Mental and neural restructuring during the treatment of depression: Do Selective Serotonin Reuptake Inhibitors enhance learning-related neural plasticity?

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Abstract

Major depressive disorder (MDD) is a highly prevalent disorders which is accompanied by hippocampal atrophy mediating impairments in learning and memory. Selective Serotonin Reuptake Inhibitors (SSRI) are the first-choice pharmacological treatment but have been criticised for low response rates and the delay until therapeutic effects are attained. Taking these criticisms into account, it is hypothesised that acute SSRI administration directly facilitates learning-related neuroplasticity which in turn improves depressive symptoms though relearning of new self-referential associations. Thereby, the role of positive environmental interactions is highlighted. The essay discusses the nootropic potential of SSRIs by focussing on enhanced synaptic plasticity, neurogenesis, and learning through increased extracellular serotonin levels. In general, serotonin has the potential to facilitate synaptic plasticity through CREB-dependent transcription of neurotropic factors such as brain derived neurotrophic factor. Additionally, increased cell proliferation in the hippocampus and improved memory performance was observed after administration of serotonergic agents. While the results are primarily based on preclinical animal studies, similar effect in humans suggest that SSRI induced neuroplasticity may be translatable to human populations.

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1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), major depressive disorder (MDD) is characterized by depressed mood and/or loss of interest and pleasure for at least two weeks. It is one of the most common mental disorders with a point prevalence of about 4 to 11 % depending on the population and the used classification system (Jane Costello, Erkanli, & Angold, 2006; Sjöberg et al., 2017; Arias-de la Torre, Vilagut, Martín, Molina, & Alonso, 2018). One study in Norway even found a life-time prevalence of 23% for all depressive-related diagnoses, including MDD, dysthymia, and depression not otherwise specified (Sund, Larsson, & Wichstrøm, 2011). Besides the high occurrence, depression has a large societal and personal burden as it is related to impaired occupational and social functioning (Saris, Aghaajani, van der Werff, van der Wee, & Penninx, 2017) as well as to a high suicide risk (Bergfeld et al., 2018).

1.1 Neurocognitive impairments in Depressive Disorders

While suicidal ideation or attempts are explicitly defined as symptoms of MDD, functional impairments are strongly related to cognitive alterations (Hammer-Helmich et al., 2018). In MDD, cognitive impairments span broadly and most commonly include declined psychomotor speed, attention, executive functioning, learning and memory (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Snyder, 2013). For example, memory biases include a higher likelihood for recalling negative autobiographical memories as opposed to positive ones. Interestingly, the cognitive deficits are present early in the episodically proceeding disease as they are already observed during the first episode and have been shown in children and adolescents with MDD (Lee et al., 2012; Wagner, Müller, Helmreich, Huss, & Tadić, 2014). It is suggested that cognitive impairments are not merely a consequence of the disorder but may contribute to the development of emotional symptoms. Indeed, it has been shown that worse cognitive functions are related to less adaptive emotion regulation, thereby affecting the

severity of the depressive symptoms (Wante, Mezulis, Van Beveren, & Braet, 2017). Hence, targeting cognitive impairments should be of major concern during the treatment of depression.

Multiple reviews suggest that biased emotional-cognitive processing is related to increased neural activation in ventrally located brain regions whereas dorsal brain regions are hypoactive in depressive disorders (Mayberg 1997; Phillips, Drevets, Rauch, & Lane, 2003; Disner, Beevers, Haugh, & Beck, 2011). Among others, dysfunctional memory retrieval such as rumination and negative self-schema activation is mediated by altered neural activity in the hippocampus and amygdala. Besides functional brain changes, structural hippocampal impairments are also related to memory dysfunctions in MDD (Travis et al., 2016). With each depressive episode the memory performance diminished by 2-3%, which is accompanied by a simultaneous progression of the atrophy of the hippocampus (Gorwood, Corruble, Falissard, & Goodwin, 2008). Hippocampal dysfunctions in MDD are especially alarming as this brain structure plays an important role for neurogenesis in adults. Neurogenesis in the hippocampus provides the neural substrate for the flexible adaption to environmental changes, which is mediated by different types of learning and memory such as pattern separation, habituation, fear conditioning, and discrimination learning (Stuchlik, 2014; Fares, Diab, Nabha, & Fares, 2019). Additionally, more general brain atrophy may also relate to hippocampal impairments as hippocampal neurogenesis affects brain network reorganization in extra-hippocampal substrates. Volume reduction in the basal ganglia, orbitofrontal cortex and subgenual prefrontal cortex (PFC) found in persistent types of MDD might be promoted by decreased neurogenesis in the hippocampus (Lorenzetti et al., 2009). Hence, targeting hippocampal impairments may be relevant for the elevation of a wide range of symptoms in MDD.

In general, MDD is a highly prevalent and severe psychiatric disorder which is characterized by hippocampal dysfunctions mediating learning and memory impairments. As cognitive impairments contribute to the severity of emotional symptoms and dysfunction in

daily live, targeting hippocampal mediated cognitive impairments has a high clinical significance during the treatment of MDD. A possibly way to reverse hippocampal atrophy may be pharmacological agents which affect neural growth and restructuring.

1.2 Hypothesized action mechanism of pharmacological treatment in MDD

The first choice of pharmacological treatment in MDD are Selective Serotonin Reuptake Inhibitors (SSRIs; Maina, Mauri, & Rossi, 2016). However, a critical review suggests exaggerated claims regarding the effectiveness of SSRI treatment due to a publication bias of significant results which is in line with studies showing low response rates (about 50%) to SSRI treatment (Turner, Matthews, Linardatos, & Tell, 2008; Bares, Novak, Brunovsky, Kopecek, & Höschl, 2017). Additionally, SSRIs are criticised for taking about 2-3 weeks until therapeutic effects are attained (Nierenberg, 2001). The two major criticisms may be explained by taking the relevance of hippocampal-dependent learning and memory during the treatment of depression into account. It is suggested that SSRIs do not affect mood per se but instead have a positive effect on hippocampal and learning impairments. The delay in therapeutic effects is explained by the time the patient needs to relearn new autobiographical memories and implement adaptive behavioural strategies. As autobiographical memories shape an individuals' self-concept and goal-oriented behaviour, the formation of positive autobiographical memories in turn causes an improvement of depressive symptoms after a delay (Lemogne et al., 2006). Furthermore, low response rates are accounted for as improvements in hippocampal-dependent learning may only elevate depressive symptoms in individuals experiencing positive environmental interactions (**Figure 1**).

The hypothesis is supported by studies showing that a single SSRI administration has the potential to immediately improve cognitive performance and modulates brain activity in regions relevant for emotional memory processing even though depressive symptoms are not directly affected (Harmer et al., 2003; Del-Ben et al., 2005; Anderson et al. 2007; Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009; Arnone et al., 2018). Furthermore, a

preclinical rodent study highlights the importance of environmental interactions for the qualitative effects of SSRIs (Alboni et al., 2017). Mice under chronic treatment with fluoxetine showed reduced depressive-related behaviour and increased neuronal growth (inferred by increased neurotrophin levels) when living in a positive, enriched environment. Contrary, mice living in a stressful environment increased their depressive-related behaviour when treated with fluoxetine compared to a placebo. The contrasting effects of SSRIs may be explained by a higher susceptibility to both beneficial and harmful influences of the environment, which is in line with the undirected susceptibility to changes model (Branchi, 2011). The undirected susceptibility to change model suggests that SSRIs enhance the capacity of neurons to dynamically adapt to environmental changes. In the context of depression, it is therefore hypothesized that SSRIs may open a window of opportunity for the relearning of new positive autobiographical memories and behavioural patterns which in turn improve depressive symptoms. In the following this hypothesis will be discussed by focussing on the nootropic effects of SSRIs.

Figure 1. *Hypothesis. Selective serotonin reuptake inhibitors (SSRIs) are expected to increase the susceptibility to environmental influences through a positive effect on learning-related neuroplasticity. Depending on the quality of environmental interactions SSRIs may either improve or deteriorate self-concept, adaptive behavioural patterns and mood.*

2. The effect of SSRIs on learning-related neuroplasticity

SSRIs modulate brain function by elevating serotonin (5-HT) levels in the synaptic cleft through serotonin transporter (SERT) blocking at the presynaptic neuron (Bymaster et al., 2002). The anti-depressive effects of elevated serotonin levels were initially discovered by coincidence during pharmacological tuberculosis and schizophrenia treatment using iproniazid and imipramine, respectively (Baumeister, Hawkins, & Uzelac, 2003; Chaiklin,

2003). Both medications block, among others, the clearance of serotonin from the synaptic cleft which was suggested to mediate the accidentally discovered reduction of depressive symptoms. Currently, a range of SSRIs have been developed showing varying specificity on the serotonergic system which are accompanied by differences in treatment efficiency and side effects (Barth et al., 2016). The importance of serotonergic modulation during the treatment of MDD was additionally supported by studies showing lower serotonin levels in depressed individuals compared to controls. As also neuroplasticity was also shown to be decreased in MDD, the cooccurrence of both low serotonin and low neuroplasticity hints to a possible relationship (Brunoni, Lopes, & Fregni, 2008). Neuroplasticity can be defined as all structural central nervous system (CNS) changes which help the individual to adapt to internal and external changes. Hence, neuroplasticity builds the cellular substrate for learning (May, 2011). In the following the effect of serotonin on different forms of learning-related neuroplasticity will be discussed.

2.1 Do SSRIs enhance synaptic plasticity?

One form of neuroplasticity is referred to as synaptic plasticity. It involves all cellular processes which modify synaptic density as well as signal transmission at the synapse (Holtmaat, Randall, & Cane, 2013). Already 50 years ago, the influential Hebbian learning approach illustrates the essentiality of synaptic plasticity for learning and memory consolidation (Hebb, 1949). Hebbian learning suggests that when a pre- and postsynaptic neurons fire action potentials simultaneously, structural changes at the synapse enhance the efficiency of the connection which is called long term potentiation (LTP). The effect of serotonin on LTP were studies in a very basic animal model. In giant marine snails (*Aplysia*) nerves cells are large enough to directly inject specific compounds and record activity over a period of days (Kandel, 2001). Adaptation of simple defensive reflexes after repeated stimulation reflect very basic form of learning. It has been shown that serotonin puffs at the synapse lead to synaptic facilitation through presynaptic second messenger signals activating

cAMP-dependent protein kinase (PKA) which in turn modulates gene transcription through cAMP response element binding protein (CREB) phosphorylation. The CREB-dependent gene transcription enables protein synthesis in the cell which is important for synaptic plasticity (**Figure 2**). Furthermore, it was shown that serotonin-initiated transcription of proteins does only facilitate synaptic growth in synapses marked by serotonin (Kandel, 2001).

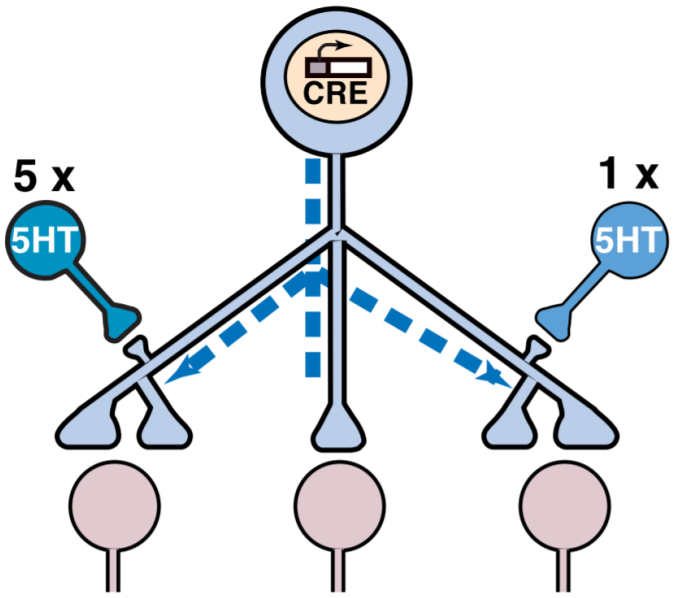

Figure 2. *Assumed effect of serotonin on synaptic facilitation. It has been shown that five puffs of serotonin (5HT) initiate CREB-dependent gene transcription which enables protein synthesis. Proteins facilitate synaptic growth only at synapses marked by serotonin. Achieved from Kandel (2001).*

Similar effects of serotonin on gene transcription were shown in a preclinical rodent study investigating CREB phosphorylation after chronic administration of two antidepressants (fluoxetine and desipramine) for 14 days (Thome et al., 2000). Fluoxetine, belonging to the group of SSRIs, has a higher selectivity to the serotonin transporter, whereas desipramine acts primarily on the noradrenalin transporter and only to a lesser extent on the serotonergic system (Jett, McGuirk, Waligora, & Hunter, 1997). In line with the hypothesis that serotonin is important for learning-related neuroplasticity, the study showed significantly increased phosphorylated CREB levels after chronic fluoxetine but only nonsignificant elevation after desipramine administration. While CREB levels were significantly increased in the amygdala,

hypothalamus, and thalamus in comparison to saline injections, effects were strongest in the dentate gyrus. The dentate gyrus is part of the hippocampus and as such, CREB-mediated protein synthesis in this region may be especially related to learning and memory (Ohline & Abraham, 2019). The rise of phosphorylated CREB seem to develop over time as a single fluoxetine administration yielded only an insignificant increase in CREB levels (Thome et al., 2000).

Among others, CREB regulates the transcription of c-fos, BDNF and multiple other neuropeptides. Both, c-fos and BDNF have been related to proliferation, differentiation and survival of neurons as well as to learning (Cruz, Rubio, & Hope, 2015; Leal, Comprido, & Duarte, 2014). In hippocampal neurons, it has been shown that BDNF mediates all types of synaptic facilitation including short-term potentiation, early LTP and late LTP (Leal, Comprido, & Duarte, 2014). Similarly, knockout mice lacking c-fos in the CNS had reduced LTP in the hippocampal CA3-CA1 synapses which correlated with impairments in spatial and associative learning tasks (Fleischmann et al., 2003). Hence, serotonin-related increase in phosphorylated CREB levels could facilitate synaptic connections through transcription of c-fos and BDNF.

Indeed, preclinical studies also show modulations in BDNF levels with increased extracellular serotonin levels. Chronic antidepressant treatment for 21 days increased BDNF mRNA levels in Sprague-Dawley rats (Nibuya et al., 1995). While all tested antidepressants (Tranylcypromine, Mianserine, Sertraline, Desipramine) increased BDNF mRNA levels in the hippocampus, Tranylcypromine was the only compound able to induce enhanced BDNF transcription in the frontal cortex. It should be noted that only sertraline is a SSRI whereas the other antidepressants enhance a range of monoaminergic transmission next to serotonin. Furthermore, in line with the insignificant CREB increase after a single fluoxetine infusion, also BDNF levels were not significantly increased after acute dosage of any tested antidepressants. Interestingly, a study investigating cultured raphe cells showed that increased

transcription of BDNF upregulates important markers for serotonergic neuron including tryptophan hydroxylase mRNA which is essential for the synthesis of serotonin (Galter & Unsicker, 2000). Increased serotonin synthesis may in turn again increase BDNF levels, lending support for a positive feedback loop between BDNF and serotonin. A positive feedback loop might explain how elevation in CREB and BDNF after acute SSRI administration may grow and become detectable by statistical tests over time.

In general, the findings of preclinical studies suggest that chronic administration of pharmacological elevating extracellular serotonin levels have the potential to facilitate synaptic growth though CREB-dependent protein transcription of neurotropic factors (e.g. BDNF). The increase in CREB and BDNF levels was consistently shown in the hippocampus. However, the reviewed studies also suggest that various antidepressant agents differ in their capacity to induce synaptic plasticity across different brain regions (Nibuya et al., 1995; Thome et al., 2000). This was supported by another rodent study comparing the effects of fluoxetine with the effects of Vorteoxitine (Chen, Du Jardin, Waller, Sanchez, Nyengaard, & Wegener, 2016). On dosage with similar SERT occupancies, synaptic formation (quantified by increased spine number spine and density) in the hippocampal C1 occurred faster and was more prominent for Vortioxitine. As inhibition of SERT was similar between both agents, differences may arise due to the specific pharmacological profiles exerting different effects on postsynaptic receptors. In line with possible differences for induced neuroplasticity, previous studies show that 5-HT_{2A}, 5-HT_4 and 5-HT_{1A} receptor activation has positive effects on memory, while 5-HT_3 receptor agonists impair memory consolidation (Hong & Menses, 1997; Buhot, Martin, & Segu, 2000). Future studies should investigate if these differences on memory performance are mediated by different capacities of SSRIs to induce synaptic growth.

In humans, the investigation of serotonergic influences on synaptic plasticity is hampered by the difficulty to obtain brain material. However, post-mortem brains of suicide victims

have been used to investigate the relationship between SSRIs and BDNF in humans (Karege, Vaudan, Schwald, Perroud, & La Harpe, 2005). BDNF levels in the ventral prefrontal cortex (vPFC), hippocampus and entorhinal cortex were compared between depressed suicide victims either taking antidepressants (mainly SSRIs) or being drug-free, suicide victims with other psychiatric or neurological diseases and a control group dying of a determined cause such as homicide or myocardial infarction. In the vPFC and hippocampus, drug-treated suicide victims had similar BDNF levels compared to controls while drug-free suicide victims showed a significant decrease in BDNF indicating that serotonergic drugs may have induced elevated BDNF levels in psychiatric suicide victims (**Figure 3**).

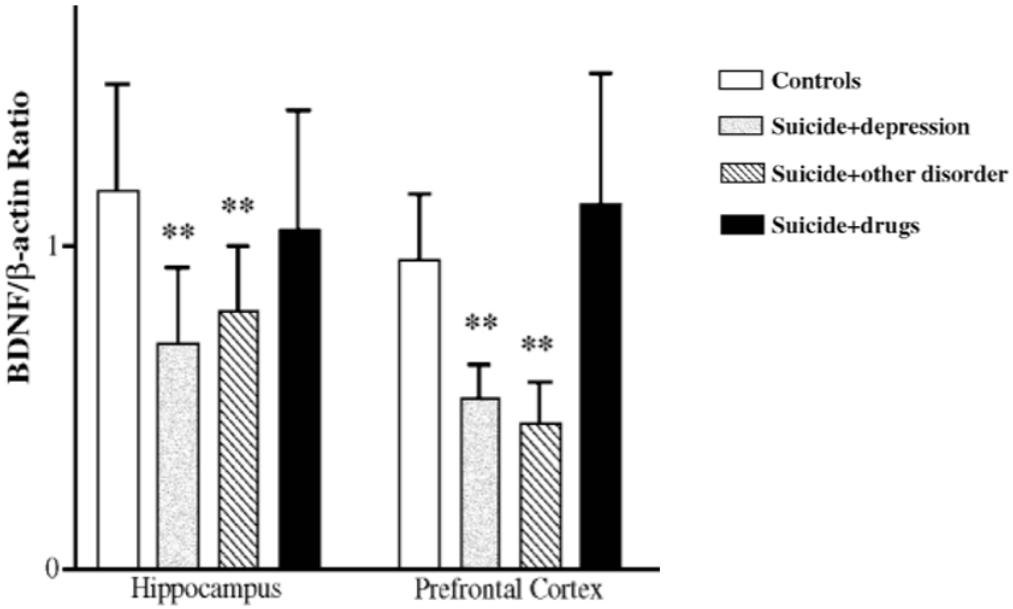

Figure 3. *Suicide victims treated with antidepressants had similar BDNF levels in the hippocampus and prefrontal cortex compared to drug-free suicide victims. Achieved from Karege et al. (2005).*

Similarly, two studies showed increased BDNF serum levels in depressed patients taking SSRIs compared to drug-free depressed patients and healthy controls (Aydemir et al., 2006; Van der Meij, Comijs, Dols, Janzing, & Oude Voshaar, 2014). However, to the best of my knowledge, no study investigated whether serum BDNF is related to BDNF levels in the CNS. Furthermore, all studies in humans relied on quasi-experimental designs which impede

the assumed causality of SSRI induced changes in neuroplasticity. Despite these limitations, studies in humans suggest increased BDNF levels after SSRI intake which suggest that serotonin induced cellular changes be translatable from preclinical to human studies.

2.2 Do SSRIs enhance neurogenesis?

Next to synaptic consolidation of experiences, other forms of neuroplasticity include axonal and dendritic sprouting or pruning of existing neurons as well as the development of new neurons from progenitor cells called neurogenesis (Balu, & Lucki, 2009). In the adult brain, neurogenesis is largely restricted to the hippocampus where approximately 700 new neurons are added each day (Spalding et al., 2013). Hippocampal neurogenesis is achieved as progenitor cells in the dentate gyrus differentiate into new neuronal cells which migrate into the granular layer where they further develop axons, dendrites and synapses. In rodents it takes at least 2-3 weeks until new-born neurons become functionally integrated in existing neural circuits and show behavioural relevance (Schoenfeld & Cameron, 2015).

Multiple animal models, relying predominately on rodents, show that hyper serotonergic cell environment increase neurogenesis (Malberg, Eisch, Nestler, & Duman, 2000; Duman, Nakagawa, & Malberg, 2001; Encinas, Vaahtokari, & Enikolopov, 2006). Neurogenesis can be observed by labelling of dividing cells in the S-phase with bromodeoxyuridine and counting the number of labelled cells in the obtained brain material after an experimental manipulation. Using this technique, Malberg and colleagues (2000) showed increased cell proliferation following the chronic administration (at least 14 days) of various antidepressants (**Figure 4**). Furthermore, other psychiatric agents such as morphine and haloperidol did not affect cell proliferation. The investigated antidepressants modulate serotonergic transmission, whereas morphine and haloperidol act primarily on opiate and dopamine receptors, respectively. Like synaptic plasticity, enhanced neurogenesis after serotonergic modulation may be also mediated by second messenger and neurotropic factor

systems (Palmer, Takahashi, & Gage, 1996; Takahashi, Palmer, & Gage, 1998). Furthermore, specific $5HT_{1A}$ receptor activation in rats was shown to increase neurogenesis (Gould, 1999).

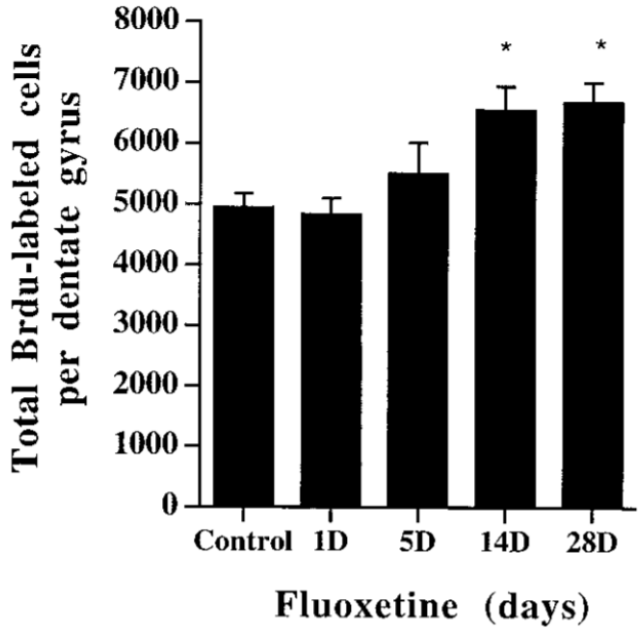

Figure 4. *Chronic administration of an SSRI (Fluoxetine) increased the number of bromodeoxyuridine labelled cells in the dentate gyrus. Bromodeoxyuridine labels cells in the S-phase reflecting neurogenesis. Achieved from Malberg et al. (2000).*

Contrary, selective serotonin deletion yielded less consistent effect on neurogenesis in the CNS. One study found that injection of a serotonin neurotoxin (5,7-dihydroxytryptamine), causing serotonin deprivation, caused a decrease in neurogenesis (Brezun, & Daszuta, 1999). However, in another study injection of 5,7-dihydroxytryptamine did not affect neurogenesis (Jha, Rajendran, Davda, Vaidya, 2006). The difference may be explained as careful protection of norepinephrine synapses was employed in the studies finding no decrease in neurogenesis whereas norepinephrine synapses were destroyed in the study observing decreased neurogenesis. Together with the observation of decreased neurogenesis by an agent decreasing both serotonin and norepinephrine level, the result suggest the relevance of norepinephrine receptors for neurogenesis. Hence, while increased neurogenesis subsequent to serotonergic antidepressants has been shown in multiple studies, the secondary

pharmacological action altering other neurotransmitter (e.g. norepinephrine) should be carefully considered.

In humans, non-invasive neuroimaging techniques such as magnetic resonance imaging (MRI) may be employed for the investigation of serotonin-induced neurogenesis. High resolution MRI determining the grey-matter volume of certain brain regions can give information on the neural density which reflects neurogenesis and changes in axon-, dendrite- and synaptic density of existing neurons. Voxel-based morphometry can detect fast structural changes in the brain as inferred based on correlations with neuroplasticity markers such as dendritic spine density, BDNF expression and neurogenesis in animal studies (Vernon, Natesan, Modo, & Kapur, 2011; Keifer et al., 2015; Biedermann et al., 2016). Together with its high test-retest reliability in humans, VBM has the potential to compare changes in local grey matter concentrations between different participants (Ashburner & Friston, 2000).

Neuroimaging studies in humans are in line with animal studies showing serotonin-induced neural growth by showing that SSRIs enhance MRI-derived hippocampal volume. For example, Arnone and colleagues (2013) found increased bilateral grey matter after two weeks of pharmacological treatment using a relative specific SSRI called citalopram in depressive patients. Similarly, SSRI administration for two years was shown to obstruct brain atrophy of cognitive impaired elderly. After two years, participants not taking SSRIs showed grey matter atrophy of -2.7%, whereas only -0.9% of grey matter was lost in participants taking SSRIs (Brendel et al., 2018). While these studies suggest a positive effect of SSRIs on grey matter volume, definite conclusions are limited as no randomized selection of a control group receiving a placebo was implemented in both studies. However, in general positive effects on hippocampal volume after chronic SSRI intake in humans are in line with preclinical studies showing increased neurogenesis, synaptic density and general neuroplasticity markers such as BDNF and CREB. Considering that structural brain changes, especially in the hippocampus, build the neural substrate for learning and memory

consolidation, it is expected that enhanced neuroplasticity after SSRI intake also facilitate cognitive performance in memory tasks.

2.3 Do SSRIs improve learning and memory?

While animal studies showing enhanced behavioural flexibility and spatial memory after SSRI administration, the question of whether SSRIs improve learning and memory is also behaviourally assessable in humans through cognitive test (Brown, Amodeo, Sweeney, & Ragozzino, 2012). A meta-analysis in humans including various types of anti-depressive medication (e.g. TCAs, SNRI, SSRI, SMS) showed that in depressed patients only SSRIs were able to significantly improve immediate memory recall which reflects learning (Prado, Watt, & Crowe, 2018). In healthy controls there was a positive effect on immediate memory which did not reach statistical significance indicating that SSRIs might be especially beneficial for learning and memory when baseline functioning is compromised (Prado, Watt, & Crowe, 2018). However, in depressed patients the memory improvement may be confounded by higher specificity of SSRIs in targeting depressive symptoms compared to the other anti-depressive compounds. Positive mood was previously related to increased task motivation, thereby possibly exaggerating the SSRI induced improvements on short-term memory in depressed individuals (Sun, Gu, & Yang, 2018).

The confounding effect of general symptoms improvement on memory and learning may be avoided by focussing on healthy individuals as done by Harmer, Bhagwagar, Cowen, & Goodwin (2002), who also included a rating scale for various mood states. In the absence of emotional changes, one acute infusion of an SSRI (escitalopram) improved delayed recall of verbal material reflecting long-term memory whereas immediate recall did not differ between the placebo and medicated group. Findings could indicate that SSRIs enhance memory consolidation instead of changing the initial encoding of memory traces which reflects learning. Similarly, the acute depletion of tryptophan, serotonins precursor amino acid, resulted in worse memory consolidation in healthy volunteers while not effecting

immediate recall (Riedel, Klaassen, Deutz, van Someren, & van Praag, 1999). A mega-analysis grouping the data of nine studies also showed impairments in delayed recall in healthy participants after tryptophan depletion (Sambeth et al., 2007). Besides these prominent memory consolidation deficits, this analysis also revealed smaller but significant impairments for immediate recall in contrast to the previous studies. The detection of the subtle learning deficits after tryptophan depletion may be due to increased power after grouping of data points. In general, serotonin seems to be especially important for the consolidation of memories as reflected by changes in delayed recall after acute SSRI infusion or tryptophan depletion while changes in immediate recall reflecting initial memory encoding are more subtle. Overall the findings suggest a ceiling effect for SSRI-induced memory enhancement as changes in learning and memory are strongest during serotonergic dysfunctions (tryptophan depletion and depressed individuals) whereas further memory improvement in healthy individuals is less consistently shown.

3. Conclusion

Combining evidence from preclinical and human studies suggest that SSRIs have a facilitating effect on learning and memory as well as on different forms of neuroplasticity including synaptic facilitation and neurogenesis. Immediate improvements in learning and memory after acute SSRI intake were most prominent in depressed individuals. Hence, it is suggested that SSRIs have the capacity to reverse learning impairments associated with MDD. In line with the hypothesis, the findings indicate increased susceptible to beneficial or harmful influences from the environment early during the pharmacological treatment.

As neural restructuring is assumed to accomplish learning and memory consolidation on a cellular level of analysis, it seems contradictory that cognitive functions improved after one acute intake of an SSRI, whereas neuroplasticity markers were only enhanced after chronic SSRI administration. With respect to synaptic facilitation, underpowered rodent studies may be unable to detect small increases in neuroplasticity markers which are however

sufficient to facilitate learning and memory. Indeed, the experiments on giant marine snails supported that there are fast-acting effects on synaptic growth induced by extracellular serotonin which could support the immediate improvement in learning and memory. Contrary, neurogenesis is a slower process which is unlikely to support early cognitive improvement. It takes about 2-3 weeks until new-born granule cells become functional integrated in neural circuits and animal studies showed increased neurogenesis after 14 days but not after 5 days of SSRI administration. Hence, SSRIs induce fast improvements in learning and synaptic plasticity, while SSRI-induced neurogenesis mirrors the delay in SSRI-induced therapeutic effects (**Figure 5**).

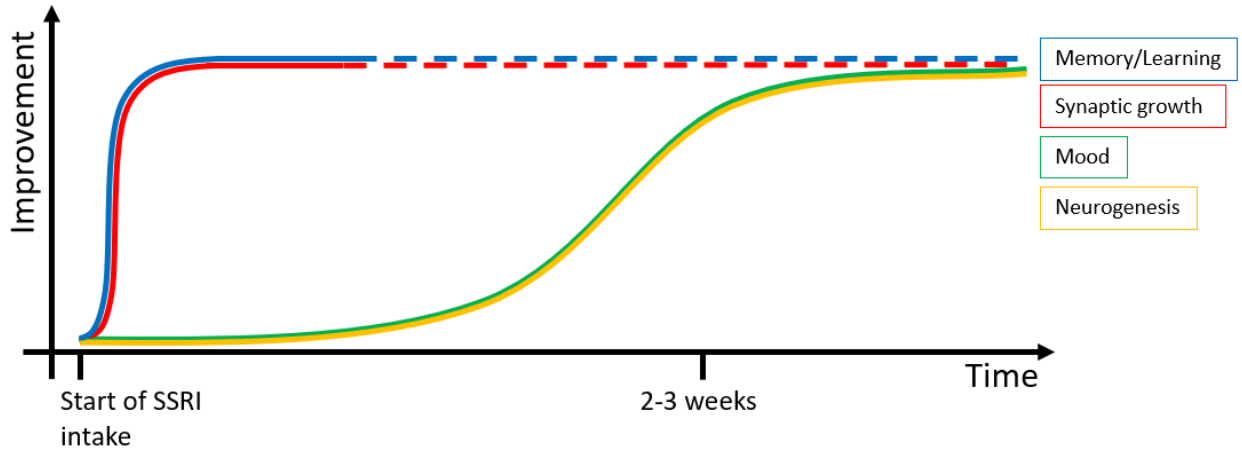

Figure 5. *Assumed effects of SSRIs on cognitive function, neuroplasticity and depressive symptoms.*

It was hypothesized that the delay in therapeutic effects is simply explained by the time it takes to learn new associations from the environment. However, the similar temporal pattern between SSRI-induced therapeutic effects and SSRI-induced neurogenesis suggest a relationship between both. While early facilitation of learning and synaptic plasticity may help to form specific positive memories, neurogenesis could be the cellular substrate to integrate the positive memories into a functional self-concept. The integration of new-born neurons into existing neural circuits may be essential in this regard. Compared to small scale synaptic changes, larger scale restructuring of neural circuits could support a stable and

integrative change in behavioural and mental patterns necessary to improve mood. A similar dissociation between fast encoding of single memory traces and slower neural system consolidation is suggested by the competitive trace theory (CTT). First, the consolidation of specific experiences is highly dependent on single memory traces in the hippocampus. Through repeated hippocampal-dependent reactivation of the memory trace, the experience becomes integrated into larger neural networks (Yassa & Reagh, 2013; Dudai, 2004). The integration into existing neural systems makes the memory more stable over time. Furthermore, it was suggested that the memory becomes decontextualized over time which may be relevant to develop a general sense of self instead of collecting multiple specific memories. In conclusion the previous literature suggests enhanced learning and synaptic plasticity early during the pharmacological treatment. Thereby, SSRIs may open a window of opportunity to form positive memories. The somewhat slower neurogenesis may integrate the learned associations in existing neural circuits which in turn improves depressive symptoms through the formation of a more positive and stable self-concept.

3.1 Implications

To optimally benefit from SSRI treatment, positive environmental interactions are essential. Indeed, it was shown that more favourable living conditions (e.g. private insurance, high income, employment) are associated with a better treatment response to SSRIs (Chiarotti, Viglione, Giuliani, & Branchi, 2017). Similarly, a combination of SSRI intake and psychotherapy yielded higher effectiveness in comparison to either treatment strategy alone (Brent et al., 2008; March et al., 2004; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004). Hence, proper guidance during the early critical phase of pharmacological SSRI treatment is assumed to be essential for better response rate as well as a possible shortening of until therapeutic effects through specific exposure to positive environmental interactions. Contrary, one should be cautious to prescribe SSRIs in unfavourable living conditions. For example, preclinical studies showed enhanced the consolidation of fear conditioning

subsequent to a single SSRI infusion (Burghardt, Sullician, McEwen, Gorman, & LeDoux, 2004; Ravinder, Burghard, Brodsky, Bauser, & Chattarji, 2013). Considering the range of cognitive impairments and different symptom representations in MDD, the specific focus on hippocampal neuroplasticity and relearning of positive associations to attain symptom remission treatment seems rather simplistic. However, the importance mental restructuring based on positive environmental interactions has been already described more than 40 years ago (Lewinsohn, 1974). The currently most widely used and most effective psychotherapy, called cognitive-behavioural therapy assumes that mental restructuring and behavioural activation are essential to elevate depressive symptoms (Mor & Haran, 2009). Interestingly, therapeutic effects of cognitive-behavioural therapy are accompanied by increased hippocampal volume which supports the hypothesis that learning-related neural growth in the hippocampus is an important pathway to improve depressive symptoms (Levy-Gigi, Szabó, Kelemen, Kéri, 2013).

Future studies may determine the exact time point at which cellular changes occur. Previous animal studies investigate discrete time points (e.g. 5, 14, and 28 days) which obscures the exact temporal course of enhanced learning-related neuroplasticity. The investigation of neuroplasticity at multiple time point may validate if the onset of therapeutic effects and neurogenesis is truly simultaneously. Furthermore, the duration of enhanced neuroplasticity may be relevant to determine how long patients possibly benefit from SSRI treatment. Another point which needs clarification involves the exact pharmacological actions facilitating learning-related neuroplasticity. The different efficiency across SSRIs suggest that not merely the inhibition of SERT enhances neuroplasticity markers but effects on other monoamines and post-synaptic serotonin receptors may play a role. Targeting the specific combination of monoamines and serotonin receptors may help to reduce side effects of pharmacological agents while simultaneously enhancing effects on learning and neuroplasticity.

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