Exploring neural correlates of depression in childhood: The relation between

amygdala:hippocampus ratios and CDI depression scores in 4-8 year olds

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Abstract

Nationally representative studies have shown that mood disorders such as depression and anxiety are widely prevalent in children, with depression acting as one of the leading causes of disability in the United States (Ghandour et al., 2018; Schmaal et al., 2016). Research on adults suggests that depression and mood regulation can be linked to brain structure and function, specifically abnormalities with the amygdala and hippocampus (Yavas et al., 2019; Gerritsen et al., 2012). Interestingly, these brain regions have been shown to undergo structural and functional changes in early childhood that correspond with critical developmental changes in behavior (e.g., Riggins et al., 2018; Stern et al., 2019). Despite these changes, there is very little research investigating the relation between the brain and depressive symptoms in children, particularly during early childhood. Furthering the understanding of the relation between structural changes in brain and depressive symptoms is critically important not only for addressing high rates of childhood depression, but also for understanding the etiology and course of depression from early childhood into adulthood. This information could inform future intervention strategies and improve our understanding of normative and non-normative development in early childhood. This study aims to fill this gap by assessing the association between amygdala and hippocampus volumes and depressive symptoms cross sectionally and longitudinally in children ages 4-8 years.

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The brain is a complex structure, and beginning to understand neural roots of pathology implicates more than an understanding of the effects of a single structure on function at a single point in time. Rather, behaviors are more likely a result of the coordination and interaction between multiple structures within the brain. This makes studies investigating the coordination between multiple brain structures crucial for furthering our understanding of complex and disordered behavior. This seems to be particularly true for the amygdala and hippocampus, which are involved in the encoding of complex memory, mood, emotion, and, therefore, association of memories with emotional context (Yavas et al., 2019; Gerritsen et al., 2012). Further research on the association between these structures to memory and emotional context suggests that the ratio of these structures (i.e., how large the amygdala is relative to the hippocampus) is associated with negative memory bias in adults, often a contributor to the development of depression (Gerritsen et al., 2012).

Interestingly, the amygdala and hippocampus have also been shown to undergo rapid structural and functional change in early stages of development (Riggins et al., 2019; Stern et al., 2018). It seems intuitive, then, that this structural change could correspond to development of depression and mood disorders in early childhood, making it critically important to investigate these structures earlier in life. However, even with our knowledge of these structural changes, there is very little research that assesses amygdala:hippocampus (AH) ratios in young children, when development is most rapid. One of the few studies assessing AH ratios in children investigated pediatric patients (ages 8-17 years) diagnosed with pediatric major depression, and found that increased AH ratios (larger amygdala compared to smaller hippocampus) were

associated with severity of anxiety symptoms (MacMillan et al., 2003). To our knowledge, there are no previous studies that investigate this association in children younger than 8 years.

Other studies have investigated the hippocampus and amygdala in isolation. In regards to the hippocampus, many studies have found that smaller hippocampal volumes are associated with depression scores. A study conducted by Pagliaccio et al. (2014) investigated the association between amygdala and hippocampus volumes and depressive symptoms and found that smaller bilateral hippocampal volumes were associated with increased depressive symptoms in 8-12 year olds. Further, studies utilizing the Child Behavior Checklist (CBCL) found that higher scores on internalizing behaviors were correlated with decreased hippocampal volume (Koolschijn et al., 2013). This finding is also consistent when controlling for several factors. For instance, higher CBCL scores were associated with smaller hippocampal volume in children even when controlling for life events and income (Barch et al, 2019). This study also establishes that the association between major depressive disorder and smaller hippocampal volumes have been observed as young as 3 years old (Barch et al, 2019). There was only one study to our knowledge that found that larger hippocampal volumes in adolescence corresponded with increased depression (Rosso et al., 2005).

In contrast, studies of the amygdala are more inconsistent. Some studies indicate no association between amygdala volumes and depressive scores in children. For instance, even though it has been found by Koolschijn et al. (2013) that higher scores on Child Behavior Checklist (CBCL) internalizing behaviors were correlated with decreased hippocampal volume, there was no significant association with amygdalar volumes (Koolschijn et al., 2013). Further, a study by Zavorontyy et al., (2018) found that amygdala volumes did not differ significantly between controls and those with major depressive disorder, but did find that the left amygdala

volume was negatively associated with total lifetime spent in depression. In other words, increased left amygdala volume predicted less time spent in depression (Zavorotnyy et al., 2018). Conversely, other studies have found that smaller amygdala volume predicts depressive symptoms in childhood. For instance, Merz et al. (2018) found that smaller amygdala volumes were significantly associated with increased depression in children, but that external factors such as socioeconomic status were correlated with smaller amygdalas in adolescence, but not earlier childhood. This could indicate some developmental difference in the structure and function of the amygdala and could be responsible for some of the inconsistent findings from previous research. These findings are consistent with a study by Ross et al. (2005) which found that depressed adolescents had significantly smaller left and right amygdala. However, as previously mentioned, studies on AH ratios have reported larger AH ratios (larger amygdala to smaller hippocampus) are correlated with problems related to mood regulation, negative memory bias, and other contributing factors to depression (Gerritsen et al., 2012; MacMillan et al., 2003).

In summary, although the literature indicates that there is evidence of a relation between amygdala, hippocampus and AH and depression scores in adult and late-childhood populations, these findings are relatively inconsistent. Further, there is a lack of research regarding this topic in young children, specifically children eight years and younger, and very limited research that investigates this association longitudinally from this age group. Thus, the aim of the present study is to be the first research to investigate the associations between these structural volumes and depressive symptoms in early childhood by using data from a cohort-sequential longitudinal study conducted on 4-to-8 year-old children. This study is particularly valuable because of its ability to investigate the association between amygdala, hippocampus and AH ratios cross-sectionally and also longitudinally as they relate to depressive scores.

Method

Participants

The present study utilized data from a dataset that was a part of a previous NIH-funded investigation (HD079518, PI Riggins). The full dataset includes 200 typically developing participants (100 females and 100 males) from ages 4-8 years (Riggins et al., 2018). Of these, 100 children were followed longitudinally for a total of three time points, each 12 months apart, using a cohort sequential design (Riggins et al., 2019; Stern et al., 2018). The focus of the current report is on Children's Depression Inventory (CDI) and MRI data that were collected from participants at the second and third assessment time points (W2 and W3). Data from W1 was excluded from this study because CDI scores were not collected at this time point.

Measures

Depressive Symptoms: Depressive symptoms were assessed using the Children's Depression Inventory (CDI; Kovacs, 1985) parent-report questionnaire. Parents of participants were administered the questionnaire which asked them to rate the degree to which they agreed with each item on the questionnaire. Responses were based on a 5-point scale (*0= not at all* and *4= Much or most of the time*) wherein parents were asked to rate the degree to which they agreed with items regarding their child's symptoms of depression. Examples of such items include "My child does not like himself or herself," and "My child seems lonely." Scores for each item were summed to determine the total score at W2 (*M*= 12.00; *SD*= 3.68) and W3 (*M*= 11.96; *SD*=4.12), with higher scores signifying greater presence of depressive symptoms and lower scores representing lower depressive symptoms.

Amygdala and Hippocampal Volumes: T-1 weighted structural magnetic resonance imaging (MRI) was used to capture amygdala and hippocampus volumes at each time point and

were processed and measured using Freesurfer (v. 5.1). Because previous research has found

significant associations between AH ratios and depressive symptoms and mood regulation issues

in adult and later childhood populations, AH ratios were calculated. This was done by dividing

amygdala volume by hippocampal volume for each participant. However, because testing the

association between depressive symptoms and AH ratios does not allow researchers to see

whether individual structures might be driving developmental change over time, structural

volumes were also assessed individually as well in order to get a clearer picture as to which

structure (if any) had a more profound association with CDI scores at each time point. In

addition to collection of amygdala and hippocampus volumes, intracranial volume (ICV) was

collected as a control for participant head size.

Results

Data Analytic Approach: In order to explore relations between amygdala volumes,

hippocampal volumes, and AH ratio volumes and depressive symptoms, I conducted analyses

using SPSS, controlling for variations in sex and ICV. Control variables were determined by

correlation analyses at W2 (Appendix A) and W3 (Appendix B). Age was excluded as a control

variable because of its high correlation to ICV. In order to address the question of whether brain

volumes were associated with CDI scores concurrently (i.e., cross-sectionally at W2 and W3),

we used linear regression to predict CDI scores based on amygdala, hippocampus, or AH ratios,

controlling for ICV and sex at W2 ($N= 61$) and W3 ($N= 58$). To assess the question of how

changes in volume were associated with *changes* in CDI scores, linear regression was utilized to

predict CDI scores at W3. ICV, sex, CDI scores at W2, and structural volumes at W2 and W3

were included as predictor variables to investigate longitudinal associations. Doing so allowed

for the assessment of a "change" score in structural volumes to be regressed against CDI scores

at W3 while controlling CDI scores at W2. 47 participants provided usable data from CDI scores and MRI scans at both W2 and W3 (*N*=47). (Note: The original plan for the third analysis was to assess the correlation between difference scores in structural volumes and change scores of CDI between W2 and W3. However, despite being widely utilized to assess developmental change, the methodological soundness of using difference scores to test for longitudinal change has also been disputed (Cronbach & Furby, 1970; Laird, 2020)). Based on research in older individuals, and based on findings from a similar cohort-sequential study on 8-12 year olds by Pagliaccio et al. (2014), we predicted that larger AH volume ratios (larger amygdala and smaller hippocampus volumes) will be correlated with depression in children between the ages of 4 and 8 years old.

AH Ratios

      Cross Sectional Analysis: It was hypothesized that larger AH ratios would predict higher CDI scores (increased depressive symptoms). In order to test this hypothesis, a linear regression was conducted in order to determine the amount of the variance observed in CDI scores at W2 that was accounted for by AH volume ratios at W2. Results did not reveal a significant association between AH ratio volumes at W2 and CDI scores at W2 (Table 1), and therefore did not support the aforementioned hypothesis. A second linear regression was performed at W3. At W3, results did not reveal any significant association between AH ratio volumes at W3 and CDI scores at W3 (Table 2).

      Longitudinal: It was hypothesized that change in AH volumes from W2 to W3 would predict CDI scores at W3. In order to test this hypothesis, a linear regression was conducted controlling for ICV, sex, CDI scores at W2 , and AH volumes at W2. Controlling for AH volumes at W2 allowed us to assess whether the change in AH volumes between W2 and W3 was associated with CDI scores at W3. However, results did not reveal any significant

association between AH volumes at W3 and CDI scores at W3, indicating that change in AH

volumes were not significantly predictive of CDI scores (Table 3, Figure 1). The only significant

predictor of CDI scores at W3 was CDI scores at W2, $p < .001$.

Hippocampal Volumes

Cross Sectional Analysis: It was hypothesized that smaller hippocampal volumes would

predict higher CDI scores (increased depressive symptoms). In order to test this hypothesis, a

linear regression analysis was conducted in order to determine the amount of the variance

observed in CDI scores at W2 that was accounted for by hippocampal volumes. However, after

controlling for ICV and sex, results revealed that hippocampal volumes at W2 did not

significantly predict CDI scores at W2 and therefore did not support the hypothesis (Table 1). A

second linear regression was conducted at W3 to assess the association between hippocampal

volumes at W3 and CDI scores at W3. After controlling for ICV and sex, results did not reveal

any significant relation between hippocampal volumes at W3 and CDI scores at W3(Table 2).

Longitudinal: It was hypothesized that change in hippocampal volumes from W2 to W3

would predict CDI scores at W3. In order to test this hypothesis, a linear regression was

conducted controlling for ICV, sex, CDI scores at W2, and hippocampal volumes at W2.

Controlling for hippocampal volumes at W2 allowed us to assess whether the change in

hippocampal volumes between W2 and W3 was associated with CDI scores at W3. However, the

linear regression did not reveal any significant association between hippocampal volumes at W3

with CDI scores at W3, indicating that the aforementioned hypothesis was not supported (Table

3, Figure 2).

Amygdala Volumes

Cross Sectional Analysis: Based on previous research, it was hypothesized that larger amygdala volumes would predict increased CDI scores (more depressive symptoms). In order to test this hypothesis, a linear regression was conducted in order to determine the amount of the variance observed in CDI scores at W2 were accounted for by amygdala volumes. If the analysis reveals a significantly positive relation between W2 amygdala volumes and W2 CDI scores, this would indicate that a significant portion of the variance observed in CDI scores at this wave were accounted for by amygdala volumes, and that increased amygdala volumes predicted higher CDI scores at W2. However, the results did not reveal a significant association between W2 amygdala volumes and W2 CDI scores (Table 1, Figure 3). Thus, the results did not support the hypothesis at W2. Similarly to W2, it was hypothesized that amygdala volumes at W3 would be positively correlated with CDI scores at W3. Contrary to results seen at W2, increased amygdala volumes at W3 were marginally related to CDI scores at W3, but did not reach traditional thresholds for significance (Table 2, Figure 4).

Longitudinal: It was hypothesized that change in amygdala volumes from W2 to W3 would predict CDI scores at W3. In order to test this hypothesis, a linear regression was conducted controlling for ICV, sex, CDI scores at W2, and amygdala volumes at W2. The analysis revealed a marginal relation between greater change in amygdala volumes at W3 and CDI scores at W3 while controlling for ICV, sex, and amygdala volumes at W2 & CDI at W2, but also did not reach traditional thresholds for significance (Table 3, Figure 5).

<div align="center">

Discussion

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The purpose of the present study was to assess whether amygdala, hippocampus, and AH volume ratios predict depressive symptoms in 4-to-8 year-olds both cross-sectionally and

longitudinally. As previously discussed, current literature investigating AH ratios and depressive symptoms indicates that increased AH ratios (larger amygdala compared to smaller hippocampal volumes) predicted increased severity of depressive symptoms in adults and anxiety in pediatric patients with MDD (MacMillan et al., 2003; Gerritsen et al., 2012). It was therefore hypothesized that increased AH volume ratios in children under 8 years of age would also predict increased depressive symptoms. However, results from our analysis did not support this hypothesis, and instead revealed no significant relation between AH ratios and depressive symptoms in 4- to-8 year-olds, both cross-sectionally and longitudinally. Similarly, no significant associations were found between hippocampal volumes and depressive symptoms cross-sectionally or longitudinally. This was particularly surprising because, when looking at previous research on the amygdala and hippocampus volumes and their association with depression in children, research on the hippocampus provided more consistent findings with smaller hippocampal volumes predicting increased depressive symptoms in children (Pagliaccio et al., 2014; Koolschijn et al., 2013; Barch et al., 2019). Therefore, the hypothesis that smaller hippocampal volumes would predict increased depressive symptoms in childhood was not supported by the present study.

While analyses revealed an association between amygdala volumes and depressive symptoms that came closer to approaching significance, these associations were still non-significant, both longitudinally and cross-sectionally. Contrary to the hypothesis, analyses at W2 and W3 both revealed that amygdala volumes were not significantly correlated to increased depressive symptoms. Similarly, longitudinal analyses revealed nonsignificant associations between growth of the amygdala between W2 and W3 and depressive symptoms at W3. These findings, though not statistically significant, do yield interesting patterns. For one, the

associations between amygdala volumes and depressive symptoms at W2 and W3 were directionally different. Results from W2 seem to corroborate findings from Ross et al. (2005) and Merz et al. (2018), which found that smaller amygdala volumes predict increased depressive symptoms in children. However, results from W3 seem to corroborate findings from Gerritsen et al., (2012) which found that, for adult participants, increased amygdala volumes predicted increased depressive symptoms, and supported findings from MacMillan et al., (2002) which found that increased amygdala volumes predicted increased anxiety for those with MDD.

It is important to note that the findings from the present study reveal nonsignificant associations between amygdala volumes and depressive symptoms. It is, therefore, likely that the results from this study corroborate findings from Koolschijn et al. (2013) and Zavorotnyy et al. (2018) which indicated no significant association between amygdala volumes and depression or depressive symptoms in children. There were no previous studies, to our knowledge, that assessed change in amygdala volumes over time in children this young. Only one study investigated change in amygdala volumes and depression in childhood, and was focused on pre-adolescence. This study revealed that for adolescent girls only, exaggerated growth of the amygdala from early adolescence to late adolescence predicted development of MDD, whereas attenuated growth of the amygdala during this time period was associated with the development of MDD in boys (Whittle et al., 2014). Therefore, future research should aim to investigate the association of the amygdala and depressive symptoms at earlier ages and into adolescence.

There are several limitations of the present study. For one, the sample utilized for this study included only typically developing children and did not sample from clinical populations. Much of the literature cited in this paper discusses the neuronal correlates of depression and samples from those clinically diagnosed with depression. It is possible, therefore, that these

results could not corroborate previous findings because this study only investigates depressive symptoms. Further, depressive symptoms were measured using a parent-report questionnaire. It is also, therefore, possible that despite the anonymity of the responses, parents could have been subject to self-report biases regarding their children's experience of psychological distress and depression. Further, it is possible that a different measure would have been more appropriate for children at this age. While the CDI has been shown to reliably reflect depressive symptoms, a review of the literature revealed that the CDI is typically administered to children who are 7 years or older. Therefore, it is possible that this measure is not as reliable when administered to the age group represented in this study, and future studies should aim to use measures such as Beck Depression Inventory II which has been validated in children ages 3-to-6 years (Beck, Steer, & Brown, 1996). Another limitation regarding the assessment of depressive symptoms is that data from the CDI were only collected at W2 and W3, and excluded W1. Including W1 could have provided even more insight into the developmental patterns of the amygdala and hippocampus and how it might relate to depressive symptoms in our sample.

There are several potential future directions for researchers investigating the association of brain structures and depressive symptoms in early childhood. For one, it is important that future research investigates how subregions of both the amygdala and hippocampus might be related to depressive symptoms. The present study only investigated total volumes of the amygdala and hippocampus when looking at these structures individually, but investigating subregions might help to address some of the heterogeneity of the research findings in this area. In a recent study by Yao et al. (2020), it was found that structural changes to different subregions of the hippocampus and amygdala were more prevalent in those with MDD than those without MDD.

Further, it should be noted that the present study utilized linear regression to assess longitudinal change in CDI scores and structural volumes, and therefore differs from other longitudinal studies that utilize difference scores, a widely used but often criticized methodological strategy. This widespread use of difference scores might be a result of several methodological limitations. For instance, in order to utilize statistical methods proposed by Laird (2020), researchers would be required to gather extremely large sample sizes, which might prove even more difficult for longitudinal studies focused on brain development in young children. It is therefore important for researchers to be both mindful of the limitations of using difference scores, but to also pursue and investigate alternative statistical techniques that take into account the difficulties of assessing longitudinal change in young children. Future research should also attempt to synthesize previous research on neuronal correlates of depression in childhood. Synthesizing all previous studies on this topic could help address the heterogeneity of the findings on this topic, investigate the different methodologies used, and better inform future investigations into this topic to improve methodology and our understanding of the etiology of depression in children.

References

Barch, D. M., Tillman, R., Kelly, D., Whalen, D., Gilbert, K., & Luby, J. L. (2019). Hippocampal

   volume and depression among young children. *Psychiatry Research: Neuroimaging*, *288*,

   21–28. https://doi.org/10.1016/j.pscychresns.2019.04.012

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *BDI-II: Beck Depression Inventory*. Pearson.

Cronbach, L. J., & Furby, L. (1970). How we should measure" change": Or should we?.

   Psychological Bulletin, *74*(1), 68.

Gerritsen, L., Rijpkema, M., van Oostrom, I., Buitelaar, J., Franke, B., Fernández, G., &

   Tendolkar, I. (2012). Amygdala to hippocampal volume ratio is associated with negative

   memory bias in healthy subjects. *Psychological Medicine*, *42*(2), 335–343.

Ghandour, R.M., Sherman, L.J., Vladutiu, C.J., Ali, M.M., Lynch, S.E., Bitsko, R.H., Blumberg,

   S.J. (2018) Prevalence and treatment of depression, anxiety, and conduct problems in

   U.S. children. *The Journal of Pediatrics*. Published online before print October 12, 2018

Koolschijn P. Cédric M.P, van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Crone, E. A.

   (2013). Hippocampal volume and internalizing behavior problems in adolescence.

   European Neuropsychopharmacology, *23*(7), 622–628.

Laird, R. D. (2020). Analytical challenges of testing hypotheses of agreement and discrepancy:

   Comment on Campione-Barr, Lindell, and Giron (2020). *Developmental Psychology,*

   56(5), 970–977. https://doi.org/10.1037/dev0000763

MacMillan S, Szeszko PR, Moore GJ, Madden R, Lorch E, Ivey J, Banerjee SP, Rosenberg DR

   (2003). Increased amygdala: hippocampal volume ratios associated with severity of

   anxiety in pediatric major depression. *Journal of Child & Adolescence*

   Psychopharmacology, 13, 65–73.

Merz, E. C., Tottenham, N., & Noble, K. G. (2018). Socioeconomic status, amygdala volume,

and internalizing symptoms in children and adolescents. *Journal of Clinical Child and*

Adolescent Psychology : The Official Journal for the Society of Clinical Child and

Adolescent Psychology, American Psychological Association, Division 53, *47*(2),

312–323. https://doi.org/10.1080/15374416.2017.1326122

Pagliaccio, D., Luby, J. L., Luking, K. R., Belden, A. C., & Barch, D. M. (2014). Brain–behavior

relationships in the experience and regulation of negative emotion in healthy children:

Implications for risk for childhood depression. *Development and psychopathology*, *26*(4 0

2), 1289.

Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., & Hancock, G. (2018). Protracted

hippocampal development is associated with age-related improvements in memory

during early childhood. *NeuroImage, 174,* 127-137. DOI:

https://doi.org/10.1016/j.neuroimage.2018.03.009

Rosso, I. M., Cintron, C. M., Steingard, R. J., Renshaw, P. F., Young, A. D., & Yurgelun-Todd,

D. A. (2005). Amygdala and hippocampus volumes in pediatric major depression.

Biological Psychiatry, *57*(1), 21-26.

Schmaal, L., Veltman, D. J., van Erp, T. G., Sämann, P. G., Frodl, T., Jahanshad, N., ... &

Vernooij, M. W. (2016). Subcortical brain alterations in major depressive disorder:

findings from the ENIGMA Major Depressive Disorder working group. *Molecular*

Psychiatry, *21*(6), 806-812

Stern, J. A., Botdorf, M., Cassidy, J., & **Riggins, T**. (2019). Empathy and hippocampal volume

in young children [Special issue]. *Developmental Psychology, 55*, 1908-1920. DOI:

http://dx.doi.org/10.1037/dev0000684

Whittle, S., Lichter, R., Dennison, M., Vijayakumar, N., Schwartz, O., Byrne, M. L., … Allen, N.

      B. (2014). Structural brain development and depression onset during adolescence: a

      prospective longitudinal study. *The American Journal of Psychiatry*, *171*(5), 564–71.

Yao, Z., Fu, Y., Wu, J., Zhang, W., Yu, Y., Zhang, Z., ... & Hu, B. (2020). Morphological changes

      in subregions of hippocampus and amygdala in major depressive disorder patients. *Brain*

      Imaging and Behavior, *14*(3), 653-667.

Yavas, E., Gonzalez, S., & Fanselow, M. S. (2019). Interactions between the hippocampus,

      prefrontal cortex, and amygdala support complex learning and memory. *F1000Research*,

      8.

Zavorotnyy, M., Zöllner Rebecca, Schulte-Güstenberg L. R, Wulff, L., Schöning S, Dannlowski,

      U., … Konrad, C. (2018). Low left amygdala volume is associated with a longer duration

      of unipolar depression. *Journal of Neural Transmission : Translational Neuroscience,*

      Neurology and Preclinical Neurological Studies, Psychiatry and Preclinical Psychiatric

      Studies, *125*(2), 229–238. https://doi.org/10.1007/s00702-017-1811-y

Table 1

Summary of regression analyses for W2 Structural Volumes and CDI scores at W2

Variables	CDI Score W2	Overall Model Fit
	β	
AH Volume Ratio	-.21	
		Adj R^2 = -0.01
ICV	.07	
		$F(3, 57) = .72$
Sex	-.03	
Hippocampal Volume	-.31	
		Adj R^2 = -0.05
ICV	.01	
		$F(3, 57) = .03$
Sex	.02	
Amygdala Volume	-.28	
		Adj R^2 = -0.01
ICV	.17	
		$F(3, 57) = .09$
Sex	.02	

*p<.05,†p<.10

Table 2

Summary of regression analyses for W3 Structural Volumes and CDI scores at W3

| Variables	CDI Score W3	Overall Model Fit
	β	
AH Volume Ratio	.21	
		Adj R^2 = -0.01
ICV	-.09	
		$F(3, 54) = .85$
Sex	.07	
Hippocampal Volume	.07	
		Adj R^2 = -0.04
ICV	-.07	
		$F(3, 54) = .23$
Sex	.10	
Amygdala Volume	0.3†	
		Adj R^2 = .01
ICV	-.19	
		$F(3, 54) = 1.26$
Sex	.04	

*p<.05,†p<.10

Table 3

Summary of regression analyses for Longitudinal Change in Volumes and CDI scores at W3

| Variables	CDI Score W3	Overall Model Fit
	β	
AH Volume Ratio W2	<-.01	
AH Volume Ratio W3	.11	
CDI W2	.74*	Adj R^2 = .57
ICV	-.04	$F(5, 41) = 13.78*$
Sex	-.02	
Hippocampal Volume W2	-.17	
Hippocampal Volume W3	.28	
CDI W2	.75*	Adj R^2 = .53
ICV	-.06	$F(5, 41) = 11.51*$
Sex	<.01	
Amygdala Volume W2	-.08	
Amygdala Volume W3	.34†	
CDI W2	.72*	Adj R^2 = .56
ICV	-.13	$F(5, 41) = 12.75*$
Sex	-.08	

*$p<.05$, †$p<.10$

Figure 1

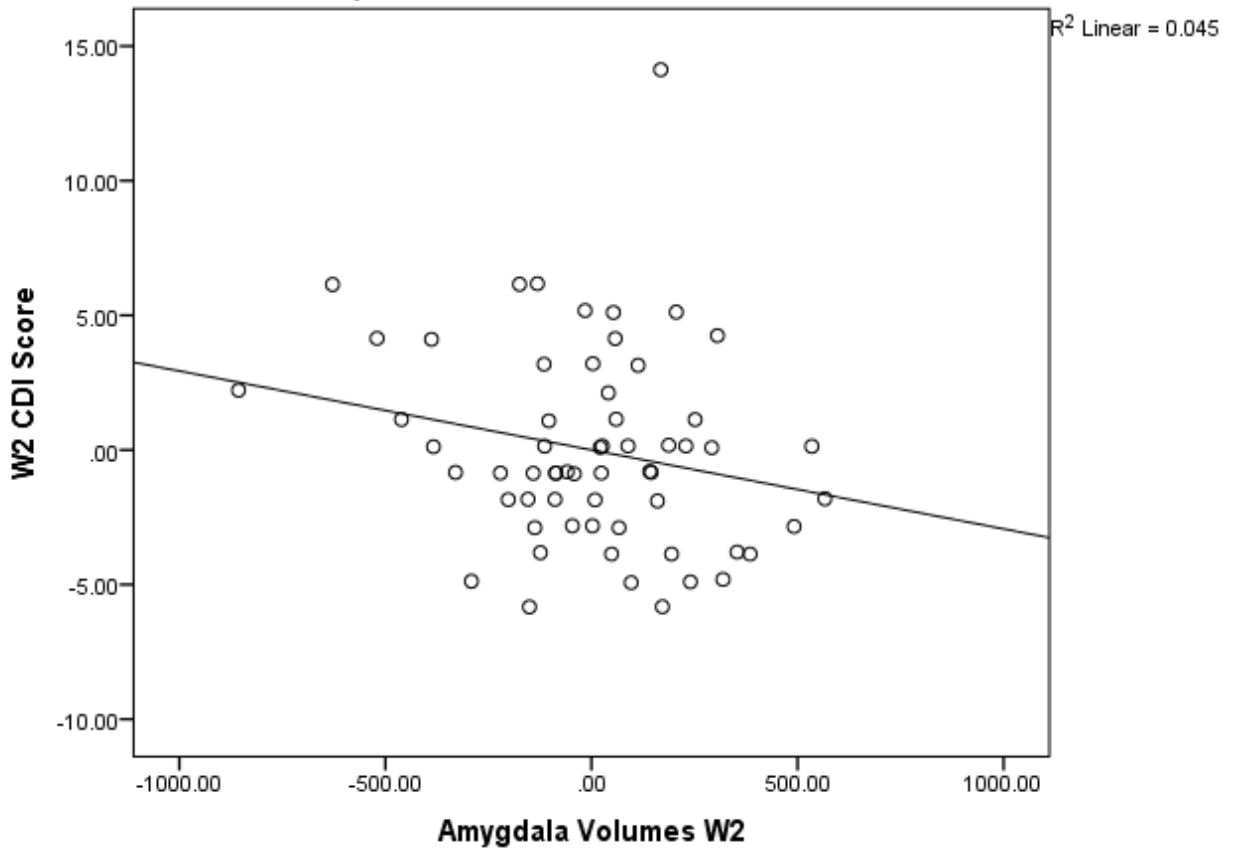*Association Between AH Ratio Change and W3 CDI Score*
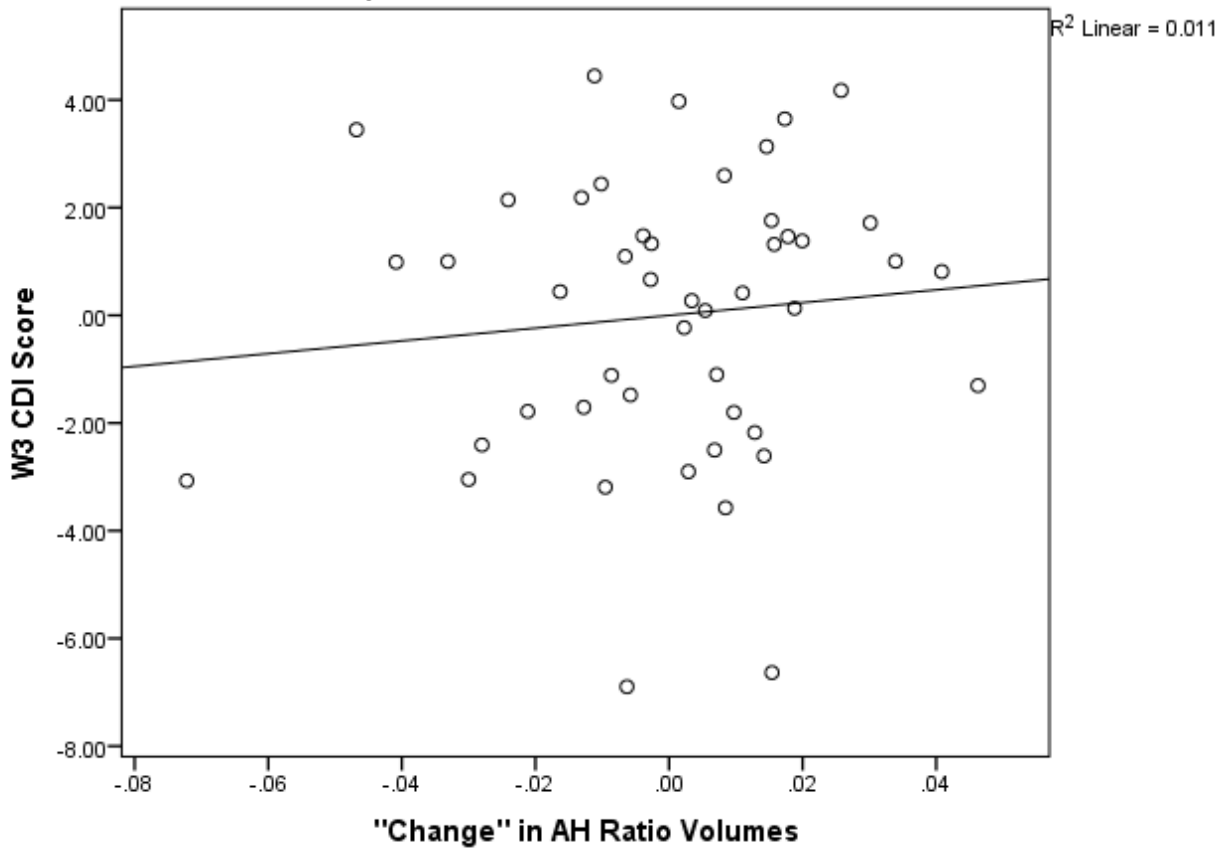
Figure 2

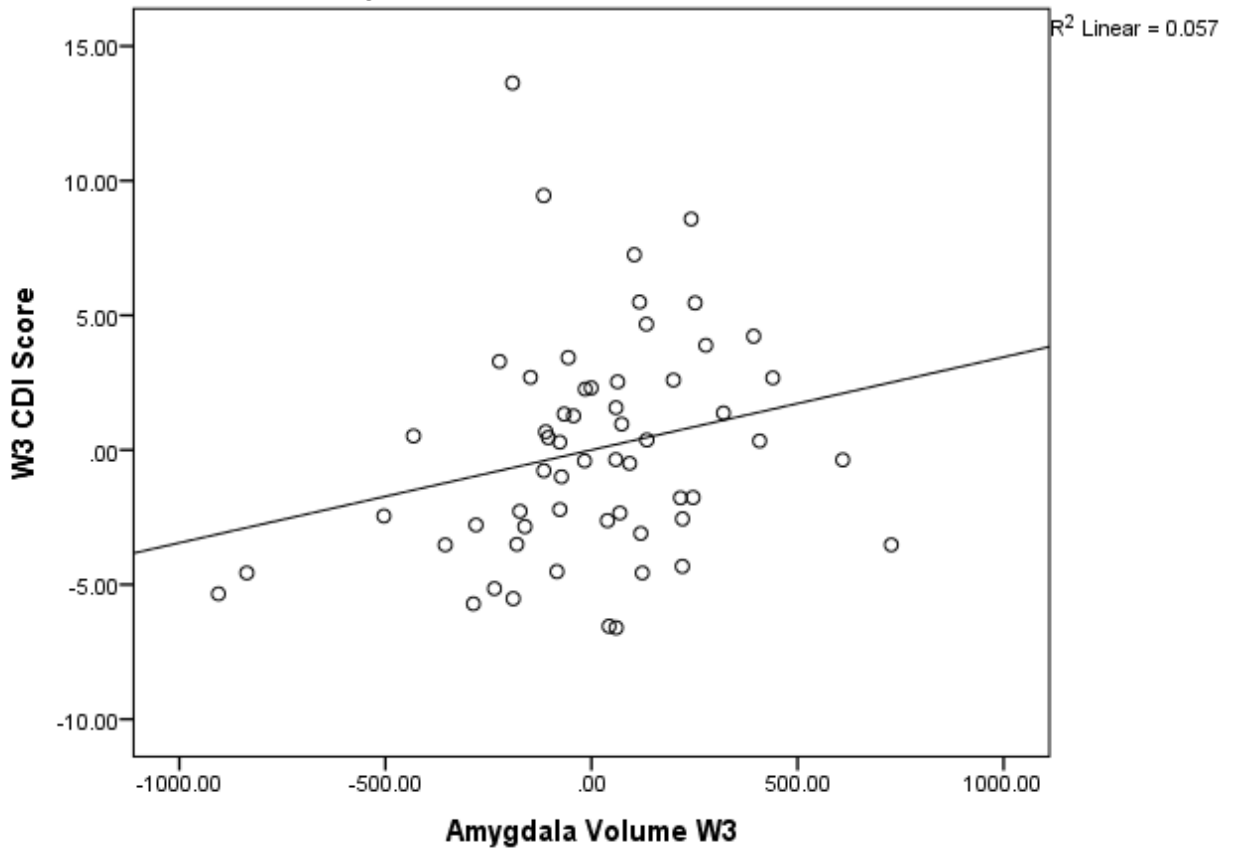*Association Between Hippocampal Volume Change and W3 CDI Score*
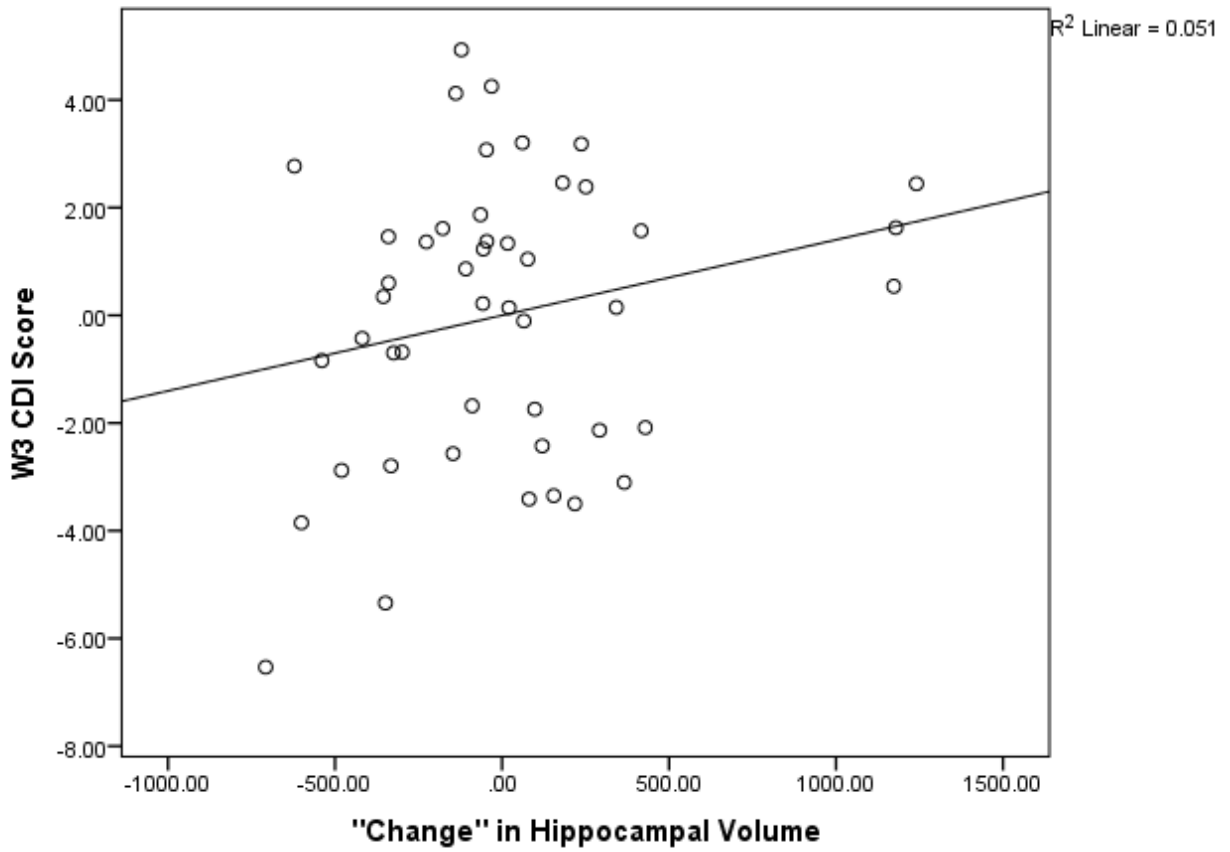
Figure 3

Cross Sectional Association Between W2 Amygdala Volumes and W2 CDI Scores
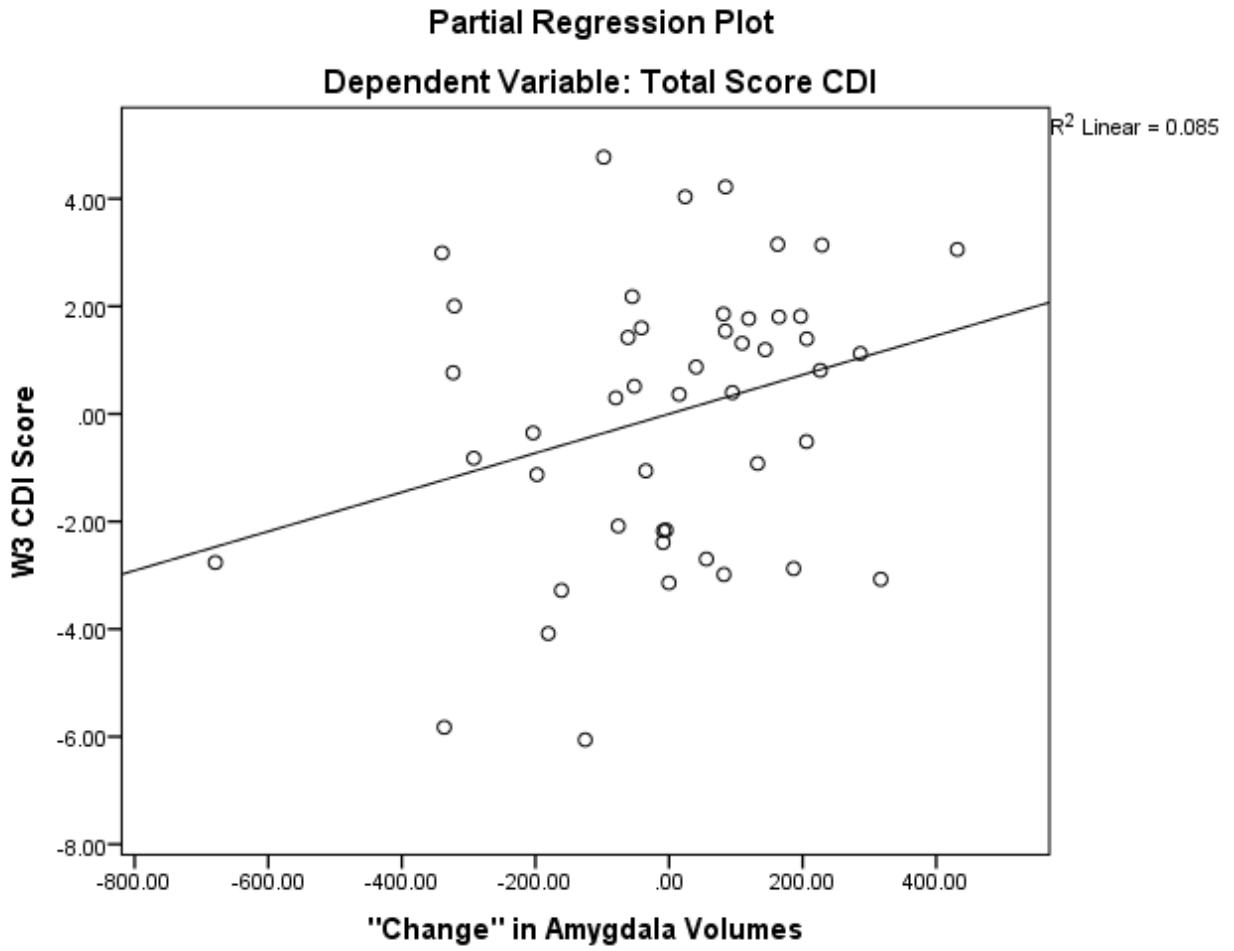
Figure 4

Cross Sectional Association Between W3 Amygdala Volumes and W3 CDI Scores

Figure 5

Association Between Amygdala Volume Change and W3 CDI Score

Partial Regression Plot

Dependent Variable: Total Score CDI

Appendix A. SPSS Correlation Table Output for W2

Correlations

		ExactAgeV1	Gender	IntraCranial Volume W2	TotalHipp_FS_W2	TotalAmyg_FS_W2	Total Score Redo
ExactAgeV1	Pearson Correlation	1	.113	.280*	.310**	.264*	.086
	Sig. (2-tailed)		.302	.013	.006	.020	.494
	N	85	85	78	78	78	65
Gender	Pearson Correlation	.113	1	.436**	.345**	.303**	.025
	Sig. (2-tailed)	.302		.000	.002	.007	.841
	N	85	99	78	78	78	65
IntraCranial Volume W2	Pearson Correlation	.280*	.436**	1	.498**	.579**	-.006
	Sig. (2-tailed)	.013	.000		.000	.000	.961
	N	78	78	78	78	78	61
TotalHipp_FS_W2	Pearson Correlation	.310**	.345**	.498**	1	.562**	-.035
	Sig. (2-tailed)	.006	.002	.000		.000	.787
	N	78	78	78	78	78	61
TotalAmyg_FS_W2	Pearson Correlation	.264*	.303**	.579**	.562**	1	-.166
	Sig. (2-tailed)	.020	.007	.000	.000		.202
	N	78	78	78	78	78	61
Total Score Redo	Pearson Correlation	.086	.025	-.006	-.035	-.166	1
	Sig. (2-tailed)	.494	.841	.961	.787	.202	
	N	65	65	61	61	61	65

Appendix B. SPSS Correlation Table Output for W3

Correlations

		TotalAmyg_FS_W3	TotalHipp_FS_W3	IntraCranial Volume W3	Total Score CDI	ExactAgeV1_W3	Gender_W3
TotalAmyg_FS_W3	Pearson Correlation	1	.601**	.586**	.213	.226*	.353**
	Sig. (2-tailed)		.000	.000	.109	.048	.002
	N	77	77	77	58	77	77
TotalHipp_FS_W3	Pearson Correlation	.601**	1	.391**	.070	.124	.265*
	Sig. (2-tailed)	.000		.000	.603	.283	.020
	N	77	77	77	58	77	77
IntraCranial Volume W3	Pearson Correlation	.586**	.391**	1	.013	.151	.386**
	Sig. (2-tailed)	.000	.000		.924	.191	.001
	N	77	77	77	58	77	77
Total Score CDI	Pearson Correlation	.213	.070	.013	1	.041	.070
	Sig. (2-tailed)	.109	.603	.924		.756	.596
	N	58	58	58	60	60	60
ExactAgeV1_W3	Pearson Correlation	.226*	.124	.151	.041	1	.044
	Sig. (2-tailed)	.048	.283	.191	.756		.693
	N	77	77	77	60	83	83
Gender_W3	Pearson Correlation	.353**	.265*	.386**	.070	.044	1
	Sig. (2-tailed)	.002	.020	.001	.596	.693	
	N	77	77	77	60	83	83

**. Correlation is significant at the 0.01 level (2-tailed).