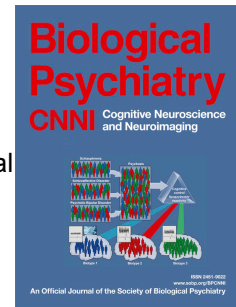


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Internalizing Symptoms & Adverse Childhood Experiences Associated with Functional
Connectivity in A Middle Childhood Sample

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Abstract

Introduction: Research has found overlapping associations in adults of resting state functional connectivity (RSFC) to both internalizing disorders (e.g., depression, anxiety) as well as a history of traumatic events. The present study aimed to extend this previous research to a younger sample by examining RSFC associations with both internalizing symptoms and adverse childhood experiences (ACEs) in middle childhood.

Method: We used generalized linear mixed models to examine associations between *a priori* within- and between-network RSFC with child-reported internalizing symptoms and ACEs using the Adolescent Brain Cognitive Development dataset ($N = 10,168$, $M_{\text{age(years)}} = 9.95$, $SD_{\text{age(years)}} = 0.627$).

Results: We found that internalizing symptoms and ACEs were associated with both multiple overlapping and unique RSFC network patterns. Both ACEs and internalizing symptoms were associated with a reduced anticorrelation between the default mode network and the dorsal attention network. However, internalizing symptoms were uniquely associated with lower within-network default mode network connectivity while ACEs were uniquely associated with both lower between-network connectivity of the auditory network and cingulo-opercular network, and higher within-network frontoparietal network connectivity.

Conclusions: The present study points to overlap in the RSFC associations with internalizing symptoms and ACEs, as well as important areas of specificity in RSFC associations. Many of the RSFC associations found have been previously implicated in attentional control functions, including modulation of attention to sensory stimuli. This may have critical importance in understanding internalizing symptoms and outcomes of ACEs.

Understanding the interrelationships between internalizing disorders (depression, anxiety) and adverse childhood experiences (ACEs) has increasingly received attention in mental health research. ACEs are strongly associated with the later development of internalizing symptoms (1–6). Therefore, understanding the shared associations (pathophysiological correlates) of ACEs and internalizing symptoms holds significance from etiological and treatment perspectives. One way to study these associations is to examine the neural correlates (e.g., resting state functional connectivity [RSFC]) associated with both ACEs and internalizing symptoms. We examined whether there are common and unique RSFC associations with reports of ACEs and internalizing symptoms in middle childhood. This information may help inform our understanding of whether ACEs and internalizing symptoms share common neural pathways that may contribute to, or be the consequence of, the development of psychopathology.

RSFC is a way to examine temporal correlations of spontaneous blood oxygenation level dependent (BOLD) activity in regions distributed across the brain and is typically obtained when the participant is not completing a task. Measures of RSFC can be used to organize brain regions into putative resting state connectivity networks by examining patterns of correlations between time-series of BOLD responses across brain regions (7). Several approaches have been taken to organizing and describing these networks. One approach groups them into two categories: “task-positive”, which are brain regions activated when stimulated by a task, and “task-negative”, which are regions deactivated when stimulated by a task (8,9). RSFC networks have been associated with different cognitive and affective processes (e.g., attentional control; Table 1 for network functions (7)). These same processes have also been associated with both psychiatric symptoms and ACES in a number of studies (7,12–19,21).

Internalizing symptoms have been associated with several RSFC patterns (17,18,22–25). Although research has not been consistent regarding directionality, disrupted connectivity between “task-positive” networks (e.g., the dorsal attention network [DAN]; Table 1 for network

functions) and sensory oriented networks (e.g., the visual network [VIS]) has been associated with internalizing symptoms (14,25). Studies have also found associations for anxiety disorders and depressive symptoms involving networks associated with attention. For example, both types of symptoms have been associated with higher within-network connectivity of the default mode network (DMN; (9,14,23,24,26–28)), lower within-network connectivity of the salience network (SAN; (14,24,29,30)), and disrupted within-network connectivity of the ventral attention network (VAN; (31–33)). MDD has further been associated with disrupted between-network connectivity of the frontoparietal network (FPN) and DAN (14,23), and heightened between-network DMN-FPN connectivity (14,23). Several of these networks have been associated with attention within or outside the body (e.g., DAN and FPN are associated with executive control of attention (7,12,15)). Consistent with these RSFC findings, research has tied internalizing disorders with altered attention (12,13).

The strong association between ACEs and later development of internalizing disorders is well-established (1–6). Therefore, it is not surprising that studies examining childhood stress/ACEs have found associations with several of the aforementioned RSFC networks associated with internalizing symptoms (5,19,20,34–36). Multiple studies have researched ACEs with varying definitions (35). We defined ACEs as stressful life events that children had little or no control over, similar to previous research (36,37). Research examining trauma and stress has found associations with lower within-network connectivity of DMN (4,38,39) and disrupted within-network connectivity of SAN (35,40). These networks are functionally associated with control of attention (Table 1; (7)) and as described above have been associated with the presence of internalizing symptoms.

The present paper was motivated by previous research examining shared associations between internalizing disorders, ACEs, and RSFC networks in adults (12). Notably, Yu et al. (12) found that both MDD and prior experience of trauma (e.g., sexual abuse) were associated with disrupted within-network DAN RSFC as well as higher between-network connectivity of

DAN-FPN RSFC (Figure 2 and Table S5 (12)). They further found reports of abuse/neglect uniquely associated with more positive: between-network connectivity of VIS and the cingulo-opercular network (CON), between-network connectivity of DAN and sensorimotor network, and between-network connectivity of CON and the auditory network (AUD). They found unique associations between MDD and RSFC (e.g., lower between-network DAN-SAN connectivity, higher within-network connectivity of DMN, Figure 2 (12)). These overlapping and unique findings motivated the current paper as, to our knowledge, no previous research has examined both the overlap and the specificity of RSFC network alterations for both internalizing symptoms and ACEs in a middle childhood sample.

It is important to examine overlapping neural associations of stress/trauma and internalizing symptoms in a middle childhood demographic. Research has found associations between levels of internalizing symptoms during early/middle childhood and internalizing disorders in adulthood (41,42) and that such symptoms can be seen as early as toddlerhood (41). Research further indicates experiencing ACEs at a younger age can lead to an increased chance of later developing depressive and trauma-related disorders (5). Although previous research has looked at neural associations of internalizing symptoms (43,44) and ACEs (45) separately, research looking at both the overlap and specificity of these report types using a middle childhood sample is lacking. Examining a younger population could shed light on whether the overlapping associations between RSFC and these symptoms found in adulthood are already present in middle childhood, potentially identifying a window of opportunity for early intervention before the onset of adolescence, a known high-risk period for increases in depression.

We aimed to replicate the findings reported by Yu et al. (12) in the middle childhood sample using data from the Adolescent Brain Cognitive Development (ABCD) Study (46). We examined overlap and specificity of within- and between-network RSFC associations with self-reports of ACEs or internalizing symptoms (Figure 1). We used 10 Gordon parcellation RSFC

networks (7) in our analyses, with networks chosen to replicate the RSFC associations found in Yu et al. (12). Analyses included all significant associations found in both the manuscript and supplement of Yu et al. (12) that can be examined in the Gordon parcellation. To more fully explore the overlap and specificity of associations, we initially examined associations with predictors of interest separately, then followed with models in which predictors of interests were jointly examined. For both ACEs and internalizing symptoms, we expected associations with within- and between-network connectivity to be found in attention-based networks (e.g., DAN within-network connectivity, DMN within-network connectivity, and DMN-FPN between-network connectivity; Table 1), similar to Yu et al. (12).

Methods

Participants

The ABCD Study is a large-scale study tracking 9-10-years-olds recruited from 21 research sites across the United States (47). The ABCD Study was approved by a central Institutional Review Board at the University of California, San Diego. Parents and children provided written informed consent and assent, respectively. Data Release 3.0 includes several waves of data, including a baseline (N=11,883) and 1-year follow-up (N=11,235), which were included in the present study. We examined data collected at baseline, with the exception of child-reported ACEs, which, although collected at the 1-year follow-up, assessed lifetime ACEs.

ABCD data were accessed from the National Institutes of Mental Health Data Archive (Acknowledgments; Supplement for study-wide exclusion criteria). Participants that did not have at least one resting state scan that passed quality assurance criteria (n=614) or had missing data (n=1,101; Supplemental Table 1) were removed from analyses. Final sample size was 10,168 individuals (Supplemental Table 1).

Measures

Adverse Childhood Events (ACEs)

The PhenX Adverse Life Events scale (36,37) measures self-reported lifetime ACEs experienced by the child. We examined youth self-reports to be consistent with Yu et al. (12)'s examination of self-reported symptoms. We also analyzed results using parent-about-child reports (Supplement). The Adverse Life Events scale has been shown to be a valid and reliable measure that is widely used to examine ACEs (36,37). This computerized instrument consists of 25 questions about events over the child's lifetime that the child experienced and had little to no control over (e.g., the death of a parent; (36,37)). Following the endorsement of ACEs, the child is asked whether this was a positive or negative event. We calculated ACEs as the summation of items that were judged by the child as negative, similar to Tiet et al. (37). 81.6% of included participants endorsed 1+ ACEs in this self-report measure (Supplemental Table 3 for prevalence of individual item endorsement).

Internalizing Symptoms

To measure internalizing symptoms, we used the validated and computerized Kiddie-Structured Assessment for Affective Disorders and Schizophrenia (K-SADS) for DSM-5 (46,48–50). K-SADS was utilized in the present study because it is the only measure of youth-reported psychopathology administered at baseline. Although we examined youth self-report to be consistent with Yu et al. (12), we also analyzed results using parent-about-child reports (Supplement). The computerized self-administered versions of the K-SADS show good to excellent concordance with the clinician-administered computerized K-SADS (50). We examined child-reported internalizing symptoms using the summation of 24 items assessing current depression symptoms ($n_{\text{questions}}=17$, $\alpha=0.832$) and Generalized Anxiety Disorder symptoms ($n_{\text{questions}}=7$, $\alpha=0.947$), as has been done in previous research using the ABCD Study dataset (51). 12.3% of included participants endorsed 1+ internalizing symptoms in this self-report measure (Supplemental Table 2 for prevalence of individual item endorsement). In contrast to Yu et al. (12), the present study examined internalizing symptoms broadly as opposed to focusing principally on diagnosis of MDD (Supplement for details). We additionally

conducted separate analyses examining youth-reported depressive symptoms from K-SADS (Supplemental Table 4) and anxiety symptoms (Supplemental Table 5), with results remaining consistent for depressive reports.

Imaging Procedure

The present study analyzed tabulated baseline imaging data from the ABCD Data Release 3.0 (DOI 10.15154/1519007). ABCD imaging procedures have been detailed in previous studies (52,53). All participants were imaged on a 3T scanner (Siemens, Phillips, or General Electric) with a 32-channel head coil and completed T1- and T2-weighted structural scans (1mm isotropic). Participants also completed four 5-minute resting-state BOLD scans, with their eyes open and fixated on a crosshair. Resting state images were acquired in the axial plane using an EPI sequence. Other resting-state image parameters varied by 3T scanner and have been previously detailed (https://abcdstudy.org/images/Protocol_Imaging_Sequences.pdf). A data analysis pipeline, using the Multi-Model Pressing Stress software package, was created in which resting state data were normalized and time course detrended. Signals of non-interest, including motion, white matter, ventricles, and whole-brain were removed by general linear model regression (52). Then frames with excessive motion were removed (>0.3 mm framewise-displacement, ≥ 5 contiguous frames, motion filtered for respiratory signals). The Fisher Z-transform of the correlation values was examined within and between each network (Supplement for additional imaging procedure details). We aimed to replicate Yu et al. (12) by examining within- and between-network RSFC that was: a) significant in their research, and b) could be replicated using the Gordon parcellation (7). This resulted in a total of 30 RSFC associations (Figure 1). Specifically, we looked at within-network connectivity associations of DMN, FPN, DAN, VIS, SAN, AUD, CON, sensorimotor mouth network (SMM), sensorimotor hand network (SMH), and VAN. We also examined RSFC between the following networks: DAN-DMN, DAN-FPN, DAN-VIS, DAN-SMM, DAN-SMH, DAN-CON, DAN-AUD, DAN-SAN, DMN-FPN, DMN-SAN, FPN-SAN, FPN-VIS, CON-VIS, CON-AUD, DAN-VAN, FPN-SMM, FPN-

SMH, FPN-AUD, CON-SMM, and CON-SMH. See Supplement for additional information [e.g., determination of between-network connectivity directionality (i.e., for anticorrelation)].

Statistical Analyses

Generalized linear mixed models (GLMM) were conducted in R lme4 package (54). All GLMMs included family unit and the 21 research sites modeled as random intercepts to account for the nested structure of the data relative to siblings and sites. All models included age, sex, and average motion (mean framewise-displacement) as covariates. We did not include race/ethnicity as a covariate in our models because previous research indicates that race/ethnicity is at least partially confounded with the likelihood of experiencing ACEs due to factors relating to systemic racism (55,56). We harmonized all scanner data across scanner types using COMBAT (57,58).

First, a GLMM examined the association between ACEs and internalizing symptoms. GLMMs were then used to analyze the associations between either ACEs or internalizing symptoms as outcomes and: 1) within-network connectivity for each of the 10 networks; 2) between-network connectivity as predictors (Imaging Procedure section above for all included between-network models). Exploratory analyses followed up any significant findings by examining whether the interaction of internalizing symptoms and ACEs was associated with RSFC metrics (Supplement). Although Yu et al. (12) did not do so, we also examined whether associations varied by sex (Supplemental Table 7). Additionally, we analyzed if our findings replicated when looking at parent-about-child reports of ACEs and internalizing symptoms (Supplemental Table 6).

Results are expressed as standardized beta estimates (β s) with 95% bootstrapped (5000 iterations) confidence intervals (CIs) and effect sizes are expressed as pseudo R-squared values (R^2_m). Analyses were False Discovery Rate corrected (FDR-corrected) across 30 comparisons for internalizing symptoms and 30 comparisons for ACEs.

Results

As expected, higher ACEs were associated with higher internalizing symptoms ($\beta=0.120$, $b=0.076$, $p<.001$, $95\%CI=0.064$, 0.088 , $R^2m=0.016$).

Internalizing Symptoms

Within-Network Connectivity Internalizing Symptoms

Table 2 and Figure 1 summarize all results. We found internalizing symptoms were associated with lower within-network DMN connectivity and higher within-network SMH connectivity, both of which survived FDR correction. Findings remained significant when adding in ACES as a predictor for RSFC (Table 3).

Between-Network Connectivity Internalizing Symptoms.

As seen in Table 2 and Figure 1, internalizing symptoms were associated with lower VIS-DAN connectivity and reduced DMN-DAN anticorrelation both of which survived FDR correction and remained significant when adding in ACES as a predictor for RSFC (Table 3).

ACEs

Within-Network Connectivity ACEs.

As seen in Table 2 and Figure 1, like internalizing symptoms (Figure 2), ACEs were associated with higher within-network SMH connectivity. ACEs were associated with lower within-network CON connectivity and higher within-network FPN connectivity. Findings survived FDR correction and remained significant when adding in internalizing symptoms as a predictor for RSFC (Table 3).

Between-Network Connectivity ACEs.

As seen in Table 2 and Figure 1, like internalizing symptoms (Figure 2), ACEs were associated with reduced DMN-DAN anticorrelation. Unlike internalizing symptoms, we found

ACEs were associated with lower AUD-CON connectivity. Findings survived FDR correction and remained significant when adding in internalizing symptoms as a predictor for RSFC (Table 3).

Discussion

The present study investigated RSFC network associations with internalizing symptoms and ACEs. Our findings point to potential overlap in connectivity associations with internalizing symptoms and ACEs (e.g., between-network DAN-DMN connectivity), and networks associated uniquely with either ACEs or internalizing symptoms (e.g., within-network DMN with internalizing symptoms; Table 2 and Figure 1). Consistent with our hypothesis, our findings partially overlapped with Yu et al. (12), in that we found reduced DMN-DAN anticorrelation associated with greater reports of internalizing symptoms. However, unlike Yu et al. (12), we found this RSFC metric was also associated with ACEs. Consistent with our hypothesis, we found associations with several RSFC metric associations involving task-positive networks (e.g., DAN, CON) and sensory information networks (e.g., SMH, VIS, AUD). These findings indicate networks implicated in various attentional control functions (e.g., DAN; Table 1) and networks implicated in sensory recognition (e.g., SMH) may have critical importance to understanding and potentially treating both internalizing symptoms and outcomes of ACEs (e.g., trauma disorders, internalizing disorders, etc.; (1)). Our findings help advance research indicating network connectivity associations with ACEs and internalizing symptoms are already evident in middle childhood.

One of our goals was to examine overlap in RSFC connectivity associations with both internalizing symptoms and ACEs. We found two overlapping RSFC associations that remained significant following FDR correction. First, internalizing symptoms and ACEs were both associated with higher within-network SMH connectivity. This finding is consistent with previous research (12), including research finding sensorimotor networks are associated with

vulnerability to panic attacks in adults (59–62), PTSD (63), depressive temperaments (64), and MDD (65). Impairments in sensorimotor connectivity have been theorized to lead to disruptions in stimuli processing (66), and increased connectivity in SMH has been associated with the preparation of the motor cortex for a threat (63) which may help explain associations between symptoms and SMH connectivity.

Second, we found internalizing symptoms and ACEs were associated with reduced between-network anticorrelation for DMN-DAN. This association was consistent with the findings of altered between-network connectivity of DMN-DAN in adults by Yu et al. (12). Our findings are also in line with previous research reporting relationships between both report types and altered between-network connectivity in regions associated with the DAN (e.g., the medial prefrontal cortex) and DMN (12,66,67). Previous research indicates the anticorrelation between DMN and DAN is associated with the modulation of attention (68,69). For example, when an individual performs a non-self-referential and goal-oriented task, within-network DMN connectivity decreases while within-network DAN connectivity correspondingly increases (68,69). Finding internalizing symptoms associated with both DMN-DAN RSFC and within-network SMH-SMH could be consistent with the hypothesis that differences in this ability of attention modulation (associated with DMN-DAN) and sensory processing (associated with SMH) may be associated with reports of internalizing symptoms and having experienced ACEs. Future research should directly examine this speculation. These shared findings could also suggest multi-finality, whereby ACEs and internalizing symptoms showed evidence in the joint models (Table 3) of both being uniquely associated with these RSFC networks.

Although there was overlap in RSFC associations, we found RSFC associations specific to reports of internalizing symptoms or ACEs. First, internalizing symptoms, but not ACEs, were associated with within-network DMN connectivity. In contrast to the present study, several studies have found within-network DMN connectivity associated with ACEs (4,38,39,70), although these studies utilized varying measures of ACEs (e.g., The Childhood Trauma

Questionnaire, Life Events Checklist, etc.). This may indicate within-network DMN connectivity alterations associated with ACEs develop over time since previous studies used samples from adult populations. We found that within-network FPN RSFC was associated with ACEs but not internalizing symptoms. Although speculative, this may suggest while both internalizing symptoms and ACEs are associated with purposeful attentional control (e.g., DMN-DAN), internalizing symptoms could be uniquely associated with dysfunctional rumination/attention to internal states (e.g., DMN-DMN associations (9,27,67)) in middle childhood, while ACEs could be more strongly associated with dysfunction in top-down (executive) attentional control abilities associated with FPN (12,73). Additionally, ACEs, but not internalizing symptoms, showed associations with CON-AUD RSFC. Further, internalizing symptoms, not ACEs, showed associations with DAN-VIS. These unique between-network connectivity alterations involve one attention-oriented network (e.g., CON) and one sensory-oriented (e.g., VIS) network. This finding is consistent with previous research on internalizing symptoms in adults (12,65). This could suggest that internalizing symptoms and ACEs are associated with an altered ability to modulate attention towards sensory stimuli, though future research is required to explicitly examine this idea. Our findings of connectivity associations between sensory- and attention-oriented networks are potentially consistent with research suggesting altered selective attention capabilities associated with depression (11). Our findings remained consistent when including both symptoms in follow-up models examining associations with these RSFC metrics, indicating unique associations are robust to the inclusion of the 'other' symptom metric (unique associations with ACE are robust to the inclusion of internalizing symptoms and vice versa).

Another goal of the present paper was to compare our findings to Yu et al. (12). We replicated some of their findings, including lower anti-correlation between-networks DMN-DAN associated with internalizing symptoms, which is consistent with other research (69). However, there were several differences in our findings compared to those of Yu et al. (12). There were multiple instances where we found *lower* network connectivity for pairs where Yu et al. (12)

reported *higher* network connectivity (e.g., within-network DMN or between-networks DAN-VIS). Yu et al. (12) also reported several RSFC associations that were not $p < .05$ in the present paper (e.g., VIS-VIS, and DAN-CON). We analyzed parent-about-child reports of ACEs and internalizing symptoms to compare to Yu et al. (12) (Supplemental Table 6). Like Yu et al. (12), we found associations between parent-reported ACEs and within-network DAN-DAN connectivity. However, parent reports generally had fewer associations than child reports for both ACEs and internalizing symptoms and generally less overlap with Yu et al. (12).

Differences between our findings and Yu et al. (12)'s may be partially attributable to the fact that they were primarily examining RSFC associated with an MDD diagnosis versus examining internalizing symptoms more broadly. To further assess overlap with Yu et al. (12), we examined our network associations using only reports of depressive symptoms (Supplemental Table 4), with findings remaining consistent with the internalizing symptom findings. We further examined network associations using reports of anxiety symptoms and found *no* significant RSFC associations (Supplemental Table 5). It should be noted Yu et al. (12) used wavelet coherence (57,72) to study functional connectivity associations while we used Pearson's correlation. This could have contributed to differences in findings between the two studies (e.g., between network DAN-VIS connectivity associations). Another possible explanation of differences could be our use of a middle childhood sample (Yu et al. (12) used an adult sample). It has been hypothesized that RSFC changes throughout development (22). Further, in the present study, youth rated lifetime ACEs using the PhenX Adverse Life Events scale, whereas, in Yu et al. (12), adults retrospectively endorsed experiences occurring before age 17 using the Childhood Trauma Questionnaire. This could explain differences in results between our study and Yu et al. (12).

Several limitations should be noted. The ABCD data used in this study are cross-sectional and, while internalizing symptoms were collected at baseline, reports of ACEs were obtained at 1-year follow-up of the ABCD study. As such, we examined lifetime ACEs, though it

is possible that some ACEs only occurred after baseline scanning, something we could not identify given the way in which the data were collected. Future studies in this sample group could examine the association between these RSFC metrics and changes in internalizing symptoms as well as the experience of ACEs over time (in a longitudinal study). Our findings were generally small in magnitude (β s < 0.06), which is expected with a large, non-clinical, heterogeneous sample (73). Further, while previous research used the Powers a priori brain parcellation (12), the ABCD Study utilizes the Gordon parcellation (7). However, it should be noted that the Gordon parcellation overlaps well with the Powers parcellation (7). The current study used tabulated RSFC data released by the ABCD Study, which precluded our ability to implement alternative RSFC data processing choices. Regardless, tabulated data were processed using methods previously shown to mitigate the negative impacts of motion (74). A limitation of the PhenX ACEs measure is it does not capture all types of ACEs (e.g., sexual abuse). Future studies should look at these reports in a clinical sample and examine associations with individual types of ACEs. Finally, there are many factors (e.g., genetic, environmental, etc.) that play into the overlap in effects of ACEs and internalizing symptoms. The present study only focuses on one aspect of this overlap (RSFC). Future research should try to further examine the overlap in effects of experiencing ACEs and internalizing symptoms (e.g., examining co-occurring cognitive and RSFC associations or examining associations between inattention symptoms and RSFC).

The current findings may have critical treatment implications including support of the potential importance of improving attentional control and integration of sensory input in both ACEs and internalizing symptoms through treatments such as Cognitive Processing Therapy (CPT; (75)). We found reports of ACEs and internalizing symptoms had unique associations with RSFC that typically included networks associated with sensory and attentional functions. (13,78) Future research should consider examining RSFC following treatments that may utilize these networks (e.g., CPT's use for treatment of trauma (75)) to examine whether these

treatments mitigate any RSFC differences in these networks. Further, future research should examine the role of other potentially influential variables, including substance use and psychotropic medication use, as the ABCD Study sample enters an age range in which these experiences become more prevalent. In summary, our findings provide important insights into the overlap and specificity of internalizing symptoms and ACEs, pointing to the importance of networks associated with the modulation of attention, including the modulation of attention to sensory stimuli.

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The ABCD data repository grows and changes over time. The ABCD data used in this report came from DOI 10.15154/1519007.

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Disclosures

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Table 1. Functions Associated with This Study's Networks of Interest.

Network	Example Associated Function(s)	Citation
Cingulo-Opercular Network (CON)	Integration of information; sustaining attention	(7,8)
Dorsal Attention Network (DAN)	Top-down attention (e.g., executive control of attention)	(7,13)
Default Mode Network (DMN)	Rumination; attention to internal states	(7,26)
Frontoparietal Network (FPN)	Executive functioning (e.g., goal-driven rapid behavior; attentional control)	(7,71)
Salience Network (SAN)	Detection of salient cues	(7,76)
Sensorimotor Hand Network (SMH)	Receives sensory input and projects motor output to hand	(7)
Sensorimotor Mouth Network (SMM)	Receives sensory input and projects motor output to mouth	(7)
Ventral Attention Network (VAN)	Bottom-up attention (e.g., acknowledging behaviorally relevant stimuli that occur unexpectedly)	(7,77)
Visual Network (VIS)	Visual processing	(7)
Auditory Network (AUD)	Audio processing	(7)

INTERNALIZING SYMPTOMS & ACES RSFC ASSOCIATIONS

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Table 2. Associations Between RSFC Estimates with Child-Reported Internalizing Symptoms or Adverse Childhood Events (ACES) ^a

	Internalizing Symptoms ^b								ACES ^b							
	<i>b</i>	Lower CI	Upper CI	β	<i>t</i>	<i>p</i>	FDR <i>p</i>	R ² <i>m</i>	<i>b</i>	Lower CI	Upper CI	β	<i>t</i>	<i>p</i>	FDR <i>p</i>	R ² <i>m</i>
Within-Network RSFC																
Cingulo-Opercular Network (CON)	-0.352	-0.648	-0.054	-0.024	-2.284	0.022	0.112	0.003	-1.032	-1.507	-0.558	-0.044	-4.306	<.001	<.001	0.006
Dorsal Attention Network (DAN)	-0.261	-0.568	0.044	-0.017	-1.641	0.101	0.303	0.002	-0.528	-1.014	-0.050	-0.021	-2.140	0.032	0.090	0.005
Default Mode Network (DMN)	-0.597	-0.937	-0.254	-0.035	-3.389	0.001	0.006	0.003	-0.326	-0.865	0.199	-0.012	-1.191	0.234	0.315	0.005
Frontoparietal Network (FPN)	-0.038	-0.383	0.308	-0.002	-0.218	0.827	0.892	0.002	0.821	0.293	1.359	0.030	3.015	0.003	0.019	0.005
Salience Network (SAN)	-0.167	-0.297	-0.038	-0.025	-2.510	0.012	0.072	0.003	-0.229	-0.430	-0.026	-0.022	-2.211	0.027	0.090	0.005
Sensorimotor Hand Network (SMH)	0.622	0.362	0.884	0.047	4.681	0.000	<.001	0.004	1.219	0.815	1.624	0.058	5.894	<.001	<.001	0.008
Sensorimotor Mouth Network (SMM)	0.103	-0.029	0.236	0.015	1.517	0.129	0.337	0.002	0.135	-0.073	0.342	0.013	1.285	0.199	0.298	0.005
Ventral Attention Network (VAN)	-0.047	-0.361	0.265	-0.003	-0.298	0.766	0.892	0.002	-0.233	-0.720	0.260	-0.009	-0.944	0.345	0.383	0.005
Auditory Network (AUD)	0.221	-0.032	0.475	0.017	1.704	0.088	0.303	0.002	-0.114	-0.521	0.285	-0.006	-0.566	0.572	0.591	0.005
Visual Network (VIS)	-0.213	-0.432	0.008	-0.019	-1.913	0.056	0.239	0.002	-0.229	-0.573	0.105	-0.013	-1.320	0.187	0.298	0.005
Between-Network RSFC																
CON-DAN	0.029	-0.384	0.445	0.001	0.135	0.892	0.892	0.002	0.467	-0.163	1.107	0.014	1.422	0.155	0.274	0.005
DMN-DAN	0.687	0.286	1.085	0.036	3.369	0.001	0.006	0.003	1.087	0.477	1.701	0.036	3.434	0.001	0.006	0.006
DMN-SAN	-0.069	-0.365	0.211	-0.005	-0.476	0.634	0.871	0.002	-0.451	-0.895	-0.008	-0.019	-1.989	0.047	0.117	0.005
FPN-DMN	-0.071	-0.504	0.375	-0.003	-0.319	0.750	0.892	0.002	0.262	-0.418	0.948	0.007	0.756	0.450	0.482	0.005
FPN-DAN	0.233	-0.216	0.686	0.010	1.006	0.314	0.620	0.002	0.357	-0.337	1.064	0.010	0.994	0.320	0.370	0.005
FPN-SAN	-0.027	-0.315	0.266	-0.002	-0.183	0.855	0.892	0.002	0.297	-0.148	0.745	0.013	1.297	0.195	0.298	0.005
FPN-VIS	-0.156	-0.526	0.205	-0.008	-0.839	0.401	0.708	0.002	-0.542	-1.109	0.035	-0.018	-1.879	0.060	0.138	0.005
SMH-DAN	-0.086	-0.503	0.326	-0.004	-0.409	0.683	0.890	0.002	-0.401	-1.042	0.236	-0.012	-1.228	0.220	0.314	0.005
SMM-DAN	-0.025	-0.311	0.260	-0.002	-0.170	0.865	0.892	0.002	0.484	0.035	0.927	0.021	2.132	0.033	0.090	0.005
SAN-DAN	-0.066	-0.344	0.213	-0.005	-0.469	0.639	0.871	0.002	0.232	-0.191	0.659	0.010	1.061	0.289	0.346	0.005
VAN-DAN	0.339	-0.059	0.738	0.017	1.670	0.095	0.303	0.002	0.683	0.057	1.294	0.021	2.171	0.030	0.090	0.005
VIS-DAN	-0.635	-0.979	-0.284	-0.036	-3.592	0.000	0.005	0.003	-0.589	-1.125	-0.051	-0.021	-2.145	0.032	0.090	0.005
VIS-CON	-0.196	-0.523	0.129	-0.012	-1.171	0.242	0.558	0.002	0.458	-0.055	0.970	0.017	1.767	0.077	0.155	0.005
AUD-CON	0.108	-0.234	0.449	0.006	0.622	0.534	0.843	0.002	-0.796	-1.322	-0.264	-0.029	-2.955	0.003	0.019	0.005
FPN-SMM	-0.151	-0.452	0.146	-0.010	-0.997	0.319	0.620	0.002	-0.112	-0.576	0.357	-0.005	-0.477	0.634	0.634	0.005
FPN-SMH	-0.052	-0.477	0.362	-0.002	-0.248	0.804	0.892	0.002	-0.525	-1.159	0.123	-0.016	-1.598	0.110	0.207	0.005
FPN-AUD	-0.153	-0.547	0.254	-0.007	-0.746	0.455	0.759	0.002	-0.679	-1.317	-0.047	-0.021	-2.140	0.032	0.090	0.005
CON-SMM	0.066	-0.198	0.333	0.005	0.488	0.626	0.871	0.002	-0.246	-0.657	0.161	-0.011	-1.172	0.241	0.315	0.005
CON-SMH	0.192	-0.202	0.581	0.010	0.973	0.331	0.620	0.002	-0.346	-0.950	0.255	-0.011	-1.128	0.259	0.324	0.005
DAN-AUD	0.299	-0.091	0.686	0.015	1.496	0.135	0.337	0.002	0.575	-0.026	1.197	0.018	1.851	0.064	0.138	0.005

^a Model: Generalized linear mixed models (GLMMs) were conducted separately examining each RSFC index as a predictor of reports of either internalizing symptoms ($n_{\text{model}} = 30$) or reports of ACEs ($n_{\text{model}} = 30$). Family unit and the 21 research sites modeled as random intercepts (to account for nonindependence of observations). Age, sex, and average motion (mean framewise-displacement) were included as covariates. The results were corrected for 30 multiple comparisons for each of the symptom types (i.e., internalizing symptoms, ACEs).

^b Abbreviations: b = unstandardized beta coefficient; CI = 95% confidence interval; β = standardized regression coefficient; t = t-test test statistic; p = p-value; FDR = False Discovery Rate; R^2_m = pseudo R-squared.

Table 3. Associations Between Both Internalizing Symptoms and Adverse Childhood Events (ACEs) with RSFC Estimates When Included in Model Simultaneously ^a

	Internalizing Symptoms ^b				ACES ^b			
	<i>b</i>	β	<i>t</i>	<i>p</i>	<i>b</i>	β	<i>t</i>	<i>p</i>
Within-Network RSFC								
Default Mode Network (DMN)	-0.0018	-0.031	-3.242	0.001	-0.0004	-0.011	-1.100	0.271
Sensorimotor Hand Network (SMH)	0.0029	0.039	3.927	<.001	0.0027	0.057	5.681	<.001
Cingulo-Opercular Network (CON)	-0.0011	-0.017	-1.722	0.085	-0.0018	-0.041	-4.274	<.001
Frontoparietal Network (FPN)	-0.0003	-0.005	-0.536	0.592	0.0010	0.027	2.755	0.006
Between-Network RSFC								
DMN-DAN	0.0014	0.028	2.982	0.003	0.0010	0.030	3.162	0.002
VIS-DAN	-0.0019	-0.033	-3.313	0.001	-0.0006	-0.017	-1.718	0.086
AUD-CON	0.0006	0.010	0.991	0.321	-0.0012	-0.032	-3.182	0.001

^a Model: Generalized linear mixed models (GLMMs) were conducted with both reports of ACEs and internalizing symptoms included as predictors of RSFC ($n_{\text{models}} = 7$). Family unit and the 21 research sites modeled as random intercepts (to account for nonindependence of observations), and age, sex, and average motion (mean framewise-displacement) included as covariates. These results included both internalizing symptoms and ACES as predictors for RSFC Estimates.

^b Abbreviations: *b* = unstandardized beta coefficient, β = standardized regression coefficient; *t* = t-test test statistic; *p* = p-value

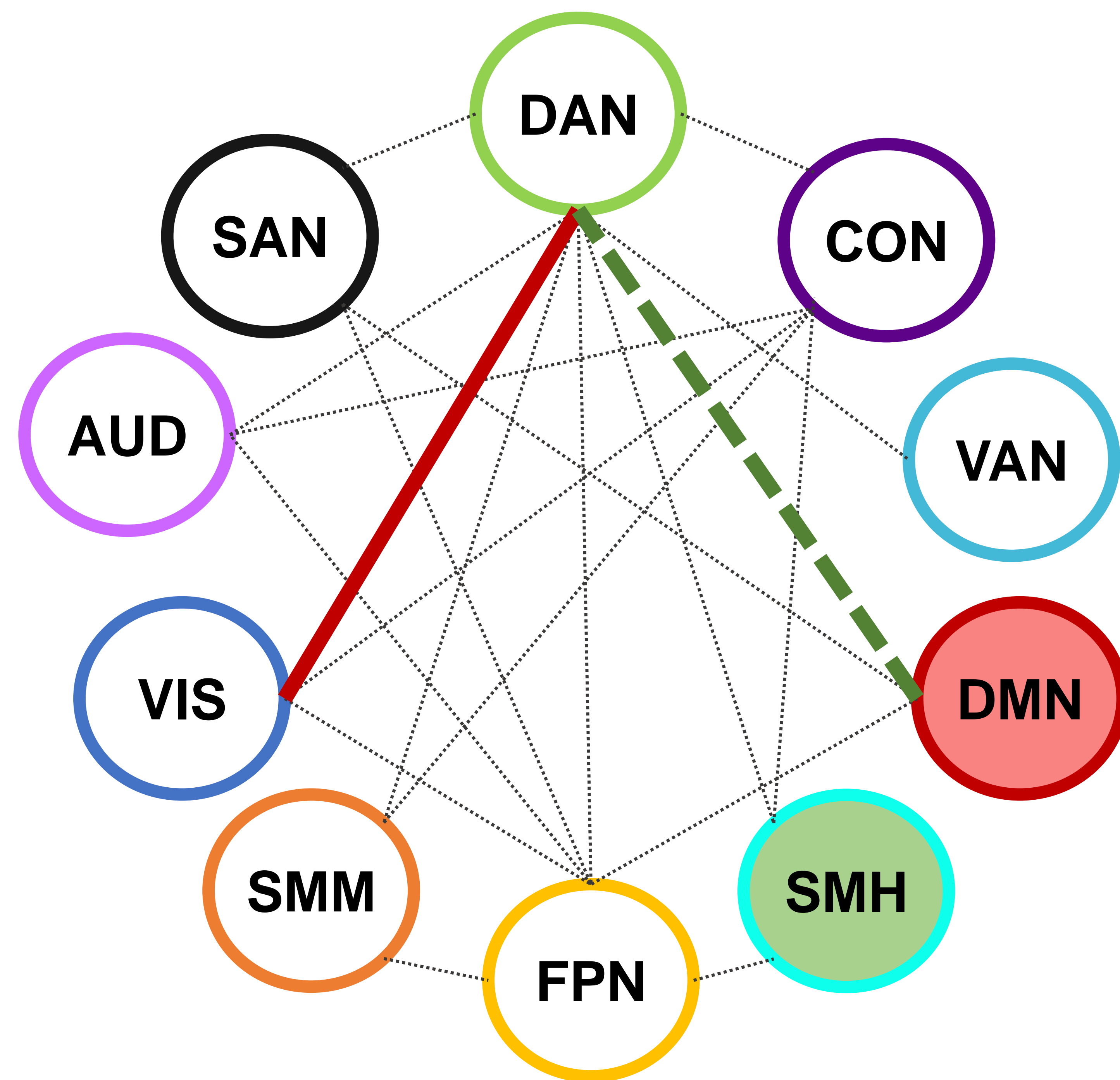
Figure 1

Figure 1: A visual summary of the results, depicting the associated connectivity for A) RSFC associations with internalizing symptoms, B) RSFC associations with ACEs. The borders of the circles in this figure (left) are color-coded to match the color of the Gordon network parcellation (bottom right).

Figure 2

Figure 2: A visual summary of differences in RSFC associated with both internalizing symptoms and ACEs. The borders of the circles in this figure (left) are color-coded to match the color of the Gordon network parcellation (bottom right).

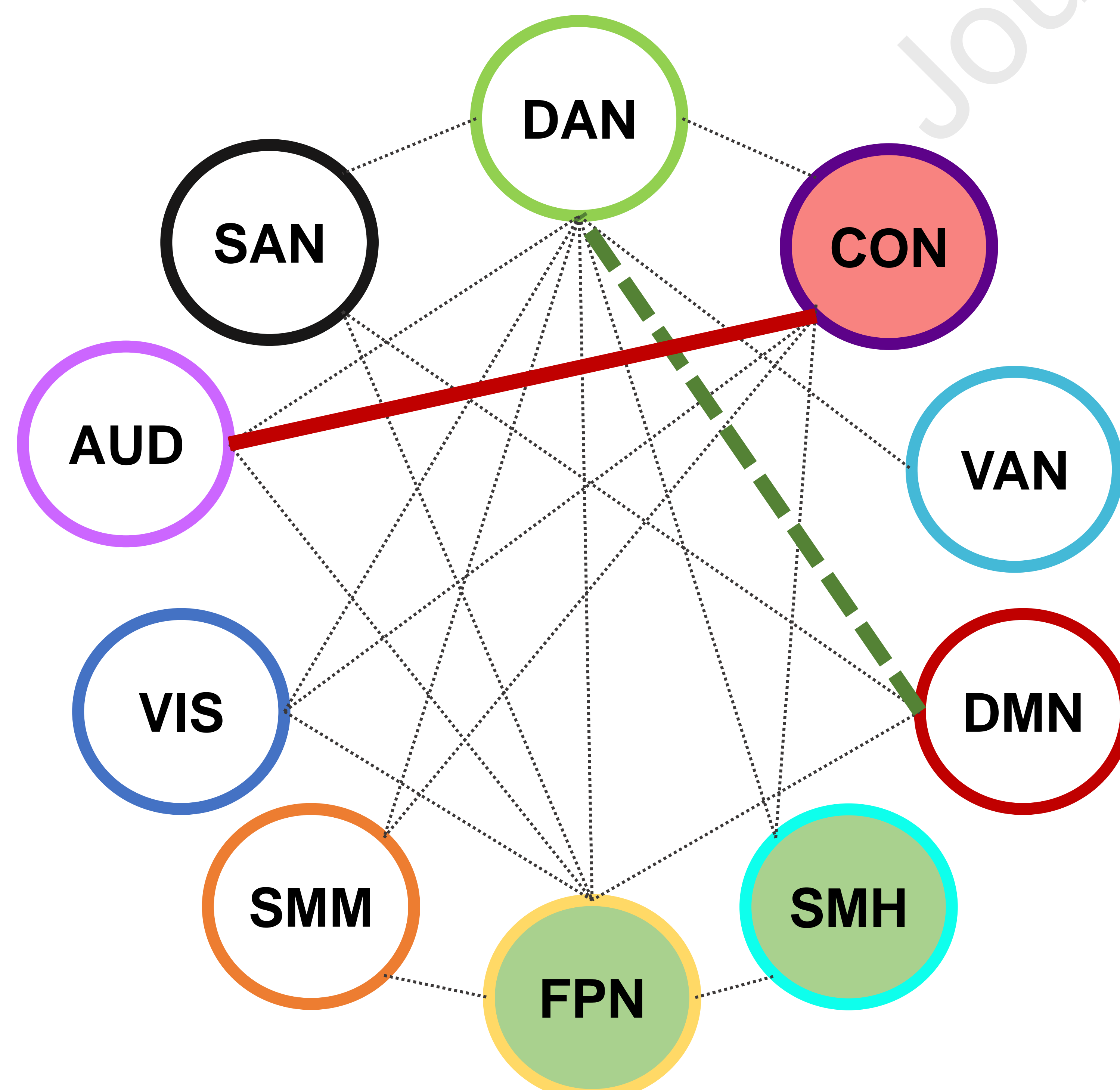
A) RSFC Associated With Internalizing Symptoms



Network Connectivity Key

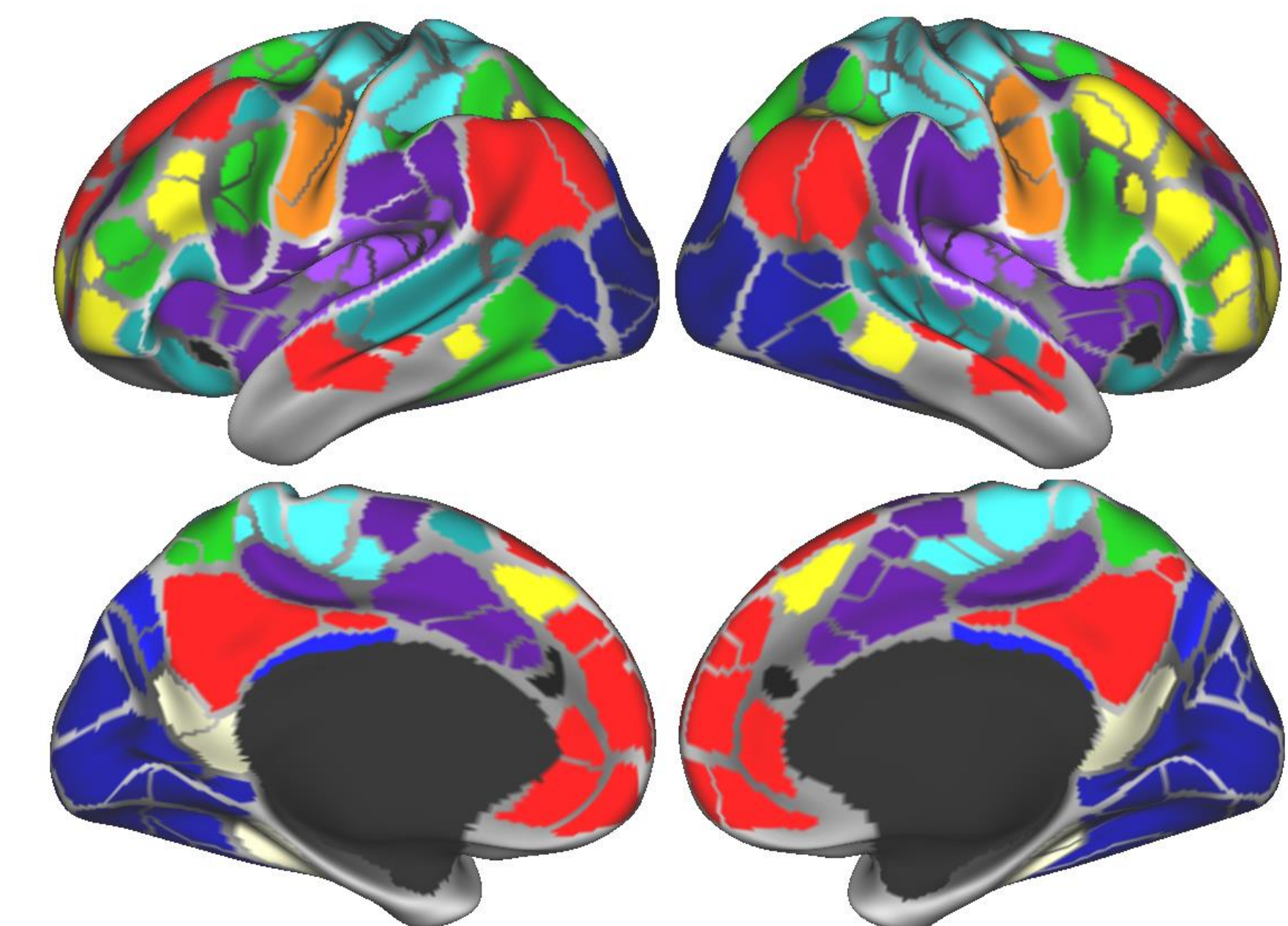
- Lower within-network connectivity
- Higher within-network connectivity
- Lower between-network connectivity
- Higher between-network connectivity
- - - Reduced anti-correlation

B) RSFC Associated With ACEs



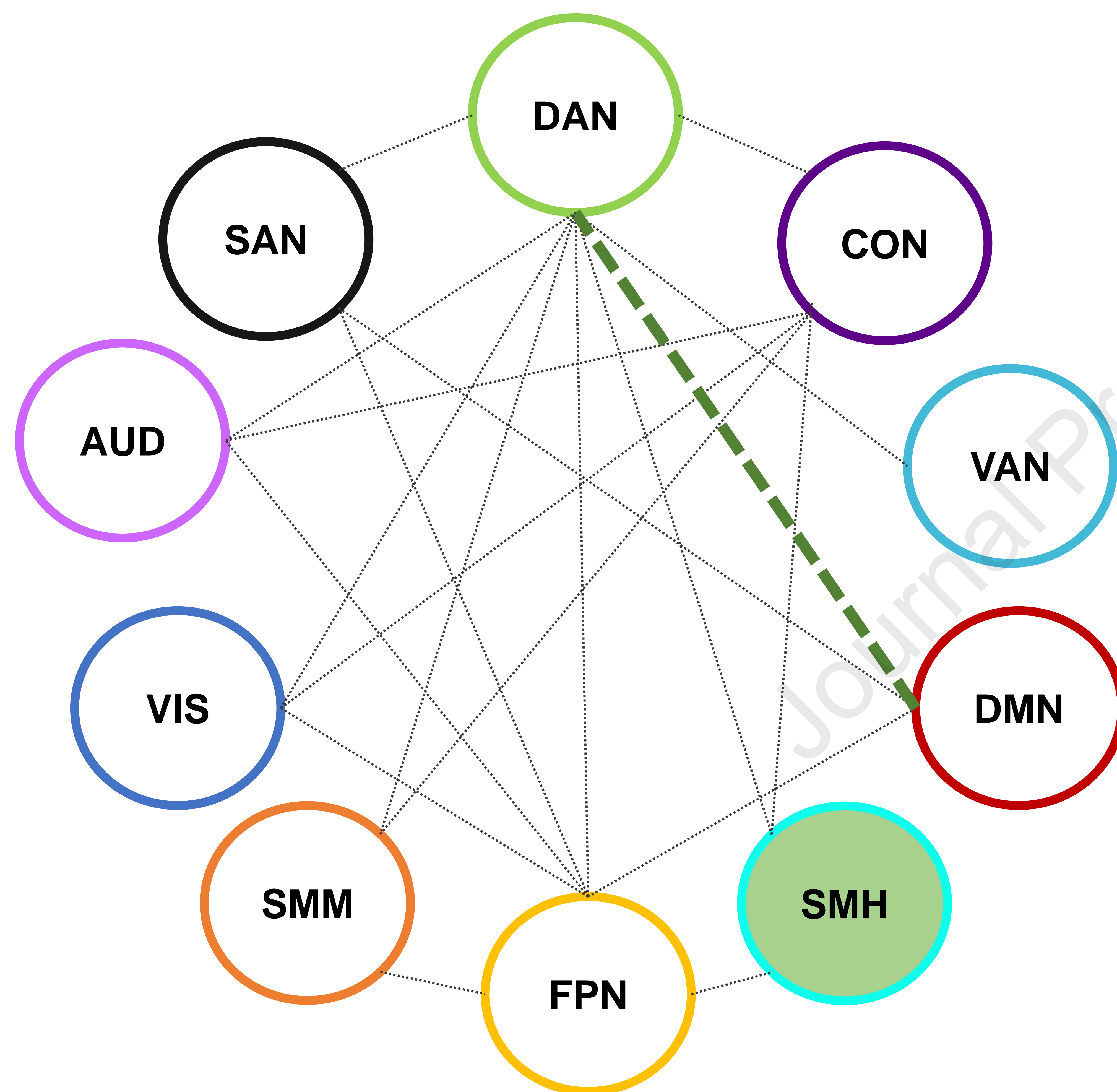
Resting State Functional Connectivity Networks

Gordon Cortical
Network Parcellation



- | | |
|--|---|
| ■ Default (DMN) | ■ Cingulo-Opercular (CON) |
| ■ Visual (VIS) | ■ SM-Hand (SMH) |
| ■ Fronto Parietal (FPN) | ■ SM-Mouth (SMM) |
| ■ Dorsal Attention (DAN) | ■ Auditory (AUD) |
| ■ Ventral Attention (VAN) | ■ Cingulo-Parietal (CPN) |
| ■ Salience (SAN) | ■ Retrosplenial-Temporal (RTN) |

RSFC Differences Seen in BOTH Internalizing Symptoms & ACEs

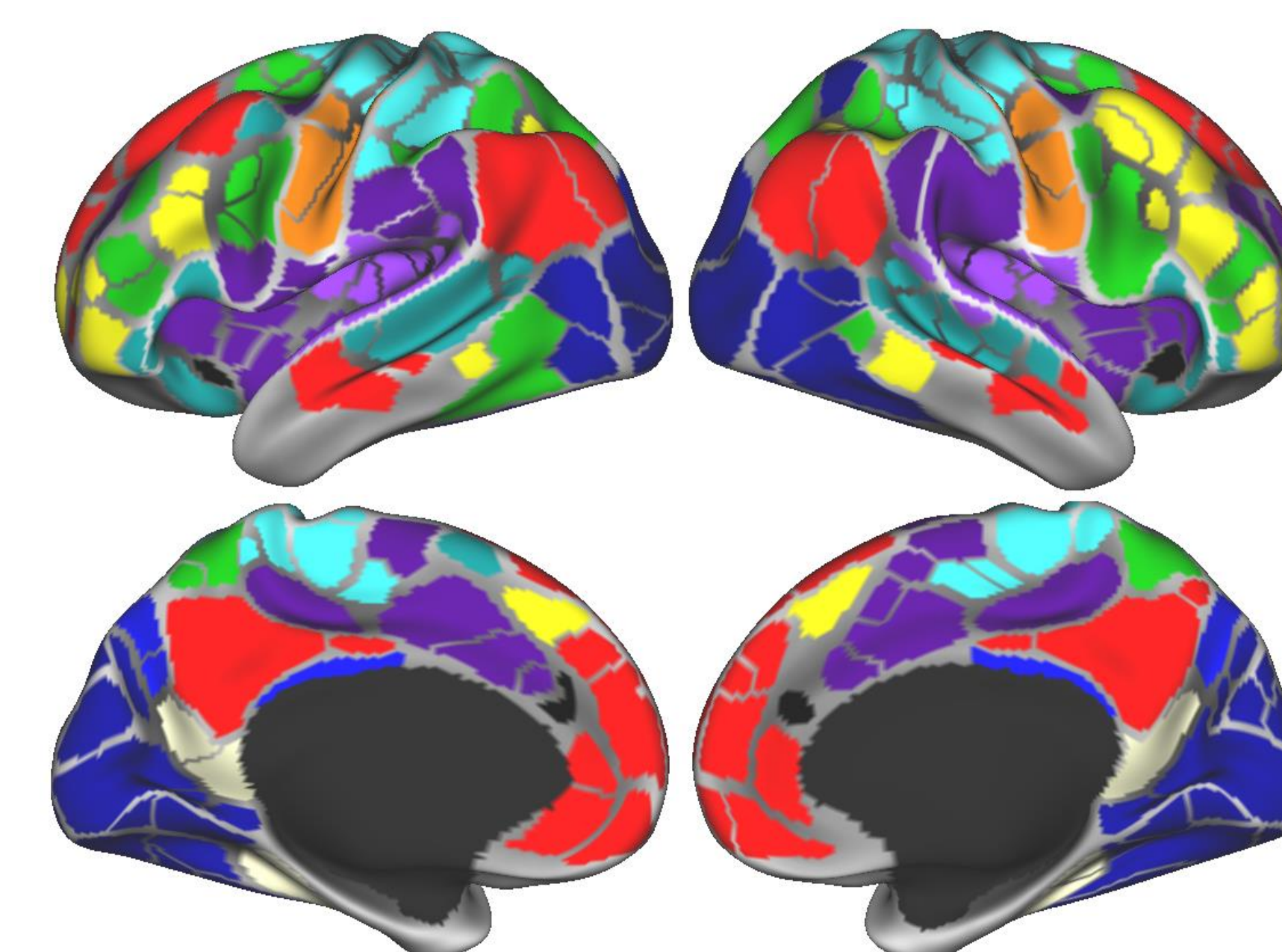


Network Connectivity Key

- Lower within-network connectivity
- Higher within-network connectivity
- Lower between-network connectivity
- Higher between-network connectivity
- Reduced anti-correlation

Resting State Functional Connectivity Networks

Gordon Cortical Network Parcellation



- | | |
|---------------------------|--------------------------------|
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