Associations of observed preschool performance monitoring with brain functional connectivity in adolescence

Kirsten E. Gilbert a,*,1, Muriah D. Wheelock b,1, Sridhar Kandala a, Adam T. Eggebrecth b, Joan L. Luby a and Deanna M. Barch a,b,c

a Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
b Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA
c Department of Psychological and Brain Sciences, Washington University in St. Louis, St. Louis, MO, USA

ABSTRACT

Monitoring one’s performance helps detect errors and adapt to prevent future mistakes. However, elevated performance monitoring is associated with increased checking behaviors and perfectionism and is characteristic of multiple psychiatric disorders. Understanding how heightened performance monitoring in early childhood relates to subsequent brain connectivity may elucidate mechanistic risk factors that influence brain and psychiatric outcomes. The aim of this study was to examine the association between performance monitoring in preschool-aged children and functional connectivity during adolescence. In the current prospective longitudinal study, we performed seed-based functional connectivity analysis using a dorsal anterior cingulate cortex (dACC) seed to assess brain-behavior relationships between observationally coded performance monitoring in preschool-aged children and adolescent functional connectivity (n = 79). We also utilized enrichment analysis to investigate network-level connectome-wide associations. Seed-based analysis revealed negative correlations between preschool performance monitoring and adolescent fc between dACC and orbitofrontal and dorsolateral prefrontal cortex while a positive correlation was observed between dACC-occipital cortex connectivity. Enrichment analysis revealed a negative correlation between preschool performance monitoring and connectivity between motor (MOT) - cingulo-opercular (CO) and salience (SN) - Reward (REW) and a positive correlation with MOT-DMN, and cerebellum (CB) - motor connectivity. Elevated performance monitoring in early childhood is associated with functional connectivity during adolescence in regions and networks associated with cognitive control, sensorimotor processing and cortico-striatal-thalamic-cortico (CTSC) aberrations. These regions and networks are implicated in psychiatric disorders characterized by elevated performance monitoring. Findings shed light on a mechanistic risk factor in early childhood with long-term associations with neural functioning.

© 2021 Elsevier Ltd. All rights reserved.
1. Introduction

Monitoring one’s performance is an aspect of cognitive control that aids in detecting and learning from errors. When adaptive, performance monitoring helps one identify errors and recognize the need to adjust to prevent future mistakes. However, elevated performance monitoring is associated with perfectionism and compulsive checking behaviors and is characteristic of multiple psychiatric disorders, including obsessive compulsive disorder (OCD), social anxiety disorder (SAD), and anorexia nervosa (Gilbert, Barclay, Tillman, Barch, & Luby, 2018; Endrass, Riesel, Kathmann, & Buhlmann, 2014; Riesel et al., 2019; Geisler et al., 2017). Specifically, perfectionism, concern over errors and cognitive inflexibility are common across OCD, SAD, and anorexia (Kaye, Wierenga, Bailar, Simmons, & Bischoff-Grethe, 2013; Levinson et al., 2019) and these disorders are often comorbid (Yilmaz et al., 2019; Kerr-Gaffney et al., 2018). Understanding trans-diagnostic brain–behavior relationships is a central goal of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) approach (Cuthbert & Insel, 2013) and recent work has highlighted the importance of investigating RDoC constructs within a neurodevelopmental framework (Mittal & Wakschlag, 2017). As such, understanding how elevated performance monitoring tendencies evident in early childhood relate to subsequent brain connectivity in adolescence may provide pertinent information regarding mechanistic risk factors that influence brain and psychiatric outcomes.

Performance monitoring is a construct centered on responding to errors. The most commonly studied neural correlate of performance monitoring is the electroencephalogram (EEG) recorded error-related negativity [ERN (Gehring, Goss, Cole, Meyer, & Donchim, 1993)]. The ERN, a negative deflection that occurs when making an error, is associated with self-monitoring and checking behaviors (Weinberg et al., 2016), and is thought to emerge from the dorsal anterior cingulate cortex (dACC) (Holroyd & Coles, 2002; Holroyd & Umemoto, 2016; Weiss et al., 2018). The dACC is a brain region repeatedly implicated in cognitive control and performance monitoring (Heilbronner & Hayden, 2016; Holroyd & Coles, 2002) and indeed, it demonstrates activation to errors in adults (Neta et al., 2015) and children (Gilbert, Perino, Myers, & Sylvester, 2020; Fitzgerald et al., 2010). Although the ERN is often equated with performance monitoring, there are other ways to assess monitoring of performance in the context of errors. Specifically, performance monitoring can also be assessed using behavioral adjustments made following an error, such as post-error slowing and post-error accuracy.

We recently established a novel developmentally appropriate observed behavioral indicator of performance monitoring in preschool-aged children utilizing the Laboratory Temperament Assessment Battery (LABTAB) (Goldsmith et al., 1995) Impossible Circles (IC) Task, where an experimenter repeatedly points out errors and criticizes the child’s drawing of circles, then provides opportunities for the child to behaviorally adjust by drawing another circle (Gilbert, Barclay, Tillman, Barch, & Luby, 2018). It should be noted that this novel observationally coded indicator assesses child emotional and behavioral concern over errors and could also tap into overlapping processes of perfectionism and ‘just right’ tendencies. Additionally, while the time scale differs (3 min of observational coding) compared to other indicators (50 msec in the ERN, seconds for a bold response to error in fMRI, milliseconds in post-error slowing), our observational task does overlap with a central aspect of performance monitoring: making an error and adjusting behavior in response to the error. Therefore, we refer to this as a purported indicator of the performance-monitoring construct. Moreover, preliminary validation demonstrated our task was associated with preschool OCD symptoms, predicted onset of adolescent OCD, and was associated with smaller dACC brain volumes across child development (Gilbert, Barclay, Tillman, Barch, & Luby, 2018), suggesting external validity with the performance monitoring construct. However, it has not yet been investigated whether this indicator of childhood performance monitoring is associated with dACC functional connectivity later in development. This is an integral next step to further our understanding of how early-emerging RDoC constructs, such as performance monitoring, demonstrate brain–behavior relationships in the context of neurodevelopment, potentially bolstering the notion that it is a mechanistic risk factor that could be targeted for early intervention.

Although the dACC is commonly implicated, a distributed set of brain regions across multiple networks - including the frontal and parietal cortex, insula, cerebellum and subcortical regions - are thought to be implicated in performance monitoring (Neta et al., 2015). As such, rather than assessing individual brain regions in isolation, network-level analysis of whole-brain connectome data, which encompasses every possible connection between brain regions, allows for a wider-lens examination. From a network-level perspective, cortical regions implicated in performance monitoring fall into three purported functional networks: the cingulo-opercular network (CO), the fronto-parietal network (FPN) and the default-mode network (DMN) (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Raichle et al., 2001; Fox et al., 2005). The CO (which includes the dACC) and the FPN are both implicated in top-down cognitive control. The CO contributes to global task maintenance, focusing on stable task control by detecting error information to adjust behavior (Dosenbach et al., 2007; Cocchi, Zalesky, Fornito, & Mattingley, 2013) while the FPN aids in integrating this information via trial-by-trial response to feedback and error adjustment (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2007; Cocchi, Zalesky, Fornito, & Mattingley, 2013; Marek & Dosenbach, 2018). Conversely, the DMN is deactivated during task performance and greater deactivation is associated with better cognitive performance (Greicius, Krasnow, Reiss, & Menon, 2003), while an inability to suppress the DMN is associated with more variability in behavioral responding during cognitive tasks (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008).
Not surprisingly, prototypical psychiatric disorders characterized by heightened performance monitoring, including OCD, SAD and anorexia, demonstrate regional and network-level functional connectivity (fc) differences including the CO, FPN and DMN in adults [e.g., (Fitzgerald et al., 2011; Weber et al., 2014; Gruner et al., 2014)]. Moreover, pediatric anxiety (SAD and generalized anxiety) demonstrates reduced striatal connectivity to the ACC, insula, cerebellum and somatosensory cortex (Gaudio, Wimerslage, Brooks, & Schioth, 2016) and across anxiety disorders, a meta-analysis implicates the DMN, the ACC and the executive control network (which overlaps the FPN and CO) (Xu et al., 2019). Moreover, supporting above-mentioned regions in fc patterns, the dACC, OFC, striatum and thalamus are involved in the cortico-striato-thalamo-cortical (CSTC) circuit (Milad & Rauch, 2012). Taken together, regions of the CSTC can be classified as part of a larger reward/emotion (REW) network (Seitzman et al., 2020; Wheelock et al., 2018), which is implicated in the etiology of OCD (Milad & Rauch, 2012), demonstrates aberrant patterns in anorexia (Uniacke et al., 2019; Gaudio, Wimerslage, Brooks, & Schioth, 2016), and aberrant cortico-striatal connectivity in SAD (Arnold Anteraper et al., 2015; Manning et al., 2015).

Although less work has been done in child and adolescent samples, pediatric OCD similarly demonstrates reduced connectivity of the rostral and dorsal ACC to the striatum and thalamus (Fitzgerald et al., 2011; Weber et al., 2014; Gruner et al., 2014) while cingulate connectivity is associated with higher compulsions and symptom severity (Fitzgerald et al., 2011; Gruner et al., 2014). Moreover, pediatric anxiety (SAD and generalized anxiety) demonstrates decreased striatal connectivity to the ACC, insula, and supplementary motor area (SMA) (Dorfman, Farber, Pine, & Ernst, 2016). In adolescent anorexia, findings indicate increased FPN, insula and DMN connectivity, decreased connectivity between executive control networks and the ACC, and fc alterations in the insula and thalamus (Boehm et al., 2014; Gaudio et al., 2015; Ehrlich et al., 2015) similarly demonstrating aberrant fc in CON, FPN, DMN and CSTC/REW. Importantly, a growing literature demonstrates that early brain response to performance monitoring in childhood predicts the onset of anxiety disorders and OCD and moderates the relationship between behavioral inhibition and SAD in childhood and adolescence (Gilbert, Barclay, Tillman, Barch, & Luby, 2018; Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015; Meyer et al., 2018; Henderson et al., 2015). Taken together, psychiatric disorders characterized by elevated performance monitoring demonstrate aberrant fc in expected regions and networks and early-emerging performance monitoring predicts onset of these psychiatric disorders. However, it is unknown whether these fc patterns are directly related to the underlying mechanism of performance monitoring. The current study examined whether an indicator of heightened performance monitoring during the preschool period predicts brain functioning using fc magnetic resonance imaging (fcMRI) later in adolescence. Understanding whether an ecologically valid indicator of performance monitoring is associated with brain connectivity later in development would aid in validating this readily observed RDoC risk factor. Indeed, an observed performance monitoring risk factor that is evident before symptom onset and is longitudinally associated with similar patterns of functional connectivity evident across multiple psychiatric illnesses is important in understanding brain-behavior associations of this purported mechanism.

To test this aim, we employed two complementary methodological approaches to assess brain-behavior associations: hypothesis-driven seed-based voxelwise connectivity and a network-level analysis. For the whole-brain seed-based approach, we used the a-priori dACC region, as it has repeatedly been implicated in performance monitoring and we have shown associations between dACC brain volume and our developmentally appropriate novel behavioral indicator of performance monitoring across development (Gilbert, Barclay, Tillman, Barch, & Luby, 2018; Neta et al., 2015). Seed-based connectivity provides a hypothesis-driven approach to investigating fcMRI relationships with the behavioral measure of preschool performance monitoring. To take a more global approach and assess relationships that may exist outside the dACC, we also used a network-level ‘enrichment’ approach. Network analysis in genomics uses statistical methods known as ‘enrichment’ or ‘over expression analysis’ to determine genome-wide associations with outcomes. These network analysis tools, recently adopted for connectome-wide association studies, have proven useful for discerning fcMRI associations with behavior and developmental outcomes (Wheelock et al., 2018; Eggebrecht, 2017; Wheelock et al., 2019). Thus, enrichment provides a data-driven approach to investigate preschool performance monitoring associations with hypothesized brain networks.

In the current prospective longitudinal study, we assessed relationships between observationally coded preschool performance monitoring and fcMRI during late adolescence. Previously in this sample, this novel indicator of heightened performance monitoring using the impossible circles task, predicted developmental trajectories of reduced dACC volume and onset of OCD (Gilbert, Barclay, Tillman, Barch, & Luby, 2018). In the current study, we aimed to assess whether early performance monitoring indexed using the IC task was associated with fcMRI collected approximately 12 years later using two complementary analysis methods, i) seed-based voxelwise analysis, and ii) connectome-wide network-level enrichment analysis. We hypothesized that heightened preschool performance monitoring would predict aberrant dACC seed-based connectivity with the OFC, and dlPFC, and from regions in the CON, FPN, DMN and CSTC/REW. We also hypothesized that elevated preschool performance monitoring would predict aberrant network-level fc within and between the CO, FPN, DMN and REW utilizing an enrichment analysis. No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

2. Methods

2.1. Participants

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/
exclusion criteria were established prior to data analysis and all measures in the study below. Participants from the Preschool Depression Study (PDS) (Luby, Beldon, Tandon, & Spitznagel, 2009) who had usable baseline observational, covariate, and adolescent (wave 4) resting state scan data were included. The PDS is an ongoing longitudinal study at Washington University School of Medicine (WUSM) that uses multiple methods to evaluate mental health and neural outcomes from preschool through late adolescence. Between 2003 and 2005, children aged 3–5 years and their primary caregivers were recruited from daycare centers, preschools and primary care centers oversampling for depression with the Preschool Feelings Checklist (Luby, Heffelfinger, Koenig-McNaught, Brown, & Spitznagel, 2004). The current sample is clinically heterogeneous with high comorbidity as 82% (n = 65) experienced at least one mental disorder across the study. Since baseline assessment, children have undergone approximately 12 annual assessments including behavioral, cognitive, clinical interview, neuroimaging and electroencephalogram tasks. Functional connectivity (fc) data used in the current study were taken from scan wave 4, when children were 14–19 years (Table 1). Of the original 292 participants who completed the baseline measurement of preschool performance monitoring, 170 participated in behavioral follow-up testing, and 148 completed an MRI scan at scan wave 4. Of these 148, 131 completed an fcMRI scan; of these, 111 participants had at least 5 min of low-motion resting state data. Of these, 79 had complete covariate data, thus 79 participants were used in the fcMRI analysis. There were no significant demographic, covariate, or performance monitoring differences between participants with versus without usable resting state data (p’s >.05). Written parental consent and child assent (child written consent when 16 years) were obtained before participation and participants were compensated. The WUSM institutional review board approved all procedures in accordance with the Declaration of Helsinki.

2.2. Observational performance monitoring

Preschool-aged children completed the impossibly perfect circles task as part of the Laboratory Temperament Assessment Battery (LABTAB) (Goldsmith et al., 1995) at baseline. The task involves an experimenter instructing the child to draw a ‘perfect’ circle and repeatedly criticizing the drawn circles for imperfections and was originally designed to elicit negative emotionality and persistence. Critiques were specific (i.e., that one has a flat side); they were not meant to help fix the errors. After 3 min of critical feedback, the experimenter admits to being harsh and praises the child’s circle drawing. The task elicits performance monitoring during a performance-focused task, which was coded using a previously validated composite (Gilbert, Barclay, Tillman, Barch, & Luby, 2018). Individual codes of frustration (1 = no signs of frustration to 4 = multiple clear facial, verbal and/or behavioral signs of frustration), diligence, care and deliberateness in actual circle drawing (1 = hurried, not paying attention to 4 = very diligent, very deliberate and slow in circle drawing), intensity demonstrated while performing the task, including the child’s focus, body tension and overall demeanor (1 = not at all, none to 4 = definitely, a lot), and child verbal self-criticism (1 = not at all, none to 4 = definitely, a lot) were rated on a 4-point scale and summed such that higher scores denote higher performance monitoring. The composite demonstrated adequate internal consistency (α = .73) and inter-rater reliability (ICC: .80; 95% CI: .67–.88).

2.3. Psychiatric symptom severity scores and diagnoses

Trained masters-level staff conducted in-person diagnostic assessments with primary caregivers at baseline using the Preschool Age Psychiatric Assessment (PAPA) (Angold & Costello, 2000) or the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997) OCD = Obsessive Compulsive Disorder; SAD = Social Anxiety Disorder; AN = Anorexia Nervosa, GAD = Generalized Anxiety Disorder; SepAnx = Separation Anxiety Disorder; PTSD = Post Traumatic Stress Disorder; Externalizing = Externalizing disorder of ADHD, Oppositional Defiant Disorder or Conduct Disorder.
deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder symptoms. Diagnoses of preschool depression were calculated. Approximately 20% of baseline tapes were reviewed by a master coder and discrepancies were discussed in case consultation with a senior child psychiatrist (J.L.L). Legal copyright restrictions prevent public archiving of the PAPA, which can be obtained from the copyright holders in the cited references.

2.4. Income-to-needs

Caregivers reported on the number of individuals in the household and family income at baseline. Socioeconomic status was computed as the total family income divided by the federal poverty level at the time of data collection, based on family size (McLoyd, 1998).

2.5. Neuroimaging data acquisition

A 3.0T Siemens Prisma scanner was used for acquiring magnetic resonance images (MRI). Two 5-min resting-state functional MRI (rs-fMRI) scans were acquired in each participant using an echoplanar imaging sequence. A T1-weighted anatomical image was acquired as referenced for the rs-fMRI data and a T2-weighted anatomical image was acquired for structural processing (see Supplemental Materials for scan sequence parameters).

2.6. Preprocessing

Freesurfer, FSL, and MATLAB scripts were used for data preprocessing. EPI, T1, and T2 images were corrected for distortions, realigned, resampled to 2 mm isotropic, and registered to the MN1152 atlas (Mazziotta et al., 2001a, 2001b; Mazziotta, Toga, Evans, Fox, & Lancaster, 1995). High motion EPI volumes were censored using a cutoff of .2 mm frame displacement. EPI data were interpolated across censored frames and bandpass filtered at .009 Hz<f<.08Hz. Participants with at least 5 min (minimum of 417 cumulative frames) of low-motion fcMRI data were included. See Supplemental Materials for additional preprocessing details.

2.7. Voxelwise statistical analysis

Whole-brain seed-based functional connectivity analysis predicted performance monitoring relationships with fcMRI using an anatomically defined dACC ROI. As we have done previously (Gilbert, Barclay, Tillman, Barch, & Luby, 2018), the Desikan-Killiany-Tourville (Klein & Tourville, 2012) parcellation of the caudal anterior cingulate was used to estimate the bilateral dACC. To examine the independent role of performance monitoring (Gilbert, Barclay, Tillman, Barch, & Luby, 2018), we included covariates of baseline age, income-to-needs, compulsions, anxiety and externalizing severity scores, sex, preschool depression diagnosis (yes/no) and adolescent day-of-scan psychotropic medication status (yes/no). Cluster extent correction was estimated using 3DClustsim (Cox et al, 2017a, 2017b) (AFNI v19.3.13) which employs 10,000 Monte Carlo simulations to control family wise error rate and the fcMRI map was thresholded at p < .001 cluster extent >50.7 voxels and visualized using Workbench (v1.3.2) (Marcus et al., 2011).

2.8. Deriving putative functional connectivity networks

Brain networks were defined using 300 regions of interest (ROI) and previously published methods (Seitzman et al., 2020; Wheelock et al., 2018). The 300 ROI compose 15 brain networks with cortical and subcortical representation including the cerebellum, basal ganglia, thalamus, hippocampus, and amygdala. Pearson r correlations were calculated between mean timeseries for all voxels in each ROI forming subject-specific connectomes. Minimal impact of retained motion artifact post scrubbing was present in connectome data (Supplemental Fi. S1) (Ciric et al., 2017).

2.9. Network-level statistical analysis

Network-level analysis examined the relationship between preschool performance monitoring and longitudinal fc data, including above-mentioned covariates. Network-level analysis was adapted from enrichment statistics in genomic research (Rivals, Personnaz, Taing, & Potier, 2006; Backes et al., 2014; Khatri et al., 2012) and used previously published methods (Eggebrecht, 2017; Wheelock et al., 2019). First, Pearson correlations between baseline performance monitoring and connectome data were calculated and binarized at threshold of P ≤ .05. Then two complementary network level tests were run to test for enrichment, a 1-degree-of-freedom χ2-test and a hypergeometric test. The χ2-test assessed enrichment for each network pair, comparing observed number of brain-behavior correlations to that would be expected if the overall number of large correlations was uniformly distributed across all network pairs. The χ2 statistic is ‘enriched’ when the number of large correlations with a network pair is greater than expected. The hypergeometric test assesses the likelihood of observing a given number of large correlations in a network pair given total possible hits for that network pair and total number of large correlations observed overall. Performance monitoring was randomly permuted 10,000 times (Eggebrecht, 2017; Backes et al., 2014) to generate a null distribution. Measured network pair associations with performance monitoring were compared to this permuted null distribution thus controlling the family-wise error rate. Only network pairs which met significance for both χ2 and hypergeometric tests are reported. Enrichment analyses were performed in MATLAB (Release 2015a, The Mathworks, Inc. Natick, Massachusetts, United States). The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author, K.G., or the last authors, J.L. or D.B., who are the P.I.’s of the study. Access will be granted to named individuals in accordance with ethical conditions governing the reuse of sensitive data. Specifically, requesters must complete a formal data sharing agreement upon written individual request. Corresponding
3. Results

3.1. Seed-based voxelwise connectivity analysis

Seed-based connectivity analysis demonstrated elevated performance monitoring was negatively correlated with dACC seed connectivity and regions within dACC, dIPFC, superior frontal gyrus, OFC, as well as a cluster spanning orbitofrontal to subgenual ACC (labeled middle orbitofrontal gyrus, xyz: 14, 28, −10) (Fig. 1; Table 2). Conversely, elevated performance monitoring was associated with greater connectivity of the dACC seed with cuneus and middle occipital gyrus. For all observed clusters, individuals with higher preschool performance monitoring had lower dACC fc within these regions (Fig. S2). Given the size of the Desikan-Killiany-Tourville dACC anatomical ROI, we additionally examined associations with a smaller, spherical dACC ROI. Despite similarities in associations with preschool performance monitoring, the results based on this functionally defined spherical dACC seed did not survive cluster-level correction (Supplemental Figure S3).

3.2. Network level analysis

To examine preschool performance monitoring associations with adolescent network-level connectivity, we employed connectome-wide enrichment analysis. Adolescent connectome data (Fig. 2A) were correlated with preschool performance monitoring after partialing out covariate variance (Fig. 2B). Network-level analysis revealed significant associations between preschool performance monitoring and adolescent DMN, CO, REW, Salience (SN), Motor (MOT), and cerebellar (CB) connectivity (Fig. 2C).

Specifically, negative correlations were observed between performance monitoring and CO-MOT and SN-REW connectivity, with higher preschool performance monitoring associated with reduced or negative connectivity between networks (Fig. 3; Supplemental Table S1). In contrast, performance monitoring was positively correlated with DMN-MOT and CB-MOT connectivity.

3.3. Secondary post-hoc analyses

Secondary post-hoc analyses were completed covarying for dACC volume (given performance monitoring predicted smaller dACC volumes in adolescence (Gilbert, Barclay, Tillman, Barch, & Luby, 2018)) and demonstrated negative...
correlations between performance monitoring and functional connectivity within OFC, dlPFC, and superior frontal gyrus as well as positive correlations with connectivity in occipital cortex remained (Fig. S4). Network-level associations remained the same after partialing out variance due to dACC volume (Fig. S5). Additionally, given the indicator of performance monitoring is made up of four independent observational codes, and the child self-criticism code demonstrated strongest predictive validity in OCD and dACC volumes in previous research (Gilbert, Barclay, Tillman, Barch, & Luby, 2018), we examined child self-critical behavior predicting functional connectivity. We observed no significant dACC seed-based clusters surviving analysis with the self-critical item. However, the self-critical item demonstrated a similar pattern of network-level associations with the MOT, CO, DMN, CB, SN, and Rew networks as well as additional associations between MOT-FPN, FPN-SN, and several other networks (see Supplemental Materials; Fig. S6). Last, given previous research demonstrates associations between preschool performance monitoring and adolescent OCD (Gilbert, Barclay, Tillman, Barch, & Luby, 2018), network level associations with adolescent OCD can be found in the Supplement and demonstrate overlapping networks: DMN, Co, Rew, and Mot (Fig. S7).

4. Discussion

These longitudinal findings demonstrate observed performance monitoring from the IC task in the preschool years is associated with adolescent dACC fcMRI and connectivity among MOT, CO, DMN, CB, SN and Rew networks. Specifically, individuals exhibiting excessive performance monitoring demonstrated less dACC seed connectivity with dlPFC, OFC and sgACC and greater dACC-visual connectivity relative to individuals with lower performance monitoring. Further, these regional findings were corroborated and expanded on with network-level analysis revealing individuals with elevated preschool performance monitoring demonstrated less CO-MOT and SN Rew and greater CB-MOT and DMN-MOT network connectivity. Both complementary analysis methods independently demonstrate a significant relationship between early childhood performance monitoring tendencies and brain

---

**Table 2** – Bilateral dACC seed-based voxelwise correlations with performance monitoring.

<table>
<thead>
<tr>
<th>X</th>
<th>y</th>
<th>z</th>
<th>Z stat</th>
<th>Hem</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>16</td>
<td>−18</td>
<td>−4.59883</td>
<td>R</td>
<td>Lateral Orbitofrontal Gyrus</td>
</tr>
<tr>
<td>−22</td>
<td>36</td>
<td>−20</td>
<td>−4.49007</td>
<td>L</td>
<td>Middle Orbitofrontal Gyrus</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>−10</td>
<td>−4.42122</td>
<td>R</td>
<td>Middle Orbitofrontal Gyrus</td>
</tr>
<tr>
<td>36</td>
<td>−86</td>
<td>14</td>
<td>3.710749</td>
<td>R</td>
<td>Middle Occipital Gyrus</td>
</tr>
<tr>
<td>24</td>
<td>46</td>
<td>16</td>
<td>−3.89615</td>
<td>R</td>
<td>Dorsolateral Prefrontal Cortex</td>
</tr>
<tr>
<td>−8</td>
<td>−82</td>
<td>24</td>
<td>3.475696</td>
<td>L</td>
<td>Cuneus</td>
</tr>
<tr>
<td>2</td>
<td>−10</td>
<td>42</td>
<td>−3.88326</td>
<td>R</td>
<td>Dorsal Anterior Cingulate</td>
</tr>
<tr>
<td>38</td>
<td>6</td>
<td>44</td>
<td>−3.99501</td>
<td>R</td>
<td>Posterior Middle Frontal Gyrus</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>48</td>
<td>−3.83533</td>
<td>R</td>
<td>Superior Frontal Gyrus</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>56</td>
<td>−3.97139</td>
<td>R</td>
<td>Superior Frontal Gyrus</td>
</tr>
</tbody>
</table>

Coordinates are reported in MNI. *Note = Hem, hemisphere.

Fig. 2 – A) Mean adolescent functional connectivity (N = 79). B) Correlation between preschool performance monitoring and adolescent functional connectivity after partialing out variance due to preschool age, sex, preschool compulsions, preschool income to needs, preschool depression, adolescent psychiatric medications, preschool internalizing, and preschool externalizing from fc and performance monitoring. C) Adolescent brain networks significantly associated with preschool overcontrol based on the network-level Chi–Square test. Mot, Motor; CO, cinguloopercular; Aud, auditory; DMN, default mode network; Mem, memory network; Vis, visual; FPN, frontoparietal network; SN, salience network; VAN, ventral attention; DAN, dorsal attention; MT, middle temporal; Rew, reward; BG, basal ganglia; Thal, thalamus; CB, cerebellum.
connectivity over a decade later. Understanding how performance monitoring may be a mechanism imparting risk for multiple psychiatric illnesses and neural aberrations later in development is vital in informing targeted early intervention, prior to disorder onset.

Investigating transdiagnostic brain–behavior relationships across development is imperative to understanding underlying mechanisms of risk for psychiatric illness. The current study provides novel information relating an observed measure of preschool performance or error monitoring with later brain connectivity employing two methodological approaches. Seed-based analyses demonstrated negative correlations between performance monitoring and dACC and prefrontal (dLPFC and OFC) connectivity. These findings parallel network-level observations of enriched performance monitoring associations with CO-MOT and SN-REW connectivity. Specifically, elevated preschool performance monitoring was negatively correlated with connectivity between these network pairs (which contained regions of the dACC, dLPFC, OFC). Given the chosen dACC region from seed-based analysis overlapped with an ROI in the CO and SN networks, the similarity between seed-based and network-level associations is expected.

In line with prior research in disorders characterized by elevated performance monitoring (Gürsel, Avram, Sorg, Brandl, & Koch, 2018; Gaudio, Wimerslage, Brooks, & Schioth, 2016; Xu et al., 2019), we observed aberrant connectivity in CO and DMN. Specifically, elevated performance monitoring was associated with decreased CO-MOT and increased DMN-MOT connectivity. Regions in the MOT, including the supplementary motor area (SMA) and the primary motor cortex, contribute to motor-related processes, including motor inhibition, response switching, and movement preparation, and have been linked with cognition (Nachev et al., 2008; Sanes & Donoghue, 2000). Although not hypothesized, anorexia has repeatedly been characterized by sensorimotor and visual network aberrations (Gaudio, Wimerslage, Brooks, & Schioth, 2016; Phillipou et al., 2016) and SAD is characterized by decreased somato-motor, motor and visual network connectivity (Dorfman, Farber, Pine, & Ernst, 2016; Liu et al., 2015). Moreover, adults and children with OCD demonstrate decreased connectivity in the SMA (Hao et al., 2019; Gruner et al., 2014), this region is an effective target for transcranial magnetic stimulation treatment for OCD (Jaafari et al., 2012) and OCD has been conceptualized as a disorder that includes sensory-motor problems (Russo et al., 2014). Taken together, associations of performance monitoring with decreased CO-MOT and increased task-negative DMN-MOT (as well as overlapping dACC-dLPFC and OFC) connectivity may be due to an inability to inhibit or shift away from errors and checking behaviors. Further, the DMN is implicated in rumination (Hamilton, Farmer, Fogelman, & Gotlib, 2015) and so, stated otherwise, a lack of integration of somatosensory or motor information with cognitive error monitoring could be
associated with repetitive and ruminative focus on food intake, checking behaviors, or social evaluation, depending on symptom presentation.

With regards to decreased CB-MOT connectivity, although the cerebellum was originally conceptualized as a motor structure (Schmahmann, 2004) recent evidence demonstrates its importance in adaptive cognitive control (Marek et al., 2018) and error processing (Neta et al., 2015), while cerebellar damage is associated with dysfunction in a range of cognitive functions, including task switching and sensory integration (Schmahmann, 2004). We speculate that overactive performance monitoring early in development could be associated with tendencies towards repetitive motor movements such as compulsions, checking behaviors and perfectionism and related somatosensory processing difficulties (MOT) that are not integrated with other cognitive control and motor functions (CB). Interestingly, the presupplementary motor area (pre-SMA), a nearby region identified as an indicator of performance monitoring in RDoC and more commonly implicated in OCD performance monitoring (de Wit et al., 2012), was not significant in current findings. Network-level findings identified a more rostral motor area in relation to CO, DMN and CB connectivity. Future work should reconcile performance-monitoring relationships within distinct regions of the supplementary motor cortex and explore the role of the motor network in learned repetitive behaviors and integration of somatosensory information processing with cognitive control and error monitoring evidenced in networks including CO, DMN and CB. Similarly, relationships between CB-MOT were in the opposite direction (greater connectivity) compared with CO-MOT (less connectivity), and as such, future research should aim to parse out the differing cognitive functions in the CB versus the CO to better understand these counterintuitive relationships.

Of note, enrichment analyses detected associations of preschool performance monitoring with greater CB-MOT connectivity that seed-based analysis did not. This association would not be apparent in voxelwise analyses if no regions from these networks were hypothesized. Both approaches offer advantages, as seed-based analysis is valuable for understanding specific, hypothesis-driven associations while enrichment analysis offers the potential to illuminate subtle connectome-wide associations that might otherwise be overlooked.

Negative correlations of performance monitoring with dACC and OFC-sgACC fc and network-level SN-REW connectivity lend support to the CTSC circuitry involvement. The SN includes the dACC and insula while the REW network includes the OFC, ventral striatum, and amygdala, all regions commonly implicated in CTSC. These overlapping results support our hypothesis and parallel past work demonstrating aberrant CSTC fc, as evidenced in OCD and anorexia (Gaudio, Wimerslage, Brooks, & Schioth, 2016; Milad & Rauch, 2012) and indirectly in SAD (Dorfman, Farber, Fine, & Ernst, 2016). In particular, the dACC and insula (in SN) demonstrate aberrant connectivity with reward regions, as increased OFC-striatal connectivity is apparent in anorexia (Unicke et al., 2019), adolescents with OCD exhibit decreased striatal-OFC and striatal-insula connectivity (Bernstein et al., 2016) and decreased insula connectivity is evident in SAD (Liao et al., 2010). Indeed, both seed-based and network level results support CTSC abnormalities in relation to the underlying mechanism of performance monitoring.

Although not identical, brain-behavior associations between preschool performance monitoring and adolescent fc parallel supplemental enrichment analyses comparing adolescents with and without a diagnosis of OCD. Specifically, adolescents with OCD demonstrated aberrations in DMN, CO, Rew, Mot, and the DAN. The former four networks parallel the performance monitoring findings, further validating the indicator as associated with risk for OCD. Indeed, given this indicator was associated with onset of OCD in adolescence, this gives further credence to using this indicator as a purported risk marker that is apparent prior to disorder onset.

Findings should be interpreted within the confines of several limitations. First, children did not undergo baseline neuroimaging scans so we cannot determine whether disruptions to functional connectivity were evident when performance monitoring was assessed. While rs-fMRI data were collected from children on three intermediate timepoints, these data were collected with both a different scanner and less advanced acquisition sequences. Further, due to the younger age range of these intermediate timepoints, rs-fMRI data were comprised of higher levels of motion-related artifacts. Therefore, the present study utilized only rs-fMRI data acquired from the fourth wave which employed more advanced HCP-style acquisition and analysis. As such, we are unable to determine whether functional connectivity differences arose prior to or after behavioral differences, nor can we infer directionality. Related, performance monitoring was not assessed during adolescence, when functional connectivity was assessed. Although performance monitoring is purportedly stable by age 9 (Buzzell et al., 2017), cognitive functioning undergoes vast developmental progression during early childhood (Posner, Rothbart, Sheese, & Voelker, 2014). As such, this indirect association should be replicated using concurrent assessments at different stages throughout child development. Second, we did not include other assessments of performance monitoring (i.e., ERN) later in development and so we are unable to validate our earlier marker and fc patterns with other neural and behavioral indicators of performance monitoring. Related, the ERN is often assessed when alone with no outside feedback provided. The current study included an experimenter who provided error feedback. Interestingly, the ERN is larger when errors occur in the presence of another person (Hajack, Moser, Yeung, & Simons, 2005), indicating the experimenter may have actually increased performance monitoring. This also hints at the issue that although we are calling this observed indicator performance monitoring, it could be tapping into more broad response to critical feedback or concern over errors, and study findings may not generalize to other measures that tap into different facets of performance monitoring. Third, performance monitoring is not inherently maladaptive, indeed, it is an adaptive aspect of cognitive functioning to detect errors and behaviorally adjust. Yet, in an inverted U-shape, too much
or too little performance monitoring is associated with psychopathology and aberrant neural functioning (Riesel et al., 2019; Pasion & Barbosa, 2020). The current measure of performance monitoring was designed to identify elevated performance monitoring deemed to be maladaptive, not the full spectrum of monitoring. As such, low levels of the current indicator of performance monitoring confound low and adaptive performance monitoring; thus we were unable to examine relationships between low performance monitoring with fc. Fourth, this cohort was oversampled for preschool depression, limiting generalizability to community samples, however depression diagnosis was accounted for in analyses.

In light of these limitations, the current study provides important new information that an observable behavioral indicator of performance monitoring in preschoolers predicts functional connectivity patterns 12 years later. Indicators of elevated performance monitoring have repeatedly been implicated as an underlying mechanism of OCD, anxiety, and anorexia (Riesel et al., 2019; Levinson et al., 2019). Findings provide preliminary evidence that an early dimensional RDoC construct may impart mechanistic risk and demonstrates fcMRI brain–behavior relationships later in development.

Author contributions

Kirsten Gilbert: Conceptualization, Writing — Original draft; Writing — Review & editing; Muriah Wheelock: Formal analysis, Data curation, Writing — Original draft; Writing — Review & editing, Visualization, Sridhar Kandala: Formal analysis, Validation, Software, Data curation; Adam T. Eggebrecht: Writing — Review & editing, Supervision Joan L. Luby: Resources, Investigation, Writing — Review & editing, Supervision, Project administration, Funding acquisition; Deanna M. Barch: Resources, Investigation, Writing — Review & editing, Supervision, Funding acquisition.

Declaration of competing interest

Dr Gilbert reports grant funding from the NIMH and Institute of Clinical and Translational Sciences (ICTS) at Washington University School of Medicine. Dr Wheelock reports grant funding from NIMH and ICTS. Dr Eggebrecht reports grant funding from NIMH. Mr Kandala reports no financial interests or potential conflicts of interest. Dr Luby reports grant funding from the NIMH. Dr Barch reports grant funding from the NIMH. All authors report no other conflict of interest.

Acknowledgements

Funding from National Institute of Mental Health to K.G. (K23MH115074), MW (K99 EB029343, T32 MH100019), A.E. (K01 MH103594) J.L. and D.B. (R01 MH090786). An earlier version of this manuscript was presented by M.W. in a poster at the FLUX, 2019 conference. We also would like to thank Scott Marek, Ph.D. for comments on analysis.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2021.05.015.

References


