



Reduced anxiety and changes in amygdala network properties in adolescents with training for awareness, resilience, and action (TARA)

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ABSTRACT

Mindfulness-based approaches show promise to improve emotional health in youth and may help treat and prevent adolescent depression and anxiety. However, there is a fundamental gap in understanding the neural reorganization that takes place as a result of such interventions. The Training for Awareness, Resilience, and Action (TARA) program, initially developed for depressed adolescents, uses a framework drawn from neuroscience, mindfulness, yoga, and modern psychotherapeutic techniques to promote emotional health. The goal of this study was to assess the effects of the TARA training on emotional health and structural white matter brain networks in healthy youth. We analyzed data from 23 adolescents who underwent the 12-week TARA training in a controlled within-subject study design and whose brain networks were assessed using diffusion MRI connectomics. Compared to the control time period, adolescents showed a significant decrease in anxiety symptoms with TARA (Cohen's $d = -0.961$, $p = 0.006$); moreover, the node strength of the Right Amygdala decreased significantly after TARA (Cohen's $d = -1.026$, $p = 0.004$). Post-hoc analyses indicated that anxiety at baseline before TARA was positively correlated with Right Amygdala node strength ($r = 0.672$, $p = 0.001$). While change in Right Amygdala node strength with TARA was not correlated with change in anxiety ($r = 0.146$, $p = 0.51$), it was associated with change in depression subscale of Anhedonia / Negative Affect ($r = 0.575$, $p = 0.004$, *exploratory analysis*), possibly due to overlapping constructs captured in our anxiety and depression scales. Our results suggest that increased structural connectivity of Right Amygdala may underlie increased anxiety in adolescents and be lowered through anxiety-reducing training such as TARA. The results of this study contribute to our understanding of the neural mechanisms of TARA and may facilitate neuroscience-based prevention and treatment of adolescent anxiety and depression.

1. Introduction

According to the World Health Organization (WHO), major depressive disorder (MDD) is the current leading cause of disability worldwide (Ferrari et al., 2013), and adolescence is an especially vulnerable period for the onset of depression (Thapar et al., 2012). Anxiety commonly

precedes and is a significant risk factor for the development of adolescent MDD. Moreover, anxiety is highly comorbid with adolescent depression (Cummings et al., 2014). Effective interventions to improve emotional health and prevent anxiety and depression in adolescents are needed. One promising approach to provide systematic training in increasing one's ability to regulate emotions is mindfulness (Vago &

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Silbersweig, 2012), which trains nonjudgmental awareness of moment-to-moment experience (Kabat-Zinn, 2003). A meta-analysis found that school-based mindfulness programs had significant positive effects on children's psychological resilience (Zenner et al., 2014). However, there is a fundamental gap in our understanding of the neural reorganization that takes place as a result of such interventions. This gap makes it difficult to optimize mindfulness interventions and apply them in a scientifically informed manner.

One mindfulness- and yoga-based program that specifically targets the developing neurocircuitry in the adolescent brain is the Training for Awareness, Resilience, and Action (TARA) (Henje Blom et al., 2014). TARA was developed by our group in alignment with the Research Domain Criteria (RDoC) of the National Institute of Mental Health (NIMH) (Insel et al., 2010). To our knowledge, it was the first treatment protocol for adolescent depression developed based on a comprehensive neuroscience theoretical framework, with a deep consideration of brain-developmental aspects. It is described in detail in our previous publication (Henje Blom et al., 2014). The treatment paradigm was created by organizing previous research findings within the RDoC framework and prioritizing the domains thought to be driving the psychopathology. The targeted constructs were sustained threat, arousal and sleep/wakefulness, loss and attention/cognitive control. This translated into a paradigm containing training of autonomic and emotional self-regulation, interoceptive attention, relational skills, value-based committed action and strengthening of intrinsic reward. To create an effective clinical intervention, we integrated approaches from several different paradigms and traditions based on their feasibility, efficacy, and congruence with our theory. This resulted in the TARA intervention: a semi-manualized 12-week group training, informed by mindfulness-, yoga-based techniques and modern psychotherapeutic approaches. In a single-arm feasibility and preliminary efficacy study, we previously demonstrated that TARA significantly improved anxiety and depression symptoms in clinically depressed adolescents (Henje Blom et al., 2016). However, the hypothesized neural changes with TARA have not yet been examined.

The goal of this study was to assess the effects of the TARA training on emotional health and structural brain networks in a non-clinical population of adolescents. Recently, it has become possible to probe structural and microstructural changes in brain circuitry non-invasively using diffusion MRI connectomics (Hagmann et al., 2010). Several studies in animals and humans highlighted myelination as a previously underestimated mechanism of brain plasticity and provided evidence for the effectiveness of diffusion MRI techniques to assess white matter changes during training (Schlaug et al., 2009; Taubert et al., 2010; Bengtsson et al., 2005), including reasoning training (Mackey et al., 2012), memory training (Engvig et al., 2012) and meditation-based training in adults (Tang et al., 2010). MRI connectomics treats the brain as a complex network ("connectome") and allows researchers to study not only local microstructural changes detected by diffusion MRI but also the global interconnection of brain regions, and to perform network analysis using graph theory (Rubinov & Sporns, 2010). MRI connectomics approach has demonstrated high test-retest reliability of graph theoretic metrics in teens (Yuan et al., 2019) and has been applied to study adolescent depression and anxiety (Tymofiyeva et al., 2017, Sharp & Telzer, 2017). Connectomics has also been used to study the brain plasticity associated with training, including working memory (Caeyenberghs et al., 2016) and mindfulness training in adults (Sharp et al., 2018). In the latter study by Sharp and colleagues, compared to active controls, the mindfulness group demonstrated a medium-effect-size increase in the strength of right insula, defined by the connection density of right insula across all connections derived from Diffusion Tensor Imaging (DTI) and tractography (Sharp et al., 2018).

In this controlled study, we expected improvement of emotional health in teens with TARA compared to the control time period and structural neurocircuitry changes, related to the three hypothesized TARA targets (Henje Blom et al., 2014, 2016): 1. *amygdala*,

characterized by hyperreactivity in depressed and anxious adolescents (e.g., Yang et al., 2010; for an overview of studies see Henje Blom et al., 2014), which TARA aims to reduce by promoting vagal and sensory afference through breathing practices and slow synchronized movement; 2. *insula*, involved in present moment sensory and interoceptive awareness cultivated through mindfulness meditation practices (for an overview of studies see Henje Blom et al., 2014); and 3. *striatum*, involved in intrinsic reward, particularly cultivated by the practices of the last TARA module (for an overview of studies see Forbes and Dahl, 2012 and Henje Blom et al., 2014).

Our primary hypotheses were: (H1) Emotional health measured using the self-report Reynolds Adolescent Depression Scale-2 (RADS-2) (Reynolds, 2002) and the Multidimensional Anxiety Scale for Children (MASC) (March 1997) will improve with TARA compared to the control time period. (H2) Node strength of the following brain regions hypothesized to be central to the efficacy of TARA will change with the intervention compared to the control time period: Right and Left Amygdala, Right and Left Insula, Right and Left Caudate (which includes Nucleus Accumbens in the atlas used in this study), and Right and Left Putamen. Our secondary hypothesis was: (H3) The improvement in emotional health will correlate with changes in node strengths of the brain regions hypothesized in H2.

2. Materials and methods

The study was approved by the Institutional Review Board (IRB) of the University of California, San Francisco. All participants in the study provided written informed assent and their parent(s) or legal guardian (s) provided written informed consent in accordance with the Declaration of Helsinki.

2.1. Participants

Thirty-six adolescent volunteers (20 females, 16 males) between the ages of 14–19 years participated in this neuroimaging study (age at the beginning of TARA: mean \pm standard deviation, 16.52 \pm 1.19 years). Adolescent participants were recruited using IRB-approved flyers posted around the University of California, San Francisco campus, neighboring areas, and local high schools. Only adolescents who reported no MRI contraindications, psychiatric diagnoses, and not taking any psychotropic medication were included in this study. Additionally, adolescents undergoing current mindfulness trainings and/or an ongoing meditation and/or yoga practice of > 20 min twice a week or more for the past two months were also excluded.

Participants received a gift card for participating in the experiment (\$50 for two MRI scans and \$100 for three MRI scans).

2.2. TARA intervention

As part of the study, all participants underwent the TARA program, a semi-manualized 12-week secular group intervention, informed by mindfulness-, yoga-based techniques and modern psychotherapeutic approaches developed by our group (Henje Blom et al., 2014, 2016). Participants attended 90-minute weekly sessions for 12 consecutive weeks, i.e. in total 18 h. Two TARA-trained facilitators led the group in exercises such as guided breathing practices, yoga-based movement synchronized with breaths, and interoceptive/sensory awareness meditation practices such as "body-scans." Sessions also included brief psychoeducational presentations and group discussions. The psychoeducation presentations aimed to provide the rationale for each of the introduced practices, and they covered topics such as stress responses, functioning of the autonomous nervous system, and strategies to improve emotion regulation. In addition, home practice instructions were given, which could encompass daily practice of anywhere between 5 min to an hour. Participants were provided with audio recordings with guided meditations, yoga-based movement sequences, and breathing

exercises.

The modular structure of the TARA intervention is as follows, with each module covered in three sessions (for details, see [Henje Blom et al., 2014](#)): **Module 1**: focuses on the ability to create a calm and safe inner state through breathing, yoga-based movement and guided “body-scan” meditations. A brief psychoeducational module on the psychophysiology of stress and respiration is provided. **Module 2**: includes attention training first targeting external stimuli, followed by sensory stimuli and interoceptive awareness. Psychoeducation is provided on the basics of brain functioning and the importance of sleep and healthy eating for emotional health. **Module 3**: focuses on recognizing, labeling, and communicating emotions. By aiding participants in identifying their emotions and applying skills from modules 1 and 2, the core skills are applied in social interaction. **Module 4**: a more cognitively based behavioral activation approach is introduced, including understanding of social triggers of negative emotions and one’s own experiential avoidance strategies and how they may impede obtaining desired life goals. A parallel focus on defining personal core values and linking them to behavior activation is a thread throughout the intervention that serves as a motivational force to increase sustainability and future engagement in salutogenic activity.

Attendance was assessed by the TARA teachers. We followed an efficacy approach that only includes data of study participants who are adequately compliant ([Armijo-Olivo et al., 2009](#)) and only analyzed data of the participants who attended at least 75% of TARA sessions.

2.3. Experimental design

The study had a *controlled within-subject design* ([Fig. 1](#)). In this study design, subjects are assessed three times: the first two assessments before and after the “waiting” period serving as a control condition, and the second and third assessments occurring before and after training. By avoiding the effect of between-subjects variance, such a design is potentially more powerful than a *randomized-controlled study design* ([Poldrack, 2000](#)).

All 36 subjects underwent two MRI scans / emotional health assessments: one immediately before the TARA training (time point B) and one immediately after the training ended (time point C) ([Fig. 1](#)). A subset of the 20 subjects had received a third, control MRI scan (time point A) and emotional health assessment 12 weeks before the training commenced. The remaining 16 subjects did not have the time point A assessments because they found out about the study and enrolled after the time point A has passed but before scheduled TARA groups started.

2.4. Emotional health self-assessment measures

Anxiety and depression symptoms were measured with the Multi-dimensional Anxiety Scale for Children (MASC) ([March 1997](#)) and Reynolds Adolescent Depression Scale-2 (RADS-2) ([Reynolds, 2002](#)),

respectively. Total T-scores were used as the main outcome with both scales.

The Reynolds Adolescent Depression Scale-2 (RADS-2) ([Reynolds, 2002](#)) is a widely used, highly valid and reliable self-report measure of adolescent depression that provides scores on four subscales that evaluate specific domains of depressive symptoms in adolescents: Anhedonia/Negative Affect, Dysphoric Mood, Negative Self-Evaluation, and Somatic Complaints ([March et al., 2006](#); [Osman et al., 2010](#); [Reynolds & Mazza, 1998](#)).

The MASC is a 39-item child-report measure of anxiety symptoms across several dimensions of anxiety. Items are rated according to four response categories ranging from 0 (“never true about me”) to 3 (“often true about me”). The MASC consists of four subscales: Physical Symptoms, Social Anxiety, Harm Avoidance, and Separation/Panic ([March 1997](#)). The MASC also yields a Total Scale score and an Anxiety Disorder Index (ADI) score to identify youth who may meet criteria for an anxiety disorder (ADI is comprised of items with the highest predictive validity of an anxiety disorder) ([March 1997](#)).

2.5. MRI data acquisition and preprocessing

Each adolescent underwent MRI scanning on a 3 T GE Discovery MR750 (General Electric Healthcare, Milwaukee, WI, USA) using a Nova 32-channel head coil (Nova Medical, Wilmington, MA, USA). We acquired a standard high-resolution T1-weighted scan for the purposes of identifying regions of interest and facilitating alignment, and a diffusion-weighted MRI scan with a spin-echo echo-planar-imaging (EPI) sequence (TR = 7.5 s, minimum TE, FOV = 25.6x25.6 cm, 128x128 matrix, slice thickness = 2 mm) for the purposes of estimating white matter tracts connecting our regions of interest and to compute water diffusion metrics reflecting white matter microstructure. Diffusion-sensitizing gradients were applied at a b-value of 1000 s/mm² along 30 non-collinear directions, and one b₀ volume was collected.

Preprocessing was done using the FMRIB Software Library (FSL 5.0.8) ([Smith et al., 2004](#)) and in-house scripts in MATLAB (MathWorks, Natick, MA). A quality assurance step was performed, in which diffusion volumes affected by motion were rejected ([Tymofiyeva et al., 2012](#)) and remaining images were corrected for eddy current distortions, affine head motion, and b-vector rotation to account for head motion. Datasets of adolescents with > 15 rejected directions were excluded from the analysis ([Chen et al., 2015](#)). DTI reconstruction, deterministic whole-brain streamline fiber tractography, and visualization were performed using the Diffusion Toolkit ([Wang et al., 2007](#)). Fiber Assignment by Continuous Tracking (FACT) was chosen with one seed per voxel and a standard threshold angle of 35°.

2.6. Network construction (Connectomics)

Network construction was performed as described previously ([Yuan](#)

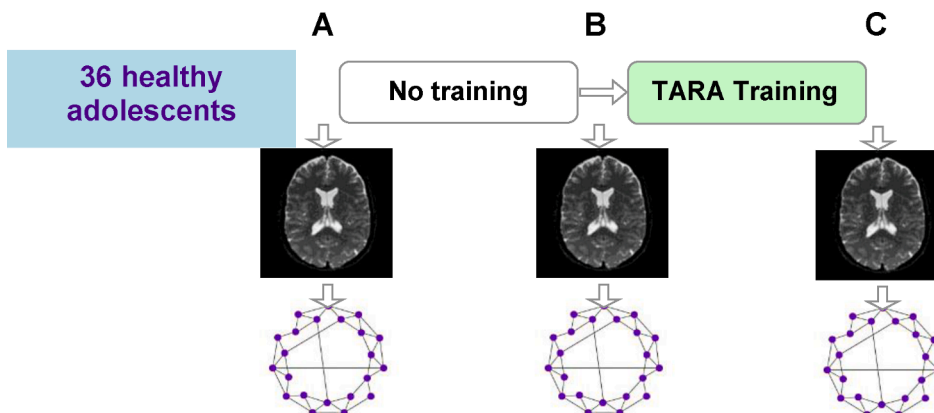


Fig. 1. Controlled within-subject study design. Adolescent subjects were assessed three times: the first two assessments before and after the “waiting” period serving as a control condition, and the second and third assessments occurring before and after training. Assessments included diffusion MRI-based structural brain network measures and emotional health self-assessment measures. The time interval between time points A and B, and between time points B and C was 12 weeks. All 36 adolescents had time points B and C. Only 20 adolescents had all three time points A, B and C.

et al., 2019). Briefly, segmentation of the cerebrum into 90 regions of interest (ROIs) was performed in DTI space using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and intermediate registration to T1-weighted images in MNI space. To assure the quality of the registration, the resulting AAL-based ROIs were visually inspected via semi-transparent overlay with the b_0 volume in fsview. The AAL-based ROIs served as network nodes, whereas connections were calculated by using as weights the average fractional anisotropy (FA) sampled along the connecting streamlines. The FA-weighted connections were represented as a 90×90 connectivity matrix, in which each row/column corresponds to a distinct node (brain ROI). The node strengths of the hypothesized brain regions were calculated as the sum of all neighboring connection weights or, in other words, the sum of connection weights between the brain region of interest and all other nodes in the network (Rubinov & Sporns, 2010). The changes in the obtained node strengths of Right and Left Amygdala, Right and Left Insula, Right and Left Caudate, and Right and Left Putamen with the intervention were expected to reflect the network-level microstructural changes in the white matter tracts connecting these regions to the rest of the brain. The choice of the connectome construction pipeline was based on previous evidence that FA-weighted networks consistently yield reliable and highly precise graph metrics in adolescents (Yuan et al., 2019), sensitive to mood disorders in youth (Tymofiyeva et al., 2017). Node strength was chosen because it is a common measure of node centrality with the most straightforward neurobiological interpretation (high interaction with many other nodes) (Rubinov & Sporns, 2010), which has been previously shown to reflect mindfulness training-related structural network changes in adults (Sharp et al., 2018).

2.7. Monitoring instruments

2.7.1. Participant acceptability of the TARA interventions

Participants were asked to complete session-by-session ratings of the TARA training using the Child Session Rating Scale (CSRS) (Campbell & Hemsley, 2009). The CSRS is a 4-item self-assessment using a 10-cm visual analog scale, with higher scores indicating better experience. Participants rated each session in terms of how much they felt listened to, how important the content and activities were to them, how much they liked the session, and their overall experience.

2.7.2. Compliance with home practice

To probe how much the participants practiced at home, we asked them to mark days on which they practiced breathing, meditation or yoga-based movements outside TARA sessions in a provided practice sheet.

2.8. Statistical analyses

To test the primary hypotheses (H1, H2), we designed a hierarchical Bayesian model that had the change in RADS-2 T-score, MASC T-score, or node strengths between time points A and B, and B and C, as the response variable and was formulated as follows:

$$S_{B,i} - S_{A,i} = \alpha + \varepsilon_{1,i}$$

$$S_{C,i} - S_{B,i} = \alpha + \delta + \varepsilon_{2,i}$$

$$\varepsilon_{1,i} \sim N[0, \sigma_1^2], \varepsilon_{2,i} \sim N[0, \sigma_2^2], \text{Corr}(\varepsilon_{1,i}, \varepsilon_{2,i}) = 0$$

where

i – individual subject

A, B, C – time points

α – mean change in the outcome variable during the waiting/control period (e.g., due to development)

δ – mean change in the outcome variable during the training period due to the training

S – the outcome variable

Markov Chain Monte Carlo methods were used to explore the posterior distribution of all parameters (α , δ , and σ^2) and conduct missing data imputation simultaneously, since not all subjects had all three data points. We used flat priors for all parameters (α , δ , and σ^2) but for σ^2 the domain was restricted to the positive reals. We fitted the model using the software Stan (Carpenter et al., 2017) using the R package *rStan* (Stan Development Team, 2018).

We chose to use this hierarchical approach over paired *t*-tests in order to preserve data from all 34 subjects as a subset of participants did not complete assessments at time point A. We additionally performed paired *t*-tests to explore changes between time points A and B, and between time points B and C, separately.

The secondary hypothesis H3 was tested using Pearson's correlation between changes in RADS-2 and MASC T-scores (between time points B and C), and the corresponding changes in node strengths of Right and Left Amygdala, Right and Left Insula, Right and Left Caudate, and Right and Left Putamen. Additional exploratory analysis for the subscales of MASC and RADS-2 was planned following the same design: correlation between changes in MASC and RADS-2 subscales and changes in node strengths of Right and Left Amygdala, Right and Left Insula, Right and Left Caudate, and Right and Left Putamen.

A post-hoc analysis using Pearson's correlation was planned, depending on the H1 and H2 testing results to assess baseline correlations between the emotional health and brain network node strengths variables.

We conservatively corrected for multiple comparisons using Bonferroni correction. For H1, with two comparisons (corresponding to the RADS-2 and MASC scores), the corrected significance level was set at 0.025. For H2 and H3, with eight comparisons (corresponding to the eight node strengths), the corrected significance level was set at 0.006.

We also tested whether there was any systematic difference between the subjects who had all three time points and those who were missing the time point A in terms of sex, age, race, ethnicity, handedness, socioeconomic status, and MASC and RADS-2 at the beginning of TARA. We performed chi-square tests and independent *t*-tests with equal variances for the categorical and continuous variables, respectively.

The statistical analyses were performed using IBM SPSS Statistics software (version 26) and R (4.0.0).

3. Results

The MRI scans and the TARA training were well-tolerated by all 36 participants. The participant acceptability of the TARA interventions as measured by the CSRS was high: averaging 8.9 out of 10.0 across all of the participants, sessions, and questions (how much participants felt listened to, how important the content and activities were to them, how much they liked the session, and their overall experience). On average, participants attended 78% of the TARA sessions. Twelve participants attended fewer than 75% of the sessions and were excluded. The number of days on which the included participants reported doing TARA practices outside the 12 weekly sessions varied considerably ranging from four days to 66 days (meaning a daily practice outside the sessions). Some of the participants, however, did not track home practice systematically during the 12 weeks of the TARA intervention and instead provided a "memory protocol" on the day of the post-TARA MRI. One adolescent's diffusion MRI dataset had > 15 rejected directions and was excluded from the analyses. Out of the remaining 23 subjects, 14 had assessments and MRIs at three time points and nine subjects had assessments and MRIs only at time points B and C. The participants who had three time points did not differ from those who had two time points in terms of sex, age, race, ethnicity, handedness, socio-economic status, and MASC and RADS-2 at the beginning of TARA (all p 's > 0.05). Demographic and baseline clinical characteristics of the study participants whose data were included in the analyses are summarized in Table 1 and in Fig. 2.

Table 1
Demographic and baseline clinical characteristics of the study participants included in the data analyses.

Number of participants included in data analyses	23
Number of participants with 3 time points	14
Sex (Female/Male)	13/10
Age before TARA (time point B), yrs. (standard deviation; range)	16.4 (1.2; 14.3–18.99)
Race	
white/Caucasian	12 (52%)
African American	0 (0%)
Asian	5 (22%)
Native American	1 (4%)
Pacific Islander	0 (0%)
other or more than one	4 (17%)
missing data	1 (4%)
Ethnicity	
Hispanic or Latino	3 (13%)
not Hispanic or Latino	20 (87%)
Socio-economic status/the highest level of education of the mother	
less than 9th grade	0 (0%)
some high school	0 (0%)
graduated high school	2 (9%)
some college	0 (0%)
graduated college	6 (26%)
professional/graduate degree	12 (52%)
do not know	1 (4%)
missing data	2 (9%)
Handedness	
right-handed	20 (87%)
left-handed	1 (4%)
missing data	2 (9%)
RADS-2 T-score before TARA (time point B)	53.9 (11.4; 39–84)
MASC-2 T-score before TARA (time point B)	58.0 (10.6; 37–80)

Our results showed a large statistically significant effect of decrease in anxiety symptoms during the TARA training compared to the control time period (Cohen’s $d = -0.961, p = 0.006$) (Table 2, Fig. 3). A medium effect size was observed for the decrease in depressive symptoms, which, however, did not reach statistical significance (Cohen’s $d = -0.609, p = 0.06$).

We also observed a large statistically significant effect of decrease in the Right Amygdala node strength with the TARA training compared to the control time period (Cohen’s $d = -1.026, p = 0.004$) (Table 2, Fig. 3).

A post-hoc analysis showed a significant positive correlation between the baseline pre-TARA MASC anxiety symptoms and the baseline Right Amygdala node strength (Pearson’s $r = 0.652, p = 0.001$) (Fig. 4), however, the change in anxiety symptoms with TARA did not correlate with the change in the Right Amygdala node strength (Pearson’s $r = 0.146, p = 0.51$).

3.1. Further non-significant results and exploratory analyses

Due to multiple comparisons and potentially due to a limited number of subjects, several associations in H2 and H3 did not reach statistical significance but displayed a medium effect size (Table 2): (H2) Left Caudate node strength increased during the TARA training compared to the control time period (Cohen’s $d = 0.639, p = 0.05$); Left Putamen node strength increased during the TARA training compared to the control time period (Cohen’s $d = 0.545, p = 0.09$); Right Caudate node strength decreased during the TARA training compared to the control time period (Cohen’s $d = -0.695, p = 0.046$); (H3) change in MASC anxiety symptoms with TARA negatively correlate with the change in the Left Putamen node strength (Pearson’s $r = -0.503, p = 0.015$); change in RADS-2 depressive symptoms with TARA negatively correlate with the change in the Left Putamen node strength (Pearson’s $r = -0.502, p = 0.015$) (Tables 3, 4).

Exploratory analyses relating change in brain metrics with change in the various subscales of the MASC and RADS-2 showed the following results correlations (uncorrected): the change in Left Putamen node strength negatively correlated with the change in RADS-2 Somatic Complaints ($r = -0.494, p = 0.017$), as well as with the change in MASC Harm Avoidance ($r = -0.462, p = 0.026$) and MASC Anxiety Disorder Index ($r = -0.450, p = 0.031$). The change in the Right Amygdala node strength correlated positively with the change in RADS-2 Anhedonia / Negative Affect ($r = 0.575, p = 0.004$) (Fig. 5). The change in the Left Caudate node strength correlated negatively with the change in RADS-2 Somatic Complaints ($r = -0.418, p = 0.047$). The change in the Left Insula node strength correlated positively with the change in RADS-2 Anhedonia / Negative Affect ($r = 0.457, p = 0.028$). See Tables 3-4 for a summary.

Finally, the exploratory paired t -tests revealed more details about the main findings of the decreased anxiety and Right Amygdala node strength with the TARA training compared to the control time period:

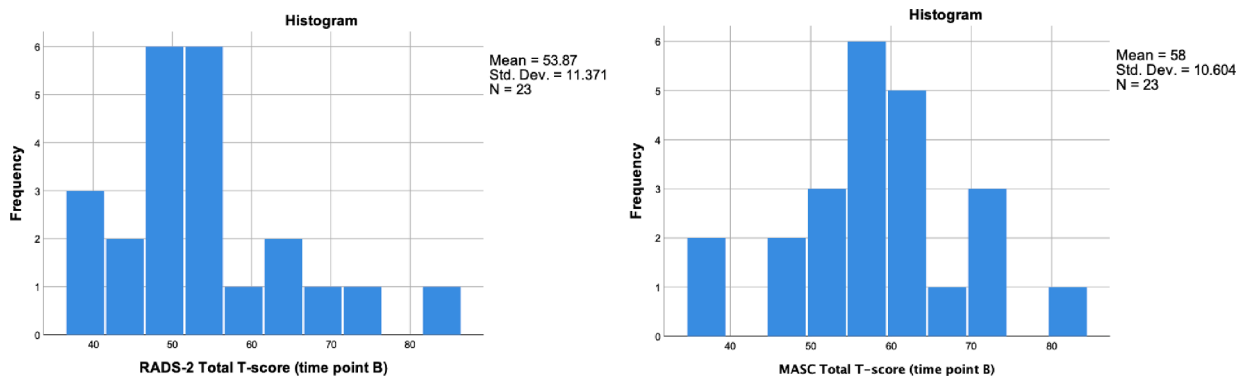


Fig. 2. Baseline pre-TARA (time point B) distribution of depressive (left) and anxiety (right) symptoms.

Table 2
Changes in depression and anxiety symptoms and node strengths during the TARA training compared to the control time period.

	RADS-2	MASC	R. Amygdala	L Amygdala	R. Insula	L. Insula	R. Caudate	L. Caudate	R. Putamen	L. Putamen
Cohen’s d	-0.609	-0.961*	-1.026**	-0.230	0.201	-0.326	-0.695	0.639	-0.303	0.545
uncorrected p -value	0.063	0.006	0.004	0.496	0.549	0.302	0.046	0.053	0.378	0.094

* significant at the 0.025 corrected level for RADS-2 and MASC (H1)

** significant at the 0.006 corrected level for node strength (H2)

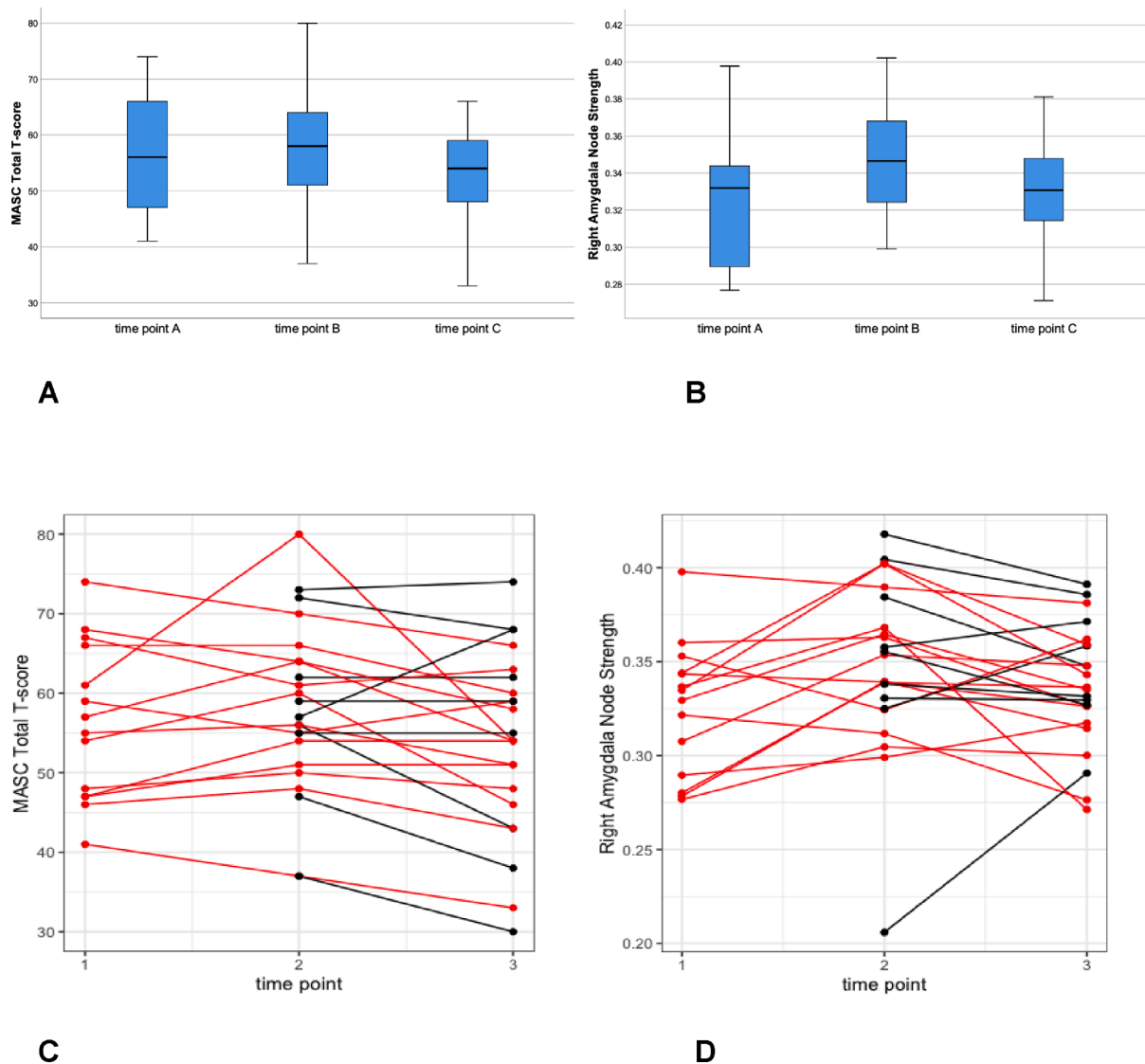


Fig. 3. Boxplots representing significant changes with TARA compared to control time period in anxiety symptoms (A) and Right Amygdala node strength (B). Plots of individual subjects' values, color-coded by those who had all three time points and those who had only two, for anxiety symptoms (C) and Right Amygdala node strength (D).

While there was a decrease in these measures between time points B and C, there was an increase in these measures between timepoints A and B (Table 5).

4. Discussion

The present study is the first to examine the structural connectome changes in adolescents with Training for Awareness, Resilience, and Action (TARA). The main findings were the large decrease in anxiety symptoms during the TARA training compared to the control time period and the large decrease in the Right Amygdala node strength during the TARA training compared to the control time period. Although not statistically significant, we observed a medium effect size in decreases in depressive symptoms with TARA compared to the control time period. The stronger effect size in the case of anxiety compared to depression symptoms can be explained by the fact that the participants were more anxious than depressed at the pre-TARA baseline (Table 1). Our post-hoc analysis also showed that higher baseline pre-TARA anxiety symptoms were associated with higher baseline Right Amygdala connectivity. While change in Right Amygdala node strength with TARA was not correlated with change in anxiety, it was associated with change

in depression subscale of Anhedonia / Negative Affect.

We used FA-weighted node strength as the MRI outcome, thus probing into the network-level microstructure (axonal ordering, axonal density, degree of myelination, etc.) of all neighboring connections of the brain regions of interest. Our post-hoc analysis showing a significant positive correlation between the baseline pre-TARA anxiety symptoms and the Right Amygdala node strength suggests that increased structural connectivity of Right Amygdala may underlie increased anxiety in adolescents. Indeed, a recent DTI study demonstrated white matter hyperconnectivity of amygdalae in adolescent rats with emotional deficits that followed chronic early-life adversity/stress (Bolton et al., 2018). The authors argued that this hyperconnectivity was causing increased activation of the corticotropin releasing factor (CRF)-producing neurons in amygdalae. Also, some human studies reported a positive correlation between amygdalar structural connectivity and anxiety (Clewett et al., 2014; Jalbrzikowski et al., 2017; Greening & Mitchell, 2015). Interestingly, the study by Bolton and colleagues also provides supporting evidence that anhedonia follows stress due to aberrant interaction of reward and anxiety circuits. In our study, change in Right Amygdala node strength with TARA was not correlated with change in anxiety but rather with a depression subscale of Anhedonia /

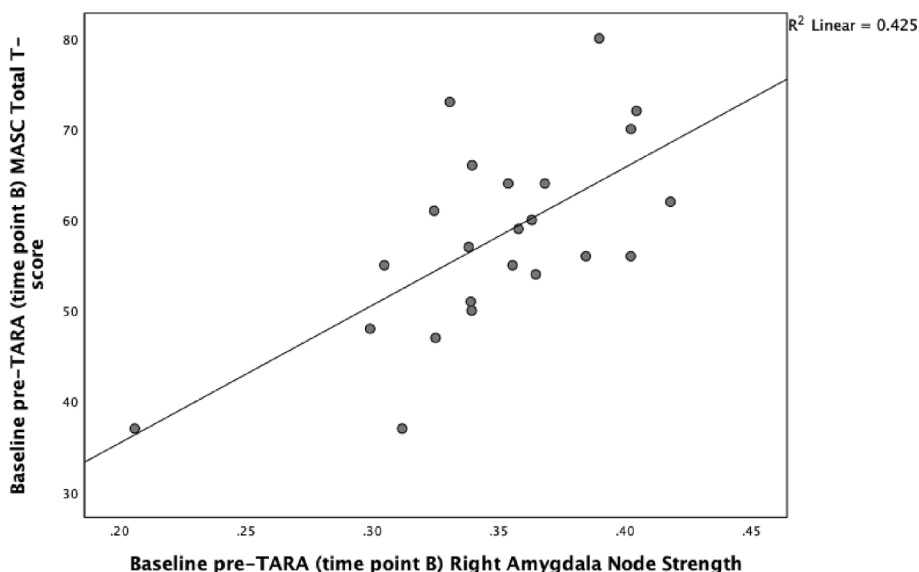


Fig. 4. A post-hoc analysis showed a significant positive correlation between the baseline pre-TARA MASC anxiety symptoms and the baseline Right Amygdala node strength (Pearson’s $r = 0.652$, $p = 0.001$).

Table 3

Correlations between changes in RADS-2 depressive symptoms in adolescents with TARA and changes in structural brain networks with TARA.

		Δ RADS-2	Δ Dysphoric Mood	Δ Anhedonia/ Negative Affect	Δ Negative Self-Evaluation	Δ Somatic Complaints
Δ Right Amygdala	Pearson Correlation	-0.009	0.154	0.575*	0.003	-0.205
	uncorrected p -value	0.968	0.484	0.004	0.990	0.348
Δ Left Amygdala	Pearson Correlation	-0.212	-0.091	0.284	-0.165	-0.203
	uncorrected p -value	0.331	0.680	0.190	0.451	0.352
Δ Right Insula	Pearson Correlation	0.009	0.224	0.390	-0.002	-0.095
	uncorrected p -value	0.966	0.304	0.066	0.994	0.668
Δ Left Insula	Pearson Correlation	-0.069	0.011	0.457*	0.076	-0.128
	uncorrected p -value	0.756	0.962	0.028	0.732	0.561
Δ Right Putamen	Pearson Correlation	-0.182	-0.049	0.000	-0.068	-0.144
	uncorrected p -value	0.406	0.826	0.999	0.758	0.512
Δ Left Putamen	Pearson Correlation	-0.502*	-0.409	-0.062	-0.368	-0.494*
	uncorrected p -value	0.015	0.053	0.778	0.084	0.017
Δ Right Caudate	Pearson Correlation	-0.204	-0.065	0.369	-0.133	-0.231
	uncorrected p -value	0.351	0.767	0.083	0.546	0.288
Δ Left Caudate	Pearson Correlation	-0.400	-0.214	-0.084	-0.369	-0.418*
	uncorrected p -value	0.058	0.326	0.705	0.083	0.047

Δ - change between time point B and time point C

**significant at the 0.006 corrected level (for Δ RADS-2 only, Hypothesis 3)

* significant at the 0.05 uncorrected level

Negative Affect (in an exploratory analysis). Possible reasons for that include non-biological derivation of the anxiety and depression scales and overlapping constructs between the two scales (for example, MASC contains an item “I have trouble asking other kids to play with me,” whereas the RADS-2 subscale of Anhedonia / Negative Affect contains a reverse-scored item “I feel like talking to other students”).

We interpret the observed changes in the structural brain network metrics with TARA compared to the control time period as an indicator of microstructural changes in the amygdalar white matter tracts that takes place with regular, anxiety-reducing TARA practices. Cellular mechanisms that potentially explain FA-weighted network changes include fiber reorganization, myelin formation, and myelin remodeling (Zatorre et al., 2012). Specifically, animal studies showed a direct link between an increase in oligodendrocytes forming the myelin sheaths and an increase in FA with training (Blumenfeld-Katzir et al., 2011). Evidence from other animal studies demonstrates that myelin sheath thickness may increase or decrease in response to experience and activity (Liu et al., 2012; Sinclair et al., 2017; Zatorre et al., 2012). While experience-dependent FA decreases are less commonly reported in human studies, we assume that the main contribution to such changes is

related to preexisting oligodendrocyte remodeling, such as change in internode length and/or thickness (Sampaio-Baptista & Johansen-Berg, 2017).

It needs to be noted that we observed an increase in the Right Amygdala node strength (and a very minor increase in anxiety) between time points A and B (Table 5). One possible explanation of this change is that participants who joined our mindfulness study had an ongoing (or anticipated) increase in stressful circumstances, which continued during the waiting period but the effect of which was reversed during the intervention.

The associations in H2 and H3 that displayed a medium strong effect size but did not reach statistical significance involved Left Caudate, Left Putamen and Right Caudate, all of which are highly dopaminergic striatal structures implicated in reward-based learning (Haber, 2011). Changes in the activity in the putamen have been previously associated with mindfulness meditation (Barentsen et al., 2010; Lazar et al., 2000; Tang et al., 2009). Meditation is also associated with dopamine release, with one research group observing a 65% increase of endogenous dopamine in the striatum during practice (Kjaer et al., 2002). Our team has also demonstrated that youth undergoing TARA training (a partially

Table 4
Correlations between changes in MASC anxiety in adolescents with TARA and changes in structural brain networks with TARA.

		ΔMASC	ΔPhysical Symptoms	ΔSocial Anxiety	ΔHarm Avoidance	ΔSeparation/ Panic	ΔAnxiety Disorder Index (ADI)
ΔRight Amygdala	Pearson Correlation	0.146	0.224	0.179	-0.132	0.315	0.047
	uncorrected <i>p</i> -value	0.507	0.304	0.413	0.548	0.143	0.832
ΔLeft Amygdala	Pearson Correlation	-0.218	-0.096	-0.060	-0.335	0.001	-0.231
	uncorrected <i>p</i> -value	0.319	0.662	0.786	0.118	0.997	0.288
ΔRight Insula	Pearson Correlation	0.002	-0.014	0.198	-0.164	0.075	-0.193
	uncorrected <i>p</i> -value	0.994	0.948	0.365	0.453	0.735	0.377
ΔLeft Insula	Pearson Correlation	0.010	0.080	0.121	-0.250	0.225	-0.122
	uncorrected <i>p</i> -value	0.965	0.716	0.583	0.251	0.302	0.578
ΔRight Putamen	Pearson Correlation	-0.095	-0.027	0.018	-0.193	-0.070	-0.251
	uncorrected <i>p</i> -value	0.665	0.904	0.935	0.376	0.750	0.249
ΔLeft Putamen	Pearson Correlation	-0.503*	-0.356	-0.312	-0.462*	-0.313	-0.450*
	uncorrected <i>p</i> -value	0.015	0.096	0.148	0.026	0.146	0.031
ΔRight Caudate	Pearson Correlation	-0.092	-0.079	-0.021	-0.212	0.264	-0.165
	uncorrected <i>p</i> -value	0.676	0.721	0.923	0.331	0.224	0.453
ΔLeft Caudate	Pearson Correlation	-0.216	-0.168	-0.039	-0.150	-0.170	-0.149
	uncorrected <i>p</i> -value	0.323	0.445	0.859	0.496	0.438	0.499

Δ - change between time point B and time point C

**significant at the 0.006 corrected level (for ΔMASC only, Hypothesis 3)

* significant at the 0.05 uncorrected level

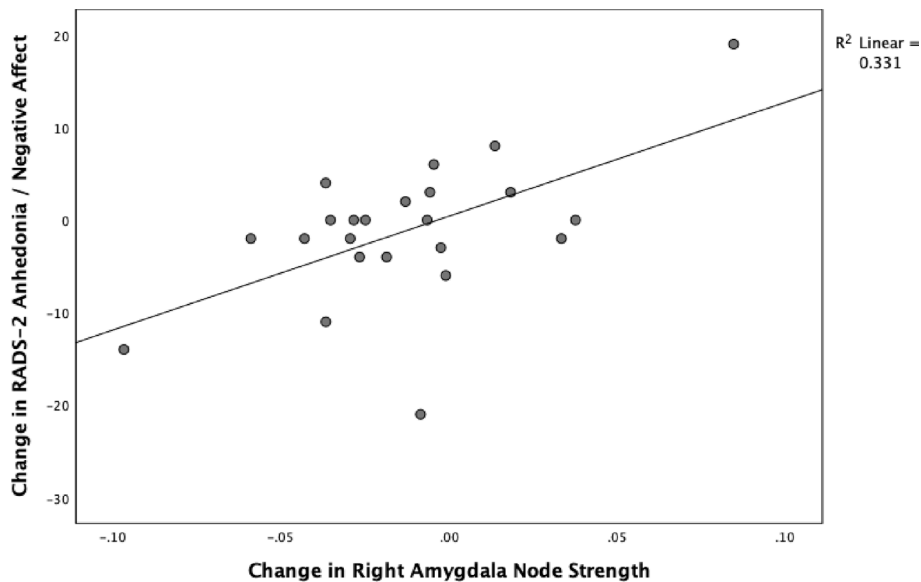


Fig. 5. An exploratory analysis showed a significant (uncorrected) positive correlation between the change in the Right Amygdala node strength and the change in RADS-2 Anhedonia / Negative Affect ($r = 0.575$, $p = 0.004$).

Table 5
Changes in anxiety and Right Amygdala node strength during the control time period (between time points A and B) and during the TARA training (between time points B and C), assessed separately using paired t-tests.

	Mean	t (paired t-test)	Number of degrees of freedom	Significance (2-tailed)
MASC _A -MASC _B	-1.857	-1.048	13	0.314
MASC _B -MASC _C	4.217	2.764	22	0.011
Right Amygdala _A - Right Amygdala _B	-0.025	-2.970	13	0.011
Right Amygdala _B - Right Amygdala _C	0.013	1.664	22	0.110

overlapping sample with this study) exhibited significant gray matter changes in a region including the Left Putamen with an effect size of Cohen's $d = 0.47$ (Yuan et al., 2020). Although non-significant, the observed associations with striatal structures in this study may reflect the intrinsic reward cultivated in particular by the practices of the last

TARA module (Henje Blom et al., 2014, 2016); future research explicitly testing this possibility in larger samples is needed. It needs to be noted that both trends towards increased and decreased node strengths were observed (Table 2), which may reflect region-dependent directionality of observed plastic changes consistent with the idea that the brain responds to environmental demands by focusing resources on task relevant networks and eliminating irrelevant processing for the purpose of energy reduction (Metzler-Baddeley et al., 2016).

The results of our study should be interpreted in light of its limitations. First, the study designed did not include randomization to the TARA intervention. However, a controlled within-subject design was utilized, which has the advantage of avoiding the effect of between-subjects variance and can be more statistically powerful than a randomized-controlled study design (Poldrack, 2000). Secondly, the study sample was relatively small, limiting the power to reliably detecting only strong effects; however, several of our non-significant findings with medium effect sizes were consistent with our hypotheses. Notably, an average medium effect size was reported (after correcting for inflation) in a meta-analysis of morphometric neuroimaging

in meditation practitioners (Fox et al., 2014) and in our voxel-based morphometry (VBM) study of youth practicing TARA (Yuan et al., 2020). Third, only adolescents without psychiatric diagnoses were included in this study, however, this information was based on self-reports and we did not conduct clinical assessment of psychiatric disorders as part of our study. Fourth, DTI tractography was used that is limited in resolving crossing fibers. Moreover, FA is considered to be a sensitive but not very specific measure, which can be impacted by a number of tissue properties, such as axonal ordering, axonal density, degree of myelination, etc. (Jones et al., 2013). Finally, the commonly used AAL atlas partitions the cerebrum into 90 relatively large regions, which might explain why, for example, no changes in the node strength of the insula were observed: the effects might get “diluted” due to the large number of connections.

In conclusion, our results indicate that increased structural connectivity of the Amygdala may underlie increased anxiety in adolescents and be lowered through stress-reducing training such as TARA. The results of this study contribute to our understanding of the neural mechanisms of TARA and may facilitate neuroscience-based prevention and clinical treatment of adolescent anxiety and depression.

CRediT authorship contribution statement

Olga Tymofiyeva: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Project administration, Funding acquisition. **Eva Henje:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Funding acquisition. **Justin P. Yuan:** Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing. **Chiung-Yu Huang:** Methodology, Formal analysis, Writing - review & editing. **Colm G. Connolly:** Conceptualization, Writing - review & editing. **Tiffany C. Ho:** Conceptualization, Resources, Writing - review & editing. **Sarina Bhandari:** Validation, Formal analysis, Investigation, Writing - review & editing. **Kendall C. Parks:** Investigation, Writing - original draft, Writing - review & editing. **Benjamin Sipes:** Validation, Formal analysis, Writing - review & editing. **Tony T. Yang:** Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition. **Duan Xu:** Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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