Establishing the Resting State Default Mode Network Derived From Functional Magnetic Resonance Imaging Tasks as an Endophenotype: A Twins Study

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Abstract: The resting state default mode network (DMN) has been shown to characterize a number of neurological and psychiatric disorders. Evidence suggests an underlying genetic basis for this network and hence could serve as potential endophenotype for these disorders. Heritability is a defining criterion for endophenotypes. The DMN is measured either using a resting-state functional magnetic resonance imaging (fMRI) scan or by extracting resting state activity from task-based fMRI. The current study is the first to evaluate heritability of this task-derived resting activity. 250 healthy adult twins (79 monozygotic and 46 dizygotic same sex twin pairs) completed five cognitive and emotion processing fMRI tasks. Resting state DMN functional connectivity was derived from these five fMRI tasks. We validated this approach by comparing connectivity estimates from task-derived resting activity for all five fMRI tasks, with those obtained using a dedicated task-free resting state scan in an independent cohort of 27 healthy individuals. Structural equation modeling using the classic twin design was used to estimate the genetic and environmental contributions to variance for the resting-state DMN functional connectivity. About 9–41% of the variance in functional connectivity between the DMN nodes was attributed to genetic contribution with the greatest heritability found for functional connectivity between the posterior cingulate and right inferior parietal nodes ($P < 0.001$). Our data provide new

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evidence that functional connectivity measures from the intrinsic DMN derived from task-based fMRI datasets are under genetic control and have the potential to serve as endophenotypes for genetically predisposed psychiatric and neurological disorders. *Hum Brain Mapp* 35:3893–3902, 2014. © 2014 Wiley Periodicals, Inc.

Key words: resting state functional MRI; default mode network; genetic control; twins; task derived; connectivity; endophenotypes

INTRODUCTION

Resting state brain activity is reflected in spontaneous low frequency fluctuations in blood oxygenation level-dependent (BOLD) signal that can be measured using functional magnetic resonance imaging (fMRI; Biswal et al., 1997). These fluctuations have an underlying pattern and have been shown to be coherent between linked regions of the brain, an observation that has led to the conceptualization of a system of resting state networks (Greicius et al., 2003; Raichle et al., 2001). The dominant network that has been identified is the default mode network (DMN), a set of brain regions whose activity is maximal during “rest” and is suspended during performance of externally cued tasks. Functional connectivity measured at rest within this network has been shown to be associated with underlying structural connections measured using Diffusion Tensor Imaging (Greicius et al., 2009; van den Heuvel et al., 2008, 2009). The DMN has been shown to play a dynamic role in normal and abnormal neural function (Anticevic et al., 2012; Lewis et al., 2009). An altered resting state DMN has been observed in a number of neuropsychiatric disorders including depression, anxiety disorders, and schizophrenia (Fox and Greicius, 2010).

There is mounting evidence that functional connectivity within the DMN is under significant genetic control, raising the possibility that it could serve as an endophenotype for brain disorders that have a genetic component (Fornito et al., 2011; Glahn et al., 2010). Supporting this are findings that increased DMN coactivation has been found both in healthy subjects with an increased genetic risk for neurodegenerative disorders (Filippini et al., 2009), and for psychiatric disorders including major depressive disorder (Rao et al., 2007) and schizophrenia (Whitfield-Gabrieli et al., 2009). Endophenotypes have been suggested to be important intermediate pathways linking genetic risk to overt expression of illness—especially for psychiatric disorders that are complex and polygenic in nature and where direct “one to one mapping” of genes to a clinical condition is not possible (Gottesman and Gould, 2003). An important step in establishing clear endophenotypes lies in determining whether these markers are influenced principally by “nature” genetic code or by “nurture” environmental factors during development. Studying genetically related individuals provides a means to disentangle the observed variance of these endophenotypes into genetic

and environmental sources. Twin studies using both monozygotic and dizygotic twins are one of the most powerful designs for this purpose (Peper et al., 2007).

Previous examinations of resting state DMN activity have utilized dedicated “resting” fMRI protocols, which involve measuring fMRI activity with no explicit experimental task control over a period of time. However, there is some evidence that valid low frequency rest-like fluctuations can be extracted from task fMRI datasets (Gavrilescu et al., 2008; Fair et al., 2007). This means that already existing large task fMRI datasets collected across a number of healthy and unique patient populations could be potentially used to investigate resting networks in these cohorts. However, this approach is yet to be validated using fMRI data collected across multiple tasks, and has not been directly tested against task independent resting data collected from the same individuals.

In this article, we use biometric modeling of a large, well-controlled twin cohort to evaluate genetic versus shared and unique environmental contributions to the DMN (Rao and Rice, 2006). The genetic influence on DMN using resting activity-derived fMRI tasks is yet to be established. Based on previous findings of significant genetic control on the resting brain using dedicated resting protocols (Glahn et al., 2010), we hypothesize that a significant component of variance in task-derived resting activity will be attributable to genetics. The goals of this study were (1) to validate resting activity extracted from task fMRI protocols (task derived) using data from five different fMRI tasks by evaluating the DMN from each of these tasks for consistency, and by comparison to data extracted from a separate dedicated (task free) resting state scan and (2) to test the degree to which this task-derived resting activity is under genetic control using genetic analysis of a large twins sample to estimate heritability of the DMN. This modeling will permit us to determine whether the DMN meets heritability criteria for endophenotype status.

MATERIALS AND METHODS

Subjects

In this study, we examined imaging data from 277 healthy individuals pooled from two study cohorts: (1) a twins cohort which included 250 healthy twins (79 monozygotic and 46 dizygotic same sex twin pairs), ranging in

TABLE I. Default mode network regions identified using the dedicated resting state scan ($P < 0.05$ FWE corrected)

DMN region	Cluster size	Primary peak location MNI coordinates			Peak Z score	Peak P value (FWE)
		x	y	z		
PCC/precuneus	8151	-10	-48	32	>10	<0.001
Left inferior parietal/temporal cortex (LIPC; BA39)	1266	-52	-64	20	6.28	<0.001
Right inferior parietal/temporal cortex (RIPC; BA39)	776	54	-62	16	5.47	0.001
L-temporal cortex (BA21)	995	-58	-34	-10	6.07	<0.001
Medial prefrontal cortex (mPFC)/ anterior cingulate cortex (ACC; BA32)	549	-6	48	12	5.36	0.002

age from 18 to 65 years (mean age: 39.7 ± 12.8 years) and comprised of 96 males and 154 females and (2) a cohort of 27 healthy participants (unrelated or nontwins) with a mean age of 24.5 ± 5.5 years (15 males and 12 females). All twins were of European ancestry and were drawn from the TWIN-E study (details of the study protocol can be found in Gatt et al., 2012). Both studies were approved by the Human Research Ethics Committee of the University of Sydney and informed written consent was obtained from all participants. All participants were English speaking and had no current/history of psychiatric illness, neurological or genetic conditions, brain injury, severe medical conditions, blood borne illnesses, alcohol/substance abuse, and sensory/motor impairments.

Image Acquisition and fMRI Protocols

MRI was performed using a 3.0-T GE Signa HDx scanner (GE Healthcare, Milwaukee, WI) at Westmead Hospital, Sydney, Australia. Acquisition was performed using an eight-channel head coil. Participants from both study cohorts performed five functional MRI tasks and a three-dimensional (3D) T1-weighted structural MRI scan. The nontwin cohort ($n = 27$) also completed a task-free resting state scan. The details of the five functional MRI tasks have been previously described (see Table I in Korgaonkar et al., 2013). Briefly, tasks assessed cognitive (selective attention using an auditory oddball task; sustained attention and working memory using continuous performance task; and impulsivity and inhibition processes using Go-NoGo task) and emotional processes (facial emotion processing at and below level of conscious awareness). The cognitive tasks used an event-related design; the emotional tasks used a mixed block/event design. For the oddball task the events consisted of a pseudorandomly arranged series of 20 high-pitched tones (targets) and 100 low pitch tones (nontargets) both applied over 50 ms with 2,400 ms interstimulus interval. Participants were instructed to respond to the high-pitched tones. The continuous performance task involved a series of 120 letters presented in either yellow (working memory or 1-back trials) or white

(baseline) for 200 ms each with an inter-stimulus interval of 2,300 ms. The task involved a “1-back” design where the participants were asked to respond only to yellow letters when they were repeated twice (1-back trials). The Go-NoGo task involved a series of representations of the word “PRESS” in either green (Go) or red (NoGo) color. The words were displayed for 500 ms with a 750-ms inter-stimulus interval. Participants were instructed to respond only to the green words. The emotion tasks involved presentation of faces representing six emotional states, presented in a pseudorandom order with block of eight different faces with the same emotion, and each block repeated five times. For the unmasked (conscious) task faces were presented for 500 ms with an interstimulus delay of 750 ms. For the masked (unconscious) task the same experimental design was used, with backward masking where the emotion was presented for 10 ms, followed by a neutral face for 490 ms. For the resting state scan, participants were presented with a black screen and instructed to keep their eyes closed and remain awake for the duration of the scan. Only the nontwin subjects performed this additional latter scan.

MR images for each functional task and the resting state scan were acquired using echo planar imaging (EPI) MR sequence with the following parameters: repetition time (TR) = 2,500 ms, echo time (TE) = 27.5 ms, matrix = 64×64 , field of view = 24 cm, flip angle = 90° . Forty contiguous axial/oblique slices with a slice thickness of 3.5 mm were acquired to cover the whole brain in each volume. For each protocol, 120 volumes were collected with a total scan time of 5 min and 8 s. Three dummy scans were acquired at the start of every acquisition. Structural MRI 3D T1-weighted images were acquired in the sagittal plane using a 3D spoiled gradient echo (SPGR) sequence (TR = 8.3 ms; TE = 3.2 ms; flip angle = 11° ; inversion time = 500 ms; number of excitation = 1; ASSET = 1.5; frequency direction: S/I). A total of 180 contiguous 1 mm slices were acquired covering the whole brain with a 256×256 matrix with an in-plane resolution of $1 \text{ mm} \times 1 \text{ mm}$, resulting in 1 mm^3 isotropic voxels. The 3D SPGR sequence was used for normalization of the functional data to MNI standard space.

Analysis of Task-Derived and Task-Free Resting State Data

Preprocessing steps

The fMRI data were preprocessed and analyzed using SPM8 software (www.fil.ion.ucl.ac.uk/spm). The details of the preprocessing methodology have been described previously (Korgaonkar et al., 2013). In brief, motion correction using realignment and unwarping, global signal removal and smoothing using an 8-mm Gaussian kernel were performed for both fMRI tasks and the resting state dataset. For normalization to stereotactic MNI space, the T1-weighted data were normalized to standard space using the FMRIB nonlinear registration tool and the fMRI EPI data were coregistered to the T1 data using FMRIB linear registration tool. Normalization warps from these two steps were stored for use in functional to standard space transformations. For each fMRI task, the BOLD responses for each experimental condition were modeled in the general linear model framework: oddball (target and nontarget trials), continuous performance (working memory, 1-back and baseline trials), Go-NoGo tasks (Go and NoGo trials), and both emotion tasks (each emotion type). Motion effects were also modeled for each task using the motion parameters (three translation and three rotational) estimated during the realignment preprocessing stage. The resting state signal (task-derived resting activity) was extracted by removing variance by modeling the BOLD signal for each of the stimuli as covariates (separately for each task), and residual images created after removing these effects. After this a band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$) was applied. For the resting state scan, only motion effects were removed and data band-pass filtered.

DMN and functional connectivity analyses

The DMN was identified using a seed based correlation approach separately for each task. This was done using the same posterior cingulate cortex (PCC) seed point used by Greicius et al. (2003). The BOLD time series for the PCC was then extracted and correlated with all voxels across the brain. Only voxels with significant correlation at $P < 0.05$ (FWE corrected for multiple comparisons) were considered as part of the DMN. The top five nodes of the DMN were identified from the task-free resting state data [PCC, L-R inferior parietal cortex (LIPC and RIPC), medial prefrontal cortex (mPFC), and L-temporal cortex; Table I]. These nodes were defined using a sphere of 5 mm diameter and then used to extract the resting state BOLD time series for both the task-fMRIs and task-free resting state datasets. Direct correlations between the node time series were performed and correlation coefficients were then estimated as measures of functional connectivity for the task-free resting dataset, each separate task dataset and for data pooled across the five tasks. In order to validate our

Figure 1.

Univariate genetic modeling using the classic twin design. Additive genetics (A), dominant genetics (D), common environment (C), and unique environment (E) variables are modeled and their contributions to the variance (a, d, c, and e, respectively) of the functional connectivity measures estimated using data from each twin and their corresponding twin. Note that C and D variables cannot be tested in the same model because they confound each other and hence ACE and ADE models are tested separately. The constraints on the covariances of these variables (indicated on the arrow connecting the variables) reflect relationships among twins, e.g., additive genetics is assumed to be 100% shared between the monozygotic (MZ) or 50% shared between the dizygotic (DZ) twins and is indicated as 1 or 0.5 on the arrow connecting A1 and A2.

approach, the strength of these correlations was compared to that with background noise [extracted using a 5-mm sphere from the cerebrospinal fluid (CSF) in the ventricles]. We also compared the DMN functional connectivity estimates for each task and for the pooled task data against the task-free resting state scan using a repeated measures analysis of variance. To validate this further using the larger twin cohort, the first- and second-born twins were considered in separate cohorts and the DMN functional connectivity estimates using data from each twin cohort were compared to that from the dedicated resting scan from the smaller nontwin cohort using the Welch test to assess equality of means.

Genetic Analysis

Univariate genetic modeling using the classic twin design (Neale and Maes, 1998) was used to estimate the genetic and environmental contributions to variance for each measure (Fig. 1). Analyses were conducted using *OpenMx* version 1.0.7 (Neale et al., 2003) on *R* version 2.13.2 (R Development Core Team, 2011). Full ACE and ADE models were fitted to each variable individually using maximum likelihood estimation. These models test the contribution of additive genetics (A), dominant genetics (D), common environment (C), and unique environment (E) to the model. The model relies on the assumption that the additive and dominant genetics are 100% shared between the monozygotic twins and 50 or

25% shared between the dizygotic twins respectively (these constraints on the covariances of these variables are indicated in Figure 1, e.g., $MZ = 1$ and $DZ = 0.5$ for A). Similarly, the common environment is 100% shared while the unique environment is not shared at all. Any residual errors are also modeled in the unique environment. The significance of the A, C (or D), and E parameters is tested by dropping each parameter from the model and comparing the fit of the resulting model fit indices. Models were compared for best fit using the Akaike's Information Criterion and the log likelihood chi-square difference test. A significant change in model fit suggests that the dropped parameter accounts for a significant component of the phenotypic variation, and should therefore remain in the model. A sub-model was rejected when a chi-square difference test had a P value < 0.05 . Covariates tested in the models included age, gender, and education.

RESULTS

Validation of Task-Derived Resting State Data

The regions for the DMN identified using the dedicated resting state scan are summarized in Table I. Figure 2 shows the DMN identified from dedicated resting state scan (Fig. 2A) compared to the task-derived resting state data (Fig. 2B–F). The spatial pattern of the DMN identified was concordant both within the task-derived resting datasets, and between the dedicated resting state and the task-derived data. Voxel-wise repeated measures analysis determined that there were no significant differences between the DMN networks. This was true for each task when compared to the dedicated resting state data, and also for a comparison between the pooled task-derived data and the dedicated resting dataset.

Figure 3 shows a plot of the correlation coefficients between the PCC and four key components of the DMN (L-IPC, R-IPC, mPFC, the L temporal cortex), as well as background noise (measured within CSF). Coefficients from the dedicated resting state data are compared to task-derived resting data from each of the fMRI tasks (Fig. 3A). The functional connectivity within the DMN was significantly higher and stronger than that with noise ($P < 0.0001$). The PCC–CSF (noise) correlation coefficients were not significantly different from zero for each of the datasets ($P > 0.05$). Repeated measures analysis for each task versus the dedicated resting state data showed no significant differences in functional connectivity estimates within the DMN consistent with the voxel level analysis above. The standard deviation across the task-derived correlation coefficients was of similar magnitude to the dedicated resting state data (average standard deviation across regions—GNG = 0.32, oddball = 0.37, working memory = 0.34, faces conscious = 0.37, and faces non-conscious = 0.38) and was similar to that seen in the dedicated resting state data (average standard

deviation = 0.34). The variance when pooled across the five functional tasks was lower than both the task and dedicated resting state data (standard deviation pooled data = 0.21).

The spatial pattern of the DMN using the twin cohort was also concordant with the dedicated resting state protocol from the smaller nontwin cohort. Considering the first- and second-born twins as separate cohorts, and the nontwin cohort as a third, no significant difference in the functional connectivity estimates between the twin cohorts and the nontwin cohort were found using the Welch test (Fig. 3A,B)—thus validating our approach using a bigger cohort dataset.

Heritability of DMN

Figure 4 shows the genetic influence on functional connectivity within the DMN. The A/E model was the least parsimonious fitting model for all the functional connectivity measures ($P < 0.001$). The common environment (C) had relatively no contribution to the variance of these measures. Heritability was found significant only for the PCC–RIPC connectivity measure ($a^2 = 0.41$; $P < 0.001$) and was at trend level only for the PCC–LIPC measure ($a^2 = 0.24$; $P < 0.1$). The A/E model estimates for connectivity measures between the DMN nodes are summarized in Table II.

DISCUSSION

In this article, we use data from a large and highly standardized twin cohort to provide the first direct evidence that specific functional connectivity paths based on low frequency resting activity are heritable. Our study focused specifically on the heritability of the DMN, which has been implicated in a number of disorders (van den Heuvel and Hulshoff Pol, 2010; Whitfield-Gabrieli and Ford, 2012). No previous twin study has examined the heritability of resting state networks. Our data showed that the genetic influence on functional connectivity within the DMN is strongest for connections between the PCC and the inferior parietal cortex. The degree of heritability of the other connections within the DMN was weak, and only the PCC–RIPC connection attained the formal criteria for an endophenotype (heritability $> 40\%$). The demonstration that these circuits are under genetic control is an important contribution in the development of this measure as a potentially important endophenotype to guide treatment decisions and prognostication in disease states.

We derived resting activity from task fMRI datasets and for the first time, demonstrate its equivalence to data extracted from dedicated task-free resting state scan. Brain activity during rest is typically measured using a dedicated protocol which involves no experimental task. Task related activity is the dominant contribution to the BOLD signal acquired in a task-fMRI dataset, however, and it has

Figure 2.

Default mode network identified ($P < 0.05$ FWE corrected) using (A) dedicated resting state data and task-derived resting data from each of the fMRI tasks— (B) auditory oddball task, (C) continuous performance task, (D) Go/NoGo task, (E) unmasked, and (F) masked emotion processing. Data from the

nontwin cohort ($n = 27$) is shown. IPC, inferior parietal cortex; L, left; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; R, right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

been suggested that this activity does not affect the underlying spontaneous BOLD fluctuations (Fair et al., 2007; Gavrilescu et al., 2008). This underlying low frequency signal can be successfully extracted, by modeling the task time series, and then removing this task-related component from the data. Using task fMRI and task-free resting data from the same cohorts, our analysis confirms that valid low frequency “rest-like” fluctuations can be derived

from task fMRI datasets, and that these low frequency fluctuations are under genetic control. Our task-derived resting data does not appear to be different from task-free resting data, raising the possibility that the DMN is unaffected by neural activity occurring on the timescale measured using our cognitive and emotional paradigms. Resting data extracted from both block and event-related fMRI task designs have previously been shown to be

Figure 3.

Validation of resting state fMRI connectivity estimates derived from fMRI tasks. **(A)** Mean and standard deviation for resting state connectivity for the five elements of the default mode network and physiological noise (CSF) extracted from each individual fMRI task dedicated paradigms and for data pooled across all five fMRI tasks, compared to that extracted from the dedicated resting state scan ($n = 27$). Functional connectivity estimates for the DMN were significantly greater than that with noise ($P < 0.0001$). No significant differences were found between task-derived resting and dedicated resting scan measurements.

(B) Replication of resting state connectivity measurements for the twin cohort (using data from the pooled five fMRI tasks; $n = 250$ twins or 125 twin pairs). Functional connectivity estimates for the twin cohorts were similar to those obtained for the dedicated resting scan from the nontwin cohort ($P > 0.05$ Welch test). IPC, inferior parietal cortex; L, left; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; R, right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

suitable for resting functional connectivity analyses; however, these authors found quantitative differences may exist for event-related task-derived data (Fair et al., 2007). This study involved three groups of 10 subjects (mixed-block, event-related, and task-free resting fMRI data) with no overlap of measurements between groups. In contrast to these findings, our current data provide solid validation for both event-related and mixed block/event task designs using data from five different cognitive and emotion processing fMRI tasks and task-free resting data—all acquired in the same individuals. All five tasks generated equivalent DMN maps, and these maps did not differ from DMN maps derived from dedicated resting state data. If the emotional or cognitive tasks caused a perturbation of the DMN then some heterogeneity would be expected between our five different tasks. Our data provide evidence that supports the use of existing nondedicated fMRI task datasets to measure resting state activity. This opens up the possibility of capitalizing on the considerable existing collections of fMRI datasets to study intrinsic brain networks with both healthy and abnormal neurodevelopment.

Genetic effects have been shown to influence the efficiency of resting functional connections across the brain,

ranging from 60% in healthy adults (Fornito et al., 2011) to 42% in children (van den Heuvel et al., 2013). Previous work using resting data from extended pedigrees has also demonstrated that up to 40% of the variance in the DMN is under genetic control (Glahn et al., 2010). Recent data in first-degree relatives of patients with schizophrenia provide further support for the role of genetics in task-free resting brain activity. First degree relatives of patients with schizophrenia exhibit both hyperactivation during tasks and hyperconnectivity of the default mode regions during rest compared to controls (Whitfield-Gabrieli et al., 2009). Our findings validate these findings of a genetic influence on the DMN for the first time using a twin design. Interestingly not all functional connections within the DMN were significant in our analysis. We found the strongest heritable influence existed for the PCC and inferior parietal cortical connections (41% for PCC–RIPC and 24% for PCC–LIPC) within the DMN. The remaining connections did not meet criteria for endophenotype status. The increased genetic control for these connections is a novel finding and promotes the candidature of this measure as an endophenotype in brain disorders. This is supported by functional studies in autism where both patients and their siblings show a failure to deactivate the PCC

and the bilateral IPC during a functional task (Spencer et al., 2012). A decreased resting state connectivity between the same DMN regions was also observed in patients with 22q11.2 deletion syndrome, a genetic disorder which represents the most significant genetic risk fac-

Figure 4.

Heritability estimates (a^2 expressed in %) for functional connectivity within the default mode network. Genetic influence for only the PCC-RIPC functional connectivity was significant ($P < 0.001$; bold connection). IPC, inferior parietal cortex; L, left; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; R, right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tors for disorders of social dysfunction and cortical connectivity such as autism spectrum disorders and schizophrenia (Schreiner et al., 2013).

Recent studies have also started to identify the actual genes involved in the regulation of DMN connectivity. Catechol-O-methyl transferase (COMT) and brain-derived neurotrophic factor (BDNF) single nucleotide polymorphisms have been associated with altered functional connectivity within the DMN (Jang et al., 2012). The COMT val158met polymorphism has been shown to be associated with high level executive function (Goldberg et al., 2003); while the BDNF val66met has been linked to memory processing and shown to play an important role in normal neuronal development (Leal et al., 2013; Tan et al., 2007). Various studies have shown links between both COMT and BDNF to psychiatric disorders such as depression (Arlt et al., 2013). Carriers of the e4 allele of apolipoprotein E, a risk marker for Alzheimer's disease, were found to have abnormal DMN connectivity in comparison to healthy noncarriers. Given the established finding of altered DMN in both mild cognitive impairment and Alzheimer's disease, these findings provide evidence that resting state functional connectivity maybe an early marker of genetic risk even before any visible symptoms (Filippini et al., 2009; Sheline et al., 2010). Our finding of genetic control over the task-derived resting activity suggests that this measure may also serve as potential candidate for studying genetic links for these and other disorders.

A potential limitation of using task-derived resting state activity is the added variance due to the type and design of functional task used. This is especially critical for between cohort comparisons of task-derived resting data

TABLE II. Additive genetics/unique environment (A/E) model estimates and significance values for the model and genetic component (A) for the connectivity measures between the default mode network (DMN) nodes

DMN connectivity	rMZ	rDZ	Standardized variance components				P values A/E model fit	P values A
			a^2	95% CI	e^2	95% CI		
PCC-RIPC ^a	0.49	-0.02	0.41	(0.22-0.56)	0.59	(0.44-0.78)	<0.001	<0.001
PCC-LIPC ^b	0.28	0.04	0.24	(0.03-0.43)	0.76	(0.57-0.97)	<0.001	0.08
PCC-mPFC	0.12	0.15	0.10	(0.00-0.29)	0.90	(0.71-1.00)	<0.001	0.53
PCC-LTC	0.16	0.16	0.17	(0.00-0.37)	0.83	(0.63-1.00)	<0.001	0.25
RIPC-LIPC	0.17	0.16	0.16	(0.00-0.35)	0.84	(0.65-1.00)	<0.001	0.30
RIPC-mPFC	0.15	0.07	0.12	(0.00-0.32)	0.88	(0.68-1.00)	<0.001	0.57
RIPC-LTC	0.12	0	0.09	(0.00-0.31)	0.91	(0.69-1.00)	<0.001	0.72
LIPC-mPFC	0.09	0.13	0.11	(0.00-0.32)	0.89	(0.68-1.00)	<0.001	0.59
LIPC-LTC	0.18	0.25	0.21	(0.00-0.40)	0.79	(0.60-1.00)	<0.001	0.13
mPFC-LTC	0.13	0.33	0.16	(0.00-0.36)	0.84	(0.64-1.00)	<0.001	0.20

Abbreviations: A, additive genetic component; a , additive genetics variance estimate; E, unique environment component; e , unique environment variance estimate; CI, confidence interval; LIPC, left inferior parietal cortex; LTC, left temporal cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; RIPC, right inferior parietal cortex.

Twin correlations for both the MZ (rMZ) and DZ (rDZ) groups for each measure are also listed.

^a $P < 0.05$ indicates significant genetic effect.

^b $P < 0.1$ indicates significant genetic effect.

where different functional tasks may have been used for different cohorts. Although we did not find significant task-related differences in resting state functional connectivity measures between any of our five tasks, we did notice a small nonsignificant difference in mean functional connectivity estimates between tasks for certain DMN node connections in our analysis. However the between cohorts variance in the same measure was almost negligible, suggesting that this is not an issue if the same fMRI task is used across cohorts. It is important to stress that in this study we have only examined the DMN. Our finding that task-derived data is equivalent to task-free resting data for this network is consistent with the concept of this network as a baseline brain activity. Previous work has shown that additional networks such as the sensory-motor, executive control, visual processing, auditory processing, frontoparietal control network can be identified from dedicated resting activity (Damoiseaux et al., 2006). Future work is needed to evaluate if these resting networks can be consistently identified using task-derived resting activity from different fMRI tasks and to further test the genetic influence on these.

In summary, our data show that valid resting brain activity can be extracted from task fMRI datasets. This means that already existing fMRI datasets could be potentially utilized to measure valid intrinsic brain networks. We also demonstrate that functional connectivity within the DMN is influenced by genetic factors providing support for the potential of this measure as a candidate endophenotypes for psychiatric and neurological disorders with genetic predispositions.

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