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Effect of stress on structural brain asymmetry.

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Abstract

There is a growing body of evidence that stressful events may affect the brain not only as a whole, but also in multiple laterality aspects. The present review is aimed at discussing the effect of stress and stress hormones on structural brain asymmetry. Differences and crossroads of functional and structural asymmetry are briefly mentioned throughout the document. The first part of this review summarizes major findings in the field of structural brain asymmetries in animals and humans from the evolutionary perspective. Additionally, effect of stress on animals is discussed generally. The second part then explores asymmetrical effects of stress on structural changes of principal brain areas - amygdala, hippocampus, neocortex, diencephalon, basal forebrain and basal ganglia from the point of normal lateralization, steroids, trauma and genetic factors. At the end we present hypothesis why stress appears to have asymmetrical effects on lateralized brain structures.

1. INTRODUCTION

Brain is considered asymmetrical if a brain region on one side is structurally or functionally different from the other side. The term asymmetry is often substituted for the term laterality, even though laterality traditionally refers only to functional asymmetry (Bryden, 1982). There are a few well-established structural and functional differences between the right and the left hemisphere. For instance, in our species, language and speech production is controlled by the left hemisphere in a vast majority of individuals, while the right hemisphere is specialized for spatial relations and emotional control (Hugdahl, 2005). Although brain asymmetry is a norm for a functional nervous system in healthy population, a large body of literature indicates abnormalities in brain asymmetry in patients suffering from several diseases, such as schizophrenia, depressive disorders, anxiety or neurodegenerative diseases (Crow *et al.* 2013, Sheng *et al.* 2013, Bruder *et al.* 2012, Ishikawa *et al.* 2014). Numerous factors may contribute to either structural as well as functional brain asymmetry, such as fetal orientation, genes, sex or hormones (Toga and Thompson, 2003). Techni-

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cally, structural brain asymmetries are related to the anatomical volumes of CNS (central nervous system) subparts (nuclei, cortical width, size of the neurons in the layers of the neocortex, archicortex etc., size of the white matter bundles and fascicles inside hemispheres between right and left side). Functional brain asymmetries are more focused on the physiological aspects and often studied in the context of neurological/psychiatric disorders (brain asymmetries in the levels of the neuromediators, in the EEG (electroencephalography) signal on the surface of the brain, genetic expression of the various factors and molecules on the neurons and neuroglia, general activity of the nuclei and white matter in the hemispheres, emotional laterality, auditory laterality, etc.). In our review we track the first group only – structural asymmetries of the brain, since these are often neglected in the literature while functional brain asymmetries are in the literature cited relatively often (Bryden, 2012, Hugdahl and Davidson, 2004).

Stress has been subject of scientific debate ever since the first use of this term in 1950 (Selye, 1950). As a nonspecific response of the body, a stress reaction aims to regain homeostasis that is compromised by a stressor (Chrousos, 2009). After a prolonged exposure to stressors, the stress response may become maladaptive and bear negative consequences for the individual (Selye, 1998), even though the adaptive and maladaptive aspects appear to be difficult to dissociate from each other (Koolhaas *et al.* 2011). Recently, the term 'stress' was proposed for conditions that are characterized by their unpredictability and uncontrollability (Koolhaas *et al.* 2011).

Brain is a clear target of stress and plays also a central role in the regulation of allostasis, which is a way of maintaining stability by changing homeostatic setpoints when a stressor is anticipated (McEwen, 1998). Low intensities of acute stress have beneficial effects on the brain and also on some mental functions (Lyons, 2002); more specifically, it promotes cognitive and emotional functioning (Boyce and Chesterman, 1990, Parker *et al.* 2005). However, more extreme and also chronic stressful life events cause a variety of negative conditions and alter several behavioral and mental functions including asymmetry dysregulation (Bob, 2008). Collectively, a hypothesis may be generated that a maladaptive stress response results in a dysfunctional hemispheric specialization.

Stress could be evoked by wide range of various conditions and situations. To name some of them, it would include pharmacologically invoked stress by means of subcutaneous pellets with corticoids, behaviorally induced stress - forbidden zones with nociceptive stimuli, visual exposure to adversary animals, experimental disruption of the natural circadian rhythms, socially induced stress and many others. In the wider context we assume as a source of stress maltreatment in the childhood, exposure to emotionally charged movies or situations, like loss of family member or friend. Important distinction is always duration of the stress – acute or chronic. Since we are interested in structural asymmetries we presume that acute stress does not have sufficient duration to promote permanent changes in the volumes of the nervous system subparts.

Experimental studies on animals showed different left-right effect of chronic stress on some brain structures (basolateral amygdala, prefrontal/prelimbic and somatosensory cortex), depending on age and other factors. Chronic exposure to nicotin differed significantly between adult and adolescent Sprague-Dawley rats. In both groups there was significant reduction in complexity of apical dendritic arborization in principal neurons of the basolateral amygdala after nicotin treatment. However, in adults nicotine increased dendritic length in the right hemisphere only while in adolescents there was no significant alteration of basilar dendritic morphology at all. In adolescents though nicotine eliminated a naturally existing right-left asymmetry. In contrast chronic nicotine exposure had no effect on right-left asymmetry of the pyramidal neurons in the infralimbic cortex in adult animals (Bergstrom *et al.* 2010).

Chronic restraint stress reduced length of the apical dendrites in the right prelimbic and infralimbic cortices (right longer then left in controls) but in left anterior cingulate cortex (no hemispheric asymmetry observed in controls) (Perez-Cruz *et al.* 2007). Restraint stress was then applied to rats during resting and activity periods. In prelimbic cortex the number of spines on proximal dendrites was higher in the left than in the right hemisphere and displayed diurnal variation: more spines appeared during resting period compared to activity period. Restraint stress during the activity period had more pronounced effects on the physiological stress parameters compared to resting period (Perez-Cruz *et al.* 2009). In case of somatosensory cortex deprivation study showed that father-deprived animals (rodent Octodon degus) have shorter and less complex basal dendrites in the left compared with the right hemisphere (Pinkernelle *et al.* 2009).

In the present review, we summarize the effect of stress on structural brain asymmetry. At the end of this review, we discuss the influence of stress on the asymmetry of specific brain regions and the relation between brain asymmetry and stress-related neuropsychological disorders.

Evolutionary and developmental views on laterality account

Traditionally, brain asymmetry has been considered a unique trait of human species and was associated with language capabilities and handedness (Shapleske *et al.* 1999). However, over the last twenty years a great body of evidence has been accumulating to support the view that animals also have several asymmetrical brain regions. Structural brain asymmetry is now considered

widespread among vertebrates (Vallortigara, 2006) as well as in invertebrates (Frasnelli *et al.* 2012). Besides brain asymmetry, even rats were demonstrated by some studies to be left or right handed (Babcock and Robison, 1989). There is evidence indicating a behavioral asymmetry dating back to the Cambrian period. Fossils of trilobites have a higher incidence of healed scars, possibly from attacks, specifically on the right posterior region of their bodies. This suggests that trilobites tended to escape by moving leftwards, or that their predators had an asymmetry in their direction of attack (Babcock and Robison, 1989).

It is speculated that some asymmetry traits such as human left-handedness evolved to provide an advantage in fighting (Faurie and Raymond, 2013). Interestingly, there is an increase in the proportion of left-handed people in human communities threatened by high levels of inter-human aggression and violence, perhaps showing the advantage of lesser action predictability in fight (Dane and Şekertekin, 2005). On the other hand, in males, trait aggression was significantly higher in strong-handers than in mixed-handers, while no difference was seen in females (Dinsdale *et al.* 2011). Overall, literature suggests that brain asymmetry may have ocurred as an adaptive response to stressors that may provide important advantages. However, there are several lines of evidence indicating that extreme or chronic stress may also lead to dysfunctional, maladaptive hemispheric specialization.

According to Best (1988) the pattern of cerebral asymmetries is developmentally rather invariant in both functional and structural way. At the same time author concedes that the structural and functional properties of the two cerebral hemispheres do change developmentally, but always in different manners because they develop within the context of an ever-present lateralization of functions, which is continuous with a lateralized gradient of neuronal differentiation and maturation. Background hypotheses for this are lateralized neuroembryological gradient and growth vector of neuronal organization (Best, 1988).

A rich body of research has demonstrated that both prenatal and postnatal early experience have a critical role in shaping the brain and that early life stress is associated with a life-long burden of risk for neuropsychiatric diseases (Jones *et al.* 2011). In the following paragraph are mentioned several studies indicating that stressful early life experience may have an impact on hemispheric specialization.

Women who experienced a high level of stressful life events were shown to have a higher risk of having mixed-handed children (Obel *et al.* 2003). Another study revealed that maternally reported stress level is related to fetal left-handed self-touches (Reissland *et al.* 2014). It has been suggested that altered intrauterine hormonal environment might predispose to atypical cerebral asymmetry (Sandson *et al.* 1992). Persons that experienced emotional childhood neglect were found to have a smaller volume of the left hippocampal white matter (Frodl *et al.* 2010). A study by Coplan also pointed to the left hippocampus as they found a decreased left mediotemporal lobe volume in macaques that experienced early life stress (Coplan *et al.* 2010). Several cytoskeletal and heat shock proteins as well as enzymes of energy metabolism were found upregulated in the left hippocampus following a denial of the expected maternal contact (Raftogianni *et al.* 2012). However, there is also evidence that maternal deprivation had a negative impact on neurons in hippocampus and on learning and memory functions, but did not influence laterality (Wang and Gondre-Lewis, 2013). Decreases in cortical thickness as well as white matter atrophy were found to be most severe in the left hemisphere in a study using a mouse model of early life neglect and abuse based on maternal separation with early weaning (Duque *et al.* 2012). A number of studies revealed alterations in the prefrontal cortex following early life stress. Smaller volume of the right orbitofrontal cortex has been found in abused children (Hanson *et al.* 2010). Reductions in the basal unit activity in the right medial prefrontal cortex have been revealed in subjects that experienced neonatal maternal separation (Stevenson *et al.* 2008). On the other hand, decreased left frontal pole has been found related to childhood stress (Hanson *et al.* 2012).

2. THE ROLE OF GLUCOCORTICOIDS IN STRUCTURAL BRAIN ASYMMETRY

One of the mechanisms explaining how stress may impact brain asymmetry is through the release of glucocorticoids although sensitivity to it is also subject of left - right asymmetry (Zou *et al.* 2001). In turn left and right hemispheres seem to have different regulatory impact on the levels of the stress hormones and overall activity of the HPA (hypothalamic-pituitary-adrenal axis) axis. It is well-established that chronic high levels of glucocorticoids exhibit adverse or even atrophic effects on hippocampal neurons and glial cells (Scheff *et al.* 1980, Woolley *et al.* 1990), which is known as glucocorticoid cascade hypothesis (Sapolsky *et al.* 1986). Chronically high levels of corticoids associated with stressful life events seem to affect both hippocampi, although the right side affliction is more pronounced (Frodl and O'Keane, 2013). Effect of high levels of glucocorticoids on bilateral hippocampal volume decrease was described by Sousa et al. (Sousa *et al.* 1998). However, Zach and colleagues (Zach *et al.* 2010) only observed a delayed decrease in the volume in the right hippocampus of Long-Evans rats following chronic corticosteron administration. Another study found that sensitivity to corticosteron, measured by long-term potentiation after neonatal novelty exposure, was higher in the right hippocampus (Zou *et al.* 2001). In accord with this finding, a higher density of mineralocorticoid receptors (Neveu *et al.* 1998) has been

found in the right hippocampus. Moreover, increased level of novelty-induced plasticity (Tang *et al.* 2008, Verstynen *et al.* 2001) has been found predominantly in the right hippocampus.

Besides glucocorticoids, HPA axis may contribute to structural brain asymmetries, although by not very well understood way. Structural asymmetry in the major limbic fiber bundles in humans (the cingulum and uncinate fasciculus) was found to be associated with cortisol awakening response (CAR). Higher neuroticism scores, which were associated with higher CAR, were also correlated with higher right relative to left cingulum fractional anisotropy. Elevated CAR was associated with the degree of fractional anisotropy asymmetry within both the cingulum and the uncinate fasciculus, but in opposing directions (Madsen *et al.* 2012c). This leads to speculations that asymmetry between left and right limbic structures have a relation to the HPA axis reactivity although it is not clear in which direction (limbic system towards HPA, HPA towards limbic system or both) (Madsen *et al.* 2012a). The role of hippocampus itself in stress regulation is possibly even more complex since left and right one have differential regulatory effects on the HPA axis. On the other side, a contrary evidence was found by a precise experiment of (Schmidt *et al.* 1999) showing that complete and selective bilateral excitotoxic lesions to hippocampus failed to disinhibit negative feedback regulation of stress response in HPA axis.

Overall asymmetry the glucocorticoids affect the brain may be left lateralized (prefrontal cortex, hippocampus) as suggested by several reports (Cerqueira *et al.* 2008, MacLullich *et al.* 2006, Silva *et al.* 2006) although in case of hippocampus mixed reports exist (Frodl and O'Keane, 2013, Zach *et al.* 2010).

However, corticosteroids themselves cannot fully explain the effect of stress on the brain, as several stress-related disorders, such as posttraumatic stress disorder (PTSD), chronic pain or fatigue exhibit low plasma levels of cortisol (Yehuda, 2009).

3. POST-TRAUMATIC STRESS DISORDER (PTSD)

Recent research indicates that adults with PTSD have a higher incidence of mixed (right-left, left-right) laterality with respect to handedness than the rest of the population (Saltzman *et al.* 2006). Traumatic events may influence patterns of brain asymmetry and induce inter-hemispheric deregulation. It has been suggested that the right hemisphere is more vulnerable to traumatic events (Bob, 2008). In a population of subjects that developed PTSD following an earthquake, grey matter volume in the right ventral anterior cingulate cortex was negatively associated with PTSD symptoms. As the anterior cingulate cortex is involved in processing of fear and anxiety (beside other functions), these results indicate that it may represent a region of increased lateralized vulnerability for PTSD symptoms (Sekiguchi *et al.* 2013).

A case study reported that the removal of the amygdala-hippocampal region due to epilepsy resulted in the presentation of PTSD symptoms (Adami *et al.* 2006). This suggests that amygdala and hippocampus are both functionally and morphologically involved in the etiology of PTSD. It may be also speculated that disconnection and asymmetry between the right and left amygdala-hippocampal region may play a role in the development of PTSD (Adami *et al.* 2006).

Indeed, PTSD is associated with a significantly smaller left amygdalar complex volume when compared to both healthy and trauma-exposed controls (Karl *et al.* 2006). Asymmetry in the volume of amygdalar complex is present in both patients that developed PTSD and subjects that were exposed to trauma, but did not develop PTSD symptoms (Woon and Hedges, 2009). PTSD patients have also a significantly smaller left hippocampus (Smith, 2005).

In addition, cerebellum seems to be also affected in patients that developed PTSD. A study revealed that the left cerebellar hemisphere volume correlated negatively with PTSD and depressive symptoms (Baldacara *et al.* 2011).

New insights into PTSD mechanism came from the studies on prefrontal cortex subareas activation during stress diferentially on the left and right side. Involvement of the ventromedial, dorsolateral and orbitofrontal cortices together with amygdala showed different reactibility of the circuitry under acute and chronic stress (Arnsten *et al.* 2015). Nevertheless, the absolute values of structural asymmetry (if present) are not documented. Maltreated youth with PTSD demonstrated decreased right ventromedial prefrontal cortex volumes, compared to both maltreated youth without PTSD and non-maltreated controls. Maltreated youth without PTSD demonstrated larger left amygdala and right hippocampal volumes compared to maltreated youth with PTSD and non-maltreated control youth. PTSD symptoms inversely correlated with right and left hippocampal and left amygdala volumes. Confirmatory masked voxel base morphometry analyses demonstrated greater medial orbitofrontal cortex gray matter intensity in controls than maltreated youth with PTSD (Morey *et al.* 2016).

Recent metaanalysis showed that hippocampal volume was reduced in subjects with PTSD, with a greater reduction in the left hippocampus. A medium effect size reduction was found in bilateral amygdala volume when compared with findings in healthy controls; however, no significant differences in amygdala volume between PTSD subjects and trauma-exposed controls were found. Significant volume reductions were found bilaterally in the anterior cingulated cortex (O'Doherty *et al.* 2015).

Interesting observations came from monozygotic twins where one male was a Vietnam combat veteran

and his identical co-twin had no combat exposure. There was smaller hippocampal volume in brain of combat veterans who suffered with more severe PTSD symptoms. Also there was negative correlation between hippocampal volume in veterans compared to their brothers w/o combat exposure indicating that smaller hippocampal volume in identical co-twins who were not themselves exposed to combat was related to more severe PTSD symptoms in their combat-exposed brothers (Gilbertson *et al.* 2010).

4. STRUCTURAL ASYMMETRIES OF THE BRAIN AND EFFECTS OF STRESS

Computational analysis of the high resolution MRI in healthy young controls confirmed already known structural asymmetries (frontal right > left and occipital left > right petalias, left > right in several language areas like planum temporale, gyrus angularis but no asymmetry in anterior language areas, right > left in cingulate sulcus and caudate nucleus) as well as shown some new ones (anterior insular cortex right > left) in both males and females (Watkins *et al.* 2001).

Amygdalar complex, hippocampus and prefrontal cortex are important regulators of the HPA axis and are rich in glucocorticoid receptors (Greenberg *et al.* 2014). Lateralized differences in the structure and functioning of the hippocampus have long been recognized (Milner, 1971), while analogous differences in other regions have attracted interest only recently. Promising would be reconstruction studies by FreeSurfer or similar software on normal or stress affected brains that would clearly give left right structural differences in hundreds of brain structures. Furthermore, there may be other brain structures involved in the stress response. Not all brain structures are affected by stress in the same way, intensity or extent. The following section discusses structural asymmetries of several brain regions: amygdalar complex, hippocampus, neocortex, diencephalon, basal forebrain and basal ganglia in humans.

5.1 Amygdalar complex

The left side is slightly larger but this could reflect a general tendency in the normal brain (1160 versus 1154 mm3 (Pruessner *et al.* 2000)). The left–right difference reaches significance in some studies (Watson *et al.* 1992), where the left amygdala was reported to be significantly larger than the right one (Achten *et al.* 1998, Szeszko *et al.* 1999). Volume of the right amygdala larger than left one is reported in (Pedraza *et al.* 2004), however most reports claim no significant difference between left and right side (for review see (Brierley *et al.* 2002)). Amygdala volume measurement in 37 patients with bipolar disorder and 37 controls showed that carriers of the short allele (SL or SS) of the 5-HTTLPR polymorphism exhibit a relatively increased volume of the right amygdala compared to homozygous L-allele carriers irrespective of diagnosis status (Scherk *et al.* 2009). Carriers may show biased results on brain MRI in PTSD where higher left amygdalar volume compared to right one is often the case (Woon and Hedges, 2009). There are not abundant reports about effects of exogenous corticosteroids administration on amygdala. In humans, cortisol levels are related to the degree of amygdala activation during functional imaging (van Stegeren *et al.* 2007). Children with adrenal hyperplasia and in many cases with postnatal corticosteroids therapy had significantly smaller amygdala volumes compared to controls (Merke *et al.* 2003). Smaller amygdala volumes were also observed in children with Cushing syndrome compared to negative controls (Merke *et al.* 2005). Amygdala volume in patients with asthma or rheumatic disease receiving chronic corticosteroid therapy compared to subjects with similar medical histories with minimal corticosteroid exposure were approximately 20% smaller on the left and 11% on the right (Brown *et al.* 2008). Bilateral magnetic resonance volumetry in 11 chronic PTSD patients showed that right amygdala is significantly smaller than the left, with the right-to-left volume ratio of 0.96 +/- 0.06. This tendency towards smaller right amygdala may be an acquired effect as a result of stress-induced plasticity; however, it was not possible to exclude predisposing condition (Pavlisa *et al.* 2006). A meta-analysis investigating the volume of the right amygdala in PTSD patients in comparison with healthy controls and PTSD patients compared with non-PTSD subjects yielded no significant results, while the left amygdala was significantly smaller in both settings (Karl *et al.* 2006). On the other hand, a more recent meta-analysis of nine studies comparing the volume of amygdala in PTSD patients with PTSD in comparison with subjects unexposed to trauma and participants exposed to psychological trauma but without PTSD showed no significant differences between the groups. Within each group, the right amygdala was significantly larger than the left one, indicating that an asymmetry in the volume of amygdala is present in both trauma exposure and PTSD (Woon and Hedges, 2009).

5.2 Hippocampus

Volumetric analysis of the hippocampal volume in healthy groups without normalization to the skull of brain yielded mixed results (almost equal number of reports finding R>L and L>R), depending on the gender, age and lifestyle (Jack *et al.* 1995). High-resolution magnetic resonance imaging technique conducted with 40 healthy volunteers using segmentation protocol to minimize inter–laboratory differences showed a larger right hippocampus (3324 mm3) compared to the left (3208 mm3 (Pruessner *et al.* 2000)), similarly as in (Horvath *et al.* 2002) and meta-analysis from the years 1990-2002 by Pedraza et al. (Pedraza *et al.* 2004). Also, 32 full-term and 184 preterm infants demonstrated rightward hippocampal asymmetry (Thompson *et al.* 2009). Volumetric analysis of the subparts of

the hippocampal complex confirmed overall rightward laterality, situated mostly in the anterior part of it – the uncus (Woolard and Heckers, 2012). Rats trained in the Morris water maze show a significantly higher rate of gene expression in the right dorsal hippocampus compared to the left one (Klur *et al.* 2009). In a meta-analysis investigating PTSD patients, 15 studies revealed that they had bilaterally reduced hippocampal volume compared to healthy controls (PTSD patients had a 6.9% smaller left hippocampal volume and a 6.6% smaller right hippocampal volume compared to controls) (Milner, 1971). PTSD patients had also a significantly smaller left hippocampus compared to patients who had been exposed to a traumatic event, but did not develop PTSD. These volume differences were smaller when comparing PTSD patients with control subjects exposed to similar levels of trauma, and larger when comparing PTSD patients to control subjects without significant trauma exposure. However, no significant right hippocampal volume difference was found in none of the 12 studies (Smith, 2005). Non-PTSD trauma-exposed patients had a significantly smaller left hippocampus when compared to healthy controls (for review see (Karl *et al.* 2006)).

5.3 Neocortex

In right-handed typically developing individuals, a mean increase in the relative thickness of the right orbitofrontal and inferior frontal cortex with age of 0.011 (0.0018) mm per year was balanced against a relative left-hemispheric increase in the occipital cortical regions of 0.013 (0.0015) mm per year. Age-related change in asymmetry in non–right-handed typically developing individuals was less extensive and was localized to different cortical regions. In ADHD, the posterior component of this evolving asymmetry was intact, but the prefrontal component was lost. Age-related change in asymmetry in non-right-handed typically developing individuals was less extensive and was localized to different cortical regions, including medial prefrontal cortex, lateral frontal gyri and supratemporal gyri in parietal lobe (Shaw *et al.* 2009). In study observing structural changes from childhood to adulthood was documented that in the frontal part of the brain, the left lateral vertices were thinner than the right, and the left medial vertices were thicker. Conversely, in the posterior part of the brain, left lateral vertices were thinner and left medial vertices were thicker than their right hemisphere counterparts. This regional asymmetry pattern, particularly in the lateral aspects of the brain, is consistent with previously reported hemispheric distortions ("Yakovlevian torque"), specifically that the right frontal region is geometrically wider than the left, and the left occipital lobe wider than the right (Toga and Thompson, 2003). Also, the lateral frontal lobes develop more rightward asymmetry while the medial frontal lobes develop more leftward asymmetry with age. In contrast, the lateral side of parietal lobes developed more leftward asymmetry and the reverse pattern, with a significant increase with age in cortical asymmetry, indicating a relative gain in left-hemispheric thickness, was seen in the posterior region centered on the middle occipital and angular gyri. Pre-adolescents showed cortical asymmetry in medial occipital lobe (right thicker than the left) and inferior frontal gyrus (right thicker than the left) and more extensive frontal (lateral right thicker than left and medial left thicker than right) and parietal lobe (lateral left thicker than right and medial right thicker than left) asymmetries continued with adolescence and even increased with aging (Zhou *et al.* 2013). Additionally, Lupinsky et al. documented in animal model that stressor induced high level of glutamate in the prefrontal cortex could be induced contralaterally by callosal neurons and in case of dopamine receptor blockage this control has marked regulatory bias - left dopaminergic input to the prefrontal cortex over the right glutamatergic prefrontal cortex stress response (Lupinsky *et al.* 2010). Volumetric reductions after chronic glucocorticoid treatment in an in vivo MRI study on the rats (Cerqueira *et al.* 2005) were predominantly found in the left cingulate cortex. This finding suggests that the left medial prefrontal cortex is more vulnerable to the effects of high corticosteroid levels and, probably also to stress. The increased vulnerability of the left hemisphere to glucocorticoid effects was subsequently reported for the human brain. A recent MRI study associated the impaired regulation of the HPA axis (hyperactivity) with a smaller left, but not right, cingulate volume (MacLullich *et al.* 2006). Chronic stress significantly suppressed cytogenesis in the medial prefrontal cortex in the rat. Hemispheric comparison revealed that the rate of cytogenesis was significantly higher in the left medial prefrontal cortex of control animals, whereas stress inverted this asymmetry yielding a significantly higher incidence of newborn cells in the right medial prefrontal cortex (Czeh *et al.* 2007).

5.4 Diencephalon

In patients without any known limbic system pathology or seizures history, there was an asymmetry in mammillary bodies in an MRI study (6.5%), although the paper unfortunately does not specify whether the left or the right one was larger (Ozturk *et al.* 2008). Sex mediated differences (present on the left side, but not on the right side) were detected in the size of the arginine-vasopressine synthesizing neurons in the hypothalamic supraoptic and paraventricular nuclei, although no size differences in oxytocin synthesizing neurons in the paraventricular nucleus were observed (Ishunina and Swaab, 1999). Left–right asymmetry was described also in zebrafish for habenular nuclear complex, epithalamus and epiphysis, also in relation to genetic influence (Bianco and Wilson, 2009). Hyperactivity of the lateral habenular nuclei but not medial habenular nuclei was observed in experimental animals as well as in humans

under stress inducing stimuli but w/o specification regarding its asymmetry (Hikosaka, 2010).

5.5 Basal forebrain

A tendency to higher neuronal density on the left side and to that of glia cells on the right side were observed in the nucleus basalis Meynerti; although only sample of 7 men and 4 women had been used (Amunts, 2006).

5.6 Basal ganglia

Leftward volume asymmetry of the globus pallidus was reported (Orthner and Seler, 1975, Kooistra and Heilman, 1988). Although volume asymmetry of the caudate nucleus and putamen shows inconsistency, a rightward asymmetry of caudate nucleus was observed (Raz *et al.* 1995). Another MRI study on 35 healthy right handers revealed a rightward asymmetry of the caudate nucleus (for the head, body and tail) and globus pallidus (both internal and external); however no asymmetry was observed in putamen (Anastasi *et al.* 2006). Volumetric measurement of the basal ganglia by automated segmentation (FreeSurfer) showed rightward asymmetry of the caudate nucleus and leftward asymmetry of the putamen and globus pallidus. Putamen and globus pallidus volume decreased with age, but caudate nucleus volume did not. The lateralization index decreased with age for putamen, but not for caudate nucleus and globus pallidus (Wyciszkiewicz and Pawlak, 2014). Nucleus accumbens tends to have a statistically significant width in the right hemisphere (Neto *et al.* 2008). The right caudate volume in the PTSD group was 9% greater compared to controls without PTSD (Looi *et al.* 2009). A histochemical study shows rightward asymmetry in the level of dopamine, dihydroxyphenylacetic and homovanillic acid in the nucleus accumbens in female offsprings of stressed mothers of rats (Alonso *et al.* 1997).

6. DISCUSSION

Increasing evidence supports the view of an early evolutionary as well as developmental origins of the brain asymmetries (Bisazza *et al.* 1998). The advancement of an asymmetrical brain may be an evolutionary survival strategy and it may be speculated that stress following fight or flight response or competition was an important underlying factor for development of this phenomena (Faurie and Raymond, 2013). This review summarizes current knowledge on the structural brain asymmetry related to stress.

The prefrontal cortex seems to be crucial structure affecting regulation of behavior in relation to stress. At the gross morphological level right prefrontal cortex tends to stimulate the activity of the HPA axis, while left one has rather inhibiting effect (Majewska, 2002). Activation of the right prefrontal cortex and at the same time inhibition of the left one is examined in major depressive syndrome, while hypo activation of the right prefrontal cortex is present in attention deficit hyperactivity syndrome (Majewska, 2002). Functional laterality of the medial prefrontal cortex (specifically orbitofrontal, ventromedial and dorsolateral subparts) provides insights into significance of the brain laterality in terms of stress. The evidence suggests that exposure to a stressor initially engages medial prefrontal cortex mechanisms preferentially in the left hemisphere. However, the initial left medial prefrontal cortex activation shifts to a predominantly right medial prefrontal cortex activation as the stressor becomes prolonged and especially when it is perceived as uncontrollable or inescapable. As conceptualized by Denenberg (Denenberg *et al.* 1986), the initial left-biased prefrontal cortex response might mediate preemptive responses to stressors before they become unmanageable and start engaging the right prefrontal cortex mechanisms involved in activating physiological stress responses. However, activation of the right prefrontal cortex would eventually come to predominate when, in the face of a prolonged and inescapable stressor, the early left prefrontal cortex-mediated responses prove to be ineffective (Lupinsky *et al.* 2010). Measurements on the EEG showed that positive affection activated left while negative right prefrontal cortex (Davidson, 2002). These functional asymmetry observations are not accompanied by the similar pattern of structural asymmetry evidence. This gap could be partly explained by the absence of universally agreed on anatomical bordering of the ventromedial and dorsolateral prefrontal cortices since these reflect rather functional parcellation.

Observation supporting assignable function of the prefrontal cortex came from the field of neuroimmunomodulation. Series of animal studies examining the effect of brain lesions (parabrachial nucleus, amygdalar complex, hippocampus, hypothalamus and prefrontal cortex) on delayed skin hypersensitivity and utilization of 3H-thymidine for synthesis of DNA after injection of muramyl dipeptide showed interesting results. More was the lesion placed in the caudal part of the nervous system (brain stem, amygdale and hypothalamus) more uniform and invariable was the immune response in terms of up/down regulation and dependency on the lesion sidedness. Higher up in the hierarchy of the nervous system (hippocampus, basal ganglia and prefrontal cortex) it became less important whether lesion was placed on the right or left side. Specifically in case of prefrontal cortex variability of up/down regulation and lesion sidedness reached almost 100% - in other words each laboratory rat reacted different way (Masek and Petrovicky, 1997, Masek *et al.* 2000). On the other hand a general pattern of immunopotentiation was been observed following selective activation of the left prefrontal cortex; in contrast, higher activity of the right prefrontal cortex was accompanied by immunosuppression (Neveu and Merlot, 2003, Vlajkovic *et al.* 1994).

Neuropsychological disorders and brain asymmetry

Communication between hemispheres brings advantages for an individual (Albert and Moss, 1988) but may, as an unwanted side-effect of the higher complexity of a lateralized brain, also provide new niches for the development of psychiatric diseases. Sophisticated strategies for the organism survival demand a more complex organization of the CNS; connecting it to functional brain laterality. Some of the unsolved questions concerning existence of brain asymmetry could be: how far would process of the lateralization progress within next hundreds of years? Is the present structural and/or functional asymmetry of the CNS only first step that would eventually end up with completely right-left specialized structures? Or is it rather opposite so that we observe terminal stage of the brain lateralization (both structural and/or functional)? If the answer is first one then we can speculate that at least some of the psychiatric diseases may be result of undergoing vast changes in the laterality evolution that has not reached maturity yet. It is understandable that laterality changes may be very sensitive to genetic factors or unfavorable conditions, especially to chronic stress. This may be the reason for the frequent association with neuro psychiatric disorders. Also, plasticity of the brain should be comprehended whether it averages especially in the young age effect of stress on the laterality or vice-versa.

Asymmetry in PTSD, a typical stress-related disorder, has been discussed. Furthermore, brain asymmetry has been found in several other disorders, such as anxiety, depression (Coan and Allen, 2004, Davidson, 1998), schizophrenia (Mitchell and Crow, 2005) or Alzheimer´s disease (Long *et al.* 2013).

A distinct asymmetry pattern found in subjects with Alzheimer´s disease may be associated with earlier occurrence of cortical atrophy in the left hemisphere compared to the right one (Thompson *et al.* 2007). Physiological aging, on the other hand, is associated with a greater decline in the right hemisphere (Albert and Moss, 1988). Stress has also been suggested as a risk factor for Alzheimer´s disease, even though causal link could not be established (Greenberg *et al.* 2014).

A stress hypothesis and a traumatogenic neurodevelopmental models have been proposed for schizophrenia (Read *et al.* 2001), suggesting that a genetic deficit may create an oversensitivity to stress that triggers the disorder. Brain asymmetry in schizophrenia is a well-known factor that plays a central role in the current neuropathological model of this disorder (Oertel-Knochel and Linden, 2011). However, a causal link between stress and asymmetry in schizophrenia has not been morphologically established yet.

Brain structures

Overall, the effects of stress on the brain were mostly detected in the amygdalar complex, hippocampus and prefrontal cortex in classical studies (Bremner *et al.* 1995, Akirav and Richter-Levin, 1999, McGregor, 1991), although the right-left distribution of these changes was studied relatively recently. Less is known about structural asymmetries in other regions, such as striatum, hypothalamus, basal forebrain or cerebellum.

Many experimental studies in rats showed that pharmacologically or behaviorally induced high levels of the stress hormones (corticosteroids or their functionally similar derivatives) decreased physical volume of the several bilateral CNS structures (hippocampus, amygdalar complex, prefrontal cortex, basal ganglia) and more importantly in some cases in an asymmetrical way. Chronic stress may thus be viewed as one of the lateralization elements that physiologically and also maybe pathologically in mammals and other vertebrate species contributed to the uneven functional and morphological segregation between the almost identical left-right CNS structures.

For example, in the volumetric studies of hippocampus we often see a different size between left and right - more pronounced atrophy in experimental chronic stress or in patients with Alzheimer disease is observed in the functionally dominant one (Zach *et al.* 2010). This may be result of its higher activity compared to the recessive one (or in other words less developed one). It is not yet fully known whether such stress induced asymmetrical atrophy could be passed to F1 generation by genetic/epigenetic means so that such condition could be considered even as an evolutionary force. We propose a hypothesis that this stress induced brain asymmetry would in the future lead to even more segregated and specialized differences between bilateral CNS structures (nc. accumbens septi, septal nuclei, basal ganglia, endopiriform nucleus in mammals, epithalamic nuclei - corpus geniculatum mediale et laterale, habenular nuclei or even hippocampi that are lateralized but still both right and left hemispheres cooperate in memory encoding and retrieval) while functionally specific cortical areas like Wernicke and Broca speech centers, fissura calcarina or frontal eye field already underwent functional lateralization in the past. This is not an issue with various sensory and motor cortical and subcortical centers operating left and right halves of the body. In such cases, stress induced lateralizations are obvious – more we exercise left or right hand the more there is functional and structural asymmetry in the corresponding brain cortical/subcortical/spinal area. The question is how for example circadian rhythms, behaviors, sleep or satiety operate from the perspective of existence of putatively lateralized centers. With regard to medicine, it is not clear whether ongoing stress-induced lateralization would elevate or decrease an incidence and outcomes of already exist-

ing or newly manifesting psychiatric diseases. Some cases of schizoid attacks, dementias or inappropriate behaviors in humans at age approx. 18-23 could be attributed to sudden change of the functional laterality due to chronic stress, bacterial or viral infection of the brain, radical change of the habitual patterns and other unknown triggers as suggested on the biochemical level (Kristofikova *et al.* 2010). In these cases patients could be diagnosed for the psychiatric disease while underlying mechanism could be switch between formerly dominant structures on one side of the brain to the other recessive ones. This presumes that in the young age both left and right structures of the CNS are not functionally developed equally and there is open potential for redirection of the functional neuronal circuits on the other side, to the structure, that did not maturate in the same pace as the functionally dominant structure. In such case the chronic stress would have selecting effect in terms of either deepening functional and subsequently morphological asymmetry or temporary functional breakdown and subsequent maturation of the recessive structure – asymmetry equilibration.

It seems obvious that bilateral structures of the brain are differently active and their function and growth does not happen symmetrically. It is still unclear, whether most of these bilateral brain structures always elicit functional one side activation and other side inhibition, as it is in the case of the prefrontal cortex and HPA axis (Masek *et al.* 2000). Situation would be probably more complex and this is also documented by high complexity of results presented above. The fact that this process could oscillate forward and backward (decrease or increase of the asymmetry) together with relatively high incidence of the psychiatric diseases in the present time leads us to idea of unfinished structural and functional lateralization of the brain during phylogenesis. Whether it would end up with the brain having left and right centers equally cooperating during specific tasks or with the brain having completely lateralized structures and their functions is a still open question. What is, however, an undoubted fact is that investigation of the brain laterality related not only to the stress, but also to the other pathological conditions of the brain has immense importance for determining the neurobiological substrate of these conditions, which is a prerequisite of future advanced prevention, profylaxis and treatment.

Summary

Although functional laterality of the brain areas were studied relatively extensively, structural asymmetries are still poorly documented, either because there was not enough interest in purely anatomical morphology or they simply do not fit with functional laterality in most cases. As for known body of literature there are relatively well documented structural asymmetries either at the gross anatomical or histological level in hippocampus, amygdalar complex, basal ganglia, part of the diencephalon, nucleus basalis Meynerti and several cortical areas, including planum temporale and prefrontal cortex. These asymmetries were studied in norm and also under different pathological conditions, mostly fitting into the group of neurological or psychiatric diseases. Although the effect of chronic stress on mentioned brain areas is asymmetrical functionally as well as structurally it is unknown to what degree these two overlap. In case of the prefrontal cortex, functional laterality shows rather rigid left – right pattern but structural asymmetry we do not know and it is possible that it rather points to open, fluctuating possibilities, depending on the context in which growth, maturation and ageing occurs. This would be promising for the treatment of the neurological or psychiatric patients since it leaves open ground for any kind of change.

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Declaration of interest statement

The authors report no conflicts of interest.

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