A Supervised Exercise Intervention for Youth at Risk for Psychosis:
An Open-Label Pilot Study

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ABSTRACT

Objective: A rapidly accumulating body of research suggests that exercise can improve symptoms and well-being in patients suffering from psychosis. Exercise may also promote neurogenesis in the hippocampus, a structure that plays an important role in the pathophysiology of psychosis. To date, there has not been an intervention focused on exercise prior to the onset of psychosis, a critical time for prevention of more serious illness.

Methods: In this pilot study, 12 young adults at ultrahigh risk (UHR) for psychosis were enrolled in a 12-week open-label exercise intervention. Participants were randomly assigned to exercise 2 or 3 times each week and exercised between 65% and 85% of maximum oxygen capacity (VO_{2max}) for 30 minutes each session under the supervision of an exercise physiologist. Positive and negative symptoms, social and role functioning, performance on neurocognitive tests, cardiovascular fitness, and hippocampal structure and functional connectivity were evaluated before and after the trial.

Results: A total of 9 participants completed the exercise intervention. Participants showed improved positive and negative symptoms and social and role functioning; improvement in multiple areas of cognition; and increased functional connectivity between the left hippocampus and occipital cortex after 12 weeks of exercise.

Conclusions: The results of this study suggest that exercise interventions are feasible in a UHR sample and may promote improvement in clinical, social, and cognitive domains as well as changes to brain function in regions impacted by the development of psychosis. These findings set the stage for an ongoing phase 2 randomized controlled trial.

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Regular physical activity is an important component to maintaining physical and mental health.[1] A growing body of innovative research suggests that exercise could be an impactful supplement to traditional treatments for psychosis.[2,3] Recent reviews illustrate a variety of aerobic, anaerobic, and combined exercise interventions, including running, walking, team sports, weight lifting, and yoga, for patients with psychosis.[3–5] Indeed, there have been exciting developments in exercise interventions in schizophrenia populations, and findings suggest that exercise may improve symptom, cognitive, cardiovascular, social and role functioning, and neurobiological domains, potentially facilitating greater quality of life and well-being for people with debilitating mental illnesses.[3,6–11] Given the demonstrated benefits of exercise interventions in those with a formal psychotic disorder, the current study aims to test the feasibility of an aerobic exercise intervention prior to the onset of the illness.

The period preceding the onset of psychosis is characterized by attenuated psychotic symptoms in both positive and negative domains and a decline in functioning.[12] Studying individuals at ultrahigh risk (UHR) for psychosis can be an important point of intervention, as the disorder typically develops in early adulthood and remains a chronic problem throughout life; intervening early in the course of the illness may help prevent or decrease the significant costs and distress caused by the illness.[13]

Previous work provides an impetus for exercise interventions prior to the onset of psychosis. Cross-sectional and prospective studies show that UHR individuals on average spend more time being sedentary, engage in less-intense exercise, and have poorer markers of cardiorespiratory fitness compared with those who did not develop the disorder or healthy controls.[14–16] In addition, UHR individuals report less motivation for getting exercise and engage in exercise that requires little social interaction compared with healthy individuals.[17,18] Adolescents at risk for psychosis are less physically active and often engage in poor health behaviors, including an increased rate of tobacco and alcohol use, compared with typically developing adolescents.[19] Taken together, individuals at risk for psychosis appear to be less physically active than typically developing young adults, which may have an impact on other markers of health and functioning.

One possible mechanism by which exercise improves cognition, as well as positive and negative symptoms, is by promoting neuroplasticity in the hippocampus.[20–22] The hippocampus has been widely cited as a major brain region impaired in psychosis.[23] This impairment has far-ranging

Clinical Points

- Few interventions can help with all of the early signs of psychosis; aerobic exercise may be a powerful treatment option with holistic benefits.
- Consider exercise in the treatment planning for young adults showing early signs of psychosis.

implications for the neurobiology underlying signs and symptoms of psychosis, as the brain region plays an important role in modulating both the biological stress response and higher order cognitive functions.[24] Furthermore, there is evidence that the structure and connections to the hippocampus are impaired prior to the onset of psychosis.[25,26] Importantly, cross-sectional research with UHR individuals suggests that smaller temporal lobe volume is related to decreased physical activity.[16] Examining the structure and function of the hippocampus may provide important insight into the neurobiological effects of exercise in UHR participants.

We recruited 12 UHR participants to complete 3 months of moderate- to vigorous-intensity aerobic exercise. The participants underwent structured clinical interviews, assessment of social and role function, cognitive testing, cardiovascular fitness testing, and structural and resting state functional neuroimaging of the hippocampus before and after the exercise intervention. The major objective of this pilot study was to establish the feasibility of an exercise intervention for UHR participants. On the basis of the noted results from patients with schizophrenia,[2,3,27] we conducted exploratory analysis of positive and negative symptoms, social and role functioning, cognition, and physical fitness. In addition, we examined change in hippocampal volume and anatomic seed-based functional connectivity.

METHODS

Participants

Adolescent and young adult UHR participants between 16 and 24 years of age (mean = 19.42, SD = 1.16) were recruited to the University of Colorado Boulder's Adolescent Development and Preventive Treatment (ADAPT) research program. An inclusion criterion for the study was that the participant reported a predominantly sedentary lifestyle of no more than 60 minutes of at least moderate physical activity per week for the past 6 months. Exclusion criteria consisted of head injury, the presence of a neurologic disorder, lifetime substance dependence, current antipsychotic medication use, and the presence of any contraindication to the magnetic resonance imaging (MRI) environment (eg, pregnant or metal in the body). The presence or lifetime history of an Axis I psychotic disorder was also an exclusion criterion. The study was approved by the University of Colorado Boulder Institutional Review Board, written consent or assent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT02155699).

Clinical Interviews

The Structured Interview for Prodromal Syndromes[28,29] was administered before and after the exercise intervention to diagnose a prodromal syndrome and track positive and negative symptom changes. A total sum score for the positive and negative symptom domain is used as an indicator of the respective dimensions of symptomatology. The Structured Clinical Interview for *DSM-IV* Axis I Disorders[30] was also administered to rule out a psychotic disorder diagnosis. Interviewers were kept blind to the prescribed exercise condition for each participant. See Supplementary Material for more information regarding criteria to determine UHR and training of clinical interviewers.

Assessment of Social and Role Functioning

Social and role functioning was assessed by trained graduate students using scales specifically designed for adolescents and young adults: the Global Functioning Scale: Social (GFS:S)[31] and the Global Functioning Scale: Role (GFS:R).[32,33] These scales provide ratings on 2 separate 10-point Likert scales, which are scored independent of symptom severity; higher scores correspond to better functioning.

Cognitive Testing

Participants completed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery of cognitive tasks before and after the exercise intervention.[34] The MATRICS battery includes tests for speed of processing, verbal and visual learning, working memory, reasoning and problem solving, attention, and social cognition. The MATRICS was administered by trained graduate students in a quiet room. Raw scores were transformed to *T* scores using established standard scores, which were used in analyses concerning pre/post differences.

Physical Fitness Assessment

Baseline and follow-up cardiovascular fitness was measured with maximum oxygen uptake (Vo_{2max}), which also served as the basis for individually tailored exercise prescriptions.[35] The participants ran on a treadmill, and the speed remained the same throughout the test, but the incline of the treadmill belt increased 2% every 2 minutes (or 2.5% for speeds 6 mph or greater). The treadmill speed was determined using participant heart rate and ratings of perceived exertion (RPE). The initial speed was set to 70% of age-predicted maximum heart rate and an RPE rating of around 13 ("somewhat hard"). Staying within these parameters generally yielded an 8- to 12-minute test result, the recommended target for Vo_{2max} testing.[36] Vo_{2max} was determined using a valid primary criterion of having achieved a plateau in Vo_2, as well as secondary criteria outlined by Pimentel and colleagues[37] including respiratory exchange ratio maximum ≥ 1.1, RPE maximum ≥ 18, and age-predicted heart rate maximum ± 10 bpm.

Table 1. Behavioral Outcome Measures for the Exercise Intervention

Variable	Preexercise, Mean (SD)	Postexercise, Mean (SD)	Cohen *d*[a]
Symptom domain[b]			
Positive	12.33 (4.91)	9.89 (4.04)	–0.61
Negative	12.75 (9.29)	9.00 (6.16)	–0.47
Global social and role functioning score			
Social	6.83 (1.19)	7.33 (1.50)	0.45
Role	6.83 (1.40)	7.22 (1.09)	0.33
Cognition *T* score			
Speed of processing	52.22 (9.30)	58.22 (13.38)	1.30
Attention	46.38 (7.84)	51.00 (6.08)	0.76
Working memory	49.00 (8.22)	51.78 (8.76)	0.92
Verbal learning	48.22 (9.40)	51.11 (9.61)	0.63
Visual learning	44.56 (8.43)	51.56 (5.96)	0.76
Reasoning and problem solving	51.56 (4.85)	55.00 (5.81)	0.47
Social cognition	47.22 (7.31)	44.22 (12.83)	–0.31
Composite	48.25 (8.41)	52.89 (9.21)	1.74
Hippocampus volume, mm^3			
Left hippocampus	0.0025 (0.00024)	0.0025 (0.00019)	0.18
Right hippocampus	0.0026 (0.00025)	0.0026 (0.00019)	0.31
Physical health			
Vo_{2max}, mL/min/kg	41.16 (8.27)	39.52 (8.58)	–0.28

[a]Cohen *d* is used to measure the change in outcome variable preexercise to postexercise intervention.
[b]A total sum score for the positive and negative symptom domain is used as an indicator of the respective dimensions of symptomatology.
Abbreviation: Vo_{2max} = maximum oxygen consumption.

Exercise Intervention

Participants were randomly assigned to 1 of 2 conditions: moderate or vigorous. The moderate condition required exercise 2 days a week at 65% of their Vo_{2max} for a total of 24 sessions. The vigorous condition required exercise 3 days a week at 85% of the participant's Vo_{2max} for a total of 36 sessions. Participants wore a Polar FT1 heart rate monitor (https://www.polar.com/us-en) throughout each exercise session, and an exercise physiologist monitored the participant's exercise in order to keep the participant's heart rate at ± 5% of the prescribed target intensity. Initial exercise sessions lasted 15 minutes at 55% of Vo_{2max} intensity and were gradually increased to 30 minutes and target intensity within the first 3 weeks. The remaining exercise sessions lasted 30 minutes and were conducted at prescribed exercise intensity. Participants were given the choice to ride stationary bikes, run/walk on treadmills, or use elliptical machines at each session. At the end of each exercise session, participants were compensated.

Structural and Resting State Functional Connectivity MRI Processing

Structural MRI scans were acquired on a Siemens 3-Tesla Magnetom TIM (total imaging matrix) Trio MRI scanner (Siemens AG, Munich, Germany) with a 12-channel head coil. Left and right hippocampus and total intracranial volume were segmented using the FreeSurfer 5.3.0 suite of automated tools.[38] Each structure was divided by the participant's total intracranial volume to control for whole brain volume.

A resting state functional connectivity MRI (fcMRI) scan was acquired. Data were preprocessed in FSL (v.5; http://fsl.fmrib.ox.ac.uk/fsl), and fcMRI analysis was performed in the CONN toolbox v.15b.[39] Connectivity between the left or right hippocampal seed region of interest was calculated with all other voxels in the brain. For more detailed methods of the structural and fcMRI analysis, see the Supplementary Material.

Data Analysis

Following a similar strategy to Nuechterlein and colleagues[7] for examining the magnitude of changes after exercise in a small sample, only the effect size estimates (Cohen *d*) were calculated for pre- and postoutcome variables.

RESULTS

Participants

A total of 12 participants (6 male, 6 female) were recruited to the exercise study, which took place over a 24-month recruitment period. Of those participants, 9 (4 male, 5 female; 75% of the sample) participants completed the exercise intervention and returned for follow-up assessment. There were 7 participants in the moderate condition that completed 24 sessions and 2 participants in the vigorous condition that completed 36 sessions. The 3 drop-outs were in the vigorous condition and completed 8, 18, and 31 sessions. Because there were few participants who completed the vigorous condition, subsequent analyses of the exercise intervention collapsed across conditions.

Social and Role Functioning and Symptom Improvement After Trial

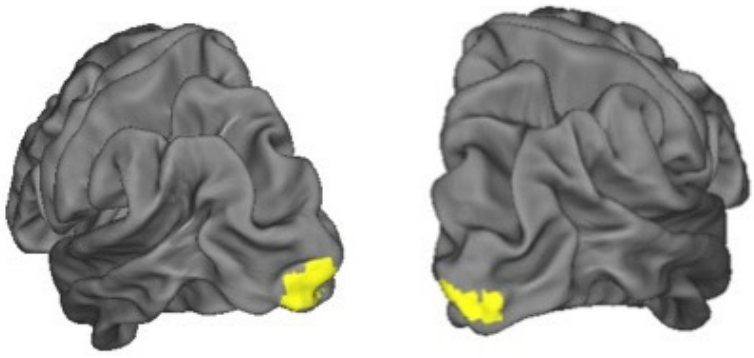
There was a small to medium improvement in social functioning ($d = 0.45$) and role functioning ($d = 0.33$).

Table 2. Results of the Left Hippocampal Seed-Based Connectivity Analysis

Direction of Connectivity	Region	Peak Cluster Size (voxels)	MNI Coordinates[a] X	Y	Z	*t* Value[b]
Baseline < Postexercise	Left occipital pole	526	−16	−104	4	9.71***
	Right occipital pole	256	32	−98	0	10.79***
	Lateral occipital cortex	63	52	−76	−6	10.96***

[a]MNI coordinates for the peak cluster location.
[b]False discovery rate–corrected, cluster level *P* values are noted for all *t* values as $*P \leq .05$, $**P \leq .01$, $***P \leq .001$.
Abbreviation: MNI = Montreal Neurological Institute coordinate system.

Figure 1. Occipital Regions Showing Increased Connectivity to the Left Hippocampal Anatomic Seed After the Exercise Intervention



Participants reported a medium to large decrease in positive symptoms after exercise ($d = -0.61$), as well as a small to medium decrease in negative symptoms ($d = -0.47$). See Table 1.

Cognitive Improvement

Participants exhibited substantial after-trial improvement in a number of cognitive domains including working memory ($d = 0.92$), verbal learning ($d = 0.63$), visual learning ($d = 0.76$), speed of processing ($d = 1.30$), attention/vigilance ($d = 0.76$), and reasoning and problem solving ($d = 0.47$). There was no improvement in social cognition ($d = -0.31$). Overall, the participants showed significant improvement on the MATRICS cognitive battery, with a large composite score improvement ($d = 1.74$).

Physical Fitness

The participants did not show improvements to physical fitness as measured by Vo_{2max} ($d = -0.28$).

Structural Imaging and Resting State Functional Connectivity

There were no changes to hippocampal volume after exercise for either the left ($d = 0.18$) or right ($d = 0.31$) hippocampus. Using the left hippocampus seed, participants showed increased functional connectivity to bilateral occipital cortices after the exercise intervention. The right hippocampus seed showed no changes in connectivity. See Table 2 and Figure 1.

DISCUSSION

In the first open-label exercise intervention for youth at risk for psychosis, we showed that exercise led to a reduction in positive and negative symptoms, improved social and role functioning, and improved cognition. These results suggest that exercise interventions are feasible within UHR samples and may help to improve important domains that are affected during the development of psychosis. Unique to this study from others in psychosis is the examination of brain structure and functional connectivity, suggesting that exercise may lead to changes in the functional organization of cortical-hippocampal networks.

As noted, we recruited a total of 12 participants to the exercise intervention. Of the 9 participants who completed the study, each attended 100% of the exercise sessions. It is important to note that the retention of participants and adherence to the aerobic exercise guidelines was in line with and in some cases better than other exercise interventions in adolescent and adult samples.[40–42] While the sample size in this study is small, it is similar to other aerobic exercise interventions in schizophrenia that have reported sample sizes between 8 and 16 participants.[2] Anecdotally, many of the participants were interested in being in the study to become more physically active and to improve their overall

health. This may have been an important motivational tool to seeking help initially, as exercise has positive social benefits and does not carry the same stigma as psychotherapy or pharmacologic treatment.[43,44] Social factors regarding the high value of exercise in the community in which the study was conducted (Boulder, Colorado) as well as monetary and other incentives may have also played a role in motivating participants to complete the intervention. For those who did not complete the exercise intervention, low motivation and loss of contact during the exercise intervention remained a substantial barrier. Innovative efforts to address adherence to exercise regimens in patients with psychosis have suggested that initial sessions of an exercise intervention include psychoeducation around exercise and goal setting.[45–47]

An important outcome of this study is the improvement of positive and negative symptoms, as well as social and role functioning. One mechanism by which exercise may improve symptoms and increase social and role function is through behavioral activation.[48,49] Another explanation from exercise interventions in schizophrenia patients suggests that exercise may promote self-esteem and confidence, leading to further engagement in the world and better well-being.[50] It is also possible that regression to the mean accounted for these results, and it will be important to conduct a controlled trial to ensure the changes are related to the intervention. The UHR period is heterogeneous in terms of symptom presentation and course; fluctuations in the intensity and distress of symptoms are common in this population.[51] Importantly, we have begun recruitment for a follow-up randomized controlled trial study incorporating a wait-listed group of UHR and healthy matched controls, which may provide further understanding of the mechanisms by which exercise can help ameliorate features of psychosis development.

Cognitive function improvement is consistent with a large body of work in human and nonhuman exercise studies.[6,8,52–54] However, there remains some controversy about whether aerobic or anaerobic exercise produces improved cognition in patients with psychosis.[48] A promising avenue of research combines high-intensity exercise and cognitive remediation training.[7] Future work examining aerobic and anaerobic exercise to improve cognition in UHR youth would be helpful for developing personalized medicine and exercise prescriptions for those at risk for psychosis.

The exercise intervention was calibrated to each individual's physical fitness level using Vo_{2max}. We were surprised to see that Vo_{2max} did not improve after the exercise intervention. However, individual differences in genetic heritability for cardiovascular performance, response to training, body composition of lipids, and glucose metabolism could potentially affect these results.[55,56] Although the finding that Vo_{2max} did not change is consistent with a number of other aerobic exercise interventions in schizophrenia patients, these results also encourage future interventions to consider including higher intensity exercise. A wealth of evidence now indicates that higher intensity aerobic exercise—particularly high-intensity interval training (HIIT)—improves cardiovascular fitness and related metabolic measures.[57] The current sample included cardiovascularly healthy but sedentary participants who exercised at 2 different intensities (ie, 65% and 85% of Vo_{2max}), and most exercised at the lower intensity; thus, it is not terribly surprising that we did not see large improvements in cardiovascular fitness. However, even without notable improvements in cardiovascular fitness in the UHR group, the results suggest that there are substantial benefits to this exercise intervention in other functional domains critical to quality of life in this population. This study thus represents an important starting point for exercise prescriptions for UHR individuals.

Consistent with other studies of UHR individuals, we did not find changes to hippocampus volume for either the left or right hippocampus.[9,58] Importantly, we used a multimodal neuroimaging approach and the finding that increased hippocampal functional connectivity of the hippocampus is an innovative development to understanding the role of the hippocampus in the neurodevelopment of psychosis. The direction and magnitude of the change in hippocampal connectivity is difficult to interpret given the lack of comparison subjects. However, it has been suggested in other studies that increased occipital-hippocampal connectivity is associated with the task-positive network and spatial memory performance.[59,60]

A diathesis stress model of psychosis suggests that neurodevelopmental abnormalities begin early in adulthood, and then brain maturational factors and stress from the environment interact with these vulnerabilities to promote the emergence of psychosis.[61–63] As noted, exercise may target brain regions thought to be a part of the abnormal neurodevelopment in psychosis. One brain region that is central to the neural diathesis stress model of psychosis—the hippocampus—is susceptible to neurogenesis and improved synaptic plasticity through regular exercise.[6,64] The current results support this model that exercise intervenes on both neurodevelopmental and behavioral levels of risk for psychosis. Importantly, we found that the exercise intervention attenuated psychotic symptoms, improved social and role functioning, and improved cognition. In addition, we saw increased functional connectivity between the hippocampus and the occipital cortex. Replication of these results and further examination of the links between these results in larger samples of UHR participants using a higher intensity exercise stimulus may produce a helpful treatment prescription for those at risk for psychosis.

This study has a number of strengths and limitations. The final sample size was small, it did not include enough participants to compare exercise conditions, and the participants did not show changes in cardiovascular fitness. The planned randomized controlled trial will improve on these limitations by including a wait-list clinical and healthy

control group, require 2 weekly sessions (as 3 sessions were less tolerable), and incorporate HIIT training, which should be a more powerful exercise stimulus for improving Vo_{2max}.[65] We assessed the participants directly after they finished the exercise intervention, and importantly, none of the participants transitioned to psychosis during the intervention. Current research suggests that as many as 35% of UHR individuals will transition to psychosis and others may experience problems with mood, anxiety, and other mental health issues.[51,66] Thus, longitudinal studies incorporating multiple domains of physical and mental health assessment are needed to see if the benefits of exercise interventions continue to improve the health and well-being of people at risk for psychosis.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

Supplementary material follows this article.

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Supplementary Material

Article Title: A Supervised Exercise Intervention for Youth at Risk for Psychosis: An Open-Label Pilot Study

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List of Supplementary Material for the article

1. **Criteria to determine ultrahigh risk and training of clinical interviewers**
2. **Detailed methods of the structural and fcMRI analysis**

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SUPPLEMENTAL MATERIAL

Clinical Interviews

The Structured Interview for Prodromal Syndromes (SIPS)[1, 2] was administered to diagnose a prodromal syndrome. Participants in the present study met SIPS criteria for a prodromal or high-risk syndrome, defined by moderate to severe but not psychotic levels of positive symptoms (rated from 3 to 5 on a six point scale) and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of schizophrenia.[3] The SIPS gauges distinct categories of prodromal symptoms including positive and negative domains. A total sum score for each domain is used as an indicator of the respective dimensions of symptomatology. Family history of psychosis was attained by asking participants if any first-degree family members had been diagnosed with a psychotic disorder. In most cases, family history was corroborated with another family member of the participant.

The Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID)[4] was also administered to rule out a psychotic disorder diagnosis. This measure has been demonstrated to have excellent inter-rater reliability in adolescent populations[5] and has been used in several previous studies focusing on adolescent populations with schizophrenia spectrum disorders.[6] Training of advanced doctoral student interviewers was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa $\geq .80$. Interviewers were kept blind to the prescribed exercise condition for each participant.

Structural Magnetic Resonance Imaging acquisition and data processing

A T1-weighted three-dimensional (3D) magnetization prepared rapid gradient multiecho sequence (MPRAGE; sagittal plane; repetition time [TR]=2530 ms; echo times [TE]=1.64 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm^3 isomorphic voxels, 192 interleaved slices; FOV=256 mm; flip angle=7^o; time=6.03 min) covering the whole brain was acquired for anatomic segmentation. A turbo spin echo proton density (PD)/T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line (AC-PC line); TR=3720ms; TE=89ms; GRAPPA parallel imaging factor of 2; .9 x .9 mm voxels; FOV=240mm; flip angle 120^o; 77 interleaved 1.5mm slices; time=5:14) was acquired to check for incidental pathology.

The processing stream involved motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[7] automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter structures,[8, 9] intensity normalization,[10] tessellation of the gray matter/white matter boundary, automated topology correction,[11] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[12]

Hippocampal target structures were segmented from the MPRAGE using the FreeSurfer suite of automated tools.[13, 14] The processing stream involved motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[7] automated Talairach transformation, segmentation of the subcortical white

matter and deep gray matter structures,[8, 9] intensity normalization,[10] tessellation of the gray matter/white matter boundary, automated topology correction,[11] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[12] FreeSurfer also calculates values for each participant's total intracranial volume (TICV; i.e., the sum of whole-brain gray matter + white matter + cerebrospinal fluid), and each structure's volume was divided by the TICV to control for whole brain volume.

Resting state functional connectivity processing

A 5 minute 34 second functional resting state blood-oxygen-level-dependent scan was acquired with a T2*-weighted echo-planar functional protocol (number of volumes =165; TR = 2,000 ms; TE = 29 ms; matrix size = 64 x 64 x 33; FA = 75°; 3.8 x 3.8 x 3.5 mm voxels; 33 slices; FOV = 240mm). During the resting state scan, participants were instructed to relax and close their eyes. A turbo spin echo proton density (PD)/ T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line; TR= 3720ms; TE=89ms; GRAPPA parallel imaging factor of 2; FOV=240mm; flip angle: 120°; .9 x .9 mm voxels; 77 interleaved 1.5mm slices) was acquired to check for incidental pathology. The fcMRI scan was kept relatively short in order to minimize anxiety and the possibility of within-scan movement. This fcMRI scan duration has been shown to yield equivalent power as longer scans.[15]

Data were preprocessed in FSL (v.5; http://fsl.fmrib.ox.ac.uk/fsl), which involved motion correction (MCFLIRT), brain extraction (BET), high-pass filtering (100 s), and spatial smoothing (6 mm FWHM). Functional images were aligned to the MNI152-T1 2-

mm brain template with a two-step procedure. First, the resting state scan was aligned to the high-resolution MPRAGE using a linear boundary-based registration method, which relies on gray/white matter boundaries.[13, 16, 17] Second, the MPRAGE was nonlinearly aligned to the template, and the two registrations were then combined in order to align the functional resting state scan to the template.

Recent papers have demonstrated the importance of properly correcting for motion by not only regressing out motion parameters, but also regressing out or eliminating specific frames with motion outliers.[18] To accomplish this, we used the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) to create confound regressors for motion parameters (3 translation and 3 rotation parameters), and additional confound regressors for specific image frames with outliers based on brain activation and head movement. In order to identify outliers in brain activation, the mean global brain activity (i.e., the mean signal across all voxels) was calculated as a function of time, and was then Z-normalized. Outliers were defined as any frames where the global mean signal exceeded 3 SD. Similarly, frame-wise measures of motion (composite measure of total motion across translation and rotation) were used to identify any motion outliers (i.e., motion spikes). Motion outliers were defined as any frame where the motion exceeded 1 mm. From the motion translation parameters we also calculated mean displacement, and used this measure as well as the number of motion and mean signal outliers in order to control for the degree of head movement.

fcMRI analysis was performed in the Conn toolbox v.15b.[19, 20] The data were band-pass filtered from 0.008 to 0.09 Hz. Seed regions-of-interest (ROIs) within the left and right, hippocampus were defined using FSL Harvard-Oxford subcortical structural

atlas.[21] The mean time-series, averaged across all voxels within each ROI, was used as a predictor regressor. Anatomical images were segmented into gray matter, white matter, and CSF with SPM8 (www.fil.ion.ucl.ac.uk/spm) in order to create masks for signal extraction. The Conn toolbox uses principal component analysis to extract 5 temporal components from the segmented CSF and white matter, which were entered as confound regressors in the subject-level GLM. This approach corrects for confounds of motion and physiological noise without regressing out global signal. We used state of the art methods to account for subject motion, as well as outliers, as suggested by Power and colleagues.[18] Accordingly, the GLM also included confound regressors for subject motion (6 parameters for translation and rotation) and frame-wise outliers identified with the ART toolbox.

Connectivity between the seed ROI was calculated with all other voxels in the brain at each time point. The *conn* toolbox used a GLM approach with connectivity measures calculated as bivariate correlations. All comparisons were defined as within-subject *T*-contrasts. Data in tables and statistical maps were first thresholded at the voxel-level at $p_{uncorr} < .001$ and then corrected at the cluster-level to a false-discovery rate (FDR) of $p < .05$.[22]

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