Front. Biol. 2016, 11(3): 182–192
DOI 10.1007/s11515-016-1412-4

REVIEW

Stress, hippocampal neurogenesis and cognition: functional correlations

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Abstract **The brain of many species including humans, harbors stem cells that continue to generate new neurons up into adulthood. This form of structural plasticity occurs in a limited number of brain regions, i.e. the subventricular zone and the hippocampal dentate gyrus and is regulated by environmental and hormonal factors. In this minireview, we provide an overview of the effects of stress and glucocorticoid hormones on adult hippocampal neurogenesis and discuss how these effects may be relevant for cognitive function and possibly, brain disease. While its exact functional role remains elusive, adult neurogenesis has been implicated in learning and memory, fear and mood regulation and recently, adult-born neurons were found to be involved in specific cognitive functions such as pattern separation (i.e. the ability to form unique memory representations) and cognitive flexibility. The process of adult neurogenesis is influenced by several factors; whereas e.g. exercise stimulates, exposure to stress and stress hormones generally inhibit neurogenesis. Effects of acute, mild stress are generally short-lasting and recover quickly, but chronic or severe forms of stress can induce lasting reductions in adult neurogenesis. Some of the inhibitory effects of stress can be rescued by exercise, by allowing a period of recovery from stress, by drugs that target the stress system, or by some, but not all, antidepressants. Stress may, partly through its effects on adult neurogenesis, alter structure and plasticity of the hippocampal circuit. This can lead to subsequent changes in stress responsivity and aspects of memory processing, which may be particularly relevant for stress related psychopathology or brain diseases that involve perturbed memory processing.**

Keywords adult neurogenesis, stem cells, hippocampus, stress, memory, pattern separation, cognition

Stress and the stress response

In our daily life, exposure to stress is difficult to avoid. Stress is diverse in nature, duration or intensity; it can be psychological in nature, such as during relationship problems (Ursin and Eriksen, 2004) or can involve biological changes, such as the occurrence of an infection. Exposure to any stress generally elicits a stress response in the body and brain that enables the individual to adapt, maintain homeostasis, and ultimately promote survival. The subjective experience of stress is highly individual, as is ones response to it, and this response depends largely on genetic make up, sex and personality traits. Gene-environment interactions, particularly during sensitive developmental periods, are further important in "programming" our hormonal and cognitive response to stress and also determine individual differences in vulnerability to disease, as reviewed before (Joëls et al., 2006,2012; Meaney et al., 2007; Binder et al., 2008; Koolhaas et al., 2011; Lucassen et al., 2013b).

The endocrinological response to stress involves first the release of adrenal (nor)epinephrine that among others, increases blood flow to essential organs. Later, the hypothalamic-pituitary-adrenal (HPA) axis is activated, a classic neuroendocrine circuit that regulates the eventual behavioral, neural and hormonal response to stress (Joëls and Baram

Received June 2, 2016; accepted June 12, 2016
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2009; Joëls et al., 2012). Activation of the HPA-axis starts with hypothalamic corticotropin-releasing hormone (CRH) production, which subsequently results in the release of glucocorticoids (GCs) from the adrenal glands (GCs; corticosterone in rodents; cortisol in man). Negative feedback of GC-release occurs when GCs bind to high-affinity mineralocorticoid (MR) and lower affinity glucocorticoid receptors (GR) in key regions of the brain (de Kloet et al., 2005). Through this, GR activation helps to maintain GC levels within physiological limits (Kretz et al., 1999; Erdmann et al., 2008) and consequently, aberrant GR expression or changes in the GR/MR ratio have been implicated in hypercortisolism, hippocampal changes, stress resistance, anxiety and depression (de Kloet et al., 2005; Ridder et al., 2005; Wei et al., 2007; Wang et al., 2012; Vinkers et al., 2014). GC-release is pulsatile and under circadian and ultradian control (Qian et al., 2012; Lucassen et al., 2013b; Fitzsimons et al., 2016), and GCs act as transcription factors that control protein expression in a slow, genomic manner, however, faster non-genomic actions exist as well (Tasker 2006; Karst et al., 2010).

Upon their release in the periphery, GCs affect energy, inflammatory responses and lipid metabolism, among others. Imbalances in GC regulation can have deleterious consequences, particularly for the brain (de Kloet et al., 2005). Specifically the hippocampus, a region important for learning and memory, is sensitive to GC increases as it contains high levels of GRs (de Kloet et al., 2005; Swaab et al., 2005; Wang et al., 2013). Indeed, GCs influence memory, fear and attention in a negative manner, particularly when exposure to stress is chronic and uncontrollable. However, positive effects of stress-such as enhanced memory have also been described and effects of stress depend on timing, type and controllability of a stressor (Joëls et al., 2006; Schwabe et al., 2012).

While functional changes after stress involve reductions in hippocampal excitability, long-term potentiation and hippocampus-dependent memory, morphological consequences of stress include hippocampal volume reductions as well as a number of cellular changes, notably dendritic atrophy and a suppressed rate of adult neurogenesis (see below) (Sapolsky et al., 1990; Czéh and Lucassen, 2007; Lucassen et al., 2014). Given its peak values after 15 min, most GC effects on brain function occur minutes to hours after the stressful event rather than in the critical first few minutes after which a threat is detected. These slow effects, as well as its morphological effects suggest that an important role of GCs in the brain is to affect future behavior and responsivity.

Effects of stress on the hippocampus may help facilitate adaptation after stressful or challenging conditions, whereas a failure to adjust behavior in response to stress could have negative consequences. Ultimately, the stress response helps to (re)direct energy and focus attention to cope with the most urgent elements of a stressor, at the cost of less urgent bodily processes that are temporarily suppressed by stress (Joëls et al., 2012).

Stress modulates adult neurogenesis

Adult neurogenesis (AN) refers to stem cells present in adult brains that continue to produce new neurons up into old age. These stem cells undergo different stages of proliferation, fate specification, migration and neuronal differentiation, before they eventually become new, functional neurons that integrate into the pre-existing, adult network of the hippocampus (Abrous et al., 2005; Toni et al., 2008; Zhao et al., 2008; Kempermann, 2012; Vivar et al., 2012; Jessberger and Gage, 2014). It has also been reported to occur in other brain structures, like the amygdala, striatum, hypothalamus and neocortex, albeit under specific conditions and with considerable differences between species (Gould, 2007).

AN is dynamically regulated by various environmental factors and declines prominently with age in many species (e.g., (Kuhn et al., 1996; Heine et al., 2004b)). Neurogenesis is potently stimulated by exercise and environmental enrichment, which notably occurs parallel to improvements in hippocampal function (Kempermann et al., 2010; Vivar et al., 2013). A strong inhibitor of AN on the other hand, is stress and GC exposure (Balu and Lucki, 2009; Lucassen et al., 2010a) as will be discussed below in more detail.

Exposure to stress during adult life is one of the best known environmental suppressors of AN. Both psychosocial (Gould et al., 1997; Czéh et al., 2002) and physical stressors (Malberg and Duman, 2003; Pham et al., 2003; Vollmayr et al., 2003) can inhibit one or more phases of the neurogenesis process (Mirescu and Gould, 2006; Lucassen et al., 2010a). In classical studies, rodents exposed to the odor of a predator generated a strong stress hormone response that was associated with significant parallel reductions in hippocampal proliferation (Tanapat et al., 1998). Both acute and chronic stressors generally suppress proliferation and many different types of stressors, including physical restraint, social defeat, inescapable foot shock, sleep deprivation, and mixed types of multiple, unpredictable or mild stressors, generally all decrease numbers of new neurons in the dentate gyrus (Gould et al., 1997; Czéh et al., 2002; Pham et al., 2003; Heine et al., 2004a; Heine et al., 2004c; Simon et al., 2005; Dranovsky and Hen, 2006; Jayatissa et al., 2006; Mitra et al., 2006; Jayatissa et al., 2009; Perera et al., 2011; Lehmann et al., 2013; Schoenfeld and Gould, 2013; Wu et al., 2014).

Notably, exceptions exist in stress inhibition of neurogenesis and negative findings have also been reported (Dagyte et al., 2009; Lyons et al., 2010; Hanson et al., 2011a; Parihar et al., 2011; O'Leary et al., 2012). These might depend on the type of stressor applied, or the species, sex or strain used (Westenbroek et al., 2004; Hanson et al., 2011b; Schoenfeld and Gould, 2013; Kanatsou et al., 2015). Inter-individual variation in the behavioral susceptibility to stress is also a relevant factor (Levone et al., 2015). In some instances, increased AN has been reported after stress, but in these studies the stressors were often predictable, controllable and/

or mild, and may actually have enriched standard laboratory housing conditions (Van der Borght et al., 2005; Parihar et al., 2011).

AN in the hippocampus is further required for the beneficial effects of an enriched environment on recovery from stress-induced changes in behavior (Schloesser et al., 2010), where stress recovery is correlated with newborn cell survival (Schloesser et al., 2010; Tanti et al., 2012). Surprisingly, housing animals in an enriched environment that includes voluntary exercise, increases GCs (Vivinetto et al., 2013), suggesting that this rise in GC levels is essential for increased AN in the hippocampus (Schloesser et al., 2010; Sampedro-Piquero et al., 2014). When rats are adrenalectomized, admittedly a highly artificial condition, environmental enrichment-induced increases in AN are no longer apparent (Lehmann et al., 2013), indicating that GCs can facilitate adult hippocampal neurogenesis under specific conditions. Again somewhat counterintuitively, exercise, which is considered a potent stimulus for AN (van Praag et al., 1999b), also stimulates GC levels, even though exercise per se reduces stress (Kannangara et al., 2011). Cessation of voluntary exercise subsequently impairs AN and can increase anxiety-like behavior (Nishijima et al., 2013) consistent with other studies that indicate that changes in AN often correlate with anxiety measures (Pham et al., 2005; Revest et al., 2009; Hill et al., 2015; Seo et al., 2015; Hu et al., 2016; Yun et al., 2016).

When no other transmitter systems are altered and the stressor is unpredictable or uncontrollable and its nature severe, stress generally reduces AN (Pham et al., 2003; Heine et al., 2004c; Simon et al., 2005; Dranovsky and Hen 2006; Jayatissa et al., 2006; Mitra et al., 2006; Jayatissa et al., 2009; Perera et al., 2011; Lehmann et al., 2013; Schoenfeld and Gould, 2013). In fact, unpredictable/uncontrollable stress can reduce multiple stages of the neurogenic process, including the initial phase of proliferation of the neural stem cells and amplifying progenitor cells, as well as subsequent neuronal differentiation phase and dendritic expansion. Exposure to GCs per se was even shown to deplete the neural precursor pool (Yu et al., 2010). Stress not only reduces proliferation and AN in many different species, it may also shift neural stem cells away from neuronal differentiation, and instead 'redirect' them toward the generation of oligodendrocytes (Chetty et al., 2014). Although not studied in great detail yet, such stress-induced fate shifts may have important functional consequences: e.g., for the myelination of axons and/or mossy fibers and hence network connectivity, particularly when they occur during early development when cell division is massive.

Although different types of stress trigger different behavioral and functional responses, adrenal GCs are considered instrumental in mediating the suppressing effects of stress on AN (Schoenfeld and Gould, 2013). The basis for this assertion is as follows. First, exogenous GC administration to animals has effects similar to those of stress on cell proliferation, neuronal differentiation and cell survival as well as on the production of oligodendrocytes and microglia responses (Mayer et al., 2006; Wong and Herbert 2006; Yu et al., 2010; Hu et al., 2012). Second, the reductions in AN after stress and many of the molecular (Datson et al., 2012) and physiological (Krugers et al., 2006) changes, can be prevented by blocking the GR, for a very short period (Mayer et al., 2006; Oomen et al., 2007; Hu et al., 2012) or by CRH antagonists (Alonso et al., 2004). Furthermore, in a transgenic mouse model of AN inhibition a transient increase in the corticosterone response to stress occurs, as well as an attenuated dexamethasone-induced suppression of corticosterone release (Snyder et al., 2011). This is indicative of a role for the newborn cells in regulating HPA axis activity. On the other hand, ablation of AN by irradiation did not impair basal HPA axis activity (Surget et al., 2011), see also (Lucassen et al., 2013a).

Although general blockers of different elements of the stress axis are thus already effective, the precise mechanism(s) by which GCs decrease the numbers of new neurons remains poorly understood. More information has become available on its molecular control (Schouten et al., 2012; Anacker et al., 2013; Miller et al., 2013). NMDA receptors, GRs and MRs are all present on newly born cells, albeit in different ratios over time, and these likely act in concert to mediate effects of stress on AN (Montaron et al., 2003; Garcia et al., 2004; Wong and Herbert, 2004, 2005). Notably, GR knockdown in newborn cells exclusively accelerates their neuronal differentiation and migration and alters their dendritic complexity. This was paralleled by reduced freezing during contextual fear conditioning. Hence, GR expression in the newborn hippocampal cells is important for structural as well as functional integration into the mature hippocampal circuits involved in fear memory (Fitzsimons et al., 2013).

Furthermore, most precursors in the brain are located closely to blood vessels (Palmer et al., 2000). Although often not distinguished in quantitative analysis, this proximity makes this population particularly sensitive to stress hormones (Heine et al., 2005) and many other peripheral factors. Astrocytes are also of relevance as they closely align the vasculature, express GRs, support the survival of developing neurons and are involved in their synaptic integration (Sultan et al., 2015). Notably, astrocytes are affected by some, but not all, types of stress (Vallières et al., 2002; Czéh et al., 2006; Banasr and Duman, 2007; Oomen et al., 2009; Wang et al., 2013).

Stress further slows down neuronal differentiation of the adult-born cells, as evidenced by the upregulation of markers indicating cell cycle arrest (Heine et al., 2004a) that may be induced by specific changes in DNA methylation (Boku et al., 2015). Stress also reduces the survival of new neurons that were born prior to the actual stressful experience. A change in “corticoid environment” (Wong and Herbert, 2006) is thought

to be mediated by stress-induced reductions in neurotrophins and survival promoting factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), (Schmidt and Duman, 2007; Wilson et al., 2014). Reductions in newborn cell survival may involve microglia, which can phagocytose new neurons. Indeed, stress influences microglia, both in terms of numbers and their responsivity. This may modulate their efficiency in clearing debris or dead neurons (Hinwood et al., 2012; Morris et al., 2013; Sierra et al., 2010) or their capacity to release neurotoxic cytokines (Kreisel et al., 2014; Sierra et al., 2014; Guadagno et al., 2015; Llorens-Martín et al., 2016).

An important aspect relevant for studies on temporal aspects of stress and AN is whether GC levels remain elevated or not after the initial exposure to stress has ended. In some psychosocial stress models, GC levels remain elevated, which has stronger suppressive effects on AN than exposure to severe, but predictable, physical stressors like restraint (Wong and Herbert, 2004). Several examples exist of a persistent and lasting inhibition of AN after an initial exposure to stress, despite a later lowering of GC levels (Czéh et al., 2002; Mirescu and Gould, 2006). In contrast, GC levels can remain elevated after a psychosocial stressor, with AN being suppressed long-term. In milder models of stress, GC levels generally normalize, yet AN remains reduced (Van Bokhoven et al., 2011; Schoenfeld and Gould, 2013). This suggests that while GCs are involved in the initial suppression of proliferation, they are not always necessary for maintaining this effect.

When studying effects of stress on AN in laboratory conditions, it is further important to realize that many variables influence the outcome (Bekinschtein et al., 2011). These variables include inter-individual genetic or gender differences in stress coping and resilience (Levine, 2005), prior handling of the animals, time of day at sacrifice and previous exposure to stressful learning tasks like the water maze, or exercise (Droste et al., 2003; Holmes et al., 2004; Ehninger and Kempermann 2006; Marlatt et al., 2012). Anatomical differences exist such as in projections to specific subregions of the hippocampus or in the larger networks, or neuromatrix (Sousa, 2016). Thus, stress effects on AN might differ between the dorsal or the ventral hippocampus depending upon the stimulus (Tanti and Belzung 2013; O'Leary and Cryan, 2014).

Many other factors may contribute to the stress-induced inhibition of AN, such as the stress-induced increase in glutamate release and NMDA receptor activation (Gould et al., 1997; Nacher and McEwen, 2006; Schoenfeld and Gould, 2013) or through stress effects on various neurotransmitter systems implicated in the regulation of AN such as GABA (Ge et al., 2007), serotonin (Djavadian, 2004), noradrenaline (Joca et al., 2007), acetylcholine (Bruel-Jungerman et al., 2011), dopamine (Domínguez-Escribà et al., 2006; Takamura et al., 2014), cannabinoids, opioids, nitric oxide, and gonadal steroids (Galea, 2008; Balu and Lucki, 2009; Mahmoud et al., 2016).

Finally, many antidepressant drugs that interfere with stress-related behavior in animals also modulate AN. The relation between stress, AN, antidepressants and psychopathology like major depression has been extensively discussed (Malberg and Duman, 2003; Santarelli et al., 2003; Dranovsky and Hen, 2006; Sahay and Hen, 2007; Lucassen et al., 2010; Perera et al., 2011; Surget et al., 2011; Tanti and Belzung, 2013; Lucassen et al., 2014; Schoenfeld and Cameron, 2015).

Changes in adult neurogenesis: functional relevance

To understand the potential functional impact of stress-modulation of adult neurogenesis, we first need to know which functional role these new neurons play in the hippocampal circuitry. In functional terms, early studies had already found that changes in AN were commonly paralleled by changes in learning and memory (Gould et al., 1999; van Praag et al., 1999a). This gave rise to the idea that AN may be relevant for at least some forms of hippocampal dependent cognition (Saxe et al., 2006; Zhang et al., 2008; Clelland et al., 2009; Aimone et al., 2010; Sahay et al., 2011a; Sahay et al., 2011b; Oomen et al., 2014). Suppression of AN, e.g. by stress or other means, has also been linked to an impairment in the animal's performance on hippocampal tasks or a change in behavior in mood or anxiety-related paradigms (Lemaire et al., 2000; Montaron et al., 2004; Montaron et al., 2006; Veena et al., 2009; Snyder et al., 2011).

Initial studies on selective elimination of newborn granule neurons administered methylazoxymethanol acetate (MAM), (Shors et al., 2001) and showed decreased cue responding in MAM-treated rats that were trained in a trace cue condition, but not in a delay condition. A similar impairment was also found in freezing in a cued fear conditioning task but not in spatial maze learning or contextual fear conditioning, among others (Shors et al., 2002). With trace fear conditioning being the most slowly learned of these tasks, this suggested that task difficulty is an important variable, and that AN may be particularly involved in more challenging memory tests such as those in which the associations are separated in time (i.e. trace conditioning).

Other studies using toxins replicated some of these findings: trace eyeblink conditioning was also impaired after temozolomide (TMZ) treatment and, consistent with earlier findings, MAM treatment did not affect contextual fear conditioning or water maze acquisition. Contrary to Shors et al. (2002) however, retention of platform location in the water maze was found to be impaired by MAM mediated ablation.

Recently, TMZ induced ablation affected water maze acquisition in juvenile but not in older animals.

Decreased contextual fear conditioning has further been demonstrated in a few studies where AN was depleted using irradiation (Winocur et al., 2006; Wojtowicz et al., 2008; Snyder et al., 2009), although exceptions exist too (Shors et al., 2002; Groves et al., 2013). The Morris water maze is one of the most widely used hippocampus-dependent spatial tasks. In contrast to impairments seen after hippocampal lesions, performance on standard spatial water maze training and probe trials is consistently spared in mice and rats that lack adult neurogenesis (Snyder et al., 2005; Wojtowicz et al., 2008; Arruda-Carvalho et al., 2011; Ben Abdallah et al., 2013; see also Snyder et al., 2016). Also here, more difficult tests that use long delays, or more subtle behavioral analyses of search strategies, identify impairments in animals lacking new neurons in some, though not all, experiments (Snyder et al., 2005; Ben Abdallah et al., 2013; Garthe et al., 2014).

A deficit in spatial performance was recently confirmed using optogenetics, that highlighted the importance of the age of the adult-born neurons as well. Four week old, but not of 2 or 8 week-old, neurons were shown to be involved in retention, but not acquisition, of the water maze (Gu et al., 2012). Studies on contextual fear conditioning and object (location) memory show mixed results and both impaired and unaffected memory performance was found. In addition to these learning tasks, animals lacking adult neurogenesis show an altered behavior in spontaneous investigation tasks (Lagace et al., 2011; Mak and Weiss 2010), which may reflect a depletion of olfactory neurogenesis, rather than of hippocampal neurogenesis.

Mice use specific strategies to solve a spatial task. Mice that lack adult neurogenesis use precise spatial strategies less frequently than normal mice, and mainly during the reversal learning trial but not during the initial learning phase (Garthe et al., 2009). In a probe trial without the platform, mice lacking adult neurogenesis search in both the original location and the new location, whereas normal mice focus much more on the newer location (Arruda-Carvalho et al., 2011). Also in an active place-avoidance spatial reversal task, mice lacking adult neurogenesis showed impairment when a reversal element was built in (Burghardt et al., 2012). Importantly, in all these reversal tasks, the novel memory for the initial platform location may interfere with the memory for the additional location. Distinguishing two similar memories may resemble aspects of pattern separation, which will be discussed below.

The specific involvement of AN in classical learning and memory tests further seems to depend on a number of factors, including species tested, the age of neurons, the phase of memory addressed and the type, design and difficulty of the test used. Together, such differences may contribute to some of the inconsistencies reported in the spatial and emotional paradigms.

Following studies that were in part based on computational models, new neurons were predicted to be important for pattern separation (Becker 2005; Aimone et al., 2009), the process by which a neural circuit reduces overlap between similar input patterns, resulting in more dissimilar output signals. Pattern separation is thought to be particularly necessary for the formation of unique, non- (or less-) overlapping representations and thus for successful memory storage.

The first study showing empirical evidence for a role of AN in pattern separation found that mice lacking neurogenesis were impaired on two spatial pattern separation tests in which spatial similarity was manipulated (Clelland et al., 2009). In particular, mice made more errors when locations were spaced closely, but not when spaced further apart (Clelland et al., 2009). Two different techniques for ablating immature neurons, X-irradiation and lentiviral mediated expression of a dominant-negative version of the Wnt protein were used. Further studies found similar results, whereby mice with impaired neurogenesis are slower to show differential freezing to highly similar contexts (Kheirbek et al., 2012b; Tronel et al., 2012).

Conversely, Sahay et al., (2011a) used a genetic manipulation to increase AN artificially. This resulted in improved context discrimination in a fear conditioning paradigm in which animals were trained to discriminate between two similar contexts across repeated sessions. Mice with increased neurogenesis were quicker to demonstrate discrimination of highly similar contexts (Sahay et al., 2011a). Furthermore, Creer and colleagues (2010) demonstrated that wheel running in mice increased AN as well as pattern separation in a touchscreen-based behavioral task, a treatment that was ineffective in aged animals that lacked running-dependent increase in AN, suggesting it was the increase in AN and not other exercise-induced effects, that were responsible for the improvements (Creer et al., 2010). Finally, brain-derived neurotrophic factor (BDNF) in the dentate gyrus was shown to be important specifically during the consolidation (but not retrieval) of memories for similar (but not dissimilar) spatial locations in an open field. BDNF was found to interact with adult-born neurons in the service of pattern separation (Bekinschtein et al., 2013; Bekinschtein et al., 2014).

For stress-related disorders such as PTSD, it has been hypothesized that impaired pattern separation may lead to overgeneralization: i.e. when events are not stored as unique representations, similar cues may be easily confused with those of the original experience (Kheirbek et al., 2012a; Besnard and Sahay 2016). Since PTSD patients experience panic attacks and relive memories in response to cues similar to those of the traumatic event, overgeneralization may be regarded as a core cognitive mechanism of this disorder. This may be particularly interesting in linking the effects of stress on adult neurogenesis to potential mechanisms of brain disease and psychopathology.

Concluding remarks

Stress and GCs commonly interfere with one or more stages of adult neurogenesis. Such inhibitory effects can normalize after a recovery period, voluntary exercise or antidepressant treatment. Adult neurogenesis has been implicated in cognitive functions and in the regulation of mood and anxiety. A reduced rate of AN may be indicative of impaired hippocampal plasticity. Lasting reductions in AN, or in the turnover rate of the DG granule cells will in time alter the overall composition of the DG cell population and can modify stress responsivity and cognition, and thereby influence overall functioning of the adult hippocampal circuit and its involvement in (aspects of) psychopathology.

Acknowledgments

PJL is supported by the HersenStichting Nederland, Alzheimer Nederland, ISAO, NWO and Amsterdam Brain & Cognition (ABC), CAO is supported by the Amsterdam Brain and Mind Project (ABMP).

Compliance with ethics guidelines

Paul J. Lucassen and Charlotte A. Oomen declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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