REVIEW ARTICLE

Changes in neuroplasticity following early-life social adversities: the possible role of brain-derived neurotrophic factor

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Social adversities experienced in childhood can have a profound impact on the developing brain, leading to the emergence of psychopathologies in adulthood. Despite the burden this places on both the individual and society, the neurobiological aspects mediating this transition remain unclear. Recent advances in preclinical and clinical research have begun examining neuroplasticity—the nervous system's ability to form adaptive changes in response to new experience—in the context of early-life vulnerability to social adversities and plasticity-related alterations following such traumatic events. A key mediator of plasticity-related molecular processes is the brain-derived neurotrophic factor (BDNF), which has also been implicated in various psychiatric disorders related to childhood social adversities. Preclinical and clinical data suggest early-life social adversities (ELSA) might be associated with accelerated maturation of social network circuitry, a possible ontogenic adaptation to the adverse environment. Neural plasticity decreases by adulthood, lessening the efficacy of treatment in ELSA-related psychiatric disorders. However, literature data suggest that by increasing BDNF/TrkB signalling through antidepressant treatment a juvenile-like plasticity state can be induced, which allows for reorganization of the social circuitry when guided by psychotherapy and surrounded by a safe and positive environment.

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INTRODUCTION

Child maltreatment, encompassing sexual, physical, or emotional abuse and physical or emotional neglect is a widespread issue affecting millions of children worldwide each year, with global prevalence rates per each subtype ranging from 12 to 36% according to self-reports.¹ Maltreatment in early life can have a devastating impact on development and increase the risk for psychopathological disorders later in life (reviewed in refs.^{2–6}). It is strongly correlated with lower socioeconomic status⁷ and lower quality of later life⁸; thus, its consequences place a serious economical burden on society.^{9,10} Child maltreatment encompasses any act or series of acts of commission or omission by a parent or other caregiver that result in harm, potential for harm, or threat of harm to a child (generally interpreted as under 18 years of age), even if harm was not intended.¹¹ It is usually divided into four types: physical abuse, sexual abuse, psychological or emotional abuse and neglect.¹¹ Among these subtypes neglect has often received less attention, even though it is one of the most common forms of maltreatment and has been suggested to be as damaging as abuse.^{11–13} In the current review, all forms of child maltreatment will collectively be referred to as early-life social adversities (ELSA).

Though studies consistently outline a link between ELSA and psychopathological disorders in adulthood, little is known about the neurobiological mechanisms behind this phenomenon. Understanding how ELSA influence brain development is crucial in order to devise effective prevention or treatment measures.

Following birth, in mammalian species the nervous system advances through critical or sensitive periods: temporary time windows during which selective brain networks display heightened plasticity, undergoing dynamic changes in response to environmental influences. These changes are gradually hardwired into the network and cannot be easily or fundamentally altered once the critical period has closed.^{14,15} Brain regions regulating social behaviour go through major reorganization in childhood and adolescence,^{16–19} and aversive social experiences could alter neuronal maturation, leading to subsequent psychopathologies. Human neuroimaging studies have also shown altered volumes in brain areas regulating social behaviour in individuals who have experienced ELSA.^{20,21} Still, morphological and functional differences seen in neuroimaging studies allow for conclusions on a larger scale only, whereas when considering treatment methods, the underlying molecular processes are of great importance.

Recently, clinical and preclinical research have begun focusing on the brain-derived neurotrophic factor (BDNF) in relation to ELSA. BDNF is one of the most investigated of the neurotrophin family of growth factors, and plays a key role in a number of plasticity-related processes, including critical period onset,^{22,23} neuronal differentiation and maturation,²⁴ synapse formation^{25,26} and modulation of synaptic strength.^{27,28} Abnormal levels of BDNF have been associated with psychiatric disorders.^{26,29} Considering BDNF's importance in plasticity, and early life as a period when plasticity is highly increased in brain networks regulating social behaviour, this review proposes that maltreatment experienced in

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early-life impacts the expression of one of the crucial plasticity-related mediators, BDNF, and the abnormal patterns of BDNF could be associated with disturbances in the development of neuronal circuits controlling social behaviour.

First, large-scale disturbances in brain morphology and function linked to ELSA will be summarized. Then the review will focus on the involvement of BDNF in plasticity-related processes. Following that, clinical and preclinical data describing association of BDNF and ELSA will be investigated. Finally, therapeutic implications will be discussed.

ELSA IS ASSOCIATED WITH PLASTICITY-RELATED FUNCTIONAL AND MORPHOLOGICAL CHANGES

Following birth, brain development undergoes a general trajectory of a rapid, non-linear increase in grey matter that peaks at around 7 years of age in humans,¹⁸ reflecting increased synaptic density.^{30,31} The overproduction of synapses is suggested to allow for outward experience to guide elimination of unused synaptic connections. This process, termed as experience-dependent synaptic pruning, occurs mainly during childhood and adolescence but can extend into adulthood in the case of the prefrontal cortex, a region showing prolonged maturation.^{31–33} Developmental curves for grey matter volume are heterochronous: sensory and motor cortices develop during the first few years, whereas higher-order association cortices continue to mature into late adolescence or even adulthood.^{33–36} Limbic structures also show regional differences in maturation rate, particularly the hippocampus and amygdala are characterized by protracted development.^{17,18,37,38} Even so, subcortical limbic structures develop earlier than prefrontal cortical control regions, a possible cause for the imbalance in emotion regulation that is prominent during adolescence, marking it as a developmental period of heightened sensitivity.³⁹

These time windows of rapid, dynamic processes when brain networks make adaptive changes in response to outward experience have been termed critical or sensitive periods.^{14,40} Maltreatment suffered during sensitive periods of heightened plasticity could be linked to abnormalities in maturation. Therefore, regions that show protracted development, i.e. their sensitive period extends for a longer time, might be at a greater risk of disturbance. Such networks are involved in the planning and execution of cognitive functions and emotion regulation. In accordance with this, research has suggested that ELSA is associated with altered function involving cognitive tasks, reaction to social or emotional stimuli, reaction to reward, resting states and functional connectivity (reviewed in refs.^{41,42}).

For example, under normal conditions functional connectivity between the amygdala and the prefrontal cortex seemingly undergoes a developmental shift from childhood to adolescence: in children under 10 years, functional connectivity between the amygdala and the prefrontal cortex is positively coupled,^{43,44} but becomes negatively coupled over the age of 10.^{43,45} This negative coupling is also reflected in white matter connectivity.⁴⁵ However, the above shift might be modified between subregions of the amygdala and the prefrontal cortex.⁴⁶ In previously institutionalized children who experienced early-life maternal deprivation (from 6 to 28 months old) but later on got adopted into stable families, the mature amygdala-prefrontal connectivity was already present at 6–10 years, which, as the authors suggest, could reflect an ontogenic adaptation to the early adversity.⁴⁷ Additionally, these affected children and adolescents showed disturbed hypothalamo–pituitary–adrenal (HPA)-axis reactivity and emotional processing.⁴⁷

In line with altered function, ELSA is associated with volumetric changes in the prefrontal cortex and limbic regions, e.g. the hippocampus and amygdala.^{21,48–52} Fibres connecting these structures, i.e. the cingulum and uncinate fasciculus are also affected.^{53–57}

A longitudinal study by Pechtel and colleagues⁵² denotes the age of 10–11 years as a sensitive period for amygdala development, when ELSA is associated with the greatest change in volume. Note that this period coincides with the aforementioned prefrontal-amygdala connectivity shift. Such sensitive periods may differ in the case of other brain regions, which, as shown before, follow distinct developmental trajectories.

Another notable example of volumetric change can be found in a longitudinal study done by Whittle and colleagues,⁵⁸ where ELSA was associated with the developmental trajectory of different hippocampal subfields depending on the gender.

Although a majority of the clinical research data regarding maltreatment comes from neuroimaging, a study was analysing post-mortem brain samples from individuals who died by suicide and had depression with or without a history of ELSA. Those with a history of ELSA had an increased number of mature myelinating oligodendrocytes along with a decreased number of immature oligodendrocyte-lineage cells in the ventromedial prefrontal cortex compared to post-mortem samples from controls and individuals with depression and without a history of ELSA.⁵⁹ This suggests that ELSA could have led to early maturation in oligodendrocytes, which could underlie white matter abnormalities seen in those who experienced maltreatment in childhood.

It must be noted that results displaying the alterations associated with ELSA are often inconsistent. This may be related to the heterogeneity of participants between each study, the differences between data sampling and analysis, the timing, type and severity of maltreatment or even research bias. The reader is directed to a meta-analysis and review done by Paquola et al.²¹ exploring the heterogeneity of grey matter changes due to ELSA, which, as stated previously, was primarily associated with alteration within the prefrontal cortex, hippocampus and amygdala. Teicher and colleagues²⁰ have also done a detailed review displaying how different types of ELSA were linked to differing changes in grey and white matter. Additionally, a meta-analysis by Riem et al.⁶⁰ has shown that experiencing multiple types of abuse has the most detrimental effect with regards to hippocampal volume. Finally, McLaughlin et al.⁶¹ propose that within ELSA, a distinction should be made between deprivation versus threatening experience, as these dimensions could have a markedly different impact on neural development.

To summarize this section, ELSA is associated with abnormalities in grey and white matter morphology, though the exact changes might differ according to the type and developmental timing of maltreatment. In most cases, these changes are reflected in altered function involving emotion regulation and higher-order cognitive tasks.

THE ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN PLASTICITY-RELATED PROCESSES

BDNF is the most investigated member of the neurotrophic growth factors, and is a major regulator of plasticity-related processes. In this section, we will give a short review on the various actions known to be exerted by BDNF.

Preclinical data

BDNF is involved in a large repertoire of plasticity-related functions, being able to do so due to its tightly regulated activity at all levels. BDNF expression is controlled by at least nine different promoters, which lead to mRNA transcripts containing a promoter-specific 5' untranslated region (UTR) spliced to the common 3' protein coding exon and either a short or long 3' UTR.^{62,63} Both 3' and 5' UTRs are involved in the spatial segregation of BDNF within the cell, localizing mRNA transcripts to either perisomatic versus dendritic, or proximal versus distal dendritic compartments, respectively.^{64,65} In the dendrites, BDNF is able to form or strengthen new synapses by recruiting

translational machinery and initiating local protein translation of synaptic components.²⁸

Whereas other growth factors are mainly secreted in a constitutive way, BDNF expression can also be induced by neuronal activity, which is predominantly attributed to promoter IV (previously known as promoter III, see 62).^{66–69} Promoter IV contains sites that can bind Ca^{2+} -dependent and cyclic AMP (cAMP)-responsive transcriptional factors, allowing activity-dependent transcription through membrane depolarization-induced Ca^{2+} -influx and cAMP signalling.^{67–71} The availability of activity-dependent transcription further depends on epigenetic modifications involving DNA methylation, histone acetylation and histone deacetylation.⁷² Importantly, environmental influences can exert an effect on BDNF expression/availability through such epigenetic mechanisms, which can also have a role in the development of psychiatric disorders.^{26,73,74}

Both mature BDNF and its precursor protein, proBDNF are biologically active and exert opposing effects. ProBDNF preferentially binds to a complex containing sortilin and the p75NTR receptor, initiating signalling cascades that can eventually lead to either long-term depression (LTD, i.e. the decrease of synaptic efficacy), pruning of the synapse, axonal/dendritic retraction or apoptosis.⁷⁵ Both proBDNF and p75NTR are expressed in higher levels during early postnatal development, where they regulate the aforementioned processes, i.e. programmed cell death, axonal/dendritic branching of rapidly proliferating and differentiating neurons and the pruning of unused synapses.^{76,77} By adulthood proBDNF and p75NTR levels decrease, though they may increase again to traumatic events, injury or inflammation.^{76,78} On the other hand, mature BDNF is expressed throughout postnatal development, reaching peak levels in adolescence, and is the major isoform present in adult life.^{76,79} Mature BDNF preferentially binds to tropomyosin receptor kinase B (TrkB) receptors and promotes cell survival, differentiation, axonal and dendritic arborization, synapse stabilization and increase in synaptic efficacy, i.e. long-term potentiation (LTP).^{25,75,77,80} BDNF/TrkB signalling also has an important role in the differentiation of diverse cell populations in the cortex and is needed for normal axonal myelination.^{24,81}

BDNF has been associated with the regulation of critical periods. Research involving critical period plasticity in the visual cortex has revealed that critical period regulation likely depends on inhibition in the central nervous system, and that precocious maturation of parvalbumin (PV)-containing GABAergic inhibitory neurons by overexpression of BDNF accelerates the onset of the critical period.^{22,23,82} Similarly, raising rat pups in an enriched environment increases BDNF expression, inhibitory neurotransmission and accelerates visual system development.⁸³ In turn, rearing animals in the dark from birth decreases BDNF levels and GABAergic neurotransmission in the visual cortex, consequently delaying critical period onset.^{84,85} Neuronal activity-dependent expression of BDNF is required for the correct development of cortical inhibition and thus critical period regulation, which is mainly mediated through promoters I and IV.^{68,86,87} It is still unclear how BDNF influences sensitive period regulation in higher-order cortices or subcortical brain regions though, as most studies focus on the better-understood sensory systems. However, the periadolescent sensitive period of the prefrontal cortex was shown to be similar to sensory critical periods, involving the maturation of local inhibitory PV-containing interneurons, and this was also suggested to be an evolutionally conserved mechanism across mammalian species.⁸⁸

To conclude, BDNF partakes in a multitude of mechanisms involving neuronal plasticity. In the context of early-life social adversities, it is especially important to note that BDNF is involved in several major events of early-life brain development, e.g. synaptogenesis, experience-dependent synaptic pruning,

myelination, maturation of local inhibitory circuitry and through that, the timing of critical and possibly sensitive periods.

THE INVOLVEMENT OF BDNF IN MEDIATING CHANGES CAUSED BY EARLY-LIFE SOCIAL ADVERSITIES

As shown in the previous sections, regions heavily involved in the regulation of social behaviour (i.e. the hippocampus, prefrontal cortex and amygdala) are characterized by protracted development, rendering them open to experience-dependent changes influenced by environmental factors for an extended period of time. ELSA affects grey matter volume and is associated with disturbances in cognitive function, including learning difficulties. Neuronal proliferation or loss and synapse formation or elimination can account for changes in grey matter volume, whereas learning depends on a balanced interaction of potentiation and depression between synapses. These processes are partly regulated by BDNF, implicating that altered BDNF-signalling could underlie morphological and functional changes caused by ELSA.

Preclinical data

Experience-dependent plasticity strongly relies on neuronal activity-dependent release of BDNF. Different environmental cues activate distinct neuronal networks, allowing for region-specific control of BDNF expression through epigenetic modifications.⁷² As such, the early-life social environment can influence BDNF levels in the hippocampus, prefrontal cortex and amygdala via epigenetic programming. Specifically, it has been shown that early-life social adversities cause abnormalities in BDNF methylation and mRNA expression patterns in the aforementioned regions, predominantly affecting activity-dependent promoters I, IV and their transcripts.^{89–92} Such patterns may lead to either reduced or increased BDNF expression (Fig. 1). In sensory critical periods, BDNF-signalling influences inhibitory circuit maturation and timing of the critical period.^{23,93} The prefrontal sensitive period has been suggested to be similar to sensory critical periods regarding its mechanisms of inhibitory circuit maturation,⁸⁸ and is possibly influenced by activity-dependent BDNF-signalling.⁹⁴ As such, inferring from studies investigating critical period plasticity in visual cortex development, reduced BDNF expression would tentatively suggest an elongated sensitive period as seen in dark rearing experiments,^{85,93,95,96} whereas increased BDNF expression would possibly lead to precocious maturation of the social circuitry.^{22,23}

In several cases, preclinical data have pointed to precocious maturation induced by ELSA. In rodents, both chronic and acute early-life stress results in precocious expression of the adult-like phenotype of fear retention and extinction.^{97,98} This has been replicated in other studies, which have additionally shown that, following early-life stress, the premature appearance of the adult-like behavioural phenotype in fear learning is accompanied by precocious maturation of the hippocampus, as shown by accelerated appearance of PV-positive interneurons.⁹⁹ This further draws parallels between visual and social network critical period regulation, as in the visual network critical period closure is dependent on the maturation of PV-positive interneurons, which is either delayed due to low BDNF levels or accelerated due to higher BDNF levels.^{23,82}

Recent results from preclinical experiments rather point to a more complex interaction, with brain region- and time-specific differences in BDNF expression and epigenetic modifications (reviewed in refs.^{100,101}). Assuming that critical period regulation in social networks is similar to visual cortex development, accelerated maturation due to early-life stress should involve increased BDNF levels shortly after the onset of stress. Some studies indeed seem to fit into this hypothesis: maternal deprivation and repeated maternal stress paradigms show an increase in exon IV

Individual differences in each model, gender effects, the direction and time course of stress-induced regional BDNF-expression and thus the timing of samples taken could be a cause of inconsistencies between studies.¹⁰⁰ The various signalling pathways that converge on and influence BDNF/TrkB signalling can also account for differences. Notable examples include glucocorticoid pathways¹⁰¹ and the serotonergic system.¹⁰⁸ Though ELSA is associated with a general hypermethylation of the BDNF and glucocorticoid-receptor genes and a general hypomethylation of the corticotrophin-releasing factor, time- and region-specific differences seen in BDNF signalling likely also apply to glucocorticoid signalling pathways.^{90,101} For example, severe stress leads to a decrease in dendritic spines and atrophy of dendrites in the hippocampus and prefrontal cortex,^{109,110} but causes hypertrophy of dendrites in the amygdala,^{110,111} suggesting differential directionality of stress-induced BDNF and glucocorticoid levels.

However, most samples were measured in adulthood, obscuring the time course of BDNF expression during development. Additionally, most clinical studies measured peripheral BDNF concentrations only. Although studies suggest that blood BDNF levels reflect brain-tissue BDNF concentrations,¹¹⁷ preclinical animal studies are needed to elucidate brain region-specific candidate mechanisms and provide cause-effect relationships.

Rodent studies suggest Val66Met sensitivity to stress. When placed in stressful settings, generated BDNF Met/Met mice

exhibited increased anxiety-related behaviours.¹¹⁹ In another study, Val66Met mice that were subjected to the forced-swim test showed the phenotype of behavioural despair at baseline, which only appeared in Val/Val mice after chronic corticosterone administration during late adolescence.¹²⁰ Hippocampal memory function of Val66Met mice was also found to be more sensitive to glucocorticoid signalling.¹²¹

Clinical data

It has been postulated that Val66Met could convey an increased susceptibility to stress. Since in rodent models ELSA mainly affects activity-dependent BDNF release, impairments in activity-dependent BDNF expression associated with the Met allele could predispose such individuals to stress-related psychiatric disorders. In a study involving major depressive disorder patients without comorbid anxiety, Met carriers were more sensitive to stress-induced downregulation of BDNF, and the decrease in BDNF was more pronounced in Met carriers with more than one type of childhood abuse.¹²² Similarly, another post-mortem study has found that Met carriers with both low and high trauma had lower BDNF mRNA than Val/Val homozygotes, and that decreases in hippocampal subfields CA2/3 and the dentate gyrus were most prominent in Met carriers with high severity of childhood trauma.¹²³

A study done by Gutiérrez and colleagues¹²⁴ has shown a greater risk for the Val/Val genotype in the development of major depression, but this heightened risk shifts to Met allele carriers when environmental factors are taken into account, emphasizing the importance of activity-dependent BDNF signalling in mediating experience-dependent changes.

However, the Val/Val genotype can also be affected by early-life adversities. In a study by Gatt et al.,¹²⁵ ELSA was associated with decreased hippocampal, prefrontal cortex and amygdala volume in Met carriers and was associated with a mixed depression-anxiety phenotype, whereas in Val/Val homozygotes increased amygdala and prefrontal cortex volumes were observed and were associated with an anxious phenotype. Val/Val and Met carriers have distinct developmental trajectories of amygdala-cortical connectivity, marking different sensitive periods in each genotype.¹²⁶ Other brain regions, e.g. cortical and hippocampal areas also show distinct developmental curves depending on the presence of the Met allele.^{127–129} In line with the above, Casey et al.¹³⁰ suggest that Val66Met susceptibility to adversity varies across the lifespan and might even be protective against certain risk factors.

Thus, development until adulthood could be summed up as a series of time points when varying patterns of regions display heightened vulnerability, allowing ELSA to exert diverse effects depending on timing and type of stress in each genotype.

THERAPEUTIC RELEVANCE OF BDNF SIGNALLING

Preclinical data

Antidepressants (AD) have been shown to upregulate BDNF/TrkB signalling, increase BDNF mRNA and protein levels and induce TrkB receptor activation in a BDNF-independent manner^{131,132} (see ref.¹³³ for review). BDNF/TrkB signalling appears to be critical in AD response, as inhibition of BDNF/TrkB signalling abolishes AD-induced behavioural effects.^{92,131,133,134} Rapid-acting antidepressants such as ketamine also involve activity-dependent BDNF release to exert their effects (reviewed in ref.¹³⁵).

It has been proposed that through enhanced BDNF/TrkB signalling ADs reactivate developmental sensitive period-like neuronal plasticity in the brain, a phenomenon referred to as induced juvenile-like plasticity (iPlasticity).¹³⁴ iPlasticity gives brain networks the capacity to be rewired in adulthood when guided by learning experience (e.g. learning a particular skill through training or re-learning social behavioural responses through

psychotherapy). Preclinical experiments have demonstrated this in multiple learning paradigms involving chronic AD treatment: fluoxetine has been shown to reactivate visual cortex plasticity in adulthood¹³⁶ and improve fear extinction in Pavlovian fear conditioning.⁷³ In another study, fluoxetine attenuated abnormal aggression induced by post-weaning social isolation but only when combined with resocialization—a preclinical model of social support, wherein rats are given the opportunity to relearn social behaviour through group housing in adulthood.⁹² Thus, fluoxetine was able to exert its beneficial effect only in positive environmental conditions. This is a highly new concept in understanding the role of BDNF-mediated antidepressant-induced plasticity, and might be the cornerstone of later pharmacological and behavioural therapeutic strategies. In line with this, enriched versus stressful environmental conditions can lead to improvement or worsening of depression-like symptoms in mice under selective serotonin reuptake inhibitor (SSRI) treatment, respectively.¹³⁷

Learning under the induced plasticity state involves upregulation of BDNF mRNA through neuronal activity-dependent promoters I and IV.^{73,92} As such, the advantage of AD treatment and resulting iPlasticity is that remodelling of the circuits via BDNF/TrkB occurs in a neuronal activity-dependent way, allowing for reorganization of brain networks that are selectively involved in the actual learning paradigm. In the context of abnormal maturation induced by ELSA, AD treatment provides an opportunity for psychotherapy to guide rewiring of the social circuitry through BDNF/TrkB signalling.⁹² However, a more complex interaction is present, as in generated Met/Met mice, fluoxetine-induced enhancement of adult hippocampal plasticity was impaired.¹³⁸

Clinical data

Living conditions were shown to influence SSRI treatment outcome in clinical cases too.¹³⁹ In patients with major depressive disorder, lower basal plasma BDNF levels have been described consistently, and chronic antidepressant treatment was associated with increased plasma BDNF levels in accordance with clinical improvement.^{140–142} A post-mortem analysis also found an AD-mediated increase of BDNF levels in multiple brain regions.¹⁴³ In non-responders, BDNF levels remained significantly lower.¹⁴² These studies indicate that the measure of peripheral BDNF levels might also have clinical relevance in relation to the clinical condition and therapeutic response.

In certain studies, ELSA was associated with treatment outcome. In a study, SSRI-mediated increase of serum BDNF did not occur in depressed patients with severe early-life trauma.¹⁴⁴ In another case, higher methylation status of BDNF exon I and IV was associated with severity of early-life trauma, depression severity, impulsivity and hopelessness. Psychotherapy decreased methylation status in responders but increased methylation in non-responders.¹⁴⁵ Importantly, BDNF serum protein levels could not be correlated with methylation status. However, the possible use of BDNF methylation as a biomarker for psychiatric disorders still requires further research (reviewed in ref.¹⁴⁶).

Polymorphisms affecting TrkB/BDNF signalling have also been shown to influence AD response. Since the Val66Met polymorphism is associated with disturbances in activity-dependent BDNF secretion, AD-mediated BDNF release could be hampered in Met carriers. Indeed, in a clinical study involving depressed patients, ketamine treatment was associated with decreased response in Val66Met.¹⁴⁷ However, other studies point to a less clear interaction.^{148–150}

To conclude, by augmenting BDNF/TrkB signalling with AD treatment, iPlasticity provides an opportunity to rewire the social network in adulthood following disturbances in brain development caused by ELSA. Exercise has also been shown to increase BDNF levels, providing a possible alternative to or enhancement of AD treatment.¹³⁴

Fig. 2 Factors that influence the developmental effect of ELSA. Effects of gender and genotype lead to a distinct developmental trajectory specific for each region. This also marks sensitive period timing and duration. Depending on the timing, duration and severity of ELSA, brain developmental trajectories can be shifted or altered, including the length of the critical period. Genotype and gender also influence treatment outcome in adulthood related to ELSA-induced psychopathologies

CONCLUSIONS

To summarize, ELSA is possibly linked to activity-dependent BDNF-signalling, which in turn alters the developmental trajectory of brain regions under their sensitive period. The nature of ELSA-associated changes are region-specific and depend on various factors, including timing, severity and type of stress, gender, genotype and the influence of other signalling pathways, e.g. the HPA-axis and the serotonergic system (Fig. 2). Preclinical and clinical data suggest ELSA might lead to accelerated maturation of social network circuitry, a possible ontogenic adaptation to the adverse environment.

Neural plasticity decreases by adulthood, lessening the efficacy of treatment in ELSA-related psychiatric disorders. However, by increasing BDNF/TrkB signalling through AD treatment a juvenile-like plasticity state can be induced, which allows for reorganization of the social circuitry when guided by psychotherapy and surrounded by a safe and positive environment. Further investigation on the role of ELSA shaping individual neural development will hopefully lead to refined treatment and prevention strategies.

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ADDITIONAL INFORMATION

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