dass etwas mit mir nicht in Ordnung sein könnte.	θ	θ	θ
10. Es macht mir Angst, wenn ich Schwierigkeiten habe, Luft zu bekommen.	θ	θ	θ
11. Wenn ich Bauchschmerzen habe, fürchte ich, dass ich richtig krank sein könnte.	θ	θ	θ

	gar nicht	manchmal	häufig
12. Es macht mir Angst, wenn ich nicht auf meine Schulaufgaben konzentrieren kann.	θ	θ	θ
13. Andere Kinder können es merken, wenn ich mich ängstlich fühle.	θ	θ	θ
14. Ungewöhnliche Körpergefühle machen mir Angst.	θ	θ	θ
15. Wenn ich Angst habe, fürchte ich, verrückt zu werden.	θ	θ	θ
16. Es macht mir Angst, wenn ich mich nervös fühle.	θ	θ	θ
17. Ich mag es nicht, meine Gefühle zu zeigen.	θ	θ	θ
18. Komische Gefühle in meinem Körper machen mir Angst.	θ	θ	θ

8.3.3 TAI

TAI-R-K	Vpnr:

Auf dieser Seite findest du eine Reihe von Situationen, die Kindern und Jugendlichen in deinem Alter Angst machen können.
Bitte gib an, wie häufig du **aus Angst vor einer Trennung von den Eltern** folgende Situationen **vermeidest**.
Es gibt keine falschen Antworten.

Ich vermeide aus Angst vor einer Trennung von den Eltern...

		nie	*selten*	*die Hälfte der Zeit*	*meistens*	*immer*
1.	allein zu Freund/ Freundin zu gehen	☐	☐	☐	☐	☐
2.	abends allein zu Hause zu sein	☐	☐	☐	☐	☐
3.	im Dunkeln einzuschlafen	☐	☐	☐	☐	☐
4.	allein bei Verwandten (z.B. Oma/ Opa) zu übernachten	☐	☐	☐	☐	☐
5.	allein zur Schule/ Kindergarten zu gehen	☐	☐	☐	☐	☐
6.	im eigenen Bett einzuschlafen	☐	☐	☐	☐	☐
7.	tagsüber allein zu Hause zu sein	☐	☐	☐	☐	☐
8.	allein bei Freund/ Freundin zu übernachten	☐	☐	☐	☐	☐
9.	allein mit einer anderen Person (z.B. Babysitter, ältere Geschwister) zu Hause zu bleiben	☐	☐	☐	☐	☐
10.	allein einzuschlafen	☐	☐	☐	☐	☐
11.	nach Hause zu kommen und niemand ist da	☐	☐	☐	☐	☐
12.	auf eine Klassenfahrt/ Ferienlager zu gehen	☐	☐	☐	☐	☐

Bitte überprüfe, ob du alle Fragen beantwortest hast.

8.3.4 ZLEL

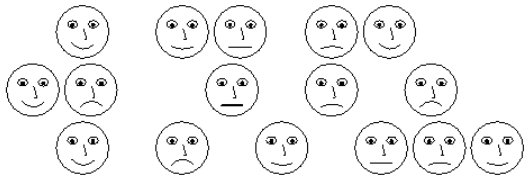
Zürcher Lebensereignisliste **ZLEL**

Name: _____ ID-Nr. _____

Geburtsdatum: _____ Datum: _____ männlich ☐ weiblich ☐

Ausgefüllt von: _____

Im letzten Jahr



*In diesem Fragebogen werden **Ereignisse oder Erlebnisse aus den letzten 12 Monaten** angesprochen, die Dir vielleicht passiert sind. Bei jedem Ereignis wirst Du zuerst gefragt, ob es Dir in den letzten 12 Monaten passiert ist. Du kannst mit "ja" oder "nein" antworten. Falls Du mit "ja" geantwortet hast, wirst Du zusätzlich gefragt, wie angenehm oder unangenehm dieses Ereignis für Dich war. Jetzt kannst Du eine der 5 Antworten auswählen, die von "sehr unangenehm" (-2) bis "sehr angenehm" (+2) reichen.*

Beispiel:

Was ist in den letzten 12 Monaten passiert?		**Wie unangenehm oder angenehm war das für Dich?**				
		sehr unange-nehm	**unange-nehm**	**weder noch**	**angenehm**	**sehr angenehm**
1. Hast Du in den Ferien eine weite Reise gemacht?	☐ **ja** ☐ **nein**	☐ _____ -2	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2

Was ist in den letzten 12 Monaten passiert?		**Wie unangenehm oder angenehm war das für Dich?**				
		sehr unange-nehm	**unange-nehm**	**weder noch**	**angenehm**	**sehr angenehm**
1. Hast Du die Schule gewechselt?	☐ **ja** ☐ **nein**	☐ _____ -2	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2
2a. Hat sich die Zahl der Menschen in Eurem Haushalt verändert? Ist jemand weggegangen?	☐ **ja** ☐ **nein**	☐ _____ -2	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2
2b. Ist jemand dazugekommen?	☐ **ja** ☐ **nein**	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2	-2
3. Bist Du umgezogen?	☐ **ja** ☐ **nein**	☐ _____ -2	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2
4a. Hat es zu Hause irgendwelche Katastrophen gegeben wie Feuer, Überschwemmung oder Einbruch?	☐ **ja** ☐ **nein**	☐ _____ -2	☐ _____ -1	☐ _____ 0	☐ _____ +1	☐ _____ +2

Herausquelle: «www.kjpd.uzh.ch/pdf/psy/zls»

4b. Ist das mehr als einmal vorgekommen?

☐ ja

☐ nein

Was ist in den letzten 12 Monaten passiert?		Wie unangenehm oder angenehm war das für Dich?				
		sehr unange-nehm	unange-nehm	weder noch	angenehm	sehr angenehm
5. Hast Du oder hat irgend jemand aus Deiner Familie oder von Deinen engen Freunden eine schwere Krankheit oder einen Unfall gehabt?	☐ ja ☐ nein					
Wer war das?						
1 ☐ ich selbst		☐	☐	☐	☐	☐
2 ☐ Mutter, Vater						
3 ☐ Geschwister						
4 ☐ nahestehender Verwandter						
5 ☐ enger Freund / enge Freundin		-2	-1	0	+1	+2
6. Warst Du oder war einer aus Deiner Familie oder von Deinen engen Freunden im Krankenhaus?	☐ ja ☐ nein					
Wer war das?						
1 ☐ ich selbst		☐	☐	☐	☐	☐
2 ☐ Mutter, Vater						
3 ☐ Geschwister						
4 ☐ nahestehender Verwandter						
5 ☐ enger Freund / enge Freundin		-2	-1	0	+1	+2

7.	Ist irgend jemand aus Deiner Familie oder von Deinen engen Freunden gestorben? Wer war das? 2 ☐ Mutter, Vater 3 ☐ Geschwister 4 ☐ nahestehender Verwandter 5 ☐ enger Freund / enge Freundin	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2

Was ist in den letzten 12 Monaten passiert?		Wie unangenehm oder angenehm war das für Dich?				
		sehr unange-nehm	unange-nehm	weder noch	angenehm	sehr angenehm
8. Hast Du ein Haustier verloren?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
9. Hast Du Dich von Freunden unter Druck gesetzt gefühlt?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
10. Hattest Du Streit oder Probleme mit einem Freund / einer Freundin?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
11. Hast Du Dich verliebt oder eine Beziehung zu einem Freund / einer Freundin begonnen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
12. Hast Du eine Verschlechterung der Beziehung zwischen den Familien-mitgliedern oder Freunden erlebt?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2

13.	Hast Du eine schlechte Prüfung gemacht oder eine schlechte Klassenarbeit geschrieben?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2		

Was ist in den letzten 12 Monaten passiert?	**Wie unangenehm oder angenehm war das für Dich?**

			sehr unangenehm	unangenehm	weder noch	angenehm	sehr angenehm
14.	Wurde ein Familienmitglied inhaftiert?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
15.	Bist Du in der Schule in Schwierigkeiten gekommen oder von der Schule verwiesen worden?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
16.	Hattest Du Ärger, Streit oder Kämpfe mit anderen Schülern oder Gleichaltrigen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
17.	Gab es in der Familie finanzielle Schwierigkeiten oder Geldsorgen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2

18.	Hast Du schlechte Zensuren oder Beurteilungen bekommen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2		
19.	Hat ein Elternteil erneut geheiratet, oder ist ein neuer Partner / eine neue Partnerin in die Familie gekommen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2		

Was ist in den letzten 12 Monaten passiert?	**Wie unangenehm oder angenehm war das für Dich?**

			sehr unangenehm	unangenehm	weder noch	angenehm	sehr angenehm
20.	Gab es Streitigkeiten oder Kämpfe zwischen Deinen Eltern?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
21.	Gab es eine Veränderung in der Beziehung zum Jungen / Mädchen, mit dem Du gehst?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
22.	Hattest Du Pläne, die ins Wasser fielen (z.B. eine Reise nicht machen)?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2

23.	Hatte ein Familienmitglied oder Verwandter Sorgen oder Probleme?	☐ ja ☐ nein	-2	-1	0	+1	+2
24.	Hattest Du Streitigkeiten oder Probleme mit dem Jungen / Mädchen, mit dem Du gehst?	☐ ja ☐ nein	-2	-1	0	+1	+2
25.	Ist eine schulische oder berufliche Veränderung bei einem Familienmitglied eingetreten (z.B. Verweis von der Schule, eine Berufsanstellung, Wechsel der Arbeitsstelle)?	☐ ja ☐ nein	-2	-1	0	+1	+2

Was ist in den letzten 12 Monaten passiert?	**Wie unangenehm oder angenehm war das für Dich?**

			sehr unange-nehm	unange-nehm	weder noch	angenehm	sehr angenehm
26.	Hattest Du Probleme oder Streitigkeiten mit Eltern, Geschwistern oder anderen Familienmitgliedern?	☐ ja ☐ nein	-2	-1	0	+1	+2
27.	Hattest Du Probleme oder Streitigkeiten mit Lehrern?	☐ ja ☐ nein	-2	-1	0	+1	+2

28.	Hattest Du Sorgen wegen Deiner Gesundheit oder Fitness?	☐ ja ☐ nein	-2	-1	0	+1	+2
29.	Gab es bei einem Familienmitglied / Verwandten Alkohol- oder Drogenprobleme?	☐ ja ☐ nein	-2	-1	0	+1	+2
30.	Hast Du eine Partnerschaft / Freundschaft beendet, oder bist Du von einem Partner / Freund bzw. von einer Partnerin / Freundin zurückgewiesen worden?	☐ ja ☐ nein	-2	-1	0	+1	+2
31.	Hat Deine Mutter oder Dein Vater ihren / seinen Arbeitsplatz verloren?	☐ ja ☐ nein	-2	-1	0	+1	+2

Was ist in den letzten 12 Monaten passiert?		Wie unangenehm oder angenehm war das für Dich?				
		sehr unange-nehm	unange-nehm	weder noch	angenehm	sehr angenehm
32. Haben Deine Eltern sich getrennt oder scheiden lassen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
33. Ist ein guter Freund / eine gute Freundin weggezogen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
34. Hat Deine Mutter (wieder) angefangen zu arbeiten?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
35. Bist Du in der Schule sitzengeblieben?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2
36. Hast Du einen Verweis von der Schule bekommen?	☐ ja ☐ nein	☐ -2	☐ -1	☐ 0	☐ +1	☐ +2

Das war ein recht langer Fragebogen!
Vielen Dank für Deine Geduld

9. Publications

9.1 Publication in scientific journals

Kneer, K.*, Reinhard J.*, Ziegler, C., Slyschak, A., Schiele, M., Vietz, M., Peters, K., Meisenzahl, E., Pauli, P., Reif, A., Deckert, J., Romanos, M., Domschke, K., Neufang, S. (2020). Serotonergic influence on depressive symptoms and trait anxiety is mediated by negative life events and frontal activation in children and adolescents. European Child & Adolescent Psychiatry, 29(5), 691-706. (*equal contribution)

Reinhard, J., Drepper, C., Weber, H., Schiele, M., **Kneer, K.,** Mittermeier, A., Frey, L., Reif., A., Domschke, K., Deckert, J., Romanos, M. (2020). Anxiety risk SNPs on chromosome 2 modulate arousal in children in fear generalization paradigm. European Child & Adolescent Psychiatry, 29(9), 1301-1310.

Kneer, K., Reinhard, J., Romanos M., Domschke, K., Neufang, S. (2019). The influence of trait anxiety and depressivity on emotional face processing. Conference Abstract in European Neuropharmacology, 29, 496-497.

9.2 Conference Proceedings

Kneer, K., Reinhard, J., Romanos, M., Domschke, K., Neufang, S. (2017). The influence of trait anxiety on structural and functional brain development. 2. *Wissenschaftskonferenz des Zentrums für Psychische Gesundheit (ZEP)*, Würzburg.

Reinhard, J., **Kneer, K.,** Romanos, M., & Neufang, S. (2017). Trait anxiety modulates fear learning and fear generalization in fronto-limbic pathways of the developing brain. *International Congress of the World Association for Stress Related and Anxiety Disorders (WASAD) in conjunction with the Collaborative Research Center SFB-TRR 58, Fear, Anxiety, Anxiety Disorders*, Würzburg. And: *Second International Summer School: Emotional Learning and Memory in Health and Psychopathology*, Leuven, Belgium.

Kneer, K., Reinhard, J., Romanos, M., Domschke, K. & Neufang, S. (2018). The influence of trait anxiety and depressivity on emotional faces processing. *31th Congress of the European College of Neuropsychopharmacology*, Barcelona, Spain. And: *Eureka Congress of the Graduate School of Life Science*, Würzburg. AND *Retreat of the Graduate School of Life Science*, Bad Kissingen.

Kneer, K. (2018). Presentation: Anxiety-related and depression-associated facets of emotional processing, Würzburg, Germany; 3. *Wissenschaftskonferenz des Zentrums für Psychische Gesundheit (ZEP)*.

Kneer, K., Reinhard, J., Romanos, M., Domschke, K. & Neufang, S. (2019). The influence of anxiety measures on emotional face processing in children and adolescents. 4. *Wissenschaftskonferenz des Zentrums für Psychische Gesundheit (ZEP)*, Würzburg.