

## A. COVER PAGE

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**Multimodal Neuroimaging of Cognitive and Emotional Networks in Young Adults  
Exposed to 9/11 as Children  
U01OH011694  
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List of Terms and Abbreviations

WTC	World Trade Center
ERP	Event Related Potential
fMRI	functional Magnetic Resonance Imaging
HEAnx+	Group of 9/11 exposed with anxiety disorders
HEAnx-	Group of 9/11 exposed without anxiety disorders
NEAnx-	Group with no 9/11 exposure with no anxiety disorder
PHQ-8	Assesses depression
GAD-7	Assesses anxiety
PCL	Assesses PTSD
PDSR	Assesses Panic
STAI	State Trait Anxiety Index
IU	Intolerance of Uncertainty
NB1	N-Back 1 working memory task
NB2	N-Back 2 working memory task
FAS	Verbal Fluency task
ENM	Directed Forgetting Memory task
TBR	To be Remembered pictures used in the ENM task
TBF	To be forgotten pictures, used in the ENM task
NPU	<b>N</b> eutral, <b>P</b> redictable and <b>U</b> npredictable task
RT	Reaction Time
FDR	False Discovering Rate

## Abstract:

Children and adolescents who experienced the trauma of the 9/11 WTC terrorist attack continue to face neuro-psychological and emotional challenges as they transition into adulthood. Previous NIOSH-funded Studies (S&W Studies: U01OH010414; U01OH011308, PI Hoven) conducted a comprehensive assessment of a representative sample (N= 1,000) of youth who were under 18 years of age on 9/11. These studies revealed that 15 years after 9/11, highly exposed individuals were 4 times more likely to have anxiety disorders compared to non-exposed controls. Anxiety disorders are associated with deficiencies in several neuronal networks, including those involved in emotional regulation, cognitive control and memory. These neurobiological circuits undergo significant development during childhood and adolescence, rendering them particularly vulnerable to trauma during this period. Yet, despite this vulnerability, there is a lack of neuroimaging studies examining these neuronal networks in young adults who were exposed to 9/11 trauma as children. As these individuals transition into adulthood with potential alternations in brain development, we investigated the neural underpinnings of emotion processing and cognitive control of memory using event related potentials (ERPs) and multimodal magnetic resonance imaging (MRI) in 57 young adults (mean age 32.8) across the following 3 subgroups: 1) 9/11 highly exposed with a life time anxiety disorder (HEAnx+; N=21); 2) 9/11 highly exposed with no anxiety disorder (HEAnx-; N=23); and 3) no 9/11 exposure with no anxiety disorder (NEAnx-; N=13). We used 2 tasks, one to assess emotional memory using the directed forgetting paradigm, and the other emotional reactivity employing the NPU paradigm. Our results indicated that the HEAnx+ group had the lowest memory performance and show the greatest difficulty in suppressing memory to the 9/11 related stimuli compared to the other groups. These behavioral results were also manifested in the ERPs demonstrating more engagement in the trauma related stimuli compared to neutral stimuli in participants in the HEAnx+ group. The fMRI findings revealed that individuals who experienced the 9/11 events and also grapple with mental health disorders exhibited heightened activation in frontal control regions in response to TBF compared to New stimuli, and to New compared to TBR stimuli. This heightened activation may reflect the challenges they face in suppressing memory for TBF, as evidenced by their poorer performance. It suggests that their brain activity is influenced by stimuli that ideally should not be remembered. There were no performance differences across groups in the NPU task. However, both the ERPs and the MRI brain activation indicated subtle, yet noteworthy differences among the groups in attentional processing of stimuli under different threat conditions. By comparing performance, brain structure, function, and connectivity between these 3 groups, we demonstrated differences in emotional reactivity and interaction of trauma memory and cognitive control processes. This study contributes to a deeper and broader neurobehavioral understanding of our unique 9/11 cohort of young adults exposed to 9/11 during childhood or adolescence.

## Study Aims:

Using MRI and ERP in well characterized groups of young adults exposed to 9/11 as children or adolescents, and matched controls, we aimed to:

1. Identify differences between exposure groups on behavioral, functional and temporal brain signals elicited during cognitive control of memory processing.
2. Identify differences between exposure groups on behavioral, functional and temporal brain signals during cognitive control of emotional processing.
3. Identify differences between exposure groups in functional and structural connectivity and brain morphometry, specifically in the prefrontal cortex and in the amygdala-hippocampal system.
4. Characterize the association between assessed brain measures and previously assessed psychosocial and biological measures across groups.

## Significant Key finding

The study included 57 participants (25 male, 32 female), ages 26-39 (mean age 32.8). Participants were categorized into groups based on their exposure to 9/11 and their mental health status: HEAnx+ were highly exposed to 9/11 with lifetime internalizing disorders (N=21), HEAnx- were highly exposed without lifetime internalizing disorders (N=23), and NEAnx- were unexposed without lifetime internalizing disorders (N=13).

Psychological and cognitive assessments were conducted revealing differences in mental health outcomes among groups, yet executive functioning appeared similar across all groups.

Emotional memory task performance varied significantly across groups, with HEAnx+ participants exhibiting the lowest memory performance, while NEAnx- participants performed best. TBR stimuli were better remembered than TBF stimuli, and neutral stimuli better than 9/11-related stimuli. HEAnx+ participants struggled notably with distinguishing old from new 9/11-related stimuli, with slower reaction times for 9/11 stimuli compared to neutral.

Brain activity exhibited the typical pattern of larger amplitude for old compared to new stimuli. However, participants in the HEAnx+ group, still grappling with childhood trauma, displayed heightened familiarity with 9/11-related stimuli, as indicated by larger ERP amplitudes, irrespective of the stimuli's classification as old or new, reflecting their poor memory performance. Similarly, the MRI data demonstrate larger activity in frontal region for the TBF compared to New stimuli in the HEAnx+ group indicating a harder time to suppress memories in this group. The ERP suggests an uncontrollable engagement with 9/11-related stimuli among HEAnx+ participants who were challenged to suppress memory for this stimulus type, leading to confusion between what was seen and what was not. The HEAnx+ group appeared to be challenged by the TBF images as was evident in the fMRI results. Despite their cognitive functioning being comparable to other groups, our findings highlight specific difficulties in the HEAnx+ group in regulating memory associated with traumatic experiences.

In the NPU task, participants performed well (~90%) across conditions and groups. RT differed significantly between positive than negative faces, aligning with established literature showing faster RT for happy expressions. RT was the slowest during the 'P' condition and fastest during the 'N' condition, demonstrating slowness in processing due to the occurrence of the unpleasant stimuli. Early ERP component indicate increase attention during the U condition, and with group difference approaching significant suggesting the attention allocation varied by the mental health and exposure to 9/11. The results of the MRI recording also demonstrated increased brain activity in frontal-parietal regions associated with attention processing during the threat conditions, further supporting the notion that early trauma exposure compound by mental health issues may result in vigilant behavior for potential threat.

Significant reductions in connectivity ( $p < 0.001$ , FDR corrected) were observed in group HEAnx+ than HEAnx-, particularly in regions associated with memory, emotion, and cognitive control. Thus, the resting state connectivity results indicate a wider disruption in the functioning of neural networks among individuals who experienced the 9/11 terror attack and later developed mental health disorders.

Our comprehensive findings from both the emotional memory and the NPU tasks, as well as from the connectivity data, highlight the profound influence of early trauma exposure compound by mental health challenges on individuals' responses to their surroundings. We observed heightened vigilance in reacting to negative stimuli whether they were related to 9/11 or unpleasant sounds, particularly among those exposed to the 9/11 terror attack and who still grapple with its lasting effects.

## Section 2: Scientific Report

### Sample Characteristics:

Our sample comprises 57 participants (Sex: M = 25, F = 32), who were between the ages 5-18 during the 9/11 terror attack. Their age range during the study varies between 26 – 39 with a mean of 32.8 years. Their race/ethnicity was as follow: 27 - White, 13 - Asian, 10 - Black, 5 - multi-ethnic and 2 reported 'other', with an overall 20 participants identifying as Latino. Participants were recruited based on their exposure to 9/11 and their mental health status, and were categorized as belonging into one of the following groups: HEAnx+ were highly exposed and had a lifetime internalizing disorders (N=21), HEAnx- were highly exposed but did not have internalizing disorders (N=23), and NEAnx were unexposed with no internalizing disorders (N=13). Our sample is based on 339 Invitations sent to potential participants. We screened 107 participants, but only those who met inclusion/exclusion criteria were invited to participate. Our recruitment effort was impacted by COVID-19 as many eligible participants relocated or refused to participate prior to screening (~100). Participants with MRI contraindications were offered participation in the EEG-only study (N=6). The study was reviewed and approved by NYSPI IRB, and informed consent was obtained from all participants.

### Psychological and Cognitive Measures (Aims 1-4):

While participants were recruited based on previous mental health assessments, we conducted an additional current mental health relevant to our research questions using PHQ-8, GAD-7, PCL, PDSR, and STAI. We also used IU as it is often associated with trauma related anxiety. Executive functioning is known to be impaired among individuals with mood disorders, therefore, we assessed working memory using NB1 and NB2 tasks and digit span forward and backwards. Cognitive fluidity was assessed using FAS, and cognitive control using task-switch in 3 level of difficulties. Current mental health significantly differed across groups, with higher GAD-7 and STAI scores observed in HEAnx+ compared to HENX- ( $F_{2,54} = 3.25, P < 0.05$  and  $F_{2,54} = 3.82, P < 0.05$ , respectively). Additionally, higher PCL scores were reported by HENX+ compared to either HEAnx- and NEAnx-, which did not significantly differ ( $F_{2,46} = 5.94, P < 0.005$ ). While Panic was more prevalent among HEAnx+, it only approached significant level, whereas scores of the PHQ-8 and IU did not differ across groups. The assessments also revealed current high anxiety or depression scores among individuals who were assigned to HENX- and NENX- groups (5 and 2 respectively), and no current mental health issues among some individuals belonging to the HANx+. Seven HANx+ participants were on anti-anxiety or anti-depressant medication during the study. Performance in the cognitive tasks demonstrated that with increasing cognitive demand, performance decreased ( $P < 0.001$ ) and reaction times increased ( $P < 0.001$ ). However, performance did not differ across the groups ( $P > 0.05$ ). Because current mental health disorders appear to be present in all groups, we ran a series of multiple linear regressions to evaluate the relationship between the psychological symptoms and cognitive assessments without considering group membership. The only significant correlation was found between STAI and combined scores of digit span ( $r = -.258, p = .026$ ). The GAD-7 approached a significant correlation with combined NB1 and NB2 scores ( $r = -.190, p = 0.079$ ). The negative correlations indicate that as anxiety symptom counts increase, performance in working memory tasks decreases.

### EEG, fMRI and Performance in the ENM Task (Aim 1):

In the ENM task participants were asked to look at 160 images in which half were 9/11-related and half were neutral. Half the images were cued TBR and half TBF. While EEG was recorded, TBR and TBF images, along with a set of new 9/11-related and neutral images were presented to assess recognition memory. For each image, participants had to indicate for if it was seen before (old) or if it was new. Memory performance (PR) and bias (Br) were computed for each participant, taking into consideration both "Hit" and "False alarm" rates. PRs were separately calculated for the TBR and TBF images, and for separately for 9/11-related and neutral images. Repeated measures mix design ANOVA with 2 Conditions x 2 Stimuli as within subject factors (TBR/TBF x 9/11-related/Neutral) by 3 Group as a between-subject factor revealed differences across conditions [ $F_{1,54} = 89.72, p < 0.0001$ ], indicating that subjects remembered TBR pictures better than TBF pictures, confirming task instructions compliance. This main effect was modulated by Condition x Group interaction [ $F_{1,54} = 5.27, p < 0.008$ ],

indicating that the groups were similar in their memory performance (low) for the TBF pictures, while memory performance for the TBR pictures varied across groups with the highest performance seen in the NEAnx-, followed by HEAnx- and showing the worst performance in the HEAnx+ group. This result supports our hypothesis that HEAnx+ will show memory impairment compared to HEAnx- and NEAnx- groups. Memory performance was significantly higher for neutral than for 9/11-related stimuli [ $F_{1,54}=14.78$ ,  $p<0.0001$ ]. This was especially apparent for the TBR condition based on significant Stimuli x Condition interaction [ $F_{1,54}=16.61$ ,  $p<0.0001$ ]. While all subjects had harder time remembering the 9/11-related images, HEAnx+ had the poorest performance compared to the other two groups. There was no significant difference in Br across groups, which show a similar bias to indicate TBF pictures as “new” [ $F_{1,54}=67.60$ ,  $p<0.0001$ ].

RTs were submitted to repeated measures mix design ANOVA with 3 conditions (New, TBR and TBF) and 2 stimuli (9/11 and neutral pictures) as within-subject factors by 3 Group as a between-subject factor. This analysis revealed main effects of Condition [ $F_{2,108}=11.64$ ,  $p<0.0001$ ] and Stimuli, [ $F_{2,54}=8.78$ ,  $p<0.005$ ], which were modulated by Condition and Stimuli interaction [ $F_{2,108}=46.45$ ,  $p<0.0001$ ], and, by Condition x Stimuli x Group interaction [ $F_{4,108}=2.90$ ,  $p<0.03$ ]. These findings indicate that identifying new stimuli was slower than identifying either TBR or TBF, with TBR stimuli having the fastest RTs. Additionally, 9/11 pictures had the slowest RTs, likely due to their high valence requiring more processing time. Interestingly, while RTs difference between 9/11 and neutral stimuli was small in TBR condition for the HEAnx- and NEAnx-, it was the smallest in the TBF condition in the HEAnx+ group.

The brain activity in the ERPs complimented these behavioral findings. We focused on two time periods of the ERPs, in the 200-280 ms and during the 400-600 ms and on selected electrodes where the effect is the largest. Repeated measure mixed design ANOVAs were performed (similar to that used for the RT data) on voltage averages of 10, 40 ms intervals (for each time interval and including Electrode as an additional factor). Our results show that very early on significant differences in brain activity to correctly remembered 9/11 related and neutral images [ $ps<0.001$ ], where the amplitudes were larger for the 9/11 related images. The typical old/new ERP effect (amplitude for old > amplitude for new) was clearly seen in the 340-660 ms [ $ps<0.03$ ], with amplitudes for old TBR are the largest, following by that of TBF images, and the smallest for new. The effects of stimulus type and old/new were interacted with Group [ $ps<0.03$ ] demonstrating differential retrieval processes among the groups. Specifically, HEAnx+ showed the highest amplitude for 9/11-related images with the smallest differences between old and new, suggesting that regardless of image condition, 9/11-related images elicit high familiarity (large P3 amplitude) and thus reducing memory performance. In contrast, NEAnx- showed the largest amplitude difference between 9/11-related and neutral images reflected also in their superior memory performance.

An hour after the EEG recording, another recognition memory assessment conducted while the participants were in the MRI scanner. Similar analysis to that described above was conducted. Analysis of the PRs revealed a main effect of conditions, [ $F_{1,54}=35.58$ ,  $p<0.0001$ ], indicating better memory retention for TBR compared to TBF pictures. However, this main effect interacted with Group [ $F_{2,54}=5.354$ ,  $p<0.008$ ], with NEAnx- participants exhibiting the highest memory performance for TBR pictures, followed by HEAnx-, and with the lowest performance observed among HEAnx+ participants. This outcome supports the hypothesis that individuals exposed to the 9/11 terror attack and suffering from internalizing disorders exhibit greater impairment in memory compared to those who were exposed but remained healthy, as well as controls. There was also a main effect of Stimuli [ $F_{1,54}=21.58$ ,  $p<0.0001$ ] and its interaction with Condition [ $F_{1,54}=7.55$ ,  $p<0.008$ ], indicating better memory performance for TBR and neutral pictures. The 3-ways interaction approached significance ( $p=0.054$ ), further showing performance differences between groups depending on the stimulus type and memory instruction (TBR vs. TBF), such that HEAnx+ had the hardest time suppressing memory for 9/11 pictures. There was no group difference in the Br measure, with all groups showing more bias for TBR pictures to be labeled as “Old” [ $F_{1,54}=32.69$ ,  $p<0.0001$ ]. Analyses of the RTs revealed main effects of Condition [ $F_{2,108}=59.96$ ,  $p<0.0001$ ], Stimuli, [ $F_{2,54}=4.03$ ,  $p=0.05$ ] which were modulated by Condition and Stimuli interaction [ $F_{2,108}=9.53$ ,  $p<0.0001$ ],

but none of the effect showed interaction with group. These findings demonstrated that, as expected, detecting new stimuli is slower than either TBR or TBF, and that high valence 9/11 pictures generated slower RTs. The lack of group difference could be attributed to the longer time available to respond to pictures in the MRI, and the slow pace of the task possibly masking potential interactions of Condition and/or Stimuli with Group.

MRI images revealed significant differences in brain activation between old and new stimuli, irrespective of groups, in bilateral visual cortex (calcarine, lingual gyrus and fusiform gyrus), hippocampus, thalamus, insula, superior parietal and supplementary motor cortex. Activation was greater for new stimuli compared to old stimuli in the left-middle temporal gyrus, bilateral supramarginal gyrus, medial superior frontal gyrus and anterior cingulate. The increase engagement of the hippocampus for old stimuli aligns with the involvement of memory regions for previously seen stimuli reported in previous studies. Brain activity recorded for the HEAnx+ group was larger than that of the HEAnx- group when comparing TBF and New stimuli in bilateral anterior cingulate and contiguous medial superior frontal cortex, and thalamus. However, there was greater activity for New than TBF stimuli in the right insula and fusiform gyrus for the HEAnx+ group. Additionally, HEAnx+ exhibited larger activity than that of HEAnx- when comparing TBR and New stimuli in right insula, right inferior frontal gyrus and left fusiform gyrus. The increase activity for New stimuli compared to either TBF or TBR stimuli (at separate brain regions) in the HEAnx+ group suggests a greater salience of New compared to Old stimuli. Overall, these results indicate that individuals exposed to 9/11 who also suffer from mental health disorders engaged frontal control regions. It is possible that the difficulty they had in suppressing memory, as seen in their poor performance, is manifested by larger activation to New or TBF stimuli that was not observed in the healthy exposed group, and underscore the complexity of their cognitive-emotional processes.

#### EEG, fMRI and Performance in the NPU Task ( Aim 2):

In the NPU task, participants were asked to discriminate between positive and negative facial expressions in 3 different task conditions. N – neutral condition serves as control condition, P – a condition in which a unpleasant sound was presented in a predictable moment, and U – a condition in which the unpleasant sound presentation was unpredictable. Performance in the NPU task was high and similar across all conditions, groups (~90% accuracy) and under both EEG recordings and fMRI scanning. The high accuracy rate remained after exposure to the unpleasant stimuli.

For the EEG task only, RT differed significantly between positive than negative faces [ $F_{1,53}=8.55$ ,  $p<0.005$ ], aligning with established literature showing faster RT for happy expressions. Not seeing this effect in the RTs of the fMRI task could be attributed to the overall slow pace of the task during the MRI scanning. Notably, in both EEG and fMRI, RT was the slowest during the 'P' condition and fastest during the 'N' condition (EEG, [ $F_{2,106}=5.43$ ,  $p<0.006$ ]; fMRI, [ $F_{2,90}=7.217$ ,  $p<0.001$ ]).

Significant differences ( $Ps<0.01$ ) between the N, P and U conditions were found in the early components (90-230 ms) of the ERP (using repeated mixed design ANOVAs for three 40 ms intervals with Electrode as additional factor), such that larger amplitude was recorded for the U condition, followed by the P and then by the N condition. Since this early ERP component signifies attention to the stimuli, our results suggest that during the U condition, participants are overall more alert expecting at some point in time to be presented with unpleasant sound stimuli. The effect of Group approached significance ( $ps<0.08$ ) stemming from differences in brain activity seen in NEAnx- compared to the exposed groups who did not differ from each other, although the activity in the HEAnx- was not as low as that of the HEAnx+ group. This differential activation suggests that more attention resources are spent by the control group during this task.

Comparing brain activity during the NPU task between P and N or U and N, irrespective of groups, revealed significant activation in bilateral fusiform gyrus, middle occipital gyrus, inferior parietal, inferior frontal gyrus, medial superior frontal gyrus and right insula. However, comparing the task's conditions showed significantly more activation in these brain areas during the U condition compared to the N condition. Additionally, there was also significant more activation in the right middle temporal, right orbitofrontal gyrus, bilateral precuneus,

left insula, and bilateral pallidum, putamen and thalamus, during the U condition. These results suggest that the presence of unexpected threat stimuli engages a frontal parietal network associated with increased attentional load, aligning with the ERP findings (mentioned above) showing increased attention during conditions with threat stimuli.

Significant larger brain activity was seen in U compared to P condition in the primary visual cortex, left inferior frontal gyrus, anterior cingulate cortex, the thalamus and the putamen. This suggests that when the occurrence of the threat stimuli is unknown, participants are more engaged in monitoring the stream of stimuli. Comparing brain activity between the P and N conditions across HEAnx+ and HEAnx- revealed significant activation differences in bilateral inferior frontal gyrus, medial superior frontal gyrus and anterior cingulate, right lateral orbitofrontal gyrus and right insula. A similar comparison between the U and N conditions demonstrated significant differences between groups in bilateral inferior frontal gyrus, right superior frontal gyrus, bilateral supplementary motor area, right insula and right amygdala. However, brain activation did not differ across the two groups when comparing U and P conditions.

In summary, the subtle, yet noteworthy differences observed among the groups in processing stimuli under different threat conditions underscore the impact of early trauma exposure compounded by mental health issues on how individuals respond to potential threat, regardless of whether they are predictable or unpredictable.

#### MRI Resting State Connectivity (Aim 3):

Significant reductions in connectivity ( $p < 0.001$ , FDR corrected) were observed in group HEAnx+ than HEAnx-, particularly in regions associated with memory, emotion, and cognitive control. Specifically, diminished connectivity in HEAnx+ was evident from hippocampus to middle temporal gyrus and occipital gyrus, from amygdala to occipital cortex extending to precuneus and temporal cortex, including hippocampus, and cerebellum, from the anterior cingulate cortex to occipital cortex and posterior cingulate cortex, and from the middle frontal cortex to precuneus. These findings suggest a broader disruption in neural network functions among individuals exposed to the 9/11 terror attack who subsequently developed mental health disorders.

#### Challenges:

1. The recruitment of participants faced significant challenges due to COVID-19 and the mandated research pause, both of which ultimately impacted the final sample size. Throughout the COVID-19 pandemic, recruitment and collection were suspended for over a year, as the IRB determined that the risks outweighed the benefit for potential participants. Upon resuming recruitment efforts, we encountered difficulties as many eligible participants relocated from New York City, diminishing our pool of eligible candidates. Additionally, during the last month of the grant period, plans to enroll additional participants were stopped by the imposed pause, halting all human subject research activities.
2. The pause also hindered data analysis, as mandated by NYSPI/NIH, which prohibited the processing and analysis of collected data. This necessitated an extensive audit procedure and awaited authorization for data analysis. Consequently, data processing was delayed. Furthermore, the research pause prevented access to prior waves of data (U01OH010414; U01OH011308, PI Hoven) crucial for completing Aim 4 of the study. Dr. Hoven informed us that the data is currently undergoing the final stages of the audit process, and we anticipate its availability soon to fulfill this aim.