Using Plasticity in the Treatment of Children with Depression

Presented to the S. Daniel Abraham Honors Program
in Partial Fulfillment of the
Requirements for Completion of the Program

Stern College for Women
Yeshiva University
May 6, 2020

Rebecca Lipsky

Mentor: Professor Lisa Chalik, Psychology

Abstract

Early Life Adversity is common, and is strongly linked to psychopathology. Researchers have sought to establish the mechanisms that create this link, and one compelling suggestion is reward learning. The deficit in reward learning has specific relevance for depression, as it relates to anhedonia, a primary symptom of depression. Current treatment options for depression in this population have not proven to be successful. A possible approach for new treatment options would involve targeting the reward learning deficit that links ELA to depression. Reward learning works through brain plasticity, which tends to be lower in this population due to accelerated stress levels at a young age. Therefore, new avenues for treatment should focus on reintroducing plasticity so that the appropriate reward learning can take place.

Table of Contents

Using Plasticity in Treatment of Children with Depression

The prevalence of psychopathology in children has steadily increased in recent years (Twenge et al., 2019). At this point, one in six U.S. youth between the ages of six and seventeen experience a mental health disorder each year (Whitney & Peterson, 2019). A concern surrounding this trend is that on top of the negative influence of these disorders during childhood, there is also a notable developmental trajectory for children who suffer from psychopathology; those who experience disorders as children are more likely to carry these disorders into adulthood, or to develop other disorders and experience other negative consequences (Chapman et al., 2004; Clark et al., 2010). This reality creates an imperative to intervene early in development by figuring out the best treatment options for children who are experiencing psychopathology, thereby mitigating the consequences both during childhood as well as into adulthood.

While researchers and clinicians have devised updated treatment options for children, not all treatment options are appropriate for all children; there are certain populations in which the current treatment options are not sufficiently effective in reducing symptoms for several disorders. One such population is children who have experienced early life adversity (ELA). ELA can be defined as negative environmental experiences that create a deviation from the norm, and are likely to require significant adaptation by the average child (McLaughlin & Sheridan, 2016). This can include experiences such as maltreatment, various forms of abuse, neglect and institutionalization. ELA is very common, with close to half of all children in the United States experiencing at least one form of adversity by the time they reach adulthood (Green et al., 2010).

Children who were exposed to ELA and develop psychopathology are less responsive to treatment than children who have psychopathology but did not experience ELA. Most of the research on this topic has investigated instances of depression (Barbe et al., 2004; Lewis et al., 2010; Nanni et al., 2012) where this relationship is particularly potent.

Several studies have shown that children exposed to ELA who suffer from depression show reduced responsiveness to the standard existing treatment options (Barbe et al., 2004; Lewis et al., 2010; Nanni et al., 2012) demonstrated that children who experienced ELA were less responsive to treatment for Major Depressive Disorder than their peers. They tested several types of adversity and several types of treatment; interestingly, they found that cognitive behavioral therapy (CBT) was particularly ineffective for this group, and that children who had a history of sexual abuse performed even better in the placebo condition than they did in the CBT condition. These findings highlight an unfortunate reality, namely that even a treatment option as ubiquitous as CBT simply does not work well enough within this population. Similarly, Nanni and colleagues (2012) showed that childhood maltreatment was associated with a heightened risk of developing recurrent and persistent depressive episodes as well as a lack of response or remission during treatment for depression.

Not only has research demonstrated that these children do not respond as well to current treatment options, but research has also established a link between ELA and psychopathology, wherein children who have experienced ELA are more prone to psychopathology (Bos et al., 2011; Green et al., 2010). This has been shown in regard to various types of adversity. ELA accounts for up to 45% of child-onset of psychopathology, and 32% of adult-onset mental health disorders (Green et. al., 2010). Additionally, in a prospective longitudinal study, Lansford and colleagues (2002) showed that ELA is linked to

poor behavioral and psychological outcomes, evaluating measures such as school grades, standardized test scores, absences, suspensions, aggression, psychological disorders, drug use, trouble with police, pregnancy, running away, gang membership, and educational aspirations. After following one cohort of children between 1987 and 1999, they found that those who had experienced ELA experienced negative impacts on their psychological well-being as well as their behavior.

Children who experienced ELA are therefore simultaneously more likely to suffer from psychopathology and less likely to benefit from existing treatment options. In this paper, I will discuss ways in which we might improve treatments for this population. To address this issue, I will first ask why children who experienced ELA do not respond to the same treatments as other children. Then, I will offer one suggestion as to how to counter the challenges that these children face.

Review of Literature

Possible Links between ELA and Psychopathology

It is crucial to understand why children with ELA are more prone to persistent psychopathology. There are several suggestions, delineated by McLaughlin and colleagues (2019), as to what creates this link.

Developmental Mechanisms

The first suggestion, and the one that most studies thus far have focused on, regards developmental mechanisms. For example, one influential mechanism is the way in which children with ELA process threat-related social information: These children show by heightened sensitivity to anger and threatening stimuli (Shackman & Pollak, 2014), and are

more likely to interpret neutral stimuli as being negative or threatening (Dodge et al., 1995). This information-processing bias is most typically found in children who experienced violence or abuse. Children who experience this type of bias are more likely to develop disorders such as anxiety and PTSD, as they exhibit fear even in safe environments (Briggs-Gowan et al., 2016).

Another suggested mechanism is the patterns through which children with ELA show emotional reactivity and emotion regulation. Firstly, these children tend to exhibit stronger emotional reactions to stressors and potentially threatening stimuli (McLaughlin et al., 2014). Secondly, these children exhibit challenges with regulating their emotions. Emotion regulation involves having control over one's emotions, as well as when and how they experience and express those emotions (Gross, 1998). Children who experienced ELA have difficulty with certain components of emotion regulation, such as disengaging from negative emotional stimuli, and modulating their emotional reactions. In addition, children exposed to ELA tend to lean more toward maladaptive strategies to cope with emotions, such as ruminating about their adverse experiences. This rumination sometimes results in PTSD, as the children overly focus on their trauma long after it is over. This also leads to a variety of internalizing and externalizing behaviors. Internalizing behaviors consist of disordered behaviors directed inwards, such as extreme inhibition, anxiety and depression. Externalizing behaviors consist of disordered behaviors directed outwards, such as aggression, bullying and hostility.

Lastly, reward processing is also a suggested developmental mechanism that could be creating the link between ELA and psychopathology. The reward-processing system in children with ELA is characterized by a hindered ability to regulate behaviors that would

result in achieving a reward (McLaughlin et al., 2019). This creates a link to depression.

Learning Mechanisms

McLaughlin and colleagues (2019) highlight a gap in the research on children with ELA; whereas previous research has accentuated potential *developmental* mechanisms, little attention has been given to potential *learning* mechanisms that could be creating this link. Learning mechanisms are important to understand, because they tend to be the targets of behavioral interventions for many forms of psychopathology. An understanding of these underlying learning mechanisms can be easily used to inform intervention efforts. Therefore, although developmental mechanisms are helpful to understand as well, learning mechanisms are the most useful to understand in order to shape intervention and treatment of disorders. In the case of children who experienced ELA, learning mechanisms could be particularly useful to understand, in order to create a framework through which new, more effective intervention options can be devised.

To address this gap, McLaughlin and colleagues (2019) discuss two types of learning mechanisms: fear learning and reward learning. Fear learning involves the acquisition of a fear response after pairings between a neutral stimulus and an aversive stimulus. This can take place in a way that is explicit, where stimuli are actively paired, or implicit, where the child simply observes pairings in the environment. In either case, a neutral stimulus that previously had no meaning becomes paired with something that induces fear, resulting in the child being afraid of the neutral stimulus. Reward learning involves the acquisition of reward contingencies that must be learned over time through active feedback (McLaughlin et al., 2019). Reward learning is notably weaker in children who experienced ELA, leaving open the possibility that this deficiency may be relevant in understanding what links ELA to

psychopathology.

Reward Learning and ELA

Though McLaughlin and colleagues (2019) discuss several possibilities, reward learning is particularly important to focus on for several reasons. First, reward learning seems to create a specific link between children who experienced ELA and depression, which is the disorder most notable for having poor treatment responses in this population. Depression is a common disorder, with approximately 3.2% of children between ages three and seventeen having diagnosed depression (Ghandour et al., 2019). It is very common to have comorbidities along with depression itself; about 3 in 4 children in this age bracket who have depression also have anxiety, and almost 1 in 2 have behavior problems (Ghandour et al., 2019). It is crucial to study the factors that may contribute to the onset of depression specifically, since it is related to many other disorders and has strong implications for early intervention with treatment due to its impacts on the future.

Second, reward learning may be relevant in treatment more generally, across a variety of disorders; various treatment options rely on the patient having some motivation to improve, and with a deficit in reward learning, these options may be less effective. Lacking a desire to experience the reward of recovery and improvement, virtually any treatment option is more challenging.

Adolescence is a time when there are typically enhancements in reward learning for both monetary and social rewards; children become more attuned to what is rewarding and beneficial to them, and how to gain more of whatever that may be. These developments are associated with increases in activity and connectivity in various areas in the brain that are important for typical functioning, such as the ventral striatum and medial prefrontal cortex

(Hauser et al., 2015). Deficits in reward learning, specifically during childhood and adolescence, can be detrimental to the normal development of important areas of the brain, and consequently can lead to depression-like behaviors.

Research with children raised in institutions (Sheridan et al., 2018; Wismer Fries & Pollak, 2017) and children who experienced maltreatment (Guyer et al., 2006) has demonstrated that when engaging in implicit learning tasks, children who have experienced adversity are less likely than other children to modify their behavior in response to increasing values of a reward. Implicit learning tasks are those in which the participant is meant to develop an understanding of an association between things, even though it is not explicitly spelled out.

In one study, for example, Wismer Fries and Pollak (2017) compared children who experienced early adversity in the form of neglectful caregiving and institutionalization with children who had more typical upbringings. All of the participants engaged in a task on a computer, wherein they would receive a reward after accurately completing a full set of trials. As the trials went on, there were implicit visual cues to depict how close the participant was to completing the task and winning the reward. The cues consisted of a rectangle on the computer screen that would either become longer or brighter as the child went through more accurate trials and became closer to receiving a reward. The researchers wanted to see how much the children understood and were motivated by those implicit cues, as would be evidenced by the degree to which they modified their behavior in response to the cues. They found that the typical children demonstrated normal reward learning; they responded more quickly when the implicit cues told them they were close to the reward. They therefore effectively paired the cues with the reward. In contrast, the children who were previously

institutionalized demonstrated no such response; they did not alter their response time in reaction to the cues, thereby demonstrating that they did not effectively pair the cues with the reward.

In addition to showing differences in reward-learning behavior, research has demonstrated that differences in reward learning between children who experienced ELA and their peers are also reflected biologically. In a study by Hanson and colleagues (2015), adult participants engaged in a card-guessing task, in which they received rewards for doing well. The researchers used functional neuroimaging in order to detect individual differences in the activity of the participants' ventral striatum during the task. They examined brain activity at the point in the task when the participants should have been processing rewards, and the ventral striatum would typically be particularly active. They found that participants who had experienced higher levels of stress and adversity during childhood and adolescence exhibited lower levels of activity in the ventral striatum at the times when they should have been processing rewards. This shows that ELA is associated with blunted reward-related ventral striatum activity in adulthood; even years after they experienced adversity during childhood, the participants were less responsive to reward.

Reward Learning and Depression

While ELA is linked generally to psychopathology, there are specific mechanisms that link ELA to specific disorders. One such example is that reward learning serves as a link between ELA and depression (McLaughlin et al., 2019), since lowered responsiveness to reward can result from ELA, and is a risk factor for and feature of depression (Forbes et al., 2007).

Additionally, studies using animal models have shown that following ELA, rats

demonstrate reduced reward learning, both behaviorally and biologically (Stuart et al., 2019). On the behavioral level, these rats have shown diminished reward-seeking behavior. On the biological level, the rats' brain regions that are typically involved in reward processing have shown less activity.

One of the key symptoms of depression is anhedonia, which is characterized by reduced responsiveness to pleasurable stimuli or typically rewarding stimuli; this symptom is directly related to alterations in the reward system. When faced with rewarding stimuli, children with typical reward functioning tend to shift their behavior in order to seek out the rewarding stimulus; they learn an association between the rewarding stimulus and a certain action, and modify their behavior in order to obtain that reward. A child with anhedonia does not view the rewarding stimuli as rewarding to the same extent as other children, and does not experience the same level of interest in obtaining the reward. As a result, when faced with a rewarding stimulus, the response of a child with anhedonia or depression is muted. This muted response reflects alterations in the reward system, including diminished motivation to obtain reward, reward-seeking behavior, and pleasure while experiencing a reward (Forbes et al., 2007). In their study, Forbes and colleagues (2007) compared eleven-year-old boys with and without depressive disorders. The participants were put in a situation where they knew that there was a high chance of getting a reward, and were able to choose either a high-magnitude reward or a low-magnitude reward. The children without depressive disorders chose high-magnitude rewards, demonstrating appropriate reward learning and behavior. In contrast, those with depressive disorders continued to choose the low-magnitude rewards just as much, failing to modulate their behavior in response to a more rewarding stimulus.

As a result of the connection, depression, like ELA, has been associated with reduced modulation of behavior in response to rewards (Morris et al., 2015). Since anhedonia is one of the gateway symptoms to depression, alterations in reward learning that trigger this symptom are strong predictors of a persistence of existing depression as well as an onset of depression later in life (Forbes et al., 2007). Therefore, it is crucial to examine how best to address this link when offering treatment to children who experienced ELA and suffer from depression.

In addition to the fact that reduced reward learning is a component of depression, which manifests as anhedonia, reduced reward learning is also associated with poor treatment response among adults with depression. A study by Vrieze and colleagues (2013) showed that reduced reward learning at study entry increased the odds of a persisting diagnosis of depression after 8 weeks of treatment. Therefore, ELA and depression are linked in two ways. Firstly, ELA can lead to depression, as reduced reward learning is a risk factor for anhedonia and depression. Secondly, ELA can perpetuate depressive disorders by hindering patients' responsiveness to treatment.

Current Treatment Options

First, I will list the available treatment options for depression, and then explain why these options have limitations when it comes to treating children who have had ELA. There are several avenues for treatment that currently exist for children who suffer from depression. Some treatment options involve a therapeutic approach, while some are psychopharmacological. Children with severe depression tend to receive both therapy and medication.

Cognitive Behavioral Therapy (CBT)

Cognitive Behavioral Therapy (CBT) is a common treatment method wherein a client engages in talk-therapy with a therapist, and the therapist seeks to have the client reevaluate negative or dysfunctional thought processes. The goal is to respond to those thoughts in a more effective way. Lewis and colleagues (2010) found that CBT was particularly ineffective for children who experienced ELA.

Interpersonal Psychotherapy (IPT)

Interpersonal Psychotherapy (IPT) is a time-constrained method of treating depression that has proven to be effective in treating depression across a range of experimental paradigms, as confirmed by a recent meta-analysis (Cuijpers et al., 2011). This type of therapy is centered around acknowledging that though not the sole cause, interpersonal relationships play a role in the emotions associated with depression. Clients talk out and mend their interpersonal conflicts with the guidance of a therapist.

Zobel and colleagues (2011) conducted a five-year follow-up of a study analyzing the efficacy of combined psychotherapy and pharmacotherapy treatment of depression, where IPT served as the psychotherapy treatment. They found that for the participants who experienced ELA, around 50% of those enrolled in the study, IPT in addition to pharmacotherapy was significantly more effective than pharmacotherapy alone. These results seem promising, indicating that a combination of treatment methods can be effective in this population. However, these findings have not been widely replicated. Additionally, in Zobel and colleagues' (2011) study, the analysis of the children who experienced ELA was only done after the fact, as it was not a primary goal of the study. Therefore, though IPT may be a hopeful avenue, there needs to be further research demonstrating its efficacy in this

population.

Behavioral Activation (BA)

Behavioral Activation (BA) focuses on increasing connection to meaningful stimuli and activities that foster feelings of motivation, pleasure, and accomplishment. McLaughlin and colleagues (2019) suggest that BA may be particularly useful for children who have experienced ELA, due to its emphasis on increasing positive and rewarding activities these children tend to miss out on. However, they acknowledge that research on the effectiveness of BA in this group has not been done (McLaughlin et al., 2019).

Positive Affect Treatment

This treatment method is similar to BA, and is specifically designed to bolster approach motivation, responsiveness to reward, and reward learning. It consists of engaging in activities that facilitate the savoring of positive experiences along with attention retraining to shift attention toward positive stimuli, as well as activities designed to engender feelings of gratitude and a desire to give to others. Positive Affect Treatment aims to reduce anhedonia, a symptom that is central to depression; it does so by aiming to improve the functioning of the reward system, something that is typically diminished due to anhedonia.

Due to its focus on reward learning, which may be the factor that creates the link between ELA and psychopathology, this would seem to be a promising treatment option. Though this treatment option has shown potential to be effective in depressed patients (Craske et al., 2016), the research is preliminary and not yet conclusive. This is true is in regard to patients who are depressed, without the additional factor of having experienced ELA. In regard to depressed patients who have experienced ELA, research has not yet been done.

SSRIs, SNRIs, TCAs

While the previous options were therapeutic, Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants (TCAs) are psychopharmacological options for treatment. They increase the activation of certain neurotransmitters, thereby leading to mood boosts, which could mitigate depressive symptoms. Vrieze and colleagues (2013) explain that though SSRIs and SNRIs are said to be effective and even address the deficits in reward learning, in practice, there is a gap; they are not addressing the problem as well as they could be in this population. This further highlights the issue with the effectiveness of the current treatment options for children who experienced ELA, and creates an imperative to devise new options that will work better for these children.

If a significant feature of children who have experienced ELA is that they exhibit reduced reward learning, an essential component of treatment for these children will be to address this deficit. However, in order to accomplish this goal, we must first understand *why* this population experiences reduced reward learning.

Directions for Future Treatment

Plasticity and ELA

In order for normal learning to take place, sufficient brain plasticity is necessary. Brain plasticity, in this context, can be understood as the brain's ability to adapt to changes in the environment and take in new information in learning and memory (Johnston, 2004). This plasticity is crucial for typical behavioral, cognitive, and emotional functioning and development to occur. While vital for learning across the lifespan, plasticity changes across

development. Specifically, plasticity is highest during childhood, and dwindles with age. Researchers (Callaghan & Tottenham, 2016) explain that this dwindling trajectory of plasticity is developmentally adaptive in low stress situations. Under normal circumstances, increased levels of plasticity during childhood favor a slow and careful processing of external information, as children learn constantly from their parents and their general environments. This allows children to soak up important information prior to reaching adulthood.

When children experience ELA, they undergo an accelerated developmental trajectory which, rather than favoring a slow and steady stage of information absorption, favors more adult-like features (Callaghan & Tottenham, 2016); this is known as the "stress acceleration hypothesis." Typically in development, children do not possess the emotional and cognitive capabilities to grapple with trauma and adversity so early on in their life. As they age, then, people develop mechanisms that allow them to handle difficulties. This theory proposes that because children with ELA have experienced adversity earlier than usual, their bodies develop faster to allow them to cope with that adversity. Consequently, whereas children typically possess and develop high levels of plasticity, allowing them to learn in novel ways as they develop, a hit of early adversity makes the child more adult-like, thereby stripping the child of this openness and ability to grapple with new information. While this change of pace is developmentally adaptive, as it allows children to react in more mature ways to their unexpectedly mature circumstances, it also can impact brain functioning in a way that could result in psychopathology.

The researchers highlight that their approach comes in contrast to many other theories, which posit that adversity leads to *deficits* in those affected; Callaghan and Tottenham (2016) identify with an evolutionary biology framework, in which adversity

simply leads to a reprioritization of systems, shifting toward an adult-like trajectory, and away from a typically adaptive, slower pace of development during childhood. This reprioritization allows a child, under normal circumstances, to learn gradually and effectively, shaping them for a healthy adulthood. Therefore, according to this theory, ELA does not necessarily lead to developmental results that are inherently bad or lacking; rather, it speeds up development, in a way that may, due to other factors, ultimately become harmful and maladaptive for the child affected.

Callaghan and Tottenham (2016) use basic animal models as the basis for their hypothesis, highlighting the behavioral and biological results of various studies that examined animals in situations of adversity. Animal models are particularly useful in studying the impacts of ELA, for several reasons. Firstly, in human studies, it is not possible to separate the effects of nature from nurture; it may be that early adversity leads to psychopathology, but there is also the genetic component that may be at play. Animal models are better able to detect causality. Secondly, animal models allow for the use of a variety of techniques that would not be possible to enact with humans; for example, researchers are able to devise simulated conditions of poverty and maternal separation that can easily be replicated across many studies. In human studies, however, it is challenging to compare adversities, as they cannot be experimentally manipulated and therefore likely differ from one another (Birnie et al., 2019).

Callaghan and Tottenham (2016) bring evidence for this proposal from some studies done on infant rat pups. These studies compared pups raised in typical environments to those raised in an impoverished home cage with reduced nesting material, an adverse caregiving experience. The pups were exposed to threat conditioning, wherein an odor was paired with a

shock. While the typically reared pups exhibited age appropriate fear-responses, first exhibiting approach behaviors and later in development transitioning to avoidance behaviors, the pups who experienced the adverse caregiving experience shifted much earlier to the avoidance behaviors. This points to accelerated development in the pups that experienced adversity.

In addition to the behavioral differences in these basic models, there were also biological differences. In the mice, for example, in addition to the behavioral acceleration of transitioning from approach to avoidance, there were correlated changes in brain activity; the amygdala, the brain region associated with fear learning, became increasingly activated. This manifested differentially across the two groups of pups: The pups who experienced adversity exhibited an increase in activation of the amygdala at an earlier point, further demonstrating the acceleration effect. In addition, Callaghan and Tottenham (2016) mention additional brain regions involved in fear learning that undergo accelerated functioning in response to adversity, such as the medial prefrontal cortex and the hippocampus.

Callaghan and Tottenham (2016) interpret these findings as evidence of developmental differences that come as a result of ELA. They posit that these results carry over to humans; children who have been exposed to ELA may have consistently lower levels of brain plasticity, which could explain why they experience alterations in the fear-learning system. These alterations can result in fear and stress related disorders, such as anxiety and PTSD.

Though the "stress acceleration hypothesis" pertains specifically to fear learning and anxiety, there is compelling evidence that this is true in regard to reward learning and depression as well. While it is unlikely that adversity speeds up *all* aspects of development,

there is reason to think that certain broader systems would be affected. In this case, it is likely that several learning systems, in addition to the fear-learning system, are affected by adversity.

Furthermore, in addition to studying fear and stress-related disorders in mice, studies have also investigated depression (Bian et al., 2015). On this level of basic models, the research, though more preliminary and limited, seems to show similar findings to that of anxiety, in that plasticity is reduced, and therefore the learning systems are impacted. Bian and colleagues (2015) utilized a maternal separation paradigm on mice. The mice experienced the maternal separation (MS) induction in one of two conditions: three hours of maternal separation at a time, or fifteen minutes of maternal separation at a time. The researchers conducted behavioral tests in order to assess how the mice differentially responded. In the tasks, they measured depression by the length of time that the mice remained immobile. They found that the mice in the MS180 (three hours of separation) condition were immobile for much longer than those in the MS15 (fifteen minutes of separation) condition, demonstrating depressive symptoms. They also found in addition to inducing depression-like behaviors, the MS180 condition also had an impact on the brain; the rats that experienced the MS180 condition also experienced a decrease in expression of some plasticity-related proteins in their brains. Bian and colleagues (2015) concluded that the depression-like behavior was linked to the decrease in expression of plasticity-related proteins, as neuroplasticity may have been inhibited.

Like the animal studies looking at anxiety, those looking at depression find similar reductions in plasticity and impacts on learning systems, including the reward system. As a result, it is plausible that the “stress acceleration hypothesis” would similarly apply to reward

learning, and in tandem, to depression.

Deficient brain plasticity may, therefore, be the underlying cause for the link between ELA and depression, in that it reduces the brain's capacity for learning. Future research should look into treatment options that cater specifically to children who experienced ELA, and are therefore less receptive to current treatment options. There are several ways in which methods of reintroducing plasticity could be incorporated into treatment methods.

Recommendations for Treatment

SSRIs

While SSRIs are already in the circulation of current treatments, it is important to note how they actively address plasticity. Serotonin plays an important role in regulating developmental plasticity, and the effective use of serotonin in this role has been demonstrated with rodents and humans (Castrén, & Rantamäki, 2010; Dayer, 2014; Kraus et al., 2017). In fact, Dayer (2014) proposes that serotonin has the ability to reinstate a juvenile-like plasticity; this would be critical for those who experienced ELA and therefore were stripped of some of their early-life plasticity. While some argue that they do not do enough to address plasticity (Vidal et al., 2011), SSRIs are a promising avenue that should be examined further. Much of the existing research discusses the function of serotonin in reintroducing plasticity within the context of early life and development, indicating that this option could be especially beneficial within this age bracket.

SSRIs are common in treatment of adults, but parents and practitioners are at times resistant to using pharmacological methods of treatment with children. Additionally, for mild depression, antidepressants are not typically the initial treatment approach. As a result, though SSRIs may helpfully address deficits in plasticity, they are not utilized frequently

with children, including those with ELA. Though the reasons for preferring non-pharmacological types of treatment for children are valid, it would be worthwhile to examine whether the benefits of SSRIs specifically in the context of ELA outweigh the reasons for avoiding their use. They may, in fact, be specifically useful in treating this population. Future research should evaluate the practicality and usefulness of this option, on its own and perhaps also in combination with therapy.

Exercise

Research has demonstrated that exercise improves brain plasticity (Voss et al., 2013). Though therapists usually promote exercise and staying active when treating depressed individuals, they do not necessarily focus on the mechanisms through which exercise influences plasticity; it is probable, then, that even when exercise is incorporated into a treatment routine, it is not done in a way to maximize the benefits. Therefore, it is important to explore the exact process by which exercise might influence plasticity.

One way in which exercise can influence plasticity is through its impact on a protein involved in brain plasticity. Much of the research has focused on neuroplasticity relating to the hippocampus, as it is typically mediated by a specific protein: brain-derived neurotrophic factor (BDNF). BDNF is key marker of neuroplasticity. In a study by Cotman and Berchtold (2002), mice that had voluntary access to a running wheel even for only a few days showed an increase in BDNF proteins, suggesting an increase in neuroplasticity. Ploughman (2008) found similar results, highlighting that when the expression of BDNF is blocked, mice show impairments in learning and memory. Exercise bolsters the amount of BDNF in the system, thus contributing to improvements in learning and memory.

Though exercise, generally, has demonstrated effectiveness in increasing plasticity, it

is important to understand whether there is a specific type or duration of exercise that would be most beneficial in clinical treatment. In terms of duration, the findings are helpful but ultimately inconclusive, for several reasons. First, most studies show that moderate long-term exercise is more effective than high-intensity exercise (Ferreira et al., 2011). However, there are also studies that show that long-term exercise is necessary (Patten et al., 2013). Additionally, while animal models are useful, it is difficult to know how closely their exercise conditions would match that of humans; it is unclear if human intervention based mostly on animal models would be as effective. Though some studies have tested humans and found that the results seem consistent with the animal models (Voss et al., 2013), further studies would be necessary in order to ascertain how much the human model lines up with the animal model. In terms of type of exercise, there is also uncertainty. Many studies with rodents have utilized a running wheel or treadmill as the exercise paradigm, indicating that this type of exercise would specifically be beneficial. However, this type of exercise may simply be used because it is easy to implement and most natural for rodents to experience. As a result, it is still unclear if a specific type of exercise would be most beneficial.

Importantly, the hippocampus is the brain region that is particularly impacted by exercise, and is also a key region involved in depression. Therefore, targeting the hippocampus through exercise is a particularly appropriate method in the context of depression.

Sleep

Research has also examined sleep as a means of enhancing brain plasticity **(**Dang-Vu et al., 2006). There are several ways in which sleep impacts brain plasticity, such as by increasing the expression of synaptic-plasticity related genes, allowing consolidation of

learning from the day, and serving as a plastic state for the development and remodeling of neural circuits (Wang et al., 2011). Therefore, sleep can both increase plasticity so that better learning can then take place during wakefulness, and allow for learning that did take place to take root and be transferred to memory. The term "sleep-dependent plasticity" refers to brain plasticity that requires sleep in order to be experienced; these levels of plasticity that appear are necessary for changes in the brain are not available during wakefulness, making sleep crucial in this role.

Gorgoni and colleagues (2013) propose practical methods for introducing sleep to cognitive rehabilitative programs; these methods can similarly be used in other clinical contexts, such as for patients with depression. They suggest that sleep can be incorporated into treatment by promoting sleep between therapy sessions, promptly treating associated sleep disorders, and improving sleep quality by ensuring an adequate environment as well as appropriate melatonin administration. These interventions could promote the positive effects of sleep on brain plasticity.

However, it is important to be careful when promoting sleep for patients with depression. Depression is strongly linked with sleep abnormalities, which can be reflected through insomnia or hypersomnia (Nutt et al., 2008). For those with insomnia, which is about three quarters of patients (Yates et al., 2007), improving the quantity and quality of sleep would undoubtedly be helpful. For those who experience hypersomnia, which is around 40% of depressed young adults (Posternak, & Zimmerman, 2001), being careful about striking the right balance when it comes to the duration and quality of sleep is vital.

A limitation of this suggestion is that oftentimes, interventions that promote sleep also require medication, given that many people need pharmaceutical sleep aids in order to

follow rules and establish new sleeping habits. Though people might gravitate toward a sleep-based approach in order to avoid using pharmaceuticals in treating younger patients, oftentimes patients require pharmaceuticals in order for this method to be effective.

These proposals for treatment would not be meant to replace current treatment options, but rather to complement them by addressing the deficit in reward learning that is clearly creating problems for children who were exposed to ELA. In addition, according to Zobel and colleagues (2011), combination treatment (psychotherapy in addition to pharmacotherapy) offers particular advantages particularly for depressed patients who experienced ELA.

Discussion

Though these suggestions offer what may be promising new avenues for effective treatment, more research should be done. Firstly, these are merely proposals; while they have all been used in some capacity with different populations and disorders, researchers should implement these options within the population of children who experienced ELA. Additionally, these options can also be tested on adults who previously experienced ELA, in order to see if plasticity can still be restored at that point. When testing these options, it would be useful to evaluate whether a combination of plasticity-enhancing treatments help in combination, and if so, what the most effective combination of methods could be.

In addition, research should be done to see if this extends to other forms of psychopathology. Reward learning is most directly related to depression. However, there are also reward-related alterations present in substance use disorders, schizophrenia, and antisocial personality disorder. Therefore, there may be potential for this type of treatment to

be useful in treatment of those disorders as well.

Interestingly, while the research presented here shows how stress-acceleration in this population leads to maladaptive maturation and acceleration, there is also evidence on the other side; there is evidence that this acceleration makes children more emotionally capable, as they are more adult-like. This might mean that children are more readily able to regulate their emotions and cope with stress appropriately. More research should be done to clarify this point.

Additionally, of the studies cited, many looked at different forms of ELA, such as caregiving adversity, poverty, and abuse. In order to really parse out whether specific types of ELA are relevant to this discussion, it would be important to look at each type of adversity separately. In this way, it would be possible to understand if specific types of adversity predict greater losses in plasticity and should be focused on more in treatment efforts.

References

Barbe, R. P., Bridge, J. A., Birmaher, B., Kolko, D. J., & Brent, D. A. (2004). Lifetime history of sexual abuse, clinical presentation, and outcome in a clinical trial for adolescent depression. *The Journal of Clinical Psychiatry*, *65*(1), 77-83. https://doi.org/10.4088/jcp.v65n0113

Bian, Y., Yang, L., Wang, Z., Wang, Q., Zeng, L., & Xu, G. (2015). Repeated three-hour maternal separation induces depression-like behavior and affects the expression of hippocampal plasticity-related proteins in C57BL/6N mice. *Neural Plasticity*, *2015*, 1-7. https://doi.org/10.1155/2015/627837

Birnie, M. T., Kooiker, C. L., Short, A. K., Bolton, J. L., Chen, Y., & Baram, T. Z. (2020). Plasticity of the reward circuitry after early-life adversity: Mechanisms and significance. *Biological Psychiatry*, *87*(10), 875-884. https://doi.org/10.1016/j.biopsych.2019.12.018

Bos, K., Zeanah, C. H., Fox, N. A., Drury, S. S., McLaughlin, K. A., & Nelson, C. A. (2011). Psychiatric outcomes in young children with a history of institutionalization. *Harvard Review of Psychiatry*, *19*(1), 15-24. https://doi.org/10.3109/10673229.2011.549773

Briggs-Gowan, M. J., Grasso, D., Bar-Haim, Y., Voss, J., McCarthy, K. J., Pine, D. S., & Wakschlag, L. S. (2016). Attention bias in the developmental unfolding of post-traumatic stress symptoms in young children at risk. *Journal of Child Psychology and Psychiatry*, *57*(9), 1083-1091. https://doi.org/10.1111/jcpp.12577

Callaghan, B. L., & Tottenham, N. (2016). The stress acceleration hypothesis: Effects of early-life adversity on emotion circuits and behavior. *Current Opinion in Behavioral Sciences*, *7*, 76-81. https://doi.org/10.1016/j.cobeha.2015.11.018

Castrén, E., & Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Developmental Neurobiology*, *70*(5), 289-297. https://doi.org/10.1002/dneu.20758

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders*, *82*(2), 217-225. https://doi.org/10.1016/j.jad.2003.12.013

Clark, C., Caldwell, T., Power, C., & Stansfeld, S. A. (2010). Does the influence of childhood adversity on psychopathology persist across the Lifecourse? A 45-Year prospective epidemiologic study. *Annals of Epidemiology*, *20*(5), 385-394. https://doi.org/10.1016/j.annepidem.2010.02.008

Cotman, C. (2002). Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences*, *25*(6), 295-301. https://doi.org/10.1016/s0166-2236(02)02143-4

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., & Dour, H. J. (2016). Treatment for anhedonia: A neuroscience driven approach. *Depression and Anxiety*, *33*(10), 927-938. https://doi.org/10.1002/da.22490

Cuijpers, P., Geraedts, A. S., van Oppen, P., Andersson, G., Markowitz, J. C., & van Straten, A. (2011). Interpersonal psychotherapy for depression: a meta-analysis. The American journal of psychiatry, 168(6), 581–592. https://doi.org/10.1176/appi.ajp.2010.10101411

Dang-Vu, T. T., Desseilles, M., Peigneux, P., & Maquet, P. (2006). A role for sleep in brain

plasticity. Pediatric rehabilitation, 9(2), 98-118. https://doi.org/10.1080/13638490500138702

Dayer, A. (2014). Serotonin-related pathways and developmental plasticity: relevance for psychiatric disorders. Dialogues in clinical neuroscience, 16(1), 29.

Dodge, K. A., Pettit, G. S., Bates, J. E., & Valente, E. (1995). Social information-processing patterns partially mediate the effect of early physical abuse on later conduct problems. *Journal of Abnormal Psychology*, *104*(4), 632-643. https://doi.org/10.1037/0021-843x.104.4.632

Ferreira, A. F., Real, C. C., Rodrigues, A. C., Alves, A. S., & Britto, L. R. (2011). Short-term, moderate exercise is capable of inducing structural, bdnf-independent hippocampal plasticity. Brain Research, 1425, 111-122. https://doi.org/10.1016/j.brainres.2011.10.004

Forbes, E. E., Shaw, D. S., & Dahl, R. E. (2007). Alterations in reward-related decision making in boys with recent and future depression. *Biological Psychiatry*, *61*(5), 633-639. https://doi.org/10.1016/j.biopsych.2006.05.026

Ghandour, R. M., Sherman, L. J., Vladutiu, C. J., Ali, M. M., Lynch, S. E., Bitsko, R. H., & Blumberg, S. J. (2019). Prevalence and treatment of depression, anxiety, and conduct problems in US children. *The Journal of Pediatrics*, *206*, 256-267.e3. https://doi.org/10.1016/j.jpeds.2018.09.021

Gorgoni, M., D'Atri, A., Lauri, G., Rossini, P. M., Ferlazzo, F., & De Gennaro, L. (2013). Is sleep essential for neural plasticity in humans, and how does it affect motor and cognitive recovery? Neural Plasticity, 2013, 1-13. https://doi.org/10.1155/2013/103949

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Archives of general psychiatry, 67(2), 113-123. https://doi.org/10.1001/archgenpsychiatry.2009.186

Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, *2*(3), 271-299. https://doi.org/10.1037/1089-2680.2.3.271

Guyer, A. E., Kaufman, J., Hodgdon, H. B., Masten, C. L., Jazbec, S., Pine, D. S., & Ernst, M. (2006). Behavioral alterations in reward system function: the role of childhood maltreatment and psychopathology. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(9), 1059-1067. https://doi.org/10.1097/01.chi.0000227882.50404.11

Hanson, J. L., Albert, D., Iselin, A. R., Carré, J. M., Dodge, K. A., & Hariri, A. R. (2015). Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Social Cognitive and Affective Neuroscience*, *11*(3), 405-412. https://doi.org/10.1093/scan/nsv124

Hauser, T. U., Iannaccone, R., Walitza, S., Brandeis, D., & Brem, S. (2015). undefined. *NeuroImage*, *104*, 347-354. https://doi.org/10.1016/j.neuroimage.2014.09.018

Johnston, M. V. (2004). Clinical disorders of brain plasticity. *Brain and Development*, *26*(2), 73-80. https://doi.org/10.1016/s0387-7604(03)00102-5

Kraus, C., Castrén, E., Kasper, S., & Lanzenberger, R. (2017). Serotonin and neuroplasticity – Links between molecular, functional and structural pathophysiology in depression.

Neuroscience & Biobehavioral Reviews, *77*, 317-326. https://doi.org/10.1016/j.neubiorev.2017.03.007

Lansford, J. E., Dodge, K. A., Pettit, G. S., Bates, J. E., Crozier, J., & Kaplow, J. (2002). A 12-Year prospective study of the long-term effects of early child physical maltreatment on psychological, behavioral, and academic problems in adolescence. *Archives of Pediatrics & Adolescent Medicine*, *156*(8), 824. https://doi.org/10.1001/archpedi.156.8.824

Lewis, C. C., Simons, A. D., Nguyen, L. J., Murakami, J. L., Reid, M. W., Silva, S. G., & March, J. S. (2010). Impact of childhood trauma on treatment outcome in the treatment for adolescents with depression study (TADS). *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(2), 132-140. https://doi.org/10.1016/j.jaac.2009.10.007

McLaughlin, K. A., DeCross, S. N., Jovanovic, T., & Tottenham, N. (2019). Mechanisms linking childhood adversity with psychopathology: Learning as an intervention target. *Behaviour Research and Therapy*, *118*, 101-109. https://doi.org/10.1016/j.brat.2019.04.008

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience & Biobehavioral Reviews*, *47*, 578-591. https://doi.org/10.1016/j.neubiorev.2014.10.012

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk. *Current Directions in Psychological Science*, *25*(4), 239-245. https://doi.org/10.1177/0963721416655883

Morris, B. H., Bylsma, L. M., Yaroslavsky, I., Kovacs, M., & Rottenberg, J. (2015). Reward learning in pediatric depression and anxiety: Preliminary findings in a high-risk sample. *Depression and Anxiety*, *32*(5), 373-381. https://doi.org/10.1002/da.22358

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*(2), 141-151. https://doi.org/10.1176/appi.ajp.2011.11020335

Nutt, D., Wilson, S., & Paterson, L. (2008). Sleep disorders as core symptoms of depression. Dialogues in clinical neuroscience, 10(3), 329.

Patten, A. R., Sickmann, H., Hryciw, B. N., Kucharsky, T., Parton, R., Kernick, A., & Christie, B. R. (2013). Long-term exercise is needed to enhance synaptic plasticity in the hippocampus. *Learning & Memory*, *20*(11), 642-647. https://doi.org/10.1101/lm.030635.113

Posternak, M. A., & Zimmerman, M. (2001). Symptoms of atypical depression. *Psychiatry Research*, *104*(2), 175-181. https://doi.org/10.1016/s0165-1781(01)00301-8

Shackman, J. E., & Pollak, S. D. (2014). Impact of physical maltreatment on the regulation of negative affect and aggression. *Development and Psychopathology*, *26*(4pt1), 1021-1033. https://doi.org/10.1017/s0954579414000546

Sheridan, M. A., McLaughlin, K. A., Winter, W., Fox, N., Zeanah, C., & Nelson, C. A. (2018). Early deprivation disruption of associative learning is a developmental pathway to depression and social problems. *Nature Communications*, *9*(1). https://doi.org/10.1038/s41467-018-04381-8

Stuart, S. A., Hinchcliffe, J. K., & Robinson, E. S. (2019). Evidence that neuropsychological deficits following early life adversity may underlie vulnerability to depression. *Pharmacological Reports*, *71*(6), 1315. https://doi.org/10.1016/j.pharep.2019.09.025

Twenge, J. M., Cooper, A. B., Joiner, T. E., Duffy, M. E., & Binau, S. G. (2019). Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005–2017. *Journal of Abnormal Psychology*, *128*(3), 185-199. https://doi.org/10.1037/abn0000410

Vidal, R., Pilar-Cuellar, F., Dos Anjos, S., Linge, R., Treceno, B., Ines Vargas, V., Rodriguez-Gaztelumendi, A., Mostany, R., Castro, E., Diaz, A., M. Valdizan, E., & Pazos, A. (2011). New strategies in the development of antidepressants: Towards the modulation of Neuroplasticity pathways. *Current Pharmaceutical Design*, *17*(5), 521-533. https://doi.org/10.2174/138161211795164086

Voss, M. W., Vivar, C., Kramer, A. F., & Van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. Trends in Cognitive Sciences, 17(10), 525-544. https://doi.org/10.1016/j.tics.2013.08.001

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., De Boer, P., Schmidt, M., & Claes, S. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry*, *73*(7), 639-645. https://doi.org/10.1016/j.biopsych.2012.10.014

Wang, G., Grone, B., Colas, D., Appelbaum, L., & Mourrain, P. (2011). Synaptic plasticity in sleep: Learning, homeostasis and disease. Trends in Neurosciences, 34(9), 452-463. https://doi.org/10.1016/j.tins.2011.07.005

Whitney, D. G., & Peterson, M. D. (2019). US national and state-level prevalence of mental health disorders and disparities of mental health care use in children. *JAMA Pediatrics*, *173*(4), 389. https://doi.org/10.1001/jamapediatrics.2018.5399

Wismer Fries, A. B., & Pollak, S. D. (2016). The role of learning in social development: Illustrations from neglected children. *Developmental Science*, *20*(2), e12431. https://doi.org/10.1111/desc.12431

Yates, W. R., Mitchell, J., Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Warden, D., Hauger, R. B., Fava, M., Gaynes, B. N., Husain, M. M., & Bryan, C. (2004). Clinical features of depressed outpatients with and without co-occurring general medical conditions in STAR*D. *General Hospital Psychiatry*, *26*(6), 421-429. https://doi.org/10.1016/j.genhosppsych.2004.06.008

Zobel, I., Kech, S., Van Calker, D., Dykierek, P., Berger, M., Schneibel, R., & Schramm, E. (2011). Long-term effect of combined interpersonal psychotherapy and pharmacotherapy in a randomized trial of depressed patients. *Acta Psychiatrica Scandinavica*, *123*(4), 276-282. https://doi.org/10.1111/j.1600-0447.2010.01671.x