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Review article

Serotonin and neuroplasticity – Links between molecular, functional and structural pathophysiology in depression

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ABSTRACT

Serotonin modulates neuroplasticity, especially during early life, and dysfunctions in both systems likewise contribute to pathophysiology of depression. Recent findings demonstrate that serotonin reuptake inhibitors trigger reactivation of juvenile-like neuroplasticity. How these findings translate to clinical antidepressant treatment in major depressive disorder remains unclear. With this review, we link preclinical with clinical work on serotonin and neuroplasticity to bring two pathophysiologic models in clinical depression closer together. Dysfunctional developmental plasticity impacts on later-life cognitive and emotional functions, changes of synaptic serotonin levels and receptor levels are coupled with altered synaptic plasticity and neurogenesis. Structural magnetic resonance imaging in patients reveals disease-state-specific reductions of gray matter, a marker of neuroplasticity, and reversibility upon selective serotonin reuptake inhibitor treatment. Translational evidence from magnetic resonance imaging in animals support that reduced densities and sizes of neurons and reduced hippocampal volumes in depressive patients could be attributable to changes of serotonergic neuroplasticity. Since ketamine, physical exercise or learning enhance neuroplasticity, combinatory paradigms with selective serotonin reuptake inhibitors could enhance clinical treatment of depression.

Contents

1. Introduction

Serotonin is an important neuromodulatory transmitter with distinctive neuroplastic capabilities. While synaptic plasticity is a well-known key mechanism in learning and memory (Dayan and Cohen, 2011; Kandel, 2001), unequivocal studies suggest that dysfunction of synaptic plasticity with neuronal atrophy and cell death contribute to the pathophysiology of depression and therapeutic response could be associated with overcoming this deficit (Duman

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and Aghajanian, 2012; Krystal et al., 2013; Shakesby et al., 2002). This suggests that problems of information processing within neuronal networks associated with neuromorphological changes underlie depression (Castrén, 2005).

Clear-cut data demonstrate that 5-HT shapes neuronal networks during development and deficiencies thereby fundamentally impact the pathophysiology and long-term outcome of brain disorders (Lesch and Waider, 2012). Beyond their known neurochemical mechanisms of action, selective 5-HT reuptake inhibitors (SSRIs) might reactivate serotonin's ability to mediate developmental plasticity (Castren and Rantamaki, 2010; Vetencourt et al., 2008). Close molecular connections between serotonergic receptors and neurotrophic proteins as brain-derived neurotrophic factor (BDNF) and intracellular signaling cascades are responsible for cytoskeletal rearrangement (Mattson et al., 2004; Rantamaki and Castren, 2008); see Table 1). Serotonin modulates glutamatergic transmission and might kindle N-methyl-D-aspartate (NMDA) receptor dependent plasticity (Bennett, 2010; Sanacora et al., 2012). Moreover, 5-HT is linked to cell adhesion molecules (Lesch and Waider, 2012), which are part of the extracellular matrix and crucial for developmental plasticity (Varea et al., 2007). Environmental effects might be a crucial modulating factor for serotonergic neuroplasticity, whereby stress and negative events were demonstrated to be functionally relevant to SSRI-mediated neuroplasticity in animal models (Alboni et al., 2017; Wu et al., 2014). Hence, data suggesting that SSRIs might reactivate developmental plasticity are sound, yet these results were made in animals and translational evidence in humans is missing.

Consistent with the neuroplasticity deficits, an increasing number of neuroimaging studies identified alterations of neuroplasticity with magnetic resonance imaging (MRI; Zatorre et al., 2012). Reductions in gray matter volume (GMV) were observed in cross-sectional studies in patients with depression (van Tol et al., 2010) and corroborated by meta-analyses (Kempton et al., 2011; Wise et al., 2016). Interestingly, SSRIs were demonstrated to increase hippocampal (Arnone et al., 2013) and other limbic GMV (Hoexter et al., 2012; see Table 2). Novel rapidly acting antidepressants in the glutamate system such as ketamine are thought to exert at least parts of their action by stimulating neuroplasticity (Krystal et al., 2013). Moreover, structural changes were demonstrated in healthy subjects with longitudinal designs in learning paradigms, associated with experience of navigation or musical training to name only a few (Draganski et al., 2006; Hyde et al., 2009; Maguire et al., 2000).

This suggests that the adult brain is able to structurally adapt to internal or external stimuli and 5-HT might play an important role. In this review we aim to summarize the current knowledge of serotonin-mediated neuroplasticity, its assumed role in depression and treatment with serotonergic antidepressants. Moreover, we discuss how neuroplasticity can be measured *in vivo* in humans and how preclinical work on serotonergic neuroplasticity could be translated to patient studies.

2. Mechanisms of neuroplasticity and their importance in the pathophysiology of depression

Neuroplasticity is an umbrella term for the brain's ability to structurally adapt to changes of the internal or external milieu (May, 2011; Pascual-Leone et al., 2005). As a specific form of neuroplasticity, synaptic plasticity refers to one of the most crucial functions of the brain – it is the ability to sense, assess and store information and to modify synaptic transmission according to subsequent stimuli (Citri and Malenka, 2008; Duman et al., 2016). Thereby regulation of synaptic numbers is often referred to as synaptogenesis or synaptic homoeostasis, which are crucial during neuronal development in early life. Neurogenesis is the term for newly born neurons (Eriksson et al., 1998). According to current knowledge in adulthood neurogenesis is restricted to the hippocampus, rudimentarily present in the olfactory bulb and possibly occurring in the striatum (Bergmann et al., 2015; Ernst et al., 2014).

2.1. Plasticity during neuronal development

Serotonin mediates autoregulatory effects in growing serotonergic neurons (Whitaker-Azmitia, 1998), catalyzes the maturation of astroglial cells (Whitaker-Azmitia, 1998) and influences target tissue maturation (Whitaker-Azmitia et al., 1996). Transgenic mice entirely lacking serotonergic neurons exhibit high perinatal mortality rates and severe deficits in respiratory control (Hodges et al., 2009). Reversible inhibition of 5-HT synthesis by blocking the brain isoform of the tryptophan hydroxylase (Tph2) during early embryogenesis with DL-P-chlorophenylalanine (PCPA) results in subtle alterations of neuronal populations as well in reduced dendritic arborization and complexity, which was independent of neurotrophin signaling (Vitalis et al., 2007).

Irreversible loss of 5-HT after replacing Tph2 with an enhanced green fluorescent protein resulted in reduced serotonergic innervation in thalamic and hypothalamic nuclei, and increased serotonergic nerves in nucleus accumbens (Migliarini et al., 2013). Most strikingly, macroscopic brain development is unaffected, while mice exhibit high lethality rates and body growth reduction. Moreover, in the hippocampus of Tph2 knockout mice BDNF was upregulated indicating presence of compensatory mechanisms. These subtle changes of serotonergic innervation upon Tph2 knockout were not detected in earlier immunohistochemistry studies *e.g.*: (Gutknecht et al., 2008). Moreover, expression of serotonergic receptor mRNA upon lack of 5-HT due to Tph2 knockout was found to be unchanged (Kriegebaum et al., 2010), which the authors trace back to preserved genetic programs independent of 5-HT itself.

Excess 5-HT produces dystrophic serotonergic neurons (Daubert et al., 2010) and migration defects in retinal projection neurons (Upton et al., 1999), thalamocortical axons (Vitalis et al., 2002) and cortical interneurons (Riccio et al., 2009). While many of the neurobiological mechanisms in control of neuroplastic changes during the brain's development seem to reduce their potency in adulthood resulting in a lower threshold for plasticity, SSRIs could lower this threshold by reactivation of developmental plasticity.

Malfunction of developmental plasticity may lead to cortical malfunctions and dystrophic serotonergic neurons as observed in neurodevelopmental disorders (Gaspar et al., 2003; Lesch and Waider, 2012; Whitaker-Azmitia, 2001). Until very recently, the impact of deficits in 5-HT-mediated neuronal development on adult emotional and cognitive function was hardly known. But, accumulating animal data demonstrate developmental periods sensitive to serotonergic and dopaminergic signaling affect later-life somatosensory, anxiety/depression-like and aggressive behavior (Suri et al., 2015). While early-life stress poses a risk factor for depression by altering hypothalamic–pituitary–adrenal (HPA) axis or hippocampus function (Frodl and O'Keane, 2013), entangling protective or aversive genetic and environmental conditions during these critical periods might pose a lucrative field of innovative investigations.

2.2. Synaptic plasticity

Cellular mechanisms controlling synaptic plasticity are thought to represent the biological correlate of learning and memory in the brain (Kandel, 2001), and can be divided into large-scale adaptations like axonal or dendritic sprouting or pruning, and smaller

Table 1
Molecular links of serotonergic proteins and types of neuroplasticity.

Protein	Links with neuroplasticity	Type of neuroplasticity	References
5-HT_{1A}	MAPK, AKT, LTD + LTP *via* NMDA, s100, BDNF, NF-κB, CREB	adult neurogenesis, dendritic maturation, neuroprotection, astroglial interaction	Druse et al., (2005); Hsiung et al. (2005); Meunier et al. (2013); Moreau et al. (2013); Whitaker-Azmitia et al. (1990); Wu et al. (2012); Zhang et al. (2016)
5-HT_{1B}	AKT, ERK, LTD	unknown	Leone et al. (2000); Mathur et al. (2011)
5-HT_{2A}	ERK[a], NMDA, kalirin−7, BDNF	synaptic plasticity, spine morphology, dendritic morphology	Jones et al. (2009); Vaidya et al. (1997)
5-HT_{2C}	NMDA, LTP	synaptic plasticity	Chen et al. (2003); Tecott et al. (1998)
5-HT_{3A}	PSA-NCAM, NMDA, LTD	neuronal migration, synaptic plasticity	Murthy et al. (2014); Varea et al. (2007); Yu et al. (2014)
5-HT_4	ERK, LTP/LTD, BDNF, CREB, AKT	spine morphology, synaptic plasticity, neurogenesis	Kemp and Manahan-Vaughan (2005); Pascual-Brazo et al. (2012); Restivo et al. (2008)
5-HT_6	ARK, ERK, BDNF	unknown	Pereira et al. (2015)
5-HT_7	MAPK, LTD, TrKB	neurite length	Rojas et al., (2014); Samarajeewa et al. (2014); Speranza et al. (2015)
SERT	BDNF	spine density	Nietzer et al. (2011)
MAO-A	NMDA, LTP	neurogenesis	Singh et al. (2013)

Abbreviations: AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinases; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinases; NMDA, N-methyl-D-aspartate receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PSA-NCAM, polysialylated neuronal cell adhesion molecule; TrKB, tyrosine receptor kinase B; ERK and MAPK belong to the same ERK/MAPK pathway.
[a] Many pathways.

changes like synapse formation or pruning (synaptic plasticity; Holtmaat et al., 2013). Short-term synaptic plasticity is essential to influence information processing and high-pass or low-pass filtering of a synapse (Citri and Malenka, 2008). Long-term synaptic plasticity is thought to underlie long-term potentiation (LTP), long-term depression (LTD) or spike-timing dependent plasticity (STDP; Citri and Malenka, 2008). Due to difficulties in obtaining cell material from the brain, little is known about synaptic plasticity in humans. Dendrite length, complexity and synaptic turnover are well controlled during neuronal development, remain rather stable in many cortical areas during adulthood, yet a subset of synapses are thought to exhibit life-long cell type-specific, experience-dependent plasticity (Chow et al., 2009; De Paola et al., 2006; Kasai et al., 2010; Trachtenberg et al., 2002).

Synaptic plasticity during aversive learning *e.g.* in fear conditioning in the hippocampus and the amygdala is thought to be controlled by LTP (Ehrlich et al., 2009; Siegelbaum and Kandel, 1991). There is evidence that the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_4 and 5-HT_7 receptor have a modulatory influence on LTP and/or LTD (see Table 1). For example 5-HT_{1A}-receptors fine-tune LTP in the amygdala during fear conditioning (Huang and Kandel, 2007; Johansen et al., 2011). Owing to the availability of elegant animal experiments (Karpova et al., 2011) and experimental techniques such as optogenetics, the molecular and cellular mechanisms of fear conditioning in the amygdala, are increasingly understood (Johansen et al., 2011; Rodrigues et al., 2004). In regard to depressogenic mechanisms, evidence with comparable quality is needed. However, synaptic dysfunctions with neuronal atrophy and reductions of glial and GABAergic interneurons in the dorsolateral prefrontal cortex (dlPFC) are found in post-mortem analyses of brains of depressive patients (and animal models of chronic unpredictable stress; Duman and Aghajanian, 2012; Underwood et al., 2012). Moreover, reductions in granule cell numbers and dentate gyrus volume were demonstrated in post mortem brains of depressive patients, which were reversed upon treatment with SSRIs (Boldrini et al., 2013). It is assumed that aversive external stimuli such as stress and trauma, in concert with hypothalamus–pituitary–adrenal (HPA) axis activation and increased production of proinflammatory cytokines (Pfennig et al., 2005; Shelton et al., 2011), might act on synaptic plasticity and result in NMDA-receptor hyperactivation (Müller and Schwarz, 2007). This could lead to astrocyte/microglia imbalance, glutamatergic overproduction and excitotoxic neuronal damage (Sanacora et al., 2008) with impact on synapse functionality.

2.3. Neurogenesis

In the hippocampus neuronal progenitor cells differentiate into new neuronal cells, migrate into the granule cell layer, grow axons and dendritic branches and build new synapses, thereby contributing new functionality to existing granule cell layer neurons (Fuchs and Gould, 2000). *In vivo* detectability of neurogenesis in humans has been difficult and due to impaired comparability between species, opinions on the functional relevance in humans diverge (Aimone et al., 2010; Powers, 2013). Yet, in humans a *post mortem* study measuring the concentration of nuclear bomb test-derived ^{14}C in genomic DNA reported a daily number of 700 new neurons with a modest decline during aging (Spalding et al., 2013). While adult-born neurons seem to pose a biological prerequisite for normal function of the hippocampus, in particular thought to mediate learning and memory formation, the distinctive purpose of neurogenesis remains open (Eriksson et al., 1998; Kempermann, 2002). It was suggested that neurogenesis is a prerequisite for the brain to continuously modulate novelty and complexity of cortical input (Kempermann, 2002). A variety of literature demonstrated activation of neurogenesis upon environmental and physical stimuli including exposure to a stressor, running, or enriched environment (Chow et al., 2013; Schoenfeld et al., 2013). Exercise (running) and enriched environment both drastically stimulate neurogenesis, while stress exerts diametrically opposite effects (Opendak and Gould, 2015).

The contribution of neurogenesis in the hippocampus to etiology of depression and antidepressive treatment has been intensively investigated but is not definitely clear (Kasper and McEwen, 2008; Malberg et al., 2000; Sahay and Hen, 2007; Santarelli et al., 2003). Blocking neurogenesis in rodents does not impact on depressive-like or anxiety behavior suggesting a negligible role of neurogenesis in the etiology of major depression

(MD; Sahay and Hen, 2007). Research from the same group suggested that cognitive deficits in depression might be attributable to impairments of neurogenesis. Reduced hippocampal volumes are well replicated in MD (MacQueen and Frodl, 2011; Videbech and Ravnkilde, 2004) and were associated with poorer treatment outcome (MacQueen and Frodl, 2011). The link to impaired neurogenesis as potential pathophysiological substrate was suggested, but causal evidence is missing (Ho et al., 2013). Other mechanisms like cellular atrophy, apoptosis, decreased glial numbers or shift in extracellular fluid content might account for hippocampal atrophy in depression (Czeh and Lucassen, 2007). Since the (subgenual) cingulate, amygdala, prefrontal cortex, insula and thalamus are also key regions in pathophysiology of depression, altered hippocampal neurogenesis is certainly not the only trigger for depression (Sahay and Hen, 2007).

However, it was proposed that neurogenesis constitutes a substrate of the behavioral consequences of antidepressant response (Sahay and Hen, 2007). Chronic treatment with SSRIs, but not acute administration, increases neurogenesis (Alenina and Klempin, 2015; Malberg et al., 2000; Santarelli et al., 2003). Increased synaptic 5-HT levels correlate with neuronal proliferation and vice versa (Brezun and Daszuta, 1999). Neurogenic effects of SSRIs vary between substances (Marlatt et al., 2010), the SERT and BDNF play a crucial role (Benninghoff et al., 2012; Homberg et al., 2014; Sairanen et al., 2005) and 5-HT_{1A} and 5-HT_4 receptors might mediate consecutive changes in gene expression (see Table 1; Gaspar et al., 2003; Lesch, 2001). There might be an age/development dependent impact of neurogenesis and proliferation of new cells with more pronounced effects of fluoxetine in adolescent vs. adult rats (Klomp et al., 2014). On the other hand, many animal models show that short-term, long-term or lifetime 5-HT depletion have opposing effects on hippocampal neurogenesis (Alenina and Klempin, 2015). Surprisingly, neuronal proliferation occurs at a normal rate upon complete depletion or dramatic reduction of 5-HT in Tph2 deficient mice and two other genetic mice models (Diaz et al., 2013; Klempin et al., 2013). The latter study found that 5-HT was required for activity-induced increases in neurogenesis. Negative results of chronic administration were reported (Marlatt et al., 2013) and neurogenesis-independent mechanisms of fluoxetine action were described (David et al., 2009). Moreover, a variety of experimental paradigms and potentially occurring compensatory mechanisms might explain contradictory results (Alenina and Klempin, 2015). Interestingly, a study in baboons demonstrated that social status and social stress impacts on hippocampal neurogenesis (Wu et al., 2014), but in this study fluoxetine resulted in a reduction of neuronal precursor cells in the dendate gyrus. The authors discuss potential acceleration of fluoxetine-enhanced maturation of young neurons, age, sex, species and methodological aspects of this contradictory finding.

This evidence underscores close links between 5-HT, reduced serotonergic functionality in depression and altered neurogenesis. However, the biological relevance, triggers and molecular mechanisms are only beginning to be understood.

3. Molecular connections between serotonin and neuroplasticity—a mechanism of action in antidepressant therapy with SSRIs

A molecular relationship between 5-HT and different types of neuroplasticity is well established (Daubert and Condron, 2010; Gaspar et al., 2003). Most work was previously performed on the 5-HT_{1A} receptor (see Table 1) and based on connections between serotonergic receptors with neurotrophins, tyrosine kinases involved in cytoskeletal rearrangement or astroglial interactions or cell adhesion molecules.

Much of serotonin's link with neurotrophins is based on rodent studies demonstrating close reciprocal connections between BDNF and 5-HT. BDNF administration to cell cultures causes growth of serotonergic neurons and dendrite lengths, and 5-HT increases BDNF mRNA in raphe neuronal cultures, which shows that BDNF promotes the function and phenotype of serotonergic neurons (for review see: Homberg et al., 2014). Moreover, results from animal (Karpova et al., 2011; Piubelli et al., 2011; Vetencourt et al., 2008; Vetencourt et al., 2011) and human subjects (Boldrini et al., 2013; Kraus et al., 2014; Nitsche et al., 2009; Serra-Millas et al., 2011) suggest enhancement of neuronal plasticity as a result of elevated 5-HT levels after treatment with SSRIs. Short-term and long-term treatment with SSRIs and electroconvulsive therapy is associated with changes in the expression of BDNF (Koponen et al., 2005; Nibuya et al., 1995). Research on the biological connections demonstrated that antidepressants activate the BDNF *via* tropomyosin receptor kinase B (TrkB) and a common transcription factor cAMP response element-binding protein (CREB; Koponen et al., 2005; Rantamaki et al., 2007). Mice with the less active form of a common genetic polymorphism in the BDNF gene (Val66Met) are insensitive to antidepressants, but this has not been translated to human Met-allele carriers (Castren and Kojima, 2017). Single studies one antidepressant response are contradictory (Castren and Kojima, 2016), and meta-analyses have found slightly better response in Met-allele carriers and Val/Met heterozygous patients (Kato and Serretti, 2010; Zou et al., 2010).

But neurotrophins could be just one neuroplastic mechanism stimulated by SSRIs. Some serotonergic receptors, beyond their traditional association with G proteins, modulate the activity of signaling pathways involved in neuronal plasticity such as extracellular-regulated kinase (ERK) or mitogen-activated protein kinase (MAPK, Cowen, 2007; Polter and Li, 2010). Although knocking out SERT or MAO and genetic polymorphisms in these impact on neuronal structure (Frodl et al., 2008b; Karabeg et al., 2013; Singh et al., 2013), effects seem to be less pronounced than manipulation of serotonergic receptors (Benninghoff et al., 2012). Many serotonergic receptors are associated with ERK or other protein kinases involved in cytoskelettal regulation in neuronal cells indicating that intracellular serotonergic signals are involved in long-term cell protective processes (see Table 1). This can be demonstrated by the 5-HT_{1A} receptor, which is able to stimulate neurogenesis and dentritic maturation in the hippocampus (Yan et al., 1997). There might be a time dependent expression pattern with peak expressions *e.g.* in the amygdala throughout the developmental period and further peaks in regions maturing in postnatal development (Bonnin et al., 2006; Mehta et al., 2007). Furthermore, 5-HT_{1A} receptors on astroglial cells release a neurite extension factor (S-100β) and induce maturation of astrocytes (Azmitia, 2001). Astrocytic 5-HT_{1A} receptors in combination with S-100β are responsible for maintenance of a mature state in adult neurons (Azmitia, 1999; Wilson et al., 1998). Withdrawal of S-100β leads to a reduction of synaptic connections between neurons (Wilson et al., 1998) and goes along with findings, that the 5-HT_{1A} receptor is required for behavioral and neurogenic effects of fluoxetine (Santarelli et al., 2003).

Another line of evidence suggests that 5-HT interacts with synaptic adhesion molecules (Lesch and Waider, 2012). Serotonin increases the polysialylated form of the neural cell adhesion molecule (PSA-NCAM), which play a role in synaptogenesis and neurite remodeling. Moreover, PSA-NCAM are considered a marker of developing neurons with decreasing expression during maturation. Fluoxetine was demonstrated to increase the expression of PSA-NCAM in the prefrontal cortex, and alter the structure connectivity and plasticity of cortical interneurons. (Guirado et al., 2014; Varea et al., 2007).

Furthermore, rapidly acting antidepressants were discovered in the glutamatergic system (Berman et al., 2000; Sanacora et al.,

2008). NMDA-antagonists such as ketamine are known to increase synaptic plasticity (Li et al., 2010), a mechanism which might demand activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors by ketamine's metabolites. Several classes of antidepressants as well as SSRIs are known to exert action on the glutamate system by influencing NMDA or AMPA receptor transcription (Sanacora et al., 2008).

Recent elegant work by demonstrated an environmental effect of neuroplasticity mediated by SSRIs in a mouse model of depression-like phenotype (C57BL/6; Alboni et al., 2017). Notably, here an opposing effect of enriched environment and chronic stress was demonstrated, suggesting that SSRIs act as catalyzers to environmental susceptibility (Branchi, 2011). This model opens up a very interesting field of environment × treatment (or gene × environement × treatment) interaction studies in human psychopharmacology research, where prospective studies are currently scarce.

In summary, 5-HT is a neurotransmitter that exerts distinct neuroplastic functions. Highly active in shaping serotonergic neurons during embryonic development and early postnatal neuronal maturation, this neuroplastic role is partially conserved in specific brain regions throughout adulthood. Many of these effects are mediated by connections to BDNF, by serotonergic receptors with direct links to neuromodulatory signaling pathways or synaptic adhesion molecules. Environmental stimuli might be overlooked factors in serotonergic neuroplasticity and adverse environmental events during antidepressant therapy might even result in negative consequences. All of the above-described mechanisms were found in animals, knowledge on the cross-connection between 5-HT and neuroplasticity in humans is only beginning to evolve. Consequently, there is big demand for translational studies in humans.

4. *In vivo* quantification of neuroplasticity: MRI, computational morphometry and translational studies

With improvements in MRI-based manual volume measurements (Mathew and Partain, 1985) and computational morphometry (Ashburner and Friston, 2000), neuroplasticity research with neuroimaging has gained growing attention. Reductions or increases of MRI-derived gray matter were detected in cross-sectional study designs in depression or anxiety disorders, navigational expertise, personality, emotional or basal brain functions (Goodkind et al., 2015; Maguire et al., 2000; Mechelli et al., 2004; Van Schuerbeek et al., 2011; Witte et al., 2010). Furthermore, longitudinal increases in gray matter measurements after motoric training received widespread attention (Draganski et al., 2004) (Table 2).

These studies were conducted with a computational analysis of MRI data. Voxel-based morphometry (VBMAshburner and Friston, 2000) or diffusion tensor imaging (DTI) yield surrogates of neuroplasticity such as GMV or fractional anisotropy and enable measurement of changes in gray matter volume and density or white matter analysis in terms of axonal direction, myelination or axon density. While many of the necessary translational approaches laid out in the next section apply for both techniques, for space reasons we will only focus on gray matter. Simply put, VBM is the comparison of local concentrations or volumes of gray matter between groups or within subjects (Ashburner and Friston, 2000). Although criticized by some authors as susceptible to bias introduced by averaging individual brain shapes to standardized brain templates (Bookstein, 2001) or lack of validity (Franklin et al., 2013), structural MRI per-se exhibits an excellent test-retest reliability (Wonderlick et al., 2009). While high resolution structural MRI at field strengths of 3 T and computerized volumetric analyses are the current state-of-the-art techniques *in vivo* to quantify gray matter microstructure at a minimal resolution around 1 mm^3 (Lenglet et al., 2012) recent advances ultra-high resolution with 7 T allow, with certain restrictions to several brain areas, a minimal resolution below 1 mm^3 (Seiger et al., 2015). The main criticism of VBM studies focused on various confounding sources such as differences in blood flow (Franklin et al., 2013) or faulty study designs, statistical methods and methodological artifacts (Thomas and Baker, 2013). Due to the fact that studies on the definitive biological explanations of structural changes observed in human neuroimaging studies are missing, and methodological faults in several studies are evident, critique of the method deserves close attention. However, as the field progresses, several neuronal and non-neuronal candidate mechanisms are discussed as underlying biological mechanisms of the VBM-signal. Most promising neuronal mechanisms underlying gray matter changes include axon sprouting, dendritic branching and synaptogenesis, or neurogenesis (in the hippocampus), while angiogenesis or astrocytic changes are discussed as non-neuronal factors (Fields, 2013; Johansen-Berg, 2012). Since the field still has to progress for better answers of the biological underpinnings of VBM, translational studies such as these presented below are crucial.

An elegantly designed study with transgenic mice expressing fluorescent proteins in pyramidal neurons (Thy1-YFP) undergoing auditory fear conditioning detected significant correlations between the VBM-signal and dendritic spine density (Keifer et al., 2015). Other morphology metrics such as glia proliferation or neuronal soma sizes were not detected, indeed suggesting neuronal processes as underpinning biological substrate of VBM studies. More translational evidence demonstrates that pronounced neuronal remodeling is associated with learning paradigms or exposure to enriched environment after only several hours (Sagi et al., 2012; Scholz et al., 2015). Moreover, neuroplastic changes associated with spatial learning were detectable by MRI-based morphometry and DTI in healthy humans and rats and post-mortem histologic analysis confirmed increases in synaptic vesicles, astrocyte activation and increase in BDNF expression (Sagi et al., 2012; Vernon et al., 2011). These very important studies suggested hippocampal cell proliferation and neurogenesis as histological correlate of learning associated changes of morphometry in human neuroimaging studies, which were sensitive already several hours after learning. Another parallel MRI/histology study in mice found that structure-specific growth associated with spatial learning (Morris water maze paradigm) correlated with GAP-43 staining, a marker of neuronal process turnover, in the hippocampus and striatum, but did not detect altered neurogenesis or astrocyte numbers (Lerch et al., 2011). And a wheel running paradigm in mice demonstrating neurogenesis in the hippocampus as best explanatory variable for GMV changes (Biedermann et al., 2016). These studies confirm that rapid, activity- and environment-dependent neuroplastic changes are detectable with MRI-based morphometry, and there are differences in the types of triggered plasticity in terms of temporal, locational and categorical domains, which demand further investigations.

5. Neuroplasticity in depression quantified with neuroimaging

Magnetic resonance imaging based morphometric studies in patients detected significant gray matter reductions in depression (Kempton et al., 2011). Patients with depression exhibit smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex and gyrus rectus, while a smaller hippocampal volume is detectable in patients during a depressive episode in comparison to patients in remission (Kempton et al., 2011). Several studies show smaller hippocampal volume asso-

Table 2
Effects of SSRI treatment on *in vivo* surrogates of neuroplasticity.

Drug	Modality	Population	Increase	Decrease	References
escitalopram/ citalopram	GMV/GMD	HC	pcc, ins, fus, front	precent/postcent, cereb, pcc	Kraus et al. (2014)
sertraline	GMV	MD	dlPFC	–	Smith et al. (2013)
fluoxetine	GMV	OCD	put	–	Hoexter et al. (2012)
citalopram	GMV	MD	hipp	–	Arnone et al. (2013)
paroxetine	gray matter[c]	PTSD	hipp	–	Vermetten et al. (2003)
mixed[a]	RD/MD	OCD	–	stria/mid	Fan et al. (2012)
unknown	WMV	MD	pariet, ofront, precent, temp, ling, hipp, cereb	put, front, precent[b]	Zeng et al. (2012)
sertraline	gray matter[c]	monkey	acc, hipp	–	Willard et al. (2015)

Abbreviations: acc, anterior cingulate cortex; cereb, cerebellum; dlPFC, dorsolateral prefrontal cortex; front, frontal cortex; fus, fusiform gyrus; ins, insula; HC, healthy controls; hipp, hippocampus; GMD, gray matter density; GMV, gray matter volume; ling, lingual gyrus; MD, mean diffusivity; MD, major depression; mid, midbrain; OCD, obsessive-compulsive disorder; ofront, orbitofrontal cortex; pariet, parietal cortex; pcc, posterior cingulate cortex; PTSD, post-traumatic stress disorder; precent, precentral gyrus; put, putamen; RD, radial diffusivity; stria, striatum; temp, temporal cortex; WMV, white matter volume.

[a] Fluvoxamine, fluoxetine, sertraline and paroxetine.
[b] Uncorrected.
[c] Manual delineation.

ciated with poorer treatment outcome and that stress-induced hypercortisolemia has a negative impact on hippocampal volume (MacQueen and Frodl, 2011; Mahar et al., 2014). Strikingly, stressful life events interact with genotypes of 5-HT metabolism and BDNF on hippocampal structure (Rabl et al., 2014). Hippocampal volume reduction in depression appears to be disease state dependent and, most importantly, treatment with SSRIs increases hippocampal volume (Arnone et al., 2013). A long-term increase of hippocampal volume according to antidepressant usage was previously demonstrated (Frodl et al., 2008a), patients, who discontinued medication did not exhibit hippocampal increase (Frodl et al., 2008a). In two independent studies MRI-based hippocampal subsegmentation demonstrated that the dentate gyrus, where neurogenesis is located, is more affected by depression than the cornu ammonis or the subiculum (Huang et al., 2013; Treadway et al., 2015). With higher MRI resolution, *e.g.* ultra-high field MRI at 7 T, treatment effects on neurogenesis in the dentate gyrus could be further substantiated. Hippocampal volume changes in depression are possibly linked to neurogenesis, yet, reductions in prefrontal cortex, basal ganglia and thalamus are thus not explainable. Alternatively, pathohistological studies speak for changes in synapses, dendrites and glial cell number as source of hippocampal atrophy, while factors such as cellular shrinkage and reduced extracellular fluid content are not ruled out, yet hard to investigate in humans (Czeh and Lucassen, 2007). Synaptic, dendritic as well as glial reductions are well substantiated in the prefrontal cortex (Cotter et al., 2002), but histologic evidence for basal ganglia and thalamus is scarce or mixed (Drevets et al., 2008; Young et al., 2004).

Studies from animal models confirm that medication-induced recovery involves changes in plasticity, dendritic morphology and density and function of synapses (for review seeLicznerski and Duman, 2013). Translational MRI/histology studies investigating depressive-like symptoms in animals are in the early stages and need to be further promoted. An animal model of heart failure associated depressive-like symptoms in rats found decreased neurogenesis and neurite outgrowth in the ventral hippocampus with an increased number of astrocytes (Suzuki et al., 2015). Congruent to this finding, in a postmortem analysis of MD patients, reduced densities and mean sizes of frontal cortex neurons and reduced hippocampal volume with increased numbers of glial cells are reported (Licznerski and Duman, 2013).

Given the amount of previous knowledge of neuroplastic effects of 5-HT, antidepressant treatment effects of SSRIs on whole brain gray matter *in vivo* with MRI-based morphometry are surprisingly scarcely investigated. We are currently not aware of any longitudinal morphometric SSRI study in rodents. Nevertheless, treatment with SSRIs was demonstrated to increase GMV in healthy human subjects (Kraus et al., 2014), in a depression model of nonhuman primates (Willard et al., 2015), and in depressive patients (Smith et al., 2013; see Table 2). Gray matter increases upon treatment with SSRIs was also shown in obsessive compulsive disorder and post-traumatic stress disorder (Hoexter et al., 2012; Vermetten et al., 2003), but replication of these results is missing. Impact on GMV of antidepressant substances with other than serotonergic mechanisms of actions is currently not available. Thereby especially new treatment forms in the glutamatergic system such as NMDA-receptor antagonist ketamine would be of special interest, since ketamine leads to increased synaptic plasticity by enhancing number and function of spine synapses (Li et al., 2010).

6. Conclusion

Serotonin is an important neuromodulatory factor regulating neuroplasticity during early development and some of these functions remain active in fully matured brains. Serotonergic dysbalance is a key pathophysiological mechanism in MD and in addition significant reductions of brain tissue in the prefrontal cortex, hippocampus, thalamus and basal ganglia are known in patients with MD. The tight molecular interaction between 5-HT and serotonergic receptors with neuronal growth factors, regulatory proteins of synaptic plasticity and neurogenesis might explain impaired neuroplasticity in depression. Animal studies show that stress and life-events during vulnerable phases in neuronal development or during adulthood could impact on these interactions between neuronal cells and neurotransmitter systems, however here more studies in humans are needed. Especially, more work is needed on the biological substrate of changes in MRI-based neuroplasticity surrogates, for example MRI/histology studies in animal models of depression or antidepressant treatment. Exciting results in animals and humans suggest novel rapid acting antidepressants such as ketamine, physical exercise or learning facilitate neuroplasticity. Additionally, SSRIs were demonstrated to enhance neurogenesis and synaptic plasticity. Valuable treatment paradigms optimally combining neuroplasticity enhancements could constitute a new strategy in clinical treatment of depression.

Conflict of interest

S. Kasper received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe and Servier. R. Lanzenberger received travel grants and/or conference speaker honoraria from AstraZeneca, Lundbeck A/S, Dr. Willmar

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