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## Review

# Stress and laterality – The comparative perspective



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## HIGHLIGHTS

- Functional hemispheric asymmetries can vary over time.
- Steroid hormones have been shown to modulate them.
- We review literature on glucocorticoids and laterality.
- We review literature on stress and laterality.
- Acute and chronic stress can affect hemispheric asymmetries.

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## ABSTRACT

Functional hemispheric asymmetries can vary over time and steroid hormones have been shown to be one of the factors that can modulate them. Research into this matter has mainly focused on sex steroid hormones (androgens, estrogens and progesterone), although there is increasing evidence that glucocorticoids which are related to the body's response to stress (e.g. cortisol or corticosterone) might also modulate functional hemispheric asymmetries. Here, we review studies in humans and non-human model species investigating the relation of stress and laterality. Results indicate a dual relationship of the two parameters. Both acute and chronic stress can affect different forms of lateralization in the human brain, often (but not always) resulting in greater involvement of the right hemisphere. Moreover, lateralization as a form of functional brain architecture can also represent a protective factor against adverse effects of stress.

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## 1. Introduction

Functional cerebral asymmetries (FCAs) have been observed in all vertebrate classes [43,81,82,95,108,116] and are of central importance for the functional organization of several cognitive systems in the human brain [80]. While some authors assume that FCAs are mostly determined by genetic factors [2] and thus should be constant over time, evidence is accumulating that FCAs are to some extent plastic and can change over the lifetime of an individual as well as within shorter timeframes [89]. Besides developmental [20] and aging [36] effects, stress has been suggested to affect FCAs (e.g. [24]). Stress has been shown to affect both brain structure and function [16,54,70], making it a likely candidate to modulate FCAs. However, no strong causal link between the variables has been drawn so far. Nevertheless, there are at least two conceivable models that could explain a link between stress and laterality.

## 2. The hormonal model

Several authors have provided evidence for the notion that fluctuating steroid hormone levels could affect FCAs (e.g. [47,49,92,125,129]). Steroid hormones can be grouped into five principal classes based on the receptors to which they bind: androgens, estrogens, progestogens, glucocorticoids, and mineralocorticoids. It must be mentioned, however, that endogenous glucocorticoids in low concentrations already fully occupy mineralocorticoid receptors in the brain [32]. Particularly female sex hormones (estrogens and progestogens) have been investigated with regard to FCAs [9,46,48]. For example, Hausmann and Güntürkün [47] tested normally cycling women with prototypical left and right-hemispheric tasks during menses (low steroid levels, e.g. for progesterone) and the midluteal phase (high progesterone levels) of the menstrual cycle. Participants showed stronger laterality during menses, whereas cerebral organization was more bilateral in the midluteal phase. A similar reduction of FCAs with higher estradiol and progesterone levels was recently also reported by Hodgetts et al. [48].

Interestingly, there is mounting evidence that, in addition to sex hormones, glucocorticoids also affect FCAs. Specifically, glucocorticoid hormones related to the body's response to stress have been implicated to play a role for FCAs by recent studies (see below). In general, encountering a stress-inducing stimulus leads to two types of neuroendocrine responses [70,130]. On the one hand, the sympathetic nervous system rapidly releases adrenaline and noradrenaline, leading to physical alterations such as increases in heart rate and breathing frequency. Notably, steroids can also act fast via their membrane receptors [44]. On the other hand, a second, slower hormonal response is regulated by the so-called hypothalamus pituitary adrenal axis (HPA-axis) [56]. In this system, the paraventricular nucleus of the hypothalamus releases both corticotrophin-releasing hormone (CRH) and vasopressin. CRH stimulates adrenocorticotropin (ACTH) release in the pituitary, which in turn initiates the release of glucocorticoids (cortisol in humans, monkeys, pigs, cats, dogs, horses, sheep and fish, and corticosterone in many commonly used non-human model-species such as rodents and birds), which can affect several aspects of neurotransmitter function and functional brain organization in general [57,69]. How can glucocorticoids modulate FCAs? For female sex hormones, it has been suggested

that circulating changes associated with the menstrual cycle affect transfer of information over the corpus callosum ([47]; but see: [21]). Specifically, Hausmann and Güntürkün [47] suggested that progesterone reduces neuronal transmission over the corpus callosum by decreasing excitatory neuronal responses to glutamate, as well as by increasing inhibitory responses to GABA. This decoupling of the two hemispheres then leads to reduction of hemispheric asymmetries due to reduced inhibition. As cortisol enhances glutamatergic transmission in different brain areas [74], and acute stress rapidly decreases GABAergic neurotransmission [8], one could conceive that stress-related cortisol release would enhance FCAs. However, recent research indicates that depending on callosal subregions and fiber type, the corpus callosum can either execute an inhibitory influence (enhancing FCAs) or an excitatory influence (diminishing FCAs) on the contralateral hemisphere [11,118]. Thus, depending on the specific task, also a reduction of FCAs compared to a non-stressed condition is conceivable. In both cases, however empirical support for this theory would need to show a significant relation between physiological measures of glucocorticoids and FCAs.

## 3. The negative emotionality model

While glucocorticoids are likely to affect FCAs, there are also cognitive mechanisms that could explain an interaction of stress and laterality. Prolonged or intense aversive stimulation evokes both a stress response and the experience of negative emotions [90]. Processing of emotions, however, is fundamentally asymmetric. For example, based on lesion studies that found a reduction of negative emotionality following right-hemisphere damage as well as a reduction of positive emotionality following left-hemisphere damage, the so-called valence hypothesis was developed [98]. This model assumes differential hemispheric control positive and negative emotions, with the right hemisphere controlling negative emotions. One could assume that the negative emotions that accompany stress caused by aversive stimulation might lead to a priming of the right hemisphere. Thus, empirical support for this model would need to show a stronger right-hemispheric response in stressful situations as compared to non-stressful ones. In contrast to the hormonal model, this model does not assume a direct link between glucocorticoids and FCAs.

## 4. Aim of the present review

Given that atypical FCAs have been related to a number of neurodevelopmental and psychiatric disorders (e.g. [64,96,97]), and given that stress can play a role in the etiology of such disorders [42, 59,91], a better understanding of the relationship between FCAs and stress is crucial for the potential use of FCAs as pathology-related endophenotypes. The stress system is a regulatory system that serves the process of adaptation and is highly conserved among vertebrates [78]. The relation of FCAs and stress has been investigated in several different species. Thus, a comparative perspective integrating data from all vertebrate classes is particularly well suited to investigate this relationship. Therefore, the present review article is aimed to present a systematic literature review and comprehensive overview of studies investigating the relationship between FCAs, stressful environments

and glucocorticoid stress hormones in fish, amphibians, reptiles, birds, non-human mammals and humans.

## 5. Chondrichthyes

In cartilaginous fishes (e.g. sharks), only one study has investigated the relationship of laterality and chronic stress. Green and Jutfelt [43] investigated the effect of increased carbon dioxide levels in the water (a constant stressor for sharks) on behavioral lateralization (turning behavior) in small-spotted catsharks (*Scyliorhinus canicula*). Compared to a control group, sharks that were exposed to increased CO<sub>2</sub>-levels for one month prior to testing showed increased behavioral lateralization. This was tested by recording 40 turning decisions in a double T-maze. The stressed sharks showed stronger lateralization on the individual level, as they preferred one side in the maze more consistently than non-stressed animals.

## 6. Osteichthyes

In bony fishes, the effect of chronic stress caused by increased CO<sub>2</sub>-levels in the water on behavioral laterality seems to be opposite to what has been observed in sharks. Jutfelt et al. [51] used a similar task as Green and Jutfelt [43] to assess the impact of exposure to increased CO<sub>2</sub>-levels in the water for 43 days on behavioral lateralization in the three-spined stickleback (*Gasterosteus aculeatus*). Unlike sharks, three-spined sticklebacks showed decreased lateralization when exposed to stress due to elevated CO<sub>2</sub>-levels. Comparable results were reported by Domenici et al. [37] for the yellowtail demoiselle (*Neopomacentrus azysron*). Taken together, these studies suggest that elevated CO<sub>2</sub>-levels represent a stressor to water-living organisms that decreases behavioral lateralization. More evidence for a relationship between laterality and stress in fish has been provided in two studies by Backström et al. [4, 5], b). These authors investigated lateralization of social signaling by carotenoid pigmentation in the Arctic charr (*Salvelinus alpinus*). By analyzing size-matched pairs of fish for left- and right-sided pigmentation before and after putting them into a competitive social situation with each other, they found that in Arctic charr, pigmentation on the right side signals aggression and dominance. Conversely, pigmentation on the left side signals responsiveness to stress.

Moreover, predatory stress has been found to affect FCAs. Brown et al. [13] could show that in *Brachyraphis episcopi*, a species of poeciliid fish, females that were wild-caught from high-predation sites as well as their laboratory-reared offspring showed stronger behavioral lateralization in a barrier detour test than fish caught from low-predation sites. However, other experiments failed to show a relationship between stress and laterality [28].

## 7. Amphibia

While amphibians clearly show FCAs, e.g. in turning behavior [122], the authors could not identify any studies systematically investigating influences of stress on lateralization in amphibians.

## 8. Reptilia

In reptiles, the effects of stress on lateralization have been investigated in the Carolina anole (*Anolis carolinensis*), an arboreal lizard. Deckel [34] investigated how mild acute stress modulated hemispheric asymmetries in regulation of territorial aggression in thirteen adult male *Anolis* lizards. Animals were tested in a stress and a non-stress condition, with stress being induced by the experimenter taking the lizards out of their cages and holding them for several seconds. After stress induction, the animals were paired with antagonistic male individuals to induce territorial aggression, a behavior that has been shown to be mediated by mainly right-hemispheric circuits as shown in a previous study by the same author [33]. While the lizards showed significant

left eye preference for aggressive movements in the non-stressed condition, left eye/right hemisphere mediated aggressive movements were significantly reduced in the stressed condition. This finding shows that acute stress can reduce FCAs in reptiles. Nevertheless, more studies with diverse reptile species are clearly needed in order to get a more comprehensive understanding of the relationship between stress and lateralization in this order.

## 9. Aves

In birds, research on the link between stress and laterality was mainly performed in the chicken (*Gallus gallus domesticus*). Salvatierra et al. [100] showed that acute stress induction by means of a 15-minute swimming test lead to flunitrazepam receptor increase in the left but not the right hemisphere. More evidence for stress effects on lateralization in chicken has been put forward by Rogers and Deng [94]. Under normal circumstances, chicken embryos develop structural asymmetry in visual projections from the thalamus to the Wulst regions of the fore-brain [93]. It is known that this asymmetry is induced by asymmetric light stimulation during incubation, which is caused by the orientation of the embryo within the eggshell that leads to occlusion of the left eye. Light entering through the egg shell stimulates only the right eye [93]. This asymmetric light stimulation leads to more projections from the left side of the thalamus to the right Wulst than vice versa. Rogers and Deng [94] showed that injection of corticosterone into chicken eggs massively influenced the development of this asymmetry in the visual projections. Compared to control animals, chicks that had been injected with corticosterone before hatching did not develop visual pathway asymmetries in response to pre-hatch light exposure. Thus, corticosterone inhibited the development of hemispheric asymmetries in chicks. Another study investigating the effects of corticosterone treatment in the domestic chick was conducted by Freire et al. [39]. These authors investigated the effect of pre- or post-hatch corticosterone administration on behavior. Specifically, they tested the birds' behavioral responses to isolation as well as performance in a simultaneous food identification and predator detection task. Chicks treated with corticosterone before hatch emitted more distress vocalizations than controls after release in a novel arena in which they were isolated. This effect was not found in chicks treated with corticosterone after hatch. In the simultaneous food identification and predator detection task, chicks treated with corticosterone pre-hatch took longer to detect the overhead image of a predator than controls. Again, no effect was found for the post-hatch corticosterone treated animals. These findings indicated that corticosterone treatment during incubation influences stress reactivity in chicks. Freire et al. [39] suggested that impairment in predator detection in animals treated with corticosterone before hatching might be caused by the effect of corticosterone on the developing visual pathway asymmetries as described by Rogers and Deng [94].

## 10. Non-human Mammalia

### 10.1. Non-primate mammals

The relationship between laterality and stress has been investigated in several different non-human mammalian species. In sheep (*Ovis aries*), da Costa et al. [27] investigated how acute stress induced by social isolation affected the animals and how viewing pictures of familiar sheep faces altered indices of stress. Sight of familiar sheep faces significantly reduced behavioral and autonomic responses to stress and lead to lower cortisol and adrenaline levels as compared to a control group. Interestingly, it also modulated mRNA expression of two activity-dependent genes (*c-fos* and *zif/268*) in different brain regions in a lateralized way. Animals in the experimental as compared to the control group showed significantly reduced expression levels in right-hemispheric brain regions controlling fear (lateral and central nuclei of the amygdala) as well as a significantly increased expression levels

in right-hemispheric brain regions relevant for emotional regulation (lateral anterior cingulate cortex and orbitofrontal cortex). This finding led da Costa et al. [27] to conclude that in sheep, the control of negative emotional experiences in response to stress is mainly organized by the right hemisphere. A more recent study by Morgante et al. [75] investigated how strongly versus weakly lateralized female sheep reacted to lamb separation, a common stressor for sheep on a dairy farm. After assessment of FCAs in several different behavioral tests (e.g. turning behavior and preferential leg use in front of an obstacle), the sheep were assigned to a strongly and a weakly lateralized group and several stress indices were recorded after lamb separation. Morgante et al. [75] reported that strongly lateralized female sheep had a stronger hormonal stress response (ACTH) after lamb separation than weakly lateralized female sheep.

In horses (*Equus ferus caballus*), Siniscalchi et al. [105] investigated limb preferences in quarter horses in different motor tasks and found that for truck loading, horses showed both higher anxiety indices and significant left forelimb preference. Siniscalchi et al. [105] concluded that this result indicates right-hemispheric dominance for control of behavior in stressful situations in horses, similar to what has been reported for humans (e.g. [65,127,128]).

In carnivores, Mazzotti and Boere [68] investigated the impact of acute stress induction by transportation and exposure to an unfamiliar environment in the cat (*Felis silvestris catus*). After acute stress induction, cortisol serum levels were measured and the animals were divided into a high and a low cortisol group. Left and right tympanic temperature was determined as a measure of emotional activation. Tympanic membrane thermometry is a non-invasive method in which the temperature of the membrane that separates the external ear from the middle ear is used as a proxy for blood flow to the brain. The temperature of the tympanic membrane is typically higher than that of incoming blood. Thus, higher blood demand in one hemisphere leads to a cooling of the temperature of the tympanic membrane on that side. While no difference in left tympanic temperature was observed between the two groups, right tympanic temperature was higher in the high cortisol group. More evidence for the relation of acute stress and laterality in carnivores was reported by Siniscalchi et al. [106]. These authors investigated hemispheric specialization in the domestic dog (*Canis lupus familiaris*) for processing different types of acoustic stimuli using a head-orienting response technique. Listening to conspecific calls led to right-sided head turning, indicating activation of the left hemisphere. In contrast, listening to a loud thunderstorm, a stimulus that could potentially induce stress in the animals, led to left-sided head turning. The authors concluded that the sound of thunderstorm increased activity of the right hemisphere, potentially associated with an increase of arousal and fear.

Several studies also investigated the relationship of laterality and stress in rodents. For example, Delrue et al. [35] investigated the influence of paw preferences on mice's reactivity to stimulation of the immune system by systemic injection of lipopolysaccharide. Interestingly, all animals showed an increase in corticosterone levels. In contrast, augmentation of plasma ACTH was only significant in right-pawed and ambidextrous mice but not in left-pawed animals. This shows that in mice, a specific configuration of FCAs might be a protective factor against adverse effects of stress. Neveu and Merlot [76] investigated whether paw preferences modulated the animals' responses to stress with regard to production of cytokines, for example interleukin-1 (IL-1). Induction of acute stress by prolonged restraint led to an increase in interleukin plasma levels only in right- but not in left-pawed mice, indicating that right-pawed mice showed a stronger stress reaction than left-pawed animals.

In rats, Carlson et al. [17] investigated the role of controlled and uncontrolled acute stress on left- and right-hemispheric dopamine systems in a learned helplessness model. Rats that received uncontrollable foot shocks showed right vs. left increase of dopamine levels in the prefrontal cortex, a pattern which was not observed in animals that were

able to control the stressor, indicating a role of the right hemisphere for behavioral stress regulation in rats. Sullivan et al. [111] later showed that such dopamine asymmetries partly depend on sex. These authors used in-vivo voltammetry to measure extracellular dopamine release after acute stress induction using either predator odor or a tail pinch stress paradigm. Male rats showed greater right-hemispheric dopamine activation in the infralimbic cortex and basolateral amygdala, while females had a leftward asymmetry in dopamine release in these structures. Sex-specific effects were also reported by Alonso et al. [1] who found that prenatal stress (as operationalized by stressing the mother during gestation) reduced behavioral lateralization in male rats, but increased it in female rats. This finding supports the idea that the effect of stress on behavioral lateralization is modulated by sex hormones. Interestingly, left-hemispheric stress effects were reported by Cerqueira et al. [18,19] who found that chronic glucocorticoid treatment led to volumetric reductions in the left cingulate cortex in rats. Further evidence for a relation of chronic stress and laterality in rats has been provided by studies investigating left-right differences in cellular changes in the medial prefrontal cortex induced by chronic stress [26,85]. Perez-Cruz et al. [85] found rightward structural asymmetries in complexity and length of dendrites of layer III pyramidal cells in the prelimbic cortex of rats. Chronic stress (21 days of immobilization) had stronger effects on the right hemisphere and the dendritic asymmetries disappeared. Thus, both left- and rightward asymmetries in the rat brain seem to be relevant for stress regulation and/or affected by stress. This conclusion is also supported by a review article by Sullivan [109] aimed at integrating these findings in relation to prefrontal cortex function. Sullivan [109] concluded that the right prefrontal cortex is dominant when it comes to activation of stress-related systems. The left prefrontal cortex, however, might play an equally important role in regulating these processes through interhemispheric inhibition (also see [110]).

## 10.2. Non-human primates

In non-human primates, few studies have directly assessed the relation of stress and laterality. For example, Tomaz et al. [115] investigated the effect of acute stress on hemispheric asymmetries in black-tufted marmosets (*Callithrix penicillata*). The authors measured left and right tympanic temperature in 24 marmosets after induction of acute stress by capturing and restraining the animals. The authors found a negative correlation between right tympanic temperature and the amount of previous experience with being captured. Animals with more experience with being captured showed lower right tympanic temperature than animals with less experience with this stressful situation. No differences between the two groups were shown for left tympanic temperature. Tomaz et al. [115] concluded that marmosets show stronger activation of the right hemisphere under acute stress. Another study by Short et al. [103] investigated the role of population variation in HPA-axis activity and reactivity for structural brain asymmetries in grey and white matter in juvenile rhesus monkeys (*Macaca mulatta*). Animals that showed higher cortisol reactivity showed less structural asymmetries in overall hemispheric grey matter tissue volume, mainly due to a decrease of grey matter volume in the right hemisphere. More evidence for a link between cortisol and lateralization in rhesus monkeys was provided in a handedness study by Westergaard et al. [123]. These authors found that the frequency of right- versus left-hand use when reaching for food was positively correlated with plasma cortisol concentrations, indicating a link between behavioral laterality and HPA-axis activity in non-human primates.

## 11. Studies in human subjects

### 11.1. Birth stress and handedness

In human participants, several lines of behavioral and neuroscientific research have addressed the question whether stress affects FCAs.

Early research investigating this topic mainly focused on the question whether birth stress is a causative factor for atypical functional lateralization, e.g. left-handedness. The first study testing this idea was conducted by Bakan et al. [7] who had 510 university students complete a handedness and a birth stress evaluation questionnaire. In the latter questionnaire, participants had to indicate stressful conditions associated with birth, such as birth of multiples, premature birth, prolonged labor, Caesarian birth, breech birth, blue baby, or breathing difficulty at birth. All participants reporting at least one of these conditions were assigned to the stress group, while all other participants were assigned to the normal group. Bakan et al. [7] found a clear significant relationship between birth stress and handedness, with birth stress being reported by 40% of left-handers and only 22% of right-handers. The authors concluded that left-handedness is a neuropathological condition caused by adverse birth circumstances. After this initial study, several authors independently investigated the relation of birth stress and FCAs, with mixed results. While some studies at least partly supported the conclusion by Bakan et al. [7], their results were often markedly weaker or only evident in subsamples (e.g. [22–24,60,83,102,119,124]). On the other hand, a considerable number of studies completely failed to find a relationship between birth stress and handedness [3,6,38,62,71,72,84,88,112,117]. In the most recent study [77], birth stress in relation to handedness and cognitive ability was assessed in a large sample of children from the British Cohort Study. While birth stress affected cognitive ability, it did not have any effect on direction or degree of hand preference. Taken together, it is as yet somewhat unclear whether birth stress affects handedness. Meta-analytic integration of conflicting study results is clearly needed before any final conclusions can be drawn. However, judging from the number of null results any effects are likely to be very subtle.

### 11.2. Behavioral studies on the effects of acute stress on FCAs

Aside from birth stress, acute stress has also been investigated in relation to FCAs. A very interesting study on interactions of birth stress and acute stress with FCAs comes from Jones et al. [50], who tested relative blood flow to the left and right hemisphere in children after induction of acute stress by means of the Trier Social Stress Test for Children (TSST-C, [15]) as compared to at rest. Jones et al. [50] found a significant negative correlation between birth weight and blood flow laterality after stress induction but not at rest, indicating that acute stress leads to more lateralized blood flow in children who had experienced more birth stress as reflected in lower birth weight. This finding suggests an interaction between effects of birth stress and acute stress and FCAs.

The impact of acute stress on FCAs in humans was also investigated by Gruzelier & Phelan [45]. These authors tested participants with a divided visual lexical decision task. In a non-stressful condition, this task yielded a right-visual field advantage, reflecting the well-known left-hemispheric dominance for processing of verbal stimuli (e.g. [79]). After acute stress induction due to examination stress, Gruzelier & Phelan [45] observed enhancement of right-hemispheric performance and a switch toward a left visual-field advantage. In a more recent behavioral study, Brüne et al. [14] investigated whether performance in a lateralized emotional dot probe task differed between participants who had been stressed with the Trier Social Stress Test (TSST, [53]) and non-stressed control participants. In this task, pairs of emotional (happy or angry) and neutral faces were presented with one stimulus in the left visual hemifield and the other one in the right visual hemifield. Subsequently, the face stimuli disappeared and a dot probe appeared at the previous location of either the emotional or the neutral face with a stimulus onset asynchrony (SOA) of 200 ms or 500 ms. Participants had to indicate which side the dot probe had been presented on. Brüne et al. [14] observed that stress lead to negative affect and a rise in salivary cortisol. Moreover, for shorter SOA, stressed participants responded faster to angry faces in the left and to happy faces in the right

visual hemifield. No asymmetry effects were observed in non-stressed controls, indicating that acute stress induced FCAs in this task.

Wittling and Pflüger [129] used a divided visual field paradigm to show an emotionally aversive movie or a neutral movie so that it was perceived primarily by the left or the right hemisphere. Right-hemispheric viewing of the aversive movie led to significantly greater increase in cortisol secretion than left-hemispheric viewing. This finding is in line with the idea that the right hemisphere might be dominant for processing of negative emotions [30]. For the neutral control movie, no differences in cortisol secretion after right- as compared to left-hemispheric viewing were observed. Wittling and Pflüger [129] concluded that the right hemisphere controls cortical regulation of cortisol secretion. The same lateralized movie presentation technique was also used to assess the impact of stress on several stress reactions mediated by the sympathetic nervous system. For example, Wittling [126] reported that right-hemispheric viewing of an aversive movie caused significantly greater increase in both systolic and diastolic blood pressure than left-hemispheric viewing. Moreover, Wittling [128] found that sympathetic heart rate regulation was predominantly under control of the right hemisphere. These findings led Wittling [128] to conclude that both the HPA-axis and sympathetic stress responses are controlled for by the right hemisphere. Evidence supporting this idea to some extent was provided by a lesion study by Lueken et al. [65]. These authors investigated the effects of unilateral stroke on both tonic and phasic HPA-axis response characteristics. Morning cortisol levels and phasic responses after induction of acute stress due to a demanding oddball task were examined in 18 left-sided and 14 right-sided stroke patients and in healthy controls. Patients with left-sided stroke showed higher morning cortisol levels than controls, while patients with right-sided stroke did not differ significantly from controls. For stressor-related phasic cortisol responses, however, both patient groups showed a reduced reaction, with right-sided patients showing more pronounced decrease. Similar to Wittling [127,128], b), Lueken et al. [65] concluded that the right hemisphere is responsible for central regulation of cortisol secretion, but given that the effect was present in both patient groups, this view might be oversimplified.

### 11.3. Neuroimaging studies

In addition to behavioral studies, some authors have also used neuroimaging to investigate the relation of acute stress and laterality. For example, Wang et al. [121] measured cerebral blood flow changes to acute stress induction by means of a challenging mental arithmetic task. Changes in regional blood flow in right ventral prefrontal cortex and left insula and putamen were positively correlated with subjective stress ratings. Moreover, changes in regional blood flow in right ventral prefrontal cortex and right orbitofrontal cortex were correlated with changes in cortisol levels and heart rate caused by acute stress induction. Wang et al. [121] concluded that the right ventral prefrontal cortex plays a central role in the brain's response to stress. Pruessner et al. [131] used the Montreal Imaging Stress Task (MIST) and compared brain activation and cortisol levels in participants between a stressful and a non-stressful condition. Based on their cortisol response, participants were grouped into responders and non-responders. Comparing these two groups in relation to the stress / no-stress contrast revealed significant activation differences in right orbitofrontal and inferior frontal gyrus, as well as in left anterior cingulate cortex.

Laterality in structural (rather than functional) brain parameters has also been linked to stress. MacLulich et al. [66] compared the volumes of anterior cingulate cortex, hippocampus, and superior frontal gyrus in two groups of healthy elderly men, one of which showed suppression while the other one showed non-suppression of cortisol levels after oral intake of dexamethasone, a synthetic glucocorticoid. Suppressors, which had intact regulation of HPA-axis function, had a larger volume of the left anterior cingulate cortex than non-suppressors, while all other structures did not differ between groups. MacLulich et al. [66]

concluded that a smaller volume of the left anterior cingulate cortex could lead to dysregulation of HPA-axis function. Interestingly, structural white matter asymmetries and stress responses have also been linked in healthy participants. Madsen et al. [67] used DTI in 69 healthy adults and determined fractional anisotropy (FA) of the left and right cingulum and uncinate fasciculus, two major fiber bundles in the limbic system. Asymmetries in these two fiber tracts correlated with the so-called cortisol awakening response, i.e. a peak in plasma cortisol levels about 30 min after awakening in the morning [40]. While a higher cortisol awakening response was positively associated with leftward FA asymmetry in the uncinate fasciculus, it was negatively associated with rightward FA asymmetry in the cingulum. Interestingly, increasing cingulum asymmetry was also related to higher neuroticism scores in the NEO Personality Inventory Revised questionnaire [25]. Since neuroticism is a personality trait that has been linked to enhanced predisposition to experience negative emotions [87] as well as the probability of developing anxiety and mood disorders [10], the findings of Madsen et al. [67] suggest that structural asymmetries of limbic white matter fiber tracts do not only modulate HPA-axis activity but may also significantly impact the development of stress-related mental illnesses.

#### 11.4. Chronic stress in humans: post-traumatic stress disorder and laterality

Posttraumatic stress disorder (PTSD; ICD-10 classification: F43.1) is a complex mental disorder that can developed due to massive stress exposure induced by a traumatic event. PTSD can lead to a number of symptoms, including re-experiencing the traumatic event, hyperarousal, and numbing and avoidance of trauma-related stimuli [52]. While a plethora of rather heterogeneous studies have investigated structural brain changes in PTSD, some meta-analytical results indicate that the amount of stress associated with PTSD differentially affects the left and right hemisphere. For example, Kühn & Gallinat [58] analyzed the findings of nine voxel-based morphometry studies in PTSD patients, reporting structural reductions in PTSD patients in two structures with cluster centers in the midline of the brain (anterior cingulate cortex and ventromedial prefrontal cortex), and also in left temporal pole and middle temporal gyrus and in left hippocampus. This is particularly interesting, as Gilbertson et al. [41] found that in monozygotic twins discordant for trauma exposure, smaller hippocampal volume represents a risk factor for the development of PTSD, rather than a neurotoxic effect of trauma. In another meta-analysis of voxel-based morphometry studies, Li et al. [63] obtained largely comparable results. PTSD patients showed volume reduction in medial prefrontal cortex, left hippocampus, left middle temporal gyrus and right superior frontal gyrus and left occipital cortex. In contrast, Meng et al. [73] reported volume reduction in left anterior cingulate cortex, left insula and right parahippocampal gyrus in PTSD patients as compared to trauma-exposed healthy subjects. Karl et al. [52] reported that in addition to smaller hippocampal volumes in PTSD patients compared to controls, patients also had smaller left amygdala volumes.

In addition to grey matter changes, differences in white matter between PTSD patients and controls have also been investigated. In a meta-analysis of seven DTI studies, Daniels et al. [29] identified significant decreases of fractional anisotropy in nine clusters and increases of fractional anisotropy in six clusters. While the strongest decrease was observed in the right cingulum, there was also a decrease in the left cingulum. Other white matter tracts with decreased fractional anisotropy in PTSD were only affected in one hemisphere, including the right posterior limb of the internal capsule, the right anterior thalamic radiation, the right anterior corona radiata, the left superior longitudinal fasciculus and three unclassified white matter clusters. Increases in fractional anisotropy were observed bilaterally in the superior longitudinal fasciculus and bilaterally in a cluster in the cingulum, as well as in two unidentified white matter clusters. Taken together, PTSD affects the volume of several different brain areas mainly comprising frontal and

limbic circuits. While none of the meta-analyses explicitly compared left- and right-hemispheric volumes in patients and controls, the fact that e.g. leftward limbic structures (hippocampus and amygdala) showed decreased FA in patients while their rightward homologues did not implies that structural asymmetries in these brain regions might be shifted toward the right hemisphere in PTSD patients as compared to controls. The notion of greater involvement of the right hemisphere in perceptual and cognitive processing in PTSD is also supported by studies investigating functional lateralization in PTSD patients (e.g. [101,107]). These studies consistently report higher incidence of mixed lateral preferences in patients as compared to healthy controls. However, since all of this evidence is rather indirect, more research explicitly targeting the relation of functional and structural asymmetries in PTSD is clearly needed before any final conclusion can be drawn.

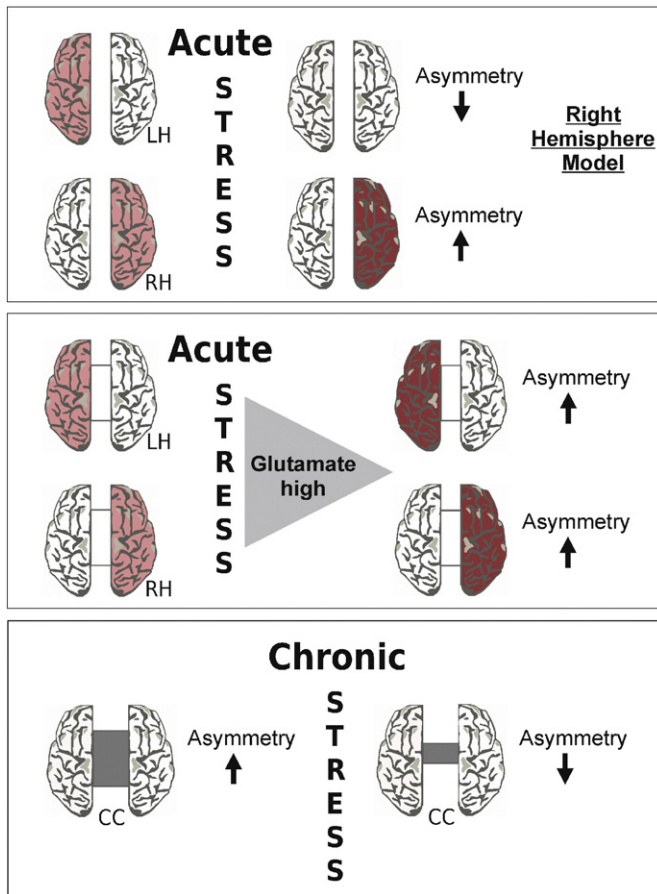
## 12. Conclusion

It is evident from the present review that the investigation of the relationship between laterality and stress is still in the early stages. In many species, the majority of published studies on this topic have neither measured stress hormone responses nor negative emotionality. This renders a decision whether the hormonal or the negative emotionality model is better suited to explain their relationship difficult. It is also a clear indication that further research is needed before any final conclusion can be drawn. It needs to be stated that the hormonal model and the negative emotionality model are not mutually exclusive. It has been suggested that the regulation of cortisol secretion in emotional situations is controlled by the right hemisphere [129]. Thus, the experience of negative emotions could theoretically affect glucocorticoid levels which in turn affect FCAs. Also, effects in the same species sometimes are contradictory. For example, Brüne et al. [14] showed an increase of lateralization after acute stress in human adults, while for birth stress, those studies that found an effect reported decreased lateralization. Thus, the relation of the stress and FCAs seems to be dependent on developmental stage as well as nature and duration of the stressor (e.g. acute vs. chronic stress). Despite the fact that more studies are needed to systematically investigate all these factors, the data outlined in the present review article indicate show a twofold relation of FCAs and stressful environments and/or glucocorticoid response. Both acute and chronic stress can modulate FCAs. In several (but clearly not all) cases they stimulate greater involvement of the right hemisphere (Fig. 1 provides schematic illustrations of the possible interplays between stress and FCAs).

This relation might be related to FCAs in the processing of emotions. Stress can induce negative emotions (e.g. [120]), and the right hemisphere has been shown to be dominant for processing of negative emotions [104,114].

In addition to this right-shift idea, interhemispheric transmission over the corpus callosum (or other commissures) might also play a role for the interplay of stress and lateralization. Importantly, this principle can also be applied to animals without a corpus callosum, as it is conceivable that a similar modulation of interhemispheric transmission might also take place for other relevant commissures, e.g. the commissura anterior in birds [61]. For example, the corpus callosum might play an important role for the interplay of chronic stress and FCAs. As patients with PTSD show reduced FCAs (e.g. [101,107]) and also reduced volume of the corpus callosum [99], one could speculate that inhibitory callosal effects are reduced in these patients, resulting in a more bilateral mode of information processing. However, the possibility that mixed lateral preferences present a risk factor for (rather than an effect of) PTSD should be further investigated.

In addition to these findings, lateralization as a principle of vertebrate brain organization can modulate HPA-axis function. Along these lines, a specific level of hemispheric asymmetry might constitute a protective factor against adverse effects of stress, as shown in the work by



**Fig. 1.** Schematic models for interactions between stress and functional cerebral asymmetries (FCAs). *Upper panel:* Due to right-hemispheric dominance in processing of negative emotions, acute stress leads to greater involvement of the right hemisphere (Right Hemisphere Model). Thus, for cognitive domains with a left-hemispheric dominance, FCAs should be reduced. In contrast, FCAs should be enhanced for cognitive domains with a right-hemispheric dominance. *Middle panel:* Steroid hormones reduce trans-callosal information transfer. Cortisol release in response to acute stress increases glutamatergic transmission and thus also increases FCAs. These models are not mutually exclusive, but can interact with each other. *Bottom panel:* Exposure to chronic stress is associated with reduced FCAs due to reduced callosal inhibition caused by e.g. reduced callosal volume.

Madsen et al. [67] and similar findings in animal model species (e.g., [76]).

As mentioned above, more empirical research is needed for practically all aspects regarding the interplay of stress and FCAs. From a phylogenetic perspective, research in more species, particularly in amphibians, reptiles and birds, is needed in order to draw conclusions about the evolutionary bases of the link between laterality and stress. From a pharmacological perspective, it would be important to investigate which effects are caused by glucocorticoid function and in which cases other agents (e.g. dopamine or noradrenaline) are the causative factor. From a neuroscientific perspective, the relation of HPA-axis activity, structural brain asymmetries and functional lateralization in PTSD patients and healthy controls demands much more exploration. This is particularly interesting for the clinical research community since atypical lateralization has been observed in a large number of psychiatric and neurodevelopmental disorders such as autism [64], depression [96] and schizophrenia [97]. Dysregulation of HPA-axis activity is one factor that patients suffering from these vastly different disorders have in common [12,31,113]. Thus, understanding the relationship between laterality, stressful environments and the binding of steroids to their brain receptors might make a significant contribution to uncovering the etiology of such mental disorders.

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