



## iPlasticity: Induced juvenile-like plasticity in the adult brain as a mechanism of antidepressants

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The network hypothesis of depression proposes that mood disorders reflect problems in information processing within particular neural networks. Antidepressants (AD), including selective serotonin reuptake inhibitors (SSRI), function by gradually improving information processing within these networks. AD have been shown to induce a state of juvenile-like plasticity comparable to that observed during developmental critical periods: Such critical-period-like plasticity allows brain networks to better adapt to extrinsic and intrinsic signals. We have coined this drug-induced state of juvenile-like plasticity 'iPlasticity.' A combination of iPlasticity induced by chronic SSRI treatment together with training, rehabilitation, or psychotherapy improves symptoms of neuropsychiatric disorders and issues underlying the developmentally or genetically malfunctioning networks. We have proposed that iPlasticity might be a critical component of AD action. We have demonstrated that iPlasticity occurs in the visual cortex, fear erasure network, extinction of aggression caused by social isolation, and spatial

reversal memory in rodent models. Chronic SSRI treatment is known to promote neurogenesis and to cause dematuration of granule cells in the dentate gyrus and of interneurons, especially parvalbumin interneurons enwrapped by perineuronal nets in the prefrontal cortex, visual cortex, and amygdala. Brain-derived neurotrophic factor (BDNF), via its receptor tropomyosin kinase receptor B, is involved in the processes of synaptic plasticity, including neurogenesis, neuronal differentiation, weight of synapses, and gene regulation of synaptic formation. BDNF can be activated by both chronic SSRI treatment and neuronal activity. Accordingly, the BDNF/tropomyosin kinase receptor B pathway is critical for iPlasticity, but further analyses will be needed to provide mechanical insight into the processes of iPlasticity.

**Key words:** brain-derived neurotrophic factor/tropomyosin kinase receptor B, dematuration, neurogenesis, neuronal plasticity, parvalbumin/perineuronal nets.

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**A**NTIDEPRESSANTS (AD), SUCH as tricyclic AD, selective serotonin reuptake inhibitors (SSRI), and monoamine oxidase inhibitors, increase the available monoamines in the synaptic cleft by, respectively, inhibiting the reuptake of serotonin and norepinephrine, selectively inhibiting the reuptake of serotonin by the presynaptic nerve terminal, and inhibiting their degradation of monoamines, thereby increasing the available monoamines in the

synaptic cleft. This increase in monoamine signaling associated with AD effects has led to what is defined as the ‘monoamine hypothesis’ of depression,<sup>1</sup> which proposes that serotonin and norepinephrine are involved in the etiology and treatment of depressive disorders and that there is a causal relation between the observed physiological effects of AD on monoamine metabolism and their behavioral outcomes.<sup>1</sup> Recently, however, the network hypothesis of depression and AD action has offered an alternative to the ‘imbalance of monoamines’ theory.<sup>2–4</sup> The network hypothesis proposes that mood disorders reflect problems in information processing within particular neural networks in the brain and that AD act by gradually improving information processing within these networks.

More recently, it has been demonstrated that AD treatment activates a state of plasticity in the adult brain that resembles plasticity during critical or juvenile periods in postnatal development. When AD-induced plasticity is combined with training (learning a particular skill or behavior), rehabilitation (restoring to health or normal state mentally and/or physically through training and therapy), or psychotherapy that guides the plastic connectivity, networks miswired by abnormal early experiences can be repaired in adulthood. In this review, we introduce the concept of and evidence for the phenomena and discuss possible underlying biological mechanisms.

### CRITICAL-PERIOD PLASTICITY

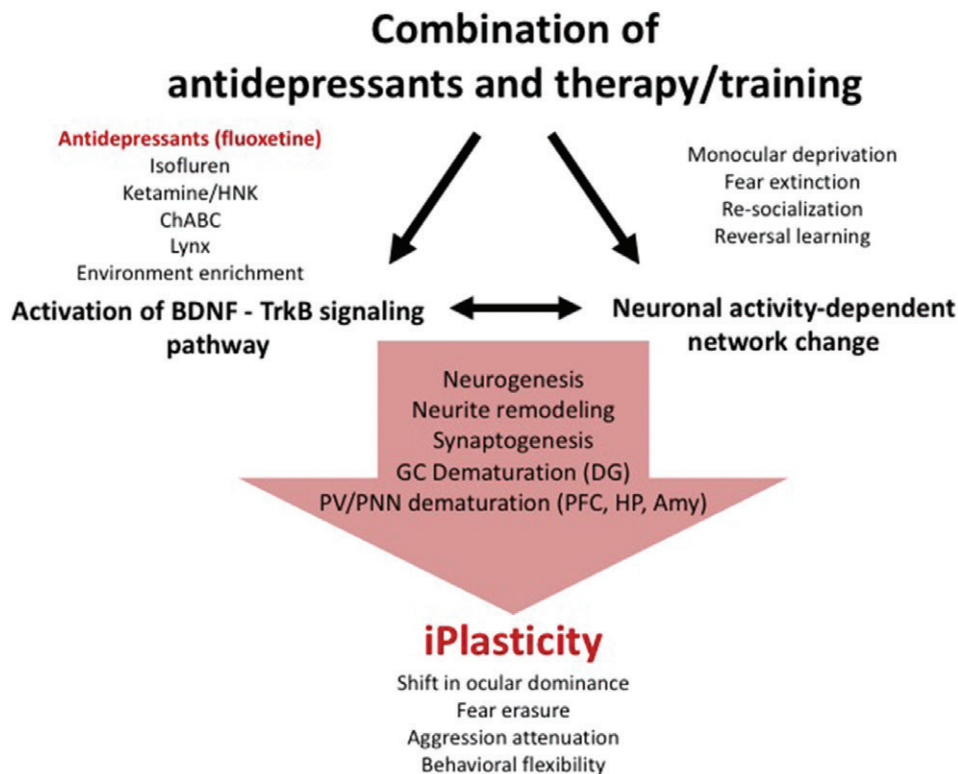
During development, the brain adapts to the environment through activity-dependent neuronal plasticity. In this process, neural networks that are originally manifested by genetic guidance are modified through experience and gradually adapt to the external and internal milieu.<sup>5,6</sup> Experience-dependent modifications peak during the critical or sensitive periods of early life<sup>7–9</sup> when neuronal networks are plastic and adjust to environmental conditions. A breakthrough in the study of critical-period plasticity was the discovery of ocular dominance columns in the kitten visual cortex by Hubel and Wiesel.<sup>10</sup> These columns, though not visible as columns by eye, are organized such that they are predominantly innervated by axons from the left or right eye. Plasticity studies have shown that activity-dependent reorganization of these columns is highest during critical periods and very restricted in adulthood after closure

of critical periods.<sup>11</sup> Abnormal visual input during critical periods, including monocular deprivation, leads to abnormal network structure within the visual cortex, including loss of innervation of a deprived eye and increased innervation of the fellow eye. These effects persist into adulthood if the pattern is not corrected during the critical period, a phenomenon known as amblyopia.<sup>12</sup> Since then, the shift in the ocular dominance paradigm in the visual cortex has been used as a robust model to study plasticity. With advances in pharmacological and genetic manipulations, our understanding of the mechanisms underlying critical periods has been growing extensively. This plasticity has been considered to permanently close at the end of the critical periods, and plasticity in adults is thought to be more restricted and to mainly involve changes in synaptic strength.<sup>13–16</sup>

This decade, however, new evidence has suggested that the adult brain is more plastic than previously expected. This is especially apparent through interventions that affect cognition and mood, such as learning, environmental enrichment, exercise, and chronic treatment with AD.<sup>17–19</sup>

### AD INDUCE JUVENILE-LIKE PLASTICITY (iPLASTICITY)

As discussed above, plasticity is a permissive state of neuronal networks that are affected by internal and environmental stimuli and ultimately display behavioral changes. Increasing evidence shows that AD can activate a plastic state in the adult brain that is comparable to that observed during developmental critical periods, and that this plastic state can be used to rewire the brain in an activity-dependent manner by stimuli such as training or rehabilitation. Our group has coined this phenomenon induced juvenile-like plasticity (iPlasticity; Fig. 1). Clinical studies have shown that combinations of AD treatment with psychotherapy or training are more effective than either treatment alone,<sup>20–23</sup> which is consistent with the iPlasticity principle. Pampallona *et al.* have shown in a clinical meta-analysis that patients suffering from depression respond better to AD treatment combined with psychotherapy than AD treatment alone.<sup>23</sup> The results of a clinical trial demonstrated that SSRI treatment combined with cognitive behavioral therapy leads to improved clinical response in SSRI-resistant depressed adolescents.<sup>22</sup> Branchi and coworkers recently showed that depressed patients



**Figure 1.** Concept of iPlasticity. Amy, amygdala; BDNF, brain-derived neurotrophic factor; ChABC, chondroitinase ABC; DG, dentate gyrus; GC, granule cell; HNK, hydroxynorketamine; HP, hippocampus; PFC, prefrontal cortex; PV/PNN, parvalbumin/ perineuronal nets; TrkB, tropomyosin kinase receptor B.

living under more favorable living conditions showed a better response to citalopram than patients living under unfavorable conditions.<sup>24</sup> In addition, Amin *et al.* showed higher efficacy of a combination of clomipramine (a tricyclic AD) and behavioral therapy in the treatment of obsessive–compulsive and phobic disorders.<sup>21</sup>

### PROOF-OF-CONCEPT EXPERIMENTS OF iPLASTICITY IN RODENT MODELS

#### Shift of ocular dominance by monocular deprivation together with chronic fluoxetine treatment

The visual cortex has become a popular model for studying brain iPlasticity as its measurements are robust, reliable, and conserved across species (including monkeys, cats, and rats).<sup>10,12,25</sup> Inputs from the left and right eye segregate into eye-specific ocular dominance columns in the visual cortex during critical periods. This plasticity declines with age.<sup>26</sup> For the segregation to be successful, it is crucial to maintain a balance between excitation and inhibition.<sup>11</sup> Even small alterations to inhibitory neurotransmission can

result in profound effects on visual cortex plasticity. For example, in transgenic mice lacking the 65-kDa isoform of the gamma-aminobutyric acid (GABA)-synthesizing enzyme GAD (GAD65), ocular dominance plasticity in response to monocular deprivation is deficient and can be rescued if GABAergic transmission is enhanced by the administration of benzodiazepines,<sup>27</sup> indicating that the critical period is dependent on inhibitory transmission. Conversely, enhancing intracortical inhibition with benzodiazepines<sup>28,29</sup> or promoting the maturation of GABA neurons via transgenic overexpression of brain-derived neurotrophic factor (BDNF)<sup>30</sup> is associated with accelerated onset of critical periods. This close relation between neuronal activity, BDNF release, and GABAergic transmission is also shown in the effects of dark rearing. If animals are raised without visual input, BDNF levels and GABAergic transmission are reduced in the visual cortex, which delays the peak of plasticity into adulthood. Infusion with diazepam, a positive allosteric modulator of the GABA<sub>A</sub> receptor,<sup>29</sup> or overexpression of BDNF,<sup>31</sup> however, abolishes the extension of the critical period. These results suggest that the GABAergic intracortical networks mature in correspondence with the critical period.

Later studies, however, have provided evidence for reactivation of critical-period-like plasticity in the adult visual cortex induced by drugs currently in clinical use and belonging to a number of pharmacological classes.<sup>25,32</sup> The first groundbreaking study showed that chronic treatment with the AD fluoxetine can reopen visual cortex plasticity in the adult rat brain.<sup>25</sup> The authors in this study combined chronic treatment with the AD fluoxetine (4 weeks) with monocular deprivation for a week in adult rats and used the following two classical assays: (i) the ocular dominance shift of visual cortical neurons in the adult brain; and (ii) the recovery of visual acuity in amblyopic adult rats whose ocular dominance had been shifted with monocular deprivation during the critical period. By recording visually evoked potentials in the binocular region of the primary visual cortex contralateral to the deprived eye, the responses of a population of neurons to patterned visual stimuli can be measured and used to evaluate visual acuity and binocularity alterations. Ocular dominance is then calculated by the contralateral-to-ipsilateral visually evoked potential ratio. While rodents naturally display contralateral eye dominance, the authors demonstrated that after chronic treatment with the AD fluoxetine, they could reinstate visual cortex plasticity in the adult rat, inducing a shift in ocular dominance towards the weaker, ipsilateral non-deprived eye. Moreover, this treatment promoted the recovery of visual functions in adult amblyopic rats. These effects were accompanied by a reduction in intracortical inhibition (as assessed by *in vivo* microdialysis) and increased BDNF protein levels (quantified by enzyme-linked immunosorbent assay). Finally, cortical diazepam administration prevented the effects induced by fluoxetine. These results indicate different roles of interneurons in the developing and mature visual cortex, or between the opening of the critical period and maintaining the state of the critical period.

Previously, Maffei *et al.*<sup>33</sup> reported that enzymatic removal of perineuronal nets (PNN), which are extracellular matrix structures mainly enwrapping the maturing synaptic circuitry of GABAergic parvalbumin-positive (PV<sup>+</sup>) inhibitory neurons, can reactivate critical period plasticity by decreasing inhibition<sup>33</sup> (discussed in the 'Cortical inhibition' section below), thereby promoting the generation of gamma oscillations.<sup>34</sup> Harauzov *et al.* pharmacologically reduced GABAergic action using GABA antagonists, picrotoxin, or 3-mercaptopropionic acid and

induced a shift in ocular dominance by monocular deprivation, which was inefficient in saline-treated animals.<sup>35</sup> The studies support the hypothesis by Takao Hensch, which posits that a reduction in intracortical inhibition promotes visual cortical plasticity in the adult brain, contrasting with a different role of GABAergic inhibition during and after the critical period. These findings are not only relevant for the clinical application of fluoxetine but also demonstrate the idea of iPlasticity and suggest new mechanisms of AD effects.<sup>36</sup>

### Fear erasure by fear extinction training with chronic fluoxetine treatment

Pavlovian fear conditioning<sup>37</sup> is another validated and popular paradigm in plasticity studies, especially in studying networks that are more complex. A variety of studies have shown that the fear and anxiety circuit is conserved across species and has been studied in both animal models and humans, and they can be modeled by the fear-conditioning paradigm in mice. Consistent throughout animal models and human studies, the fear and anxiety circuit involves the prefrontal cortex, amygdala, and hippocampus, which are each responsible for different aspects of fear.<sup>38–40</sup> The primary choices of treatment in such conditions are either extinction through exposure therapy<sup>41</sup> or pharmacotherapy, mostly using SSRI AD.<sup>42</sup> Exposure therapy extinguishes or suppresses fear responses by repeatedly exposing the subject to the fear-inducing stimulus under a safe environment; however, the effect of extinction is transient and a spontaneous recovery typically appears. Additionally, clinical experience has shown that a combination of AD treatment and psychotherapy is more effective than either treatment alone.<sup>23</sup> Our group has shown that chronic treatment with the AD fluoxetine can extinguish long-term fear memory only when it is combined with extinction training, while fluoxetine alone is ineffective and extinction training alone leads to spontaneous recovery.<sup>43</sup> In the study, we used the common cued and contextual fear conditioning protocol consisting of the fear conditioning/acquisition phase, extinction training in a chamber different from the one used in the conditioning/acquisition phase, spontaneous recovery (same chamber as extinction training), and fear renewal (the chamber used for conditioning) phases. Chronic fluoxetine treatment was started either 3 weeks before fear

conditioning or immediately after conditioning, and was continued throughout the whole experiment. While control water-treated mice recovered and renewed conditioned fear in context A and B, respectively, after extinction training fluoxetine-treated mice showed attenuated fear recovery and renewal. Aiming to identify possible underlying mechanisms, we found that fluoxetine treatment reduced the percentage of PNN-positive neurons expressing PV, but upregulated polysialylated neuronal cell-adhesion molecule (PSA-NCAM) and KCC2, which are increased during postnatal development. In addition, electrophysiological experiments showed that fluoxetine treatment increased synaptic plasticity in the lateral amygdala, as measured by increases in field excitatory postsynaptic potential responses and long-term potentiation (LTP) induction. Furthermore, BDNF-knockout mice and infection with a BDNF-expressing lentivirus in the basolateral amygdala demonstrated that an absence of or overexpression of BDNF blocked or enhanced the effect of fluoxetine treatment on fear erasure, respectively. Together, the study suggested that fear erasure induced by a combination of fluoxetine treatment and extinction training relies on a shift of PV-containing and PNN-containing neurons towards a juvenile or immature state in the basolateral amygdala and CA1 region of the hippocampus through the activation of the BDNF/tropomyosin kinase receptor B (TrkB) pathway, which opens a window of plasticity in the adult brain.

#### **Attenuation of aggression by resocialization together with chronic fluoxetine treatment**

Rat models of early social neglect were previously established by post-weaning social isolation.<sup>44,45</sup> This model can be used to investigate early adversity-induced aggression and explore novel possibilities for intervention.<sup>46</sup> The characteristic feature of social isolation is the increase in biting attacks that are preferentially aimed at vulnerable body parts of the opponent (head, throat, and belly) in a resident-intruder test.<sup>44,45</sup> Resocialization of isolated rodents in the adult phase has been proposed as a laboratory model for behavioral therapy,<sup>47</sup> but resocialization failed to decrease the social isolation-induced escalation of aggression, which confirms the assumption that this paradigm induces long-term changes in emotional processing.<sup>48,49</sup> We

hypothesized that there is a critical period for suppression of social aggression that is lost during early isolation, and that resocialization is not effective in adult animals after the closure of this critical period. However, resocialization as an adaptive process to environmental factors might be enhanced by reopening the critical period by chronic fluoxetine treatment in adulthood. In fact, a combination of resocialization therapy and chronic fluoxetine treatment in isolated rats largely reversed escalated aggression, while neither treatment alone exerted significant effects.<sup>50</sup> In resocialization-resistant early-isolation-induced aggressive rats, BDNF expression is reduced in the amygdala and medial prefrontal cortex (mPFC). Only combined treatment with fluoxetine and resocialization was able to recover BDNF expression via epigenetic regulation (DNA methylation) in the mPFC. In addition, experiments using TrkB inhibitors demonstrated that behavioral improvement after combined treatment was dependent on TrkB activity. Furthermore, cholera toxin subunit B, a retrograde tracer combined with FosB immunostaining, showed that the input from the ventral hippocampus (vHP) to the mPFC was specifically strengthened by combined treatment. These results suggest that BDNF expression in the mPFC and vHP–mPFC pathway is an important mediator of the reduced aggression induced by resocialization combined with chronic fluoxetine treatment. Together, synergistic interactions between psychosocial therapy and temporarily increased plasticity by SSRI specifically ameliorate escalated aggression induced by socially adverse early experiences.

#### **Increased behavioral flexibility by spatial reversal learning together with fluoxetine treatment**

The effects of fluoxetine on spatial learning have been assessed in several studies. It has been shown that both one-time (acute) and prolonged (chronic) fluoxetine treatment caused a significant improvement in reference spatial memory in rats.<sup>51</sup> However, some studies show negative effects or no effects of fluoxetine treatment on spatial learning skills.<sup>52–55</sup> Thus, it is still unclear whether chronic fluoxetine treatment can improve spatial learning. Considering that typically used spatial learning tasks are designed to identify spatial learning deficits, we hypothesized that chronic fluoxetine treatment specifically affects more complex learning tasks, such as

reversal learning and behavioral flexibility.<sup>56</sup> In this case, an individual learned response to a single decision among multiple options was elicited during an initial learning or acquisition phase. After obtaining the desired level of performance, the task pattern was reversed or altered: A previously incorrect option was now correct and the previously correct option incorrect. To test this more complex spatial learning task, we used an IntelliCage (NewBehavior AG, Zurich, Switzerland), in which transponder-implanted female mice were group-housed.<sup>57,58</sup> In the IntelliCage protocol, during the acquisition phase, water-deprived mice are granted access to water in a certain corner chamber. Then, the next corner becomes available for drinking in a clockwise manner during the acquisition phase. If a mouse enters the correct corner, the door opens upon nose poke and water becomes available. Thus, animals have to patrol the corners to find the correct chamber that offers water access. After the mice have learnt the clockwise pattern for water access and display low-error trials, the direction switches to the opposite direction, counterclockwise. Our studies indicate that chronic treatment with fluoxetine does not affect acquisition of spatial memory (clockwise pattern) but does improve 'reversal' learning (counterclockwise pattern) (Umemori and Castrén, manuscript in preparation). These results indicate that chronic fluoxetine enhances behavioral flexibility of the spatial learning process, which may reflect the same underlying phenomenon of iPlasticity.

### Effects of AD under adverse environmental stimuli

If AD treatment acts permissively to potentiate responses to environmental stimuli, then AD treatment under adverse stimuli might worsen the state of a patient. Recently, Branchi and coworkers provided experimental evidence suggesting that this, indeed, may be the case.<sup>59</sup> They exposed mice to stress and then either switched the mice to an enriched environment (EE) or continued stress while treating them with an SSRI or a vehicle. While SSRI treatment counteracted an anhedonia-like state in mice kept in an EE, fluoxetine treatment of stressed mice significantly elevated depression-like behavior when compared to vehicle treatment.<sup>59</sup> These data emphasize that plasticity does not have a direction, but rather that favorable stimuli promote adaptability while unfavorable stimuli are maladaptive.

### AD OTHER THAN SSRI AND FACTORS MEDIATING iPLASTICITY

All AD drugs increase TrkB signaling in the brain<sup>60</sup> (see below), and BDNF signaling through TrkB has been shown to be necessary and sufficient for fluoxetine-induced iPlasticity, indicating that most if not all AD might induce plasticity. In agreement with this notion, preliminary findings show that tiareptine, an AD not acting through serotonin reuptake inhibition<sup>61</sup> reactivates ocular dominance plasticity in the adult rat visual cortex (Maya-Vetencourt, Cattaneo, and Castrén, unpublished).

Ketamine, an anesthetic compound and a non-competitive NMDA receptor antagonist,<sup>62</sup> has been shown to induce a fast and long-lasting AD effect in treatment-resistant patients with bipolar disorder and depression.<sup>63–65</sup> Moreover, administration of ketamine also decreases suicidal ideation in treatment-resistant depressed patients.<sup>64,66,67</sup> One feature of ketamine is its fast-acting production of AD effects, which can already be observed within 4 h after a single administration,<sup>68</sup> whereas other conventional AD take several weeks to produce AD effects.<sup>69</sup> In the fear-conditioning paradigm, a combination of acute (single) administration of ketamine and fear extinction training promotes the erasure of conditioned fear<sup>70</sup> similarly to that observed for chronic treatment with fluoxetine.<sup>43</sup> Despite its fast and long-lasting AD effects, the psychotomimetic effects of the compound are concerning. A possible way to overcome this problem may be to instead use specific intermediate compounds produced during the metabolism of ketamine, such as norketamine and hydroxynorketamine (HNK).<sup>71</sup> In rodent models, HNK appears to provide the same AD-like effects as ketamine, but without its NMDA-binding capacity. Interestingly, this promotes the expression of BDNF through activation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated currents.<sup>72</sup> It will be important to use appropriate experimental models to test whether ketamine and HNK might induce plasticity in the same manner as fluoxetine.

Electroconvulsive stimulation (ECS) is a non-drug-based alternative approach in the treatment of psychiatric diseases.<sup>73</sup> Previous studies have shown an involvement of neural plasticity in the therapeutic effects of ECS in human patients.<sup>74–76</sup> In rodent models, it has been shown that ECS increases the expression of BDNF and its receptor TrkB<sup>73,77,78</sup> in

cortical and limbic areas and increases the duration of their expression, especially in the granular layer of the dentate gyrus.<sup>78</sup> In addition, it has been observed that ECS increases neurogenesis<sup>79,80</sup> and synaptogenesis.<sup>81–83</sup>

Morishita *et al.* showed that Lynx, a bungarotoxin-like endogenous pro-toxin that binds to nicotinic acetylcholine receptors and decreases their sensitivity to acetylcholine, is expressed in the visual cortex only after the closure of the critical period, and that adult Lynx-deficient mice show ocular dominance plasticity, indicating a role for Lynx in restricting visual cortex plasticity.<sup>84</sup> The same paper also demonstrated that an inhibitor of acetylcholinesterase, physostigmine, restored the visual cortex of monocularly deprived adult mice,<sup>84</sup> indicating that the ability to induce iPlasticity is not restricted to AD drugs.

Finally, Maffei and coworkers have demonstrated that housing rats in an EE, which provides high motor-sensory stimulation, produces similar iPlasticity effects to fluoxetine in the adult visual cortex and restores visual acuity in a rat model of amblyopia.<sup>18,85</sup> In addition, it has been shown that an EE can improve other plasticity-related features of the brain, such as memory and learning<sup>86</sup> and neurogenesis in the hippocampus.<sup>87</sup> These results provide a promising view regarding a non-pharmacological way to reactivate plasticity in the adult brain.

In summary, iPlasticity is induced by several drugs acting on different neurotransmitter systems. Additional experiments are needed to test whether iPlasticity is a common phenomenon shared by all AD drugs<sup>88</sup> such as monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors<sup>1</sup> and inhibitors of histone deacetylase.<sup>89</sup>

## iPLASTICITY, NEUROGENESIS, AND DEMATURATION

In addition to iPlasticity, AD drug treatment has been shown to promote adult neurogenesis and dematuration in the hippocampal dentate gyrus. Below, we will introduce these plastic phenomena and discuss their potential relationship to iPlasticity.

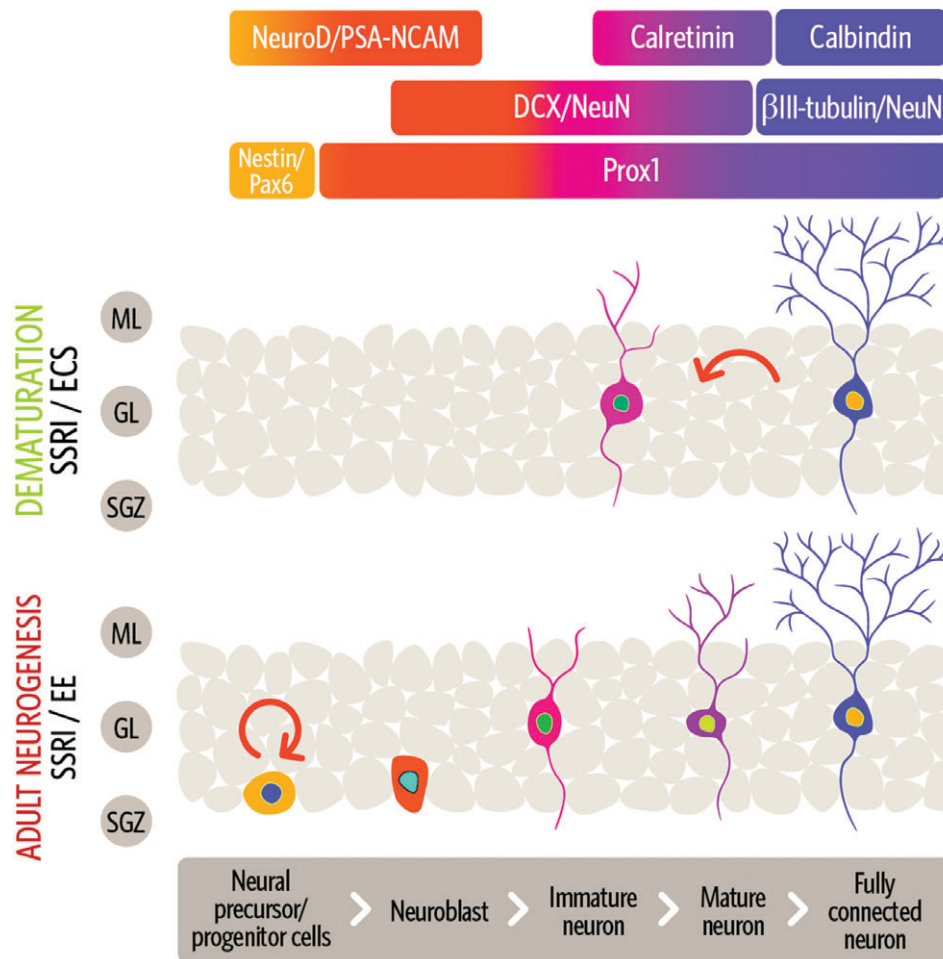
### Adult neurogenesis

Neurons are known to newly arise in both the dentate gyrus and the subventricular zone of adults, and comprise up to 10% of the entire granule cell

(GC) population in the dentate gyrus (DG).<sup>90</sup> Adult hippocampal neurogenesis is associated with pattern separation, which is the ability to differentiate overlapping contextual representations.<sup>91</sup> Chronic SSRI treatment has been shown to stimulate all stages of adult neurogenesis, including the proliferation, differentiation, and survival of adult-born granule cells (abGC)<sup>19,92–101</sup> (Fig. 2<sup>102,103</sup>). Fluoxetine does not affect the division of stem-like cells but increases symmetric divisions of early progenitor/precursor cells.<sup>104</sup> Chronic SSRI treatment prompts young abGC to rapidly mature with heightened synaptic plasticity and to integrate into the DG.<sup>92,93,105,106</sup> Young abGC are highly active and have elevated plasticity for a few weeks,<sup>106–108</sup> and eventually become functionally similar to the mature, developmentally born GC 8 weeks after neurogenesis.<sup>106,108</sup> In addition, chronic fluoxetine treatment has been shown to affect the dendritic arborization of immature neurons that express doublecortin and to enhance LTP in a neurogenesis-dependent manner.<sup>109</sup>

The 5-HT<sub>1A</sub> receptors on mature DG GC are critical for the AD response, as absence of the serotonin 1A receptor (5HT<sub>1A</sub>R, a receptor required for the SSRI response) specifically abolishes from DG GC the effects of fluoxetine on behavior and on the hypothalamic–pituitary–adrenal axis.<sup>110</sup> These observations suggest that the involvement of the serotonergic system in neurogenesis in the DG is most likely due to SSRI action itself.

Chronic corticosterone exposure (mimicking the effect of chronic stress)<sup>100,111,112</sup> and an unpredictable chronic mild stress prompt a depressive-like state and have decreased numbers of newly born cells in the DG of the adult hippocampus, which are completely recovered from after 2–3 weeks of fluoxetine treatment.<sup>96,100</sup> In addition, it has been reported that there are neurogenesis-dependent and neurogenesis-independent ameliorating effects of fluoxetine on anxiety, as well as on depression-like behaviors caused by chronic corticosterone exposure or an unpredictable chronic mild stress paradigm.<sup>96,113</sup> However, periodic food restriction induces iPlasticity in the adult visual cortex and this effect was shown to be mimicked by a periodic increase in corticosteroid release,<sup>114</sup> demonstrating that short-lasting and chronic treatment with corticoids have opposite effects on plasticity. In addition, studies using focal radiation or genetic manipulation demonstrated that ablation or impairment of the neurogenic niche attenuate AD effects on



**Figure 2.** Model of dematuration and adult neurogenesis in the dentate gyrus (DG) by chronic selective serotonin reuptake inhibitors (SSRI) treatment. The upper section indicates expression markers of each neuron state.<sup>102,103</sup> In the middle section, a mature neuron change to an immature state by dematuration after chronic SSRI treatment or electroconvulsive stimulation (ECS). In the bottom section, chronic SSRI treatment or environmental enrichment (EE) promote the proliferation of progenitor granule cells in the DG and rapid maturation of young adult-born cells and integration into the DG. Finally, the matured adult-born cell is functionally similar to other mature cells. The picture is combined and modified from Zhang and Jiao<sup>102</sup> and Segi-Nishida.<sup>103</sup> DCX, doublecortin; ML, molecular layer; GL, granule layer; PSA-NCAM, polysialic acid neural cell adhesion molecule; SGZ, subgranular zone. Copyright © 2017 Segi-Nishida. Copyright © 2015 Juan Zhang and Jianwei Jiao.

depression-related behaviors, indicating that hippocampal neurogenesis is required for some AD effects.<sup>93,95,96,115</sup> An EE has also been reported to increase adult neurogenesis in the DG of mice housed in an EE<sup>87</sup> and in young and aged rats when housed in an EE.<sup>116,117</sup> In addition, ketamine has been shown to promote synaptogenesis in the rodent PFC<sup>118</sup> and neurogenesis in the hippocampus.<sup>119</sup>

These observations indicate that a range of AD treatments exert effects on adult neurogenesis and ameliorate depression-like behaviors. However, it

is unknown whether neurogenesis is involved in iPlasticity, especially in the visual cortex and brain regions related to fear erasure, social behavior, and reversal spatial learning. Adult neurogenesis after chronic SSRI treatment has also been reported to occur in the amygdala,<sup>120</sup> PFC,<sup>121</sup> hypothalamus, and habenula,<sup>122</sup> but not in the visual cortex. Thus, the neurogenesis and their maturation promoted by fluoxetine might contribute to the formation of new networks, although further studies are needed.



### Dematuration of dentate gyrus by chronic fluoxetine treatment

As discussed above, chronic fluoxetine treatment is generally known to increase adult neurogenesis in the hippocampal DG, but some studies have reported that the behavioral effects of AD do not always coincide with increased neurogenesis.<sup>98,99,123–125</sup> Thus, not only neurogenesis but also functional modifications of existing neurons would be necessary for AD action.<sup>126</sup> Kobayashi *et al.* found that chronic fluoxetine treatment reverts the molecular and functional properties of GC to an immature state in the DG of the hippocampus<sup>126,127</sup> (Fig. 2), which is a substrate for both cognition and mood regulation.<sup>128</sup> This 'dematuration' is characterized by downregulated expression of mature GC markers, such as calbindin, desmoplakin, tryptophan-2,3-dioxygenase, and interleukin-1 receptor type I, as well as by upregulated immature-like GC markers, including calretinin.<sup>121,126,129</sup> The dematured GC induced by chronic fluoxetine treatment exhibited electrophysiological features of actual immature or developing GC, such as the following: (i) higher excitability upon somatic current injections and active membrane properties resembling those in young GC; (ii) enhanced long-term depression at the perforant path synapse, but reduced LTP; and (iii) mossy fiber synaptic facilitation reduced to the juvenile level. Mossy fiber-CA3 pyramidal cell synapses formed by immature-like GC exhibit smaller frequency facilitation<sup>126</sup> than 3-week-old young mice.<sup>130</sup> Chronic fluoxetine treatment had no significant effects either on the expression level of calbindin or on frequency facilitation in 5-HT4-receptor-deficient mice, suggesting that the 5-HT4 receptor plays a critical role in the dematuration of GC<sup>126</sup> and in adult neurogenesis in the DG, and that these phenomena are closely associated.<sup>129</sup> Thus, the serotonergic system seems to be important probably due to SSRI action on the maturity of GC in the DG. Recently, it has been shown that a brief neuronal activation by ECS induces dematuration of the mature GC. Namely, in all GC of the DG, there was observed reduced expression of the mature GC markers and physiological properties of immature GC (such as elevated somatic intrinsic excitability and smaller frequency facilitation at the dentate-to-CA3 synapse) were observed.<sup>131</sup> In addition, while a single ECS lasts a short time, repeated ECS causes long-lasting (greater than 2 weeks) dematuration in an NMDA-receptor-dependent but not serotonergic-dependent manner.<sup>131</sup> These results suggest that altered functioning

of the mature dentate GC is commonly involved in the cellular mechanisms of physical and chemical AD treatments.<sup>132</sup> A dematuration-like response to fluoxetine also occurred in interneurons in other brain regions, such as the PFC,<sup>121,133</sup> amygdala,<sup>43</sup> and the visual cortex (Umemori, Winkel, and Castrén, unpublished observations). In these brain areas, chronic fluoxetine treatment caused a decrease in the number of PV-positive or PV/PNN double-positive interneurons,<sup>43,134</sup> which are negatively associated with plastic or immature states of PV interneurons, suggesting that dematuration of PV interneurons in these areas is important for iPlasticity (discussed in the 'Cortical inhibition' section). These findings strongly support the idea of iPlasticity, namely that AD produce an immature or plastic state and a heightened adaptability to neuronal activity in response to internal or external stimuli (or both)<sup>19,32</sup> during the maturation process. An immature DG is also observed in gene-modified and drug-induced mice showing psychiatric-disease-like phenotypes.<sup>127,135–138</sup>

In the human brain, dematuration of GC in the DG has been observed in postmortem brains of bipolar and schizophrenic patients, as well as in alcoholics.<sup>139–141</sup> It has been suggested that dematuration in the DG might be an endophenotype of certain psychiatric diseases.<sup>127,138</sup> In addition, it has been shown that destabilized cage activity was accompanied by increased anxiety-related behaviors after high doses and long-term treatment with high-dose fluoxetine.<sup>142</sup> Moreover, maladaptive effects were observed after the combination of chronic fluoxetine treatment and stress as described above.<sup>59</sup> Given the concept of iPlasticity, psychiatric-disease-like phenotypes or behavioral consequences might be produced by a combination of dematuration with maladaptive, unstable, or uncontrolled environmental factors (also discussed in the section above, 'Effects of AD under adverse environmental stimuli').

Taken together, iPlasticity, neurogenesis, and dematuration are all induced after chronic treatment with AD and increase plasticity in neuronal networks in several regions of the brain, which promotes the adaptation to environmental signals. Although these three plastic phenomena are induced by the same treatment and share at least some properties, it is premature to conclude that they are all reflections of a single underlying mechanism. It will be important in future studies to directly compare these phenomena to each other and investigate the biological mechanisms underlying them to reveal

whether they are produced by the same mechanism and, if so, what this mechanism might be.

### MECHANISTIC INSIGHTS INTO iPLASTICITY: NEURONAL AND SYNAPTIC CHANGES AFTER CHRONIC FLUOXETINE TREATMENT

The behavioral consequences of iPlasticity have been described in the context of several brain networks, but the actual biological mechanisms underlying iPlasticity are not fully understood. In this last section, we will discuss the observed biological phenomena and possible underlying mechanism of iPlasticity at the level of neuronal circuits, cells, and molecules.

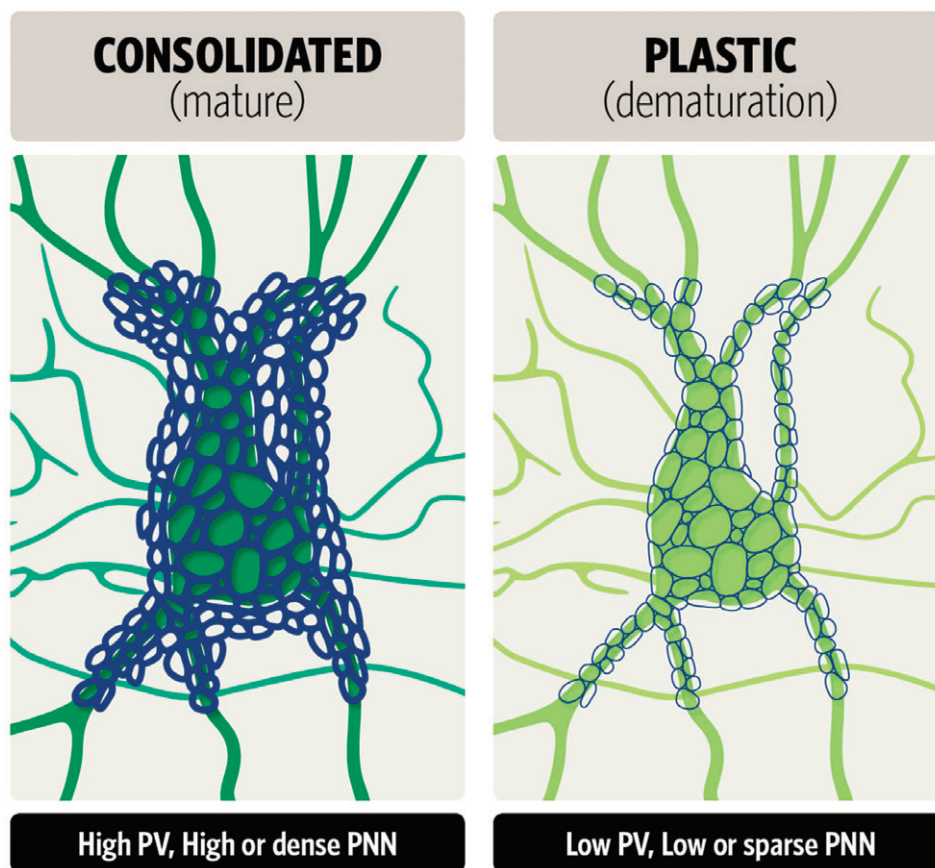
#### Cortical inhibition

The establishment of an excitation and inhibition balance is crucial for a successful critical period and disturbances in this balance can lead to maladapted networks across different brain regions, including the visual and insular cortex.<sup>27,143,144</sup> Critical orchestrators of inhibitory network activity are PV<sup>+</sup> interneurons, whose activity is tightly regulated.<sup>36</sup> PV interneurons are known for fast-spiking capability and for projection onto the axosomatic region of principal neurons.<sup>145</sup> Hence, PV interneurons are capable of strongly regulating principal neuron output (feedforward inhibition) by shaping oscillatory activity.<sup>146,147</sup> Previous research has shown that the maturation of the PV<sup>+</sup> interneurons coincides with the production of PNN, whose functions are still largely unknown but should involve the regulation of synaptic plasticity and neuroprotection.<sup>33,143,148–150</sup> Both maturation of PV<sup>+</sup> interneurons and PNN production promote the closure of critical periods and restrict plasticity of the adult brain, hence being referred to as ‘molecular brakes’ whose inactivation and removal, respectively, is thought to reset the excitation–inhibition balance.<sup>11,143</sup> Recent research has focused on PV and PNN and the underlying mechanisms of critical periods and adult plasticity (Fig. 3<sup>151</sup>). Thus far, accumulated evidence suggests that resetting the PV network to an immature state and removing PNN from the network can induce critical-period-like plasticity or iPlasticity in distinct brain regions.<sup>33,34,134</sup> For example, in the visual cortex, PNN removal results in a decrease in PV activity and subsequent promotion of gamma oscillations

mediated through pyramidal cells, finally resulting in ocular dominance plasticity.<sup>34</sup> Disruption of PNN in the amygdala has been shown to enhance the erasure of drug addiction with extinction training.<sup>152</sup> Removal of PNN in the hippocampus resulted in disrupted contextual and trace fear memory and their removal from the medial prefrontal cortex impaired long-term trace- and conditioned-stimulus-elicited fear memory in the trace fear conditioning task.<sup>153</sup>

Interesting work has been published by Donato *et al.*, who proposed a new concept of PV network states that correlate with brain plasticity and consolidation.<sup>154</sup> While fear conditioning that involves memory consolidation results in a network state mainly composed of PV cells expressing high levels of PV, an EE, an established way to induce plasticity in the brain, promotes a network state mainly composed of PV cells expressing low levels of PV<sup>154</sup> (Fig. 3). A high-PV/consolidated network is attained by enhanced excitation from local pyramidal cells or external input as memories are consolidated. In contrast, a low-PV network is maintained by increased inhibitory input from vasoactive intestinal peptide neurons, which are readily engaged by neuromodulators under EE conditions. Therefore, low or high PV states are paralleled by increased inhibition or excitation, respectively, of PV cells themselves.<sup>154</sup>

Cellular regulators of this change in PV expression likely involve molecules maintaining their mature state through PNN, which interact and release factors such as neurotrophins (BDNF and GDNF) and homeoproteins (Otx2).<sup>155</sup> Recently, the microstructure of PNN has been shown to be of a heterogeneous nature with uniform (nonpolar) and node-enriched (polar) patterns of chondroitin sulfate distribution within a single mesh.<sup>151</sup> This pattern might be related to the molecular composition of the PNN of the neuronal cell surface and might be functionally connected to the regulation of synaptic signaling processes, including synaptic plasticity.<sup>151</sup> While the function of PNN is still incompletely understood, evidence points towards a role in neuronal protection from oxidative stress.<sup>156</sup> Considering the fast-spiking properties of PV interneurons, metabolic demand is high and mitochondrial density is increased, which specifically renders PV cells particularly sensitive to oxidative stress.<sup>156</sup> Therefore, to ensure the control of feedforward inhibition and rhythmic neuronal synchrony, protection through PNN might maintain the fast-spiking activity of PV cells in adulthood and limit their intrinsic vulnerability.



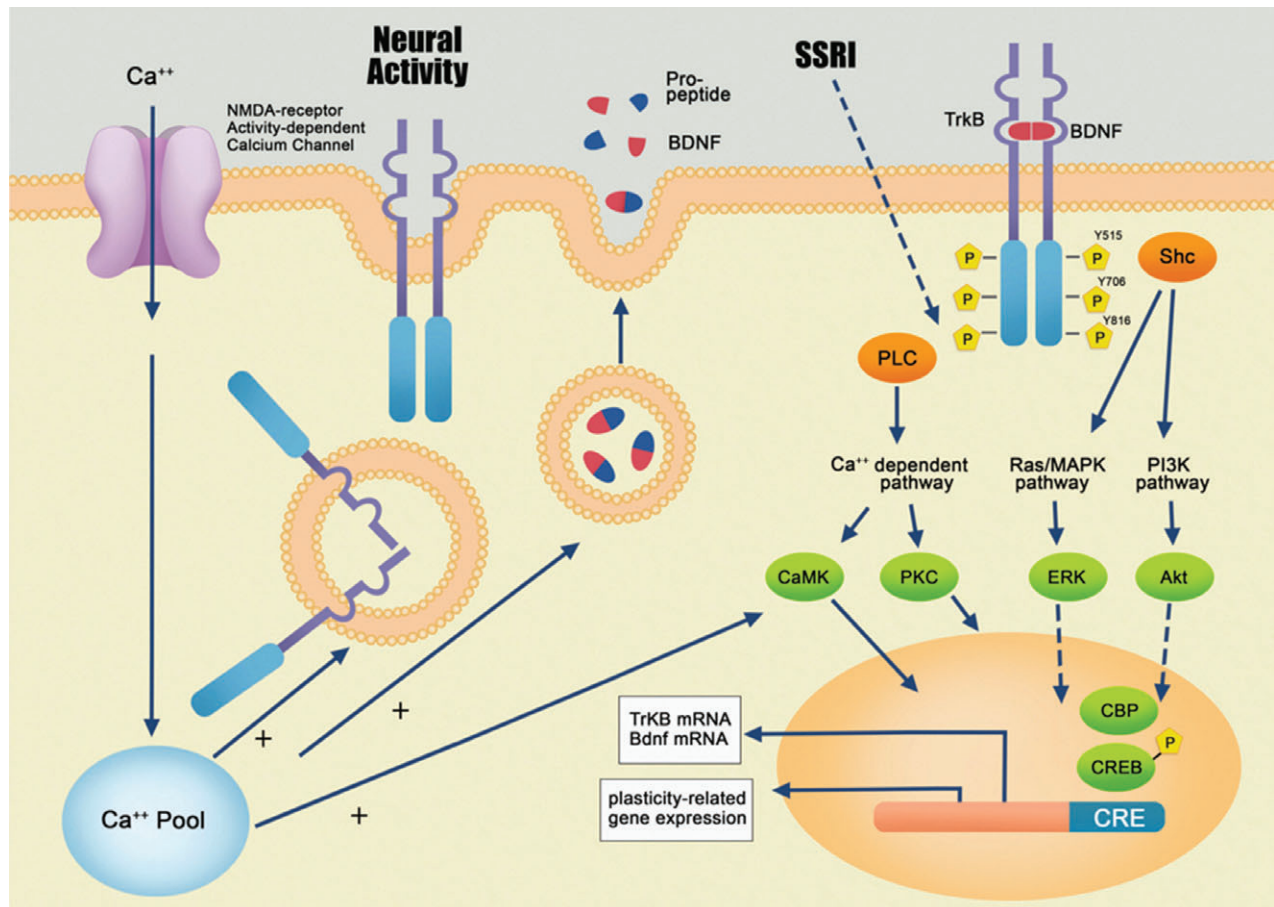
**Figure 3.** Dematuration of parvalbumin (PV)/perineuronal nets (PNN) interneurons. PNN surround synaptic boutons on neuronal soma and proximal dendrites and consist of chondroitin sulfate proteoglycans (CSPG) assembled on the hyaluronan scaffold of PV interneurons. The development of PNN is controlled by synaptic activity and their formation terminates the critical period of synaptic plasticity, consolidating the neuronal network. CSPG has a unique geometric structure of polygonal mesh shapes with the number of vertices varying from three to nine. Sizes of the mesh vary.<sup>151</sup> A reduction in PV (green) and PNN (blue) expression is associated with a plastic and immature network observed in iPlasticity by chronic SSRI treatment.

### The BDNF/TrkB pathway

As described above, previous studies have indicated that the activation of BDNF signaling through TrkB is a key molecular pathway in iPlasticity in the adult brain<sup>19,25,43,88,157,158</sup> (Fig. 4<sup>159–183</sup>). One possible molecular mechanism of iPlasticity is a synergy of SSRI-induced and activity-dependent activation of the BDNF/TrkB pathway (Fig. 4).

Neurotrophins, including nerve growth factor, BDNF, neurotrophin-3, and neurotrophin-4, play a key role in supporting neurons and neuronal survival during development.<sup>184,185</sup> These family members bind to two types of receptors, namely the Trk-family members (nerve growth factor to TrkA, BDNF and neurotrophin-4 to TrkB, and neurotrophin-3 to TrkC) and a common low-affinity

neurotrophin receptor (p75<sup>NTR</sup>).<sup>159,186–192</sup> Generally, AD treatment positively regulates BDNF levels both in animal models and humans. In rodents, BDNF mRNA and protein expression are increased in the hippocampus, cortex, and amygdala after long-term AD therapies, such as electroconvulsive therapy or commonly used AD drugs.<sup>25,43,78,193–197</sup> Phosphorylation of TrkB and downstream signaling is also increased by AD. Specifically, AD act by phosphorylating the phospholipase C  $\gamma$ -binding site (Y816) independently of BDNF.<sup>198</sup> Interestingly, plasticity represented as LTP and learning seems to be mediated by signaling through the TrkB- phospholipase C  $\gamma$  pathway, as deletion of the Y816 residue disrupts LTP and results in deficient learning.<sup>175,199</sup>



**Figure 4.** Brain-derived neurotrophic factor (BDNF)/tropomyosin kinase receptor B (TrkB) pathway. BDNF is synthesized as a precursor protein (pro-BDNF) that is proteolytically processed into mature BDNF by intracellular proteases and/or extracellular proteases.<sup>159–161</sup> Synthesis, release, and action of BDNF are regulated by neuronal activity. BDNF mRNA increases after neuron depolarization<sup>162</sup> and BDNF levels are mediated by calcium-calmodulin-dependent protein kinases (CaMK).<sup>163</sup> TrkB is a tyrosine kinase membrane protein highly expressed in both presynaptic axons and postsynaptic densities.<sup>164–166</sup> TrkB activation promotes spine formation, neuronal survival, and long-term potentiation.<sup>167–171</sup> TrkB consists of the following three main domains: an extracellular domain where the ligand (usually BDNF) binds, a transmembrane domain, and a cytosolic domain, which contains the catalytic sites that are responsible for a transphosphorylation reaction.<sup>172</sup> Binding of BDNF to the recognition site increases its affinity for the TrkB monomer, stabilizing to form a TrkB dimer.<sup>173</sup> This dimerization activates the catalytic sites, and each TrkB phosphorylates the other on specific tyrosine residues (Y706).<sup>174</sup> Secondary messenger molecules (such as sarc homology containing [Shc] and phospholipase C gamma [PLCγ]) bind to the phospho-tyrosines in positions 515 (Y515) and 816 (Y816) and activate the Ras/Erk and PIP3/Ca<sup>++</sup> dependent pathways, respectively. The latter pathway leads to activation of protein kinase C (PKC) and eventually to the phosphorylation of cyclic AMP response element binding protein (CREB).<sup>175</sup> CREB in turn induces gene expression involved in neuroplasticity.<sup>176–182</sup> Neuronal activation and high-frequency stimulation facilitate the localization of TrkB from intracellular pools to the cell surface, requiring a Ca<sup>++</sup> influx.<sup>183</sup> Akt, cellular homolog of murine thymoma virus akt8 oncogene; CBP, CREB-binding protein; ERK, extracellular signal-regulated kinase; P, phosphorylation.

Hence, BDNF signaling through TrkB is necessary and sufficient for AD behavioral responses<sup>200</sup> and for effects in iPlasticity induced by fluoxetine treatment.<sup>43</sup> Clear examples of the BDNF–TrkB pathway implication for AD effects have been reported; BDNF

knockout mice do not respond to AD treatment,<sup>201–205</sup> whereas BDNF infusion into the DG of the rat hippocampus produces an AD-like effect in learned helplessness in forced-swim-test paradigms.<sup>206</sup> Further, the overexpression of a dominant-

negative TrkB leads to a loss of AD efficacy,<sup>201</sup> whereas TrkB overexpression and increasing TrkB signaling results in AD-like behavioral effects.<sup>207</sup> In addition to TrkB and BDNF, other downstream molecules of the BDNF/TrkB pathway are also regulated by AD. For example, AD treatment upregulates the expression of CREB<sup>2,208</sup> and CREB overexpression in the rat hippocampus induces an AD-like behavior.<sup>209</sup> Evidence for increased BDNF in human patients after chronic AD treatment has also been reported; post-mortem tissues had an increased level of BDNF in the hippocampi of depressed patients receiving long-term AD therapy.<sup>210</sup> Besides SSRI, ketamine at low doses seems to increase the expression of BDNF.<sup>210</sup> Ketamine does not exhibit an AD response in an inducible BDNF knockout or in conditional TrkB knockout mice.<sup>211</sup> Also, mice with the Met allele of the BDNF V66M mutation, in which the cleavage site in pro-BDNF is mutated (Fig. 4), are resistant to ketamine.<sup>212</sup> Finally, an EE has been associated with increased levels of BDNF in the rat cortex and hippocampus.<sup>18,213</sup> In addition, heterozygous BDNF knockout mice (BDNF+/-) have impaired response in exploratory behavior and impaired adult neurogenesis induced by an EE.<sup>214,215</sup> These results suggest that ketamine and EE affect BDNF expression similarly to SSRI.

The BDNF/TrkB pathway is also known to be involved in adult hippocampal neurogenesis stimulated by both chronic AD treatment and voluntary exercise.<sup>95,216</sup> AD specifically act through the BDNF/TrkB pathway, enhance neuronal turnover and promote long-term survival of newborn neurons.<sup>95,217</sup> In addition, BDNF can promote differentiation and maturation of newborn cells by enhancing GABA release and is thought to at least partially mechanistically act through TrkB localized in PV-expressing GABAergic interneurons.<sup>218</sup>

Synthesis, release, and action of BDNF are regulated by neuronal activity, experience, and environmental stimulation (Fig. 4). At the cellular level, BDNF mRNA increases after depolarization of hippocampal culture cells via non-NMDA glutamate receptors, mainly by AMPA-receptor pathways.<sup>162</sup> In addition, changes in BDNF levels are mediated by calcium-calmodulin-dependent protein kinases.<sup>163</sup> Recent studies have demonstrated that BDNF expression displays an all-or-nothing type of response that only takes place when neuronal activity reaches a certain threshold.<sup>219</sup> *In vivo*, an activity-dependent change in BDNF levels is also observed after

environmental stimulation; limbic seizures increase BDNF mRNA expression in the rat forebrain<sup>220</sup> and BDNF synthesis in the visual cortex is regulated by visual stimulation. While darkness decreases mRNA BDNF levels, subsequent light exposure rapidly restores normal mRNA BDNF levels.<sup>221</sup> Localization of TrkB to the cell membrane is also regulated in a neuronal activity-dependent manner. TrkB is rapidly recruited to the plasma membrane by translocation from intracellular stores after neuronal activation accompanied by depolarization and subsequent increase of cAMP levels.<sup>222</sup> High-frequency electric stimulation also facilitates the movement of TrkB from intracellular pools to the cell surface, which requires a Ca<sup>2+</sup> influx.<sup>183</sup> These results clearly show the activity-dependent regulation of the BDNF/TrkB pathway.

Taken together, the BDNF/TrkB pathway is involved in all processes of synaptic plasticity, including neurogenesis, neuronal differentiation, synaptic strength, and gene regulation of synaptic formation, and is activated by both chronic SSRI treatment and neuronal activity. Thus, this pathway is considered a key factor of iPlasticity. However, further research is needed to understand at the molecular level the synergic relationship between increased synaptic plasticity and training/behavioral guidance via the SSRI-induced and activity-dependent BDNF/TrkB pathway.

## CONCLUSIONS AND FUTURE DIRECTIONS

The concept of iPlasticity is a state in the adult brain that resembles plasticity during critical or juvenile periods in postnatal development. iPlasticity permits rewiring of neuronal networks that adjust to internal or external stimuli, such as training or rehabilitation in an activity-dependent manner. The concept has thus far been demonstrated in rodent brains, such as in the visual cortex, amygdala, and prefrontal cortex, and is mediated by activation of the BDNF/TrkB pathway. However, its detailed mechanisms remain unknown. Further molecular and network analyses will be needed to provide deeper and mechanical insight into the processes of iPlasticity and open up possibilities for treatment of neuropsychiatric disorders, including amblyopia, post-traumatic stress disorder, and social illness.

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## DISCLOSURE STATEMENT

The authors declare no competing financial interests.

## AUTHOR CONTRIBUTIONS

J.U. and E.C. conceived of and designed the review. J.U., F.W., G.D., M.L., and E.C. wrote the draft. J.U. and M.L. drew or made drafts of the figures.

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