The stressed brain - discovering the neural pathways to risk and resilience

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Chapter 1

General introduction

"The greatest glory in living lies not in never falling, but in rising every time we fall"
- Nelson Mandela - Long Walk to Freedom (1994)

Although often used to refer to a negative state in day-to-day life, responding to stress is an adaptive phenomenon that is essential for the wellbeing of an individual. During our lives we are exposed to a series of challenges that we attempt to overcome. These challenges or stressors may vary from everyday hassles to severe traumatic events. The human organism always strives to reach and maintain a point of equilibrium that enables maximum functionality of the individual, and these balancing scales are a constant interplay between an individual's resources and the situation the individual finds itself in (Selye, 1979). Reaching and maintaining this balance (homeostasis) through biological and behavioral adaptation has been defined by the term allostasis (McEwen, 1998). Under influence of challenges or stressors the body activates various mechanisms, a process that is called the stress response. During a stress response (described in more detail in Box 1) energy is produced and redirected in order to provide resources to deal with the stressor as quickly and efficiently as possible, thus attempting to restore balance. However, there is a high degree of intra-individual variation in how individuals respond to stressors, and in some instances specific types of stressors or frequently repeated stressors can result in maladaptive psychological and neurobiological processes. Furthermore, when these reactions persist they can result in the development of various psychiatric disorders. There is a long history of research into the psychological mechanisms that provide protection (resilience) or confer risk factors (vulnerability) with regard to developing psychiatric symptoms after experiencing chronic or traumatic stress.

So far, research into the biology of vulnerability and resilience to severe stress has largely been driven by animal studies. More recently, the advent of neuroimaging techniques like positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) has enabled us to start to investigate human brain structure and function in vivo. As this is a relatively recent development, information on brain mechanisms that are related to vulnerability to traumatic stress is less extensive compared to the knowledge on psychological mechanisms. This is even more the case for the neural mechanisms involved in resilience, as traditionally the focus in behavioral neuroscience has always been on vulnerability and psychopathology.

This thesis aims to elucidate on brain mechanisms involved in vulnerability and resilience, and therefore consists of two sections. In the first section (Chapters 2 -5) the neural characteristics associated with a history of stress-related adverse

events of both exogenous nature (childhood maltreatment) and endogenous nature (Cushing's disease) will be addressed. In the second section (Chapters 6 - 8) the neural structural and functional characteristics that are related to resilience to severe stress are investigated using both structural and functional MRI techniques.

Traumatic stress

There is great variety in the types of stressors that elicit a stress response in humans. Situations like losing, winning, physical exercise, social rejection or life threatening situations, all activate the stress system. The most severe acute stressors are called traumatic stressors. In the diagnostic and statistical manual of mental disorders 4th edition (DSM-IV; (American Psychiatric Association, 2000) (exposure to) a traumatic experience is defined as follows:

(A.1.) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. (A.2.) The person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

Criterion A.2. has been omitted from the newest version (DSM-V; (American Psychiatric Association, 2013) in order to improve diagnostic accuracy and in order to further objectify the definition (Friedman et al., 2011), but the research in this thesis uses the DSM-IV definition. Traumatic events are quite common as the prevalence of experiencing a traumatic event at least once in our lives is estimated above 80% in Western countries including the Netherlands (de Vries and Olff, 2009), and the majority of people will even experience multiple traumatic events in their respective lives (Ogle et al., 2013).

Animal studies have shown that exposure to severe or prolonged stress in early-life leads to increased reactivity of the HPA axis, which in turn probably enhances the risk to develop psychiatric symptomatology (Liu et al., 1997; Flinn et al., 2011), including negative mood and cognitions, anxiety and symptoms related to memory of the traumatic event (i.e., intrusions and nightmares). In research, a distinction is often been made between exposure to early life stress (like childhood maltreatment) and traumas experienced in later life. In clinical practice most patients with trauma-related symptoms are diagnosed with major depressive disorder, anxiety disorder, posttraumatic stress disorder (PTSD), or a combination of these disorders. As these three classes of disorders are all associated with dysfunction of the HPA-axis, they are also referred to as stress-related disorders (Sachar et al., 1970; Arana et al., 1985; Arborelius et al., 1999; de Kloet et al., 2006). Childhood emotional maltreatment

consists of both emotional abuse (i.e., systematically criticizing or belittling) and emotional neglect (i.e., not providing the emotional support and care needed, ignoring the child's needs). Although childhood emotional maltreatment does not meet the criteria for a traumatic event as defined by the DSM-IV, it is considered one of the major precursors of developing stress-related disorders in later life (Gibb et al., 2007; Spinhoven et al., 2010).

The association between exposure to severe stressful situations and an increased vulnerability to develop psychiatric symptomatology has lead scientists to start investigating changes in neural correlates that are induced by severe stress, particularly when exposed in childhood. Animal studies using adverse environmental paradigms such as maternal separation, loss, or isolation rearing provided evidence of persistent changes in brain structure as a result of exposure to stressful early-life experiences (Fabricius et al., 2008; Oreland et al., 2010). These changes include decreased neurogenesis and reductions in dendritic branching and dendrite length, and were found to be predominantly present in the prefrontal cortex, the amygdala and the hippocampus, which are all constituents of the limbic system (Sanchez et al., 2001; McEwen, 2008). In human studies on the effect of childhood maltreatment on gray matter volumes, affected structures are mostly situated within the medial prefrontal cortex and the hippocampus (Cohen et al., 2006; Tomoda et al., 2009; Treadway et al., 2009; Frodl et al., 2010; van Harmelen et al., 2010). One theory on the pathway through which childhood maltreatment leads to persistent changes in the brain is through exposure to chronic stress and altered HPA-axis functioning (Shonkoff et al., 2009; Doom et al., 2013; Doom et al., 2014).

Although changes in brain structure under influence of exposure to stressful experiences in early life have been clearly demonstrated, changes in brain function are still poorly understood. Because adverse events like childhood maltreatment predispose for the development of psychopathology in later life, it is important to examine these persistent changes in brain function. These changes can tell us something about the pathways that lead from childhood maltreatment to vulnerability for psychiatric disorders. If these pathways are better understood, treatment methods could be adjusted accordingly.

In Chapter 2, the persisting effects of exogenous adverse experiences, in particular repeated exposure to childhood emotional maltreatment, on brain function are investigated. 88 participants (44 participants with a history of childhood emotional maltreatment, and 44 matched healthy controls) were drawn from the large-scale longitudinal Netherlands Study of Depression and Anxiety (NESDA; (Penninx et al., 2008). Using functional magnetic resonance imaging (fMRI), differences in resting-

state functional connectivity (RSFC) were examined for four resting-state networks: the limbic network, the salience network, the default mode network, and a network seeded by a location in the medial prefrontal cortex based on volumetric differences found in previous research (van Harmelen et al., 2010).

Severely stressful experiences, like childhood emotional maltreatment are exogenous factors that typically influence HPA-axis functioning and are associated with an increase in vulnerability towards developing stress-related psychiatric symptomatology. There are also examples of endogenous factors that impose similar effects. The next section will describe such an endogenous cause: Cushing's disease.

Cushing's disease

Cushing's disease represents a unique model for examining the effects of prolonged exposure to high levels of endogenous cortisol on the human brain as well as for examining the relation between these effects and psychiatric symptomatology. In Cushing's disease a pituitary adenoma produces adrenocorticotropic hormone (ACTH), which in turn stimulates the release of glucocorticoids by the adrenal cortex. Normally, the HPA-axis is regulated by a negative feedback mechanism (see box 1), however, as the production of ACTH is stimulated by the pituitary adenoma, the HPA axis is unable to regulate itself, causing an increase in the level of cortisol, which is named hypercortisolism (Nieman and Ilias, 2005; Newell-Price et al., 2006). Cushing's disease is a rare disease with an estimated prevalence of 39.1 per million and an incidence rate of 2.4 cases per million each year (Etxabe and Vazquez, 1994). Physical features that are related to Cushing's disease include, obesity (predominantly abdominal), moon face, high blood pressure, plethora, acne, increased bruisability, striae, weak bones and muscles, hirsutism and glucose intolerance (Newell-Price et al., 1998). In addition to these physical symptoms, psychiatric symptoms have been reported in concert. The psychiatric symptomatology related to Cushing's disease overlaps with the symptomatology present in stress-related disorders, as both symptoms of depression and anxiety are reported (Kelly et al., 1996; Sonino and Fava, 2001).

On a structural brain level hypercortisolism has been associated with decreases in hippocampal volume (Starkman et al., 1992), an area rich in both GR and MR, and therefore very sensitive to hypercortisolism. An important function of the hippocampus is memory functioning, which has also been found to be impaired under influence of hypercortisolism (Whelan et al., 1980; Mauri et al., 1993).

Cushing's disease is treated using transsphenoidal surgery, in some cases followed

by postoperative radiotherapy and/or hydrocortisone substitution, dependent on the outcome of the surgery. Remission occurs with the re-instatement of normalized basal and ACTH-stimulated cortisol values. Following successful treatment of hypercortisolism, both the physical features and the psychiatric symptoms improve substantially (Cohen, 1980; Kelly et al., 1996), which coincides with a reversibility of the reductions in brain volume (Starkman et al., 1999; Bourdeau et al., 2002; Starkman et al., 2003). However, despite improvement, symptoms persist when compared to healthy controls as patients with long-term remission of Cushing's disease display increased prevalence of depression and anxiety (Tiemensma et al., 2010a), cognitive impairments (Tiemensma et al., 2010b), and decreased quality of life (van Aken et al., 2005; Tiemensma et al., 2011). The persistence of these symptoms lead us to hypothesize that in Cushing's disease brain structure and function are permanently changed under influence of long term exposure to hypercortisolism. To examine this, our group conducted an MRI study in which 25 patients in long-term remission of Cushing's disease were compared with 25 healthy controls matched for age, gender and level of education. T1-weighted scans and diffusion tensor imaging (DTI) scans were used to examine gray matter volume and white matter integrity, and resting-state scans were used to examine RSFC, results of which are reported in Chapter 3-5 (see below). In addition, task-related MRI scans were used to examine brain function during cognitive performance, emotional processing, and during encoding and retrieval of emotional stimuli (results are not reported in this thesis).

Reductions in gray matter volume under influence of exposure to hypercortisolism are well documented. However, less is known about the persistence of these reductions and their relation to persistent behavioral impairments. This is addressed in Chapter 3, where differences in brain volume are investigated in patients in long-term remission of Cushing's disease and in healthy controls, using a voxel-based morphometry (VBM) approach. The relation between these brain volumes and psychiatric symptomatology in the patient group are studied in concert.

In Chapter 4 structural brain abnormalities in remitted Cushing's disease are further explored, using diffusion tensor imaging (DTI). DTI is an imaging technique, which enables the mapping of the diffusion of (predominantly water) particles in tissue (for more information see box 2). Using these DTI scans, the degree in which particles are restricted in the direction of their diffusion can be calculated. This is called fractional anisotropy (FA), and FA values in white matter are a measure for the integrity of the white matter. In Chapter 4, white matter integrity in patients in long term remission of Cushing's disease is investigated by extracting FA values from DTI scans, and subsequently using these in a tract-based spatial statistics approach. The

region-of-interest analysis focuses on FA values in the bilateral cingulate cingulum, the bilateral hippocampal cingulum, the bilateral uncinate fasciculus and corpus callosum. An exploratory whole brain analysis is used to detect changes in FA values in white matter outside our a priori defined regions-of-interest. In addition, the association between FA values in the white matter tracts resulting from our region-of-interest analysis and psychiatric symptomatology reported by the patients with long-term remission of Cushing's disease is determined.

In Chapter 5 functional connectivity in remitted Cushing's disease is explored. Using a probabilistic independent component analysis, three a priori hypothesized functional brain networks are identified: The limbic network, the default mode network, and the salience network. Resting-state functional connectivity differences between patients with long-term remission of Cushing's disease and healthy controls are investigated for each of these networks using a dual-regression method. In addition, the strength of resting-state functional connectivity was studied in relation to the psychiatric symptomatology displayed by the patients.

The brain characteristics of resilience to trauma

As described in a previous section experiencing a traumatic event is quite common, with an estimated prevalence of around 80% in Western countries (de Vries and Olff, 2009). Prevalence estimations for the development of PTSD after trauma exposure vary greatly based on type of trauma and age of exposure (Stein et al., 1997; Creamer et al., 2001; Alisic et al., 2014). However, it is clear that not everyone who experiences a traumatic event will develop trauma-related psychiatric symptoms. This notion is supported by figures from The United States National Comorbidity Survey showing an estimated 7.8% of the population in the US develops a PTSD at least once in their lives, which is a lower incidence rate compared to trauma exposure (Kessler et al., 1995). Clearly, there is a degree of inter-individual variation in the way individuals respond and adapt to severe stress, with a spectrum ranging from vulnerable individuals on the one side to resilient individuals on the other. In simple terms of outcome, resilience can be defined as the absence of psychopathology after experiencing a traumatic event. Usually, however, more complex and dynamic definitions of resilience are used in the literature. These describe resilience as a dynamic, multidimensional process encompassing positive adaptation within the context of significant adversity, and also, from a more psychobiological standpoint, as short-term and long-term responses that reduce allostatic load (Curtis and Cicchetti, 2003; Charney, 2004; Cicchetti and Rogosch, 2009).

In the search for protective and risk factors, the first evidence came from large-scale epidemiological studies that attempt to map characteristics and incidence

rates of trauma exposure and PTSD. Evidently, the nature of the traumatic event is an important risk factor, with sexual assault being the strongest predictor of PTSD for women and combat exposure for men (Kessler et al., 1995; Stein et al., 1997; Creamer et al., 2001). Although men are more prone to experience a traumatic event, women are more likely to develop PTSD (Kessler et al., 1995; Breslau et al., 1999). The experience of prior trauma and especially trauma in childhood was found to be a risk factor, but also the lack of social support posttrauma and having a family history of psychopathology were found to be important determinants in the development of PTSD (Ozer et al., 2003). These risks or vulnerability factors however do not give an answer to the question why some individuals thrive, adapt or 'bounce back' in the face of adverse events, while others break down and develop psychiatric symptoms. Over the years, research has therefore focused on investigating psychological mechanisms that protect an individual from the negative effects of trauma. These include, but are not limited to, emotion regulation, self-esteem, executive functioning (i.e., problem-solving skills and planning), active coping strategies, optimism and internal locus of control (Masten, 2001; Southwick et al., 2005; Masten, 2007; Cicchetti, 2010). In addition, personality traits are also associated with an individual's level of resilience. High neuroticism is directly related to an increased chance for developing PTSD (Breslau et al., 1991; Nakaya et al., 2006), whereas low neuroticism, and high traits of extraversion, conscientiousness, openness and agreeableness are related to a resilient personality profile (Friborg et al., 2005; Campbell-Sills et al., 2006).

In contrast to the knowledge on psychological factors that are involved in resilience, not much is known about the neural mechanisms that underlie resilience to traumatic stress. To review the state of the art knowledge regarding these mechanisms at the start of this part of the thesis we conducted a thorough literature review, resulting in Chapter 6, which provides an oversight of studies that investigate characteristics of brain structure and function related to resilience to trauma. One of the key conclusions of this review concerns the designs that are being used to examine resilience. Most studies use a design comparing trauma-exposed non-PTSD (resilient) individuals with PTSD individuals. With this comparison it remains unclear whether differences found between these two groups should be attributed to trauma-related symptomatology in the patient group, or to the resilience in the control group. Therefore, some suggestions on how to operationalize resilience in behavioral neuroscience are provided. One of these suggestions is to add another control group to the design, consisting of individuals who have not experienced trauma and do not have a history of psychopathology. The advantage of including this control group to the design is that it enables the disentangling of effects related to resilience from effects related to psychopathology. In both chapter 7 and 8 this

design is applied to investigate neural mechanisms that are specific to resilience to traumatic stress.

In Chapter 7, resting-state functional connectivity related to resilience to childhood maltreatment is investigated. Individuals with a history of childhood maltreatment without psychopathology (n = 11; resilient group) are compared to both individuals with a history of maltreatment and psychopathology (n = 11; vulnerable group) and a healthy control group (n = 11), consisting of individuals without a history of childhood maltreatment and without psychopathology. The same networks as in Chapter 3 are examined: limbic network, default mode network, salience network, and a network seeded by a location in the medial prefrontal cortex.

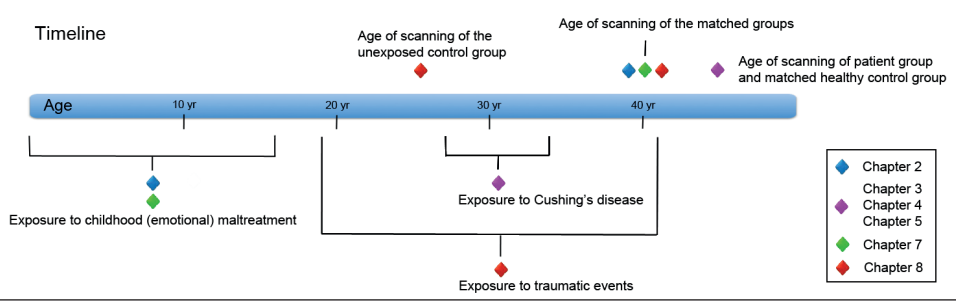
To be able to further investigate the neural mechanisms of resilience to trauma an MRI study was conducted using a highly relevant group within the context of trauma exposure and resilience: Dutch police officers. By virtue of their profession, Dutch police officers have a very high chance of encountering multiple traumatic events. It is therefore very important that these individuals are as resilient as possible, and to ensure this police officers are subjected to strict selection criteria and training methods. There are indications that these methods are effective as there is no evidence that police officers suffer from more trauma-related psychopathology compared to non trauma-related occupations (van der Velden et al., 2013). However, these training and selection methods are based on psychological and personality constructs that are known be indicative of resilience, might potentially be enhanced by additional information on the neural mechanisms that underlie resilience to trauma. In our study, police officers that were exposed to multiple profession related traumatic events but with no history of psychopathology (n = 29; resilient group) are compared to police officers with trauma exposure and a history of psychopathology (n = 33; vulnerable group) and to recruits from the police academy who were not exposed to traumatic events and had no history of psychopathology (n = 19; control group). T1-weighted scans and diffusion tensor imaging scans are used to examine gray matter volume and white matter integrity, and resting-state scans are used to examine resting-state functional connectivity. In addition, task-related fMRI scans are used to examine brain function during implicit emotion regulation, emotional working memory performance, and during social stress (results of the task-related fMRI scans are not reported in this thesis).

Using the T1-weighted scans and diffusion tensor imaging scans characteristics of gray matter volume and white matter integrity related to resilience to stress are reported in Chapter 8. Moreover, the relationship between these characteristics and resilience related behavior are examined, as well as the association between

white matter integrity characteristics, which is a measure for structural connectivity, and functional connectivity measured with resting-state MRI scans.

Finally, in Chapter 9, a summary is provided of the empirical studies reported in this thesis and the findings are integrated and discussed. A timeline is provided (Figure 1) to give an oversight for each of the Chapters when severe stress / hypercortisolism exposure occurred and when MRI measurements where assessed.

Figure 1. Timeline of severe stress / hypercortisolism exposure and time of scanning for each of the Chapters.



The stress response (BOX 1)

The primary system in the brain that initiates and regulates the stress response is the limbic system. It consists of various brain structures including the medial prefrontal cortex, insula, amygdala, hippocampus, hypothalamus and nucleus accumbens (Morgane et al., 2005; Shin and Liberzon, 2010). The amygdala is a key structure in the initiation of the stress response, as it is activated when faced with a stressor (Cahill et al., 1996; Irwin et al., 1996; Whalen, 1998; Shin and Liberzon, 2010), signaling the hypothalamus to activate the autonomic nervous system. The autonomic nervous system controls involuntary functions like heartbeat, blood pressure, constriction, and dilation of blood vessels, and regulates these through the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system promotes action, whereas the parasympathetic nervous system promotes generation and preservation of energy, mainly by putting all systems to a phase of rest, aside from digestion, which is activated. During a stressor the autonomic nervous system switches on the sympathic nervous system through the release of the hormone epinephrine by the adrenal glands as well as norepinephrine by the locus coeruleus (Berridge and Waterhouse, 2003). The release of these hormones result in a number of physical reactions, including increases in heart rate, increases in respiratory rate, stimulation of glycogenolysis in the liver and muscles (Arnall et al., 1986). These reactions all result in increases

of energy availability throughout the body, but most importantly in the muscles. This rise in energy provides an individual with the resources needed to adapt to the situation as best as possible. On a behavioral level, this results in the fight-or-flight response (Cannon, 1929), although responses of freeze, fright and faint have also been observed when exposed to severe stressors (Bracha, 2004). The sympathetic nervous system reaction on a stressor is a rather fast process, with the release of epinephrine and norepinephrine being initiated within milliseconds after the stressor presents itself (Morilak et al., 2005).

A simultaneously activated, but much slower mechanism is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is activated under influence of the same signaling of the amygdala to the hypothalamus. The hypothalamus secretes corticotropin-releasing hormone (CRH), which in turn stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH signals the adrenal cortex to produce and release glucocorticoid hormones (in humans also known as cortisol) to the bloodstream (Riedemann et al., 2010). The release of glucocorticoids by the adrenal cortex happens between three and seven minutes after the initial activation of the HPA axis (Bassett and Cairncross, 1975). Glucocorticoids can pass the blood-brain barrier, reaching the brain where they will bind on either the mineralocorticoid receptors (MR) or the glucocorticoid receptors (GR). MR have a seven to ten fold greater affinity for binding glucocorticoids when compared to GR (Reul et al., 2000), which means they are occupied the majority of the time, whereas GR only get occupied when substantial amount of glucocorticoids are available (i.e., during awakening or during a stress response). The GR are expressed throughout most of the brain, with the strongest expression in the hippocampus. MR expression is more localized in specific areas of the brain, with the strongest expression in the hippocampus as well, and moderate expression in the amygdala and hypothalamus (Reul and de Kloet, 1986). By binding to these receptors, glucocorticoids regulate the HPA axis as negative feedback occurs on the secretion of both CRH in the hypothalamus and ACTH in the pituitary gland (Wintermantel et al., 2005).

The activation of the HPA-axis is a much slower process compared to the epinephrine/norepinephrine release, and the role of the HPA-axis is to fine-tune and terminate the initial stress response (Radley et al., 2008). Glucocorticoids facilitate the fight-or-flight response by increasing the availability of energy. This happens through increasing the mobilization of glucose (Rizza et al., 1982; Dinneen et al., 1993), by increasing metabolism of proteins and fatty acids (Horber and Haymond, 1990; Djurhuus et al., 2002), and by inducing insulin resistance (Rizza et al., 1982). In addition, glucocorticoids protect an individual

from overactivation of the immune system in the case of tissue damage by suppressing the immune response (Palacios and Sugawara, 1982; Elenkov, 2004). This is the reason that glucorticoids are also used as an immunosuppressive drug proscribed for the treatment of various disease related to a dysfunction of the immune system.

Diffusion Tensor Imaging (Box 2)

Diffusion tensor imaging (DTI) is a special imaging technique, which allows the mapping of diffusional properties of predominantly water molecules in brain tissue. In neuroscience, DTI is typically used to measure integrity of white matter tracts throughout the brain. White matter tracts are myelinated nerve cell projections, which connect various gray matter areas enabling signal transmission between these areas. The myelin sheath acts as an insulator, thus increasing the speed of transmission of signals through the nerve. Diffusion inside the white matter tracts is restricted by the myelin sheath and the cell membrane. Hence, it is faster in the direction aligned with the tract and slower in the perpendicular direction. A DTI scan uses information obtained by scanning in multiple gradient directions (in the case of the studies described in this thesis 32 directions were used) to compute for each voxel the diffusion tensor, which has the shape of an ellipsoid (See Figure 2). The shape of the ellipsoid can be defined by three eigenvectors: one describing the principal long axis, one describing the width, and one describing the depth of the ellipsoid. Each of the eigenvectors has a length, which is called the eigenvalue (λ). The eigenvalue along the principal axis (λ1) is also called the axial diffusivity (AD). The average of the other two eigenvalues (λ2 and λ3) is called the radial diffusivity (RD). Furthermore the mean of the three eigenvalues is called the mean diffusivity (MD). Using the three eigenvalues the fractional anisotropy (FA) value can be calculated (See formula 1 (Mori and Zhang, 2006). FA is a sensitive marker for measuring white matter integrity and its values are scaled between 0 (isotropic) and 1 (anisotropic). However, it is also non-specific, meaning it gives no information about the structural properties underlying abnormalities in white matter tissue. In this thesis, finding differences in FA values is therefore always followed by post-hoc analyses of the AD, RD, and MD in those regions. Decreased diffusion along the principal direction of the fiber (AD) indicates axonal loss (Budde et al., 2009), while increased diffusion perpendicular to the principal direction of the fiber (RD) indicates demyelination (Song et al., 2005; Alexander et al., 2007). In addition, an increase in overall water diffusion in all directions (MD) is also an indication for demyelination (Horsfield and Jones, 2002), but could be caused by the presence of edema as well (Alexander et al., 2007).

Figure 2. Eigenvectors of the diffusion tensor model

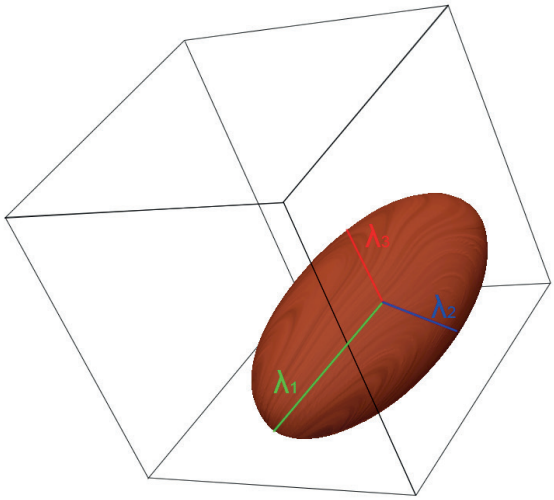


Figure 2 depicts the three eigenvectors describing the ellipsoid of the diffusion tensor model. λ1 (green) describes the length of the first eigenvector, describing the length of the ellipsoid. λ2 and λ3 describe the length of the second and third eigenvectors, which describe the width and the depth of the ellipsoid.

Formula 1. Computing FA from the eigenvalues

$$\mathrm{FA} = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}},$$

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