A Study Proposal Investigating the Effects of a Mindfulness Intervention on Prefrontal Asymmetry in Children at Risk for Depression

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A study by Davidson and Fox (1989) found that 10-month-old infants who cried in response to maternal separation were more likely to show increased right-biased prefrontal activation during a preceding resting baseline, as compared to infants who did not cry in response to this challenge. Research suggests that differences in prefrontal activation begin to emerge quite early in life, possibly even as early as infancy (Davidson, 1998). Both in infants and adults, individual differences in resting electrophysiological measures of prefrontal activation seem to be associated with differences in their affective style (Davidson, 1998). Put simply, affective style refers to how individuals regulate and respond to their emotions (Davidson, 1998). Given that virtually all forms of psychopathology involve some malfunction in emotional processes, researchers believe that certain aspects of individuals' affective style may predict depressive symptoms (Davidson, 1998). Thus, it appears as though underlying differences in prefrontal activation may help explain children's susceptibility to depression.

Individual differences in children's prefrontal activation may be influenced by two important factors – low socioeconomic status (SES) and parental history of depression (Allen & Reznik, 2015; Gilman et al., 2002). Both of these factors significantly increase children's risk of developing depression as they tend to skew their prefrontal activation patterns to being more right focused.

Collectively, this posits the need to intervene during childhood in order to modify patterns of prefrontal activation that predict depression risk. Targeting children who are at risk for depression is crucial as they may otherwise face serious developmental and functional consequences with regards to this disorder. This study proposal involves testing an intervention with promise in modifying a biomarker of depression risk in young children.

Prefrontal Asymmetry as a Biomarker for Depression

Prefrontal asymmetry, a relative measure of the difference in electroencephalogram (EEG) alpha power between the right and left frontal regions, is a potential biomarker of depression risk that may be targeted with an intervention (Allen & Reznik, 2015). The term biomarker broadly refers to any characteristic that can be objectively measured and evaluated and that can influence or predict the incidence of outcome or disease (Strimbu & Tavel, 2010). In this case, prefrontal asymmetry may be considered a biomarker as it is a neurophysiological characteristic that can help distinguish those that are at risk for depression from those that are not.

Prefrontal asymmetry, commonly referred to as (resting) frontal EEG asymmetry (i.e., measure of asymmetry at baseline), is divided into two components—left and right EEG asymmetry (Vuga et al., 2008). EEG activity in the alpha band (typically 8-13 Hz) is understood as an inverse correlate of cerebral activity (Debener et al., 2000). Consequently, greater right-frontal EEG activation is taken to indicate increased relative left-frontal cortical activation (Pickens et al., 2001). Greater relative left activity is correlated with positive alpha EEG asymmetry values (Vuga et al., 2008). On the other hand, greater left-frontal EEG activation is taken to indicate increased relative right-frontal cortical activation (Pickens et al., 2001). Increased relative right activity is associated with negative alpha EEG asymmetry values (Vuga et al., 2008). EEG studies have identified right-biased prefrontal asymmetry as a potential biomarker in those at risk for depression (Davidson, 1998).

Notably, research suggests that prefrontal asymmetry in the alpha band is correlated with affective style and motivational bias, both in children and adults (Vuga et al., 2008). Understanding this correlation is crucial because both anhedonia (loss of interest of pleasure in activities that tend to be enjoyable) and depressed mood (negative affect) are central to depression. This has implications for children at risk for depression as asymmetry patterns emerging in childhood may predict the development of depression later in life. Resting EEG asymmetry studies have found support for increased left-frontal activity being associated with positive affect and the tendency for approach motivation (readiness of engagement with one's environment) (Davidson, 1998; Vuga et al., 2008). On the other hand, increased right-frontal activity is indicative of negative affect and negative motivational bias (withdrawal tendency) (Davidson, 1998; Vuga et al., 2008). Individuals at risk for depression reflect relatively less left prefrontal activity and greater right prefrontal activity, thus implying increased negative affect (Allen & Reznik, 2015). Given that differences in affective style and motivational bias pertain to specific hemispheres of the brain, researchers have reason to assume that resting frontal asymmetry patterns may in fact be understood in the context of a stable, trait-like biomarker for depression (Coan & Allen, 2004; Vuga et al., 2008).

Stability in frontal EEG asymmetry has been studied across various age groups, ranging from infancy to adulthood. Literature in this field reflects fair to moderate stability in frontal EEG asymmetry in infants aged 3- to 6-months, and preschoolers and school-aged children aged 3- to 9-years (Vuga et al., 2008). Research with adults also suggests moderate long-term stability in frontal EEG asymmetry (Vuga et al., 2008).

Studies measuring the relationship between individual differences in prefrontal asymmetry and affective style have heavily relied on the use of resting-state (baseline) EEG measures (Coan et al., 2006). Coan et al. (2006) report that researchers' growing use of resting-state measures draws from the dispositional model of frontal affective style. This model proposes that individuals have a predominant tendency to respond to situations with either approach (indexed by relatively increased left-frontal activity) or withdrawal (indexed by relatively increased right-frontal activity) related affect (Coan et al., 2006). Consequently, this approach reflects that individual differences in frontal EEG activity recorded during one condition are preserved during the following condition based on the assumption that resting frontal asymmetry is the primary indicator of one's affective style. On the other hand, Coan et al. (2006) suggest a novel approach to test for individual differences in frontal EEG asymmetry—the capability model. This model posits that individual differences in frontal EEG asymmetry are much more pronounced when participants are subject to emotionally evocative conditions (emotional challenge) as compared to resting conditions. Moreover, the model suggests that individual differences derived from emotionally challenging conditions will exhibit greater stability over time as compared to those derived during resting-state conditions. Overall, the extent of stability in frontal EEG asymmetry spanning from infancy to adulthood can provide support for the idea that prefrontal asymmetry may be a stable biomarker for depression.

Prefrontal Cortical Development in Childhood

Understanding prefrontal cortical development during childhood offers credibility for the idea that prefrontal asymmetry, although viewed as a stable biomarker for depression, may be modifiable to some extent. The prefrontal cortex (PFC) in humans is situated at the anterior end of the frontal lobe and is responsible for higher-order cognitive processes such as executive function (Diamond, 2002). Tsujimoto (2008) notes that PFC undergoes considerable maturation during early childhood. Certain periods of life are characterized by marked changes in the abilities associated with PFC, these periods being 3 to 6 years, and 7 to 11 years (Diamond, 2002). Biologically speaking, some processes which occur during this period of maturation include reduction of synaptic and neuronal density, dendritic growth, and an increase in both gray and white matter (Tsujimoto, 2008). The development of PFC is thought to lay the groundwork for higher cognitive functions during the period from early childhood to preschool age (Tsujimoto, 2008). Overall, PFC undergoes one of the longest periods of development in comparison with other brain regions, taking over two decades to reach full maturity in humans (Diamond, 2002). The developmental trajectory of PFC may pave the way for the effectiveness of an early intervention targeting prefrontal asymmetry in children at risk for depression.

Mindfulness as an Intervention for Modifying Prefrontal Asymmetry

Having identified prefrontal asymmetry as a potential biomarker for depression, it is worth investigating how mindfulness may modify this biomarker in order to prevent the development of depression in children at risk. As discussed earlier, prefrontal asymmetry is associated with depressive symptoms, i.e., negative affect and withdrawal tendency (Davidson, 1998). One particular intervention that has shown promise in decreasing negative affect and increasing intrinsic motivation in individuals is mindfulness practice (Donald et al., 2020; Schroevers & Brandsma, 2010). Practicing mindfulness involves paying attention to the present moment and extending one's awareness to any ongoing experiences, non-judgmentally (Kabat-Zinn, 2003). Barnhofer and colleagues (2010) argue that engaging in mindfulness practice is thought to inhibit the incessant cycles of negative mood and cognition which may otherwise persist and augment in depressed individuals. Consequently, this may be conducive to the implicit cultivation of positive affect (Barnhofer et al., 2010). Research by Davidson and colleagues (2003) suggests that intensive training in mindfulness meditation leads to significant changes in resting prefrontal asymmetry such that there is greater left-frontal activation post intervention compared to baseline.

One specific type of mindfulness practice is loving-kindness or *metta* meditation which explicitly aims to cultivate positive states of mind (Barnhofer et al., 2010). This form of meditation allows individuals to develop unconditional regard and nonexclusive love for all beings (Barnhofer et al., 2010). Barnhofer and colleagues (2010) studied the effects of both loving-kindness and mindfulness meditation on prefrontal asymmetry in previously depressed individuals and found that both forms of meditation produced comparable positive effects. In terms of prefrontal asymmetry, individuals who practiced either form of meditation showed an increase in relative left prefrontal activation from baseline to post-test, indicating increased approach motivation and positive affect. This provides support for interventions rooted in mindfulness and loving-kindness/compassion training with regards to their effectiveness in modifying prefrontal asymmetry.

In studying the relationship between mindfulness and the brain, Treadway and Lazar (2010) note that sustained mindfulness practice has effects on brain function and structure. Mindfulness is thought to be associated with both state and trait like effects (Treadway & Lazar, 2010). State effects refer to alterations that occur in individuals while they are actively engaged in mindfulness practice whereas trait effects occur over a longer period of time as a result of sustained mindfulness practice and long-term modifications in brain activity and structure (Treadway & Lazar, 2010). Treadway and Lazar (2010) propose that understanding trait effects may provide a better understanding of why mindfulness is useful for treating chronic conditions such as depression. Considering that prefrontal asymmetry may be a stable, trait-like biomarker for depression, how might mindfulness practice modify this biomarker in children at risk for depression?

Investigating the effects of mindfulness training as an intervention for prefrontal asymmetry in children at risk for depression may allow for a better understanding of whether this biomarker is modifiable and to what extent. Given that prefrontal asymmetry patterns start to manifest quite early in life, it may be plausible to intervene early in order to modify it. This may help prevent the development of depression in the at-risk population, especially in children from low socioeconomic backgrounds who have parents with a history of depression.

Goal of the Current Study

The proposed study is a randomized controlled trial aimed at investigating the effects of a preschool-based mindfulness intervention on prefrontal asymmetry in children at risk for depression. Baseline data will be collected within 3 weeks of the start of the intervention and post data will be collected within 3 weeks of the end of the intervention. I hypothesize that children in the intervention group will demonstrate a shift in prefrontal asymmetry from being right-biased to being more left-focused. Children in the waitlist control group will exhibit a general stability in prefrontal asymmetry, reflecting comparable levels of right-biased prefrontal activation at pre- and post-test.

Proposed Method

Participants

This study sample will consist of 90 preschool children roughly between the ages 3 and 5 years. The sample size for this proposed study was calculated using a power analysis[1]. Children will be recruited from five different preschools in the South Side area, Chicago, IL. This particular location is chosen because of its demographic – families in this area come from predominantly low-income backgrounds and have higher chances of being eligible for the study,

[1] Sample size was calculated based on an estimated 2% increase in left prefrontal activation for children who receive the mindfulness intervention, and to allow for the proposed study to have 80% power.

as highlighted by the inclusion criterion below (Chicago Metropolitan Agency for Planning [CMAP], 2020). The sample will be gender balanced, indicating an equal ratio of boys (N = 45) to girls (N = 45). Based on the demographics of South Chicago, I anticipate that a majority of these children will be of African American ethnic background, and some may be Hispanic or Latino (CMAP, 2020). Parents will be asked to report on their child's race and ethnicity, age, and gender using a short questionnaire.

Participants' eligibility for the study will be based on specific inclusion and exclusion criteria. Children from low socioeconomic households will be considered eligible for the study as research suggests that low SES can predict right-biased prefrontal asymmetry as early as childhood (Gilman et al., 2002). Participants' socioeconomic status will be determined by obtaining information from their parents regarding their annual household income (less than $25,000, $25,000 to $49,999, $50,000 to $74,999, etc.), educational attainment (less than high school graduate, high school graduate or equivalent, some college but no degree, associate degree, etc.), and housing size (0 to 1 bedroom, 2 bedrooms, 3 bedrooms, etc.). Upon reviewing these data, families who fall under the low socio-economic category will be followed up. Another inclusion criterion is mothers' history of depression as this is known to be correlated with relatively greater right prefrontal activation in their offspring (Allen & Reznik, 2015). Mothers will be asked to report on any prior history of depression/depressive episodes using a questionnaire and will then be followed up with a structured clinical interview for diagnostic purposes. Children must also be predominantly right-handed to be eligible for this study. Handedness will be assessed using the Edinburgh Handedness Inventory as it can have an impact on asymmetry patterns due to the differential brain organization of left- and right-handed individuals (Vuga et al., 2008). While prefrontal asymmetry is not an inclusion criterion for this study, collecting baseline data on this measure will help compute the effects of the mindfulness intervention on children's prefrontal asymmetry.

Children whose parents (one or both) have a past history or current symptoms of ADHD or schizophrenia will be excluded from the sample. Adults who have these disorders also tend to exhibit frontal asymmetry patterns which may manifest in their offspring (Horan et al., 2014; Keune et al., 2015). For the scope of this study, I intend to have a sample that is reflective of prefrontal asymmetry patterns as associated with depression alone. Information regarding parents' history of other disorders will be obtained as part of the depression questionnaire.

Kindness Curriculum Intervention

The Kindness Curriculum (KC), developed by the Center for Healthy Minds at the University of Wisconsin-Madison, is a mindfulness-based curriculum designed for young children, typically ages 3 to 5 years (Flook et al., 2015). Previous research investigating the impact of KC on preschoolers suggests improvements in children's emotion regulation, resilience, prosocial behavior, cognitive skills, and self-regulation skills (Flook et al., 2015).

The curriculum will be implemented in classroom-based settings in five preschools in South Chicago and will include brief (15 to 30 minutes) lessons and activities rooted in mindfulness, kindness, and compassion. Teachers will be trained for KC and will conduct lessons and activities from the curriculum twice a week, for 12 consecutive weeks. Using random assignment, preschool classrooms will either receive the KC intervention or will be placed in the waitlist control group in order to measure the effects of the intervention on children's prefrontal asymmetry. For ethical purposes, including a waitlist control group will ensure that children who may not receive the intervention as part of the study will still be given a chance to benefit from KC post data collection. Once the sample is selected, 45 children (nested within 10 preschool classrooms with an average of 15 children each) will receive the KC intervention whereas the remaining 45 children (nested within a different set of 10 preschool classrooms with an average of 15 children each) will carry on with their regular preschool curriculum. Sampling from 20 different classrooms will improve the chances of selecting children who meet the inclusion criteria and are willing to participate in the study.

Materials

The Mood Induction Stimulus for Children (MISC) will be utilized as the stimulus for this study. The capability model proposed by Coan et al. (2006) provides support for the use of emotionally evocative tasks (in comparison with resting-state tasks) as a means to elicit more pronounced individual differences in prefrontal asymmetry. The following description of the stimulus is adapted from Pickens et al. (2001).

MISC is a videotape comprised of eight distinct mood-inducing vignettes that are controlled for affective intensity and duration. The stimulus consists of three consecutive segments: a 15-second baseline which includes a star-field and soft background music that is used as a comparable resting-state recording, a 30-second episode (emotionally valent vignette), and a 15-second closing that serves as a resolution to the story. This stimulus pattern is repeated until eight vignettes (8 star-fields, 8 episodes, and 8 resolutions) are presented, totaling the presentation time up to 8 minutes. The vignettes consist of black and white static line drawings of "Zudok," a fictional character from outer space who is placed in various different situations that are verbally narrated and accompanied by mood appropriate music. For instance, one vignette depicts a *sad* episode wherein Zudok's dog is lost but is found again during the closing segment. The vignettes include negatively and positively valanced episodes that are presented in the following order: 1) Zudok enjoying a birthday party (*happy)*, 2) Zudok losing his dog (*sad)*,

3) Zudok having his blocks knocked over by a friend (*angry*), 4) Zudok experiencing a thunderstorm (*fear*), 5) Zudok being informed that his grandfather is sick (*sad*), 6) Zudok getting lost in a mall (*fear*), 7) Zudok being denied permission to stay up and watch television (*angry*), and 8) Zudok going to a circus (*happy*).

Procedures

Measures of children's prefrontal asymmetry pre- and post-intervention will be obtained via EEG. Electroencephalography is a widely used neuroimaging technique that helps detect electrical activity generated by the brain using electrodes placed onto the scalp. The proposed study will be reviewed by the Institutional Review Board. Participants will be ensured of no/minimal risk of physical or psychological harm if they choose to participate in this research study. Participant visits will take place at a research facility housed in Northwestern Memorial Healthcare, Chicago, IL. Participants' families will be reimbursed for travel expenses to and from the testing location (maximum $20 per participant). Prior to each of the two testing sessions, verbal assent will be obtained from each child along with written informed consent from the child's legal guardian who will accompany them during visits.

EEG recordings will be obtained whilst children are being presented with the 8-minute MISC videotaped vignettes. Children will be instructed to remain seated and pay close attention to the stimulus being presented. They will be told that the video is about a child from outer space. A lycra stretchable electrode cap will be positioned on the child's head based on the International 10-20 System (Vuga et al., 2008). Using electrode gel, electrodes will be placed at the following frontal sites: F3, F4, F7, and F8. These specific frontal lobe sites are chosen as they are commonly studied in the prefrontal asymmetry literature and seem to be indicative of depression-related prefrontal asymmetry in the lateral and medial regions of the frontal cortex

(Coan & Allen, 2004; Vuga et al., 2008). EEG recordings will be obtained against a vertex (Cz) reference; however, Cz-referenced data will not be included in EEG data analysis (Vuga et al., 2008). Electrode impedances will be set below 5kΩ (Vuga et al., 2008). An additional component of EEG data acquisition is recording horizontal and vertical eye movements as part of artifact scoring. EEG artifacts refer to any electrical activity that does not have cerebral origin (Pickens et al., 2001). To facilitate this, an electro-oculogram (EOG) channel will be used – one electrode will be positioned above the child's right eye and another will be placed on the outer canthus of the right eye (Pickens et al., 2001). EEG signals will be passed through a bioamplifier with high and low frequency filers of 1 and 100 Hz respectively (Pickens et al., 2001; Vuga et al., 2008). Signal output from the amplifiers will be directed to a computer device. Data will be sampled at a rate of 512 Hz (Pickens et al., 2001; Vuga et al., 2008). Data will be acquired and analyzed using equipment and software from the James Long Company (Caroga Lake, N. Y.).

EEG Data Analysis

EEG data will be analyzed with the help of an EEG analysis software package. Data will be scored for artifacts using the EOG channels and artifact-data will be subsequently eliminated from the analysis (Vuga et al., 2008). Notably, the MISC videotaped vignettes are composed of spatially static visuals that will help prevent any major eye movement in participants (Pickens et al., 2001). Data from children who may have a difficult time focusing on the stimulus will be excluded as they might present as outliers in the dataset. Distractibility/disengagement will be determined by tracking the frequency and duration of a child's gaze away from the screen (a higher score in either category will be the basis for exclusion of data).

Data will be subjected to Fourier analyses using a 1-second artifact-free Hanning window with 50% overlap (Pickens et al., 2001; Vuga et al., 2008). EEG data will be analyzed by epochs corresponding to the three segments of MISC: 15-second neutral baseline epoch, 30-second emotionally valent episode, and 15-second closing (Pickens et al., 2001). Based on the evaluation of power distribution among preschool children, the alpha band for this study is set as 6.5 to 10.5 Hz in 3- to 5-year-old children (Vuga et al., 2008). EEG data analysis will result in alpha power values for the right and left hemispheres for each of the three stimulus segments.

Children's EEG asymmetry scores will be computed by measuring the difference between natural logarithm (ln) of EEG alpha power at the right recording site and the left recording site – ln(right) – ln(left), e.g., for sites F3/F4 = ln(F4) – ln(F3) (Vuga et al., 2008). As noted earlier, cortical activity is inversely correlated with EEG alpha power (Debener et al., 2000). Furthermore, positive alpha asymmetry scores are indicative of greater left cortical activation whereas negative alpha asymmetry scores are correlated with increased right cortical activation (Vuga et al., 2008).

Discussion of Possible Results

The present study aims to investigate the effects of a 12-week preschool-based mindfulness intervention on prefrontal asymmetry in children at risk for depression. I predict that children who receive the intervention will demonstrate a small shift in prefrontal asymmetry such that it is more left-focused (increased left prefrontal activity as compared to right prefrontal activity) whereas those in the waitlist control group will exhibit a general stability in prefrontal asymmetry (greater right prefrontal activity as compared to left prefrontal activity at both pre- and post-test) (see Appendix).

If the hypothesis were to be supported as discussed above, this would suggest that mindfulness may be an effective intervention for modifying prefrontal asymmetry, a potential biomarker for depression, quite early on in life. However, it is important to consider the contrary wherein the data obtained may not be in line with the hypothesis. A small effect size may be one reason why it may be difficult to establish a statistically significant difference in children's prefrontal asymmetry scores when comparing data from the two groups. Secondly, the duration and intensity of the mindfulness intervention may not be sufficient to promote a shift in children's prefrontal asymmetry. Twelve weeks may be too brief for inducing changes in the biomarker given its moderate stability during preschool years (Vuga et al., 2008). Not all children who receive the intervention may fully engage with the Kindness Curriculum lessons and activities. It is likely that children may miss parts of the intervention due to absences from preschool. These factors may contribute to individual differences in the effectiveness of the mindfulness intervention.

Data from the proposed study may also be understood in the context of a dose-response relationship. A dose-response relationship describes the magnitude of a response as a function of stimulus exposure. In this case, measures of children's prefrontal asymmetry may be directly associated with their engagement with the intervention. Children who show a greater stability in prefrontal asymmetry prior to the intervention may reflect a stronger shift in asymmetry post-intervention as mindfulness training may be particularly effective for these subjects. On the other hand, these children may demonstrate minimal change in prefrontal asymmetry merely because their brain patterns may be resistant to modification. Adapting this lens may allow us to distinguish children who are more resistant to alterations in prefrontal asymmetry as compared to those who are less resistant, thus helping to determine a minimal "dosage" of the intervention that may produce lasting effects in children who are at risk for depression.

If mindfulness practice seems to produce changes in children's prefrontal asymmetry, it may be worth investigating the underlying mechanisms of this relationship. Malinowski (2013) suggests that enhancing attentional processes is central to mindfulness-based practices. Training of attentional skills in children who are at risk for depression may help improve their ability to recognize their emotions, especially those experiencing increased negative affect. Attention may act as a possible mediator in the relationship between mindfulness and prefrontal asymmetry and testing for this mediating effect may help uncover the cognitive mechanisms driving this change.

Overall, mindfulness may show promise as an intervention for modifying prefrontal asymmetry in children at risk for depression as it predicts increased left cortical activation which is associated with greater positive affect and approach motivation, both characteristics that reflect reduced risk of depression (Davidson, 1998; Davidson et al., 2003). Findings from the proposed study may help determine the effectiveness of a mindfulness-based intervention for preschoolers at risk for depression, allowing researchers to work toward disseminating the Kindness Curriculum in preschool settings in order to promote children's well-being.

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Appendix

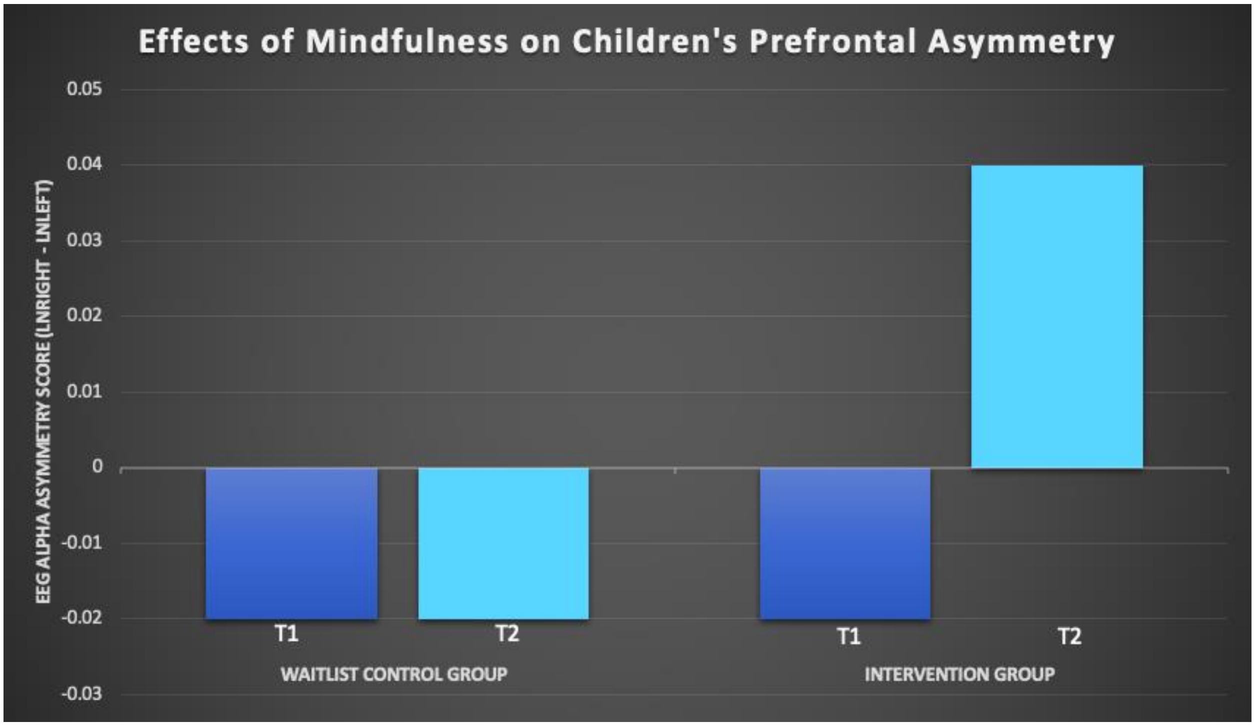

Figure 1. Children's mean prefrontal asymmetry score as predicted by their assignment to the waitlist control group or the mindfulness intervention group. Prefrontal asymmetry is measured at two timepoints – T1 (baseline data) and T2 (post-data). Positive alpha asymmetry scores reflect greater left prefrontal activation and negative alpha asymmetry scores indicate greater right prefrontal activation.