Age-differences in information flow in executive and sensorimotor brain networks during childhood and adolescence

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Abstract

Objective: Mental disorders often emerge during adolescence, and age-related differences in connection strengths of brain networks (static connectivity) have been identified. However, little is known about the directionality of information flow (directed connectivity) in this period of brain development.

Methods: We employed dynamic graphical models (DGM) to estimate directed functional connectivity from resting state functional magnetic resonance imaging data on 979 participants aged 6 to 17 years from the healthy brain network (HBN) sample. We tested for effects of age, sex, cognitive abilities and psychopathology on directionality.

Results: We show robust bi-directionality in information flow between visual-medial and visual-lateral nodes of the network, in line with prior studies in adult samples. Furthermore, we found that age in this developmental sample was associated with directionality of information flow in sensorimotor and executive control networks, yet we did not find associations with cognitive abilities or psychopathology.

Discussion: Our results revealed that directionality in information flow of large-scale brain networks is sensitive to age during adolescence, warranting further studies that may explore trajectories of development in more fine-grained network parcellations and in different populations.

Introduction

The brain undergoes tremendous changes throughout life, where childhood and adolescence is a particularly sensitive developmental period for brain maturation processes (Blakemore, 2012). A vital part of the brain's maturation happens in the functional networks that show pronounced reorganization in order to facilitate neural efficiency and integration of information, as indicated by connectome studies in healthy children and young individuals as well as in clinical populations in the same age range (Insel, 2010; Keshavan, Giedd, Lau, Lewis, & Paus, 2014; Kolskar et al., 2018; Rausch et al., 2016; Schweinsburg, Nagel, & Tapert, 2005). This supports that this time period is a sensitive phase, where there is large alterations in the functional interconnections between brain regions as a whole that link to when different mental disorders emerge (Insel, 2010).

The primary method to study functional brain interconnections so far has been to estimate static functional connectivity between brain regions, where research has shown that the functional connectome in healthy children and adolescents becomes more specialized (Li, Deng, He, Zhai, & Jia, 2019). Resting-state networks (RSNs) also become more coherent and stable during this time-period (Hoff, Van den Heuvel, Benders, Kersbergen, & De Vries, 2013), and evidence has indicated aberrant connectivity in individuals with pre-clinical psychiatric symptoms (Kaufmann et al., 2017), which is in line with the brain dysconnectivity hypothesis in mental disorders (Connolly et al., 2013; Di Martino et al., 2011; Hamm et al., 2014). Only recently has directed functional connectivity received interest as a field that could yield new knowledge about the connections between brain regions by estimating directionality in neural information flow. Riley et al. (2018) examined effective connectivity, the causal influence that one node exerts over another (Bielczyk et al., 2019; Friston, 2011), in a neurodevelopmental sample and observed that there are differences between sexes in relation to how memories are encoded in the hippocampus. In another neurodevelopmental study by Hwang, Velanova, and

Luna (2010) the authors observed that improvements in inhibitory control were linked to strengthening of top-down connectivity for regions implicated in cognitive control networks, while similar findings were found in relation to top-down processing for a language network (Bitan et al., 2006). Further, it has been shown that there are differences in directionality in adolescent boys with externalizing behavior disorders compared to a control group (Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009) and for children with Attention Deficit Hyperactivity Disorder (ADHD) (Zhao, Zheng, Yang, & Tian, 2017). However, the literature on connection directionality is scarce, calling for validation of earlier findings and for new insights using novel approaches. In particular, we do not currently know if and how the direction flow in the communication between brain networks is implicated in mental traits and disorders, including cognitive abilities. Given that cognitive deficits are seen across mental disorders, connecting these behavioral and clinical characteristics is crucial for gaining a better understanding of how higher-order processing is characterized in children and adolescence. Such integrative understanding is also important given that no consensus has been reached when it comes to the disorder-specific connectivity alterations that characterize particular mental disorders and the known overlap of symptoms (Craddock & Owen, 2010; Jollans & Whelan, 2018) and the pleiotropy between disorders (Demontis et al., 2019; Grove et al., 2019; Hibar et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Talkowski et al., 2012).

Dynamic graphical models (DGM) is a Bayesian approach for examining directed functional connectivity using dynamic linear models (Schwab et al., 2018). As such, it implements a state space model that is linear and Gaussian in form. This includes statistically stationary properties as it uses a hidden Markov modelling approach, although it incorporates time varying coefficients and as a result can provide information about directionality in the form of a binary view of coupling between two brain regions for each connectivity direction.

Here, we used DGM and publicly available resting-state functional magnetic resonance imaging (rsfMRI) data from the Healthy Brain Network (HBN) project (Alexander et al., 2017) to study brain network information flow in children and adolescents and its associations with age, sex, cognitive abilities and psychopathology. We hypothesized that information flow would be strengthened with increasing age (Bitan et al., 2006; Hwang et al., 2010), that there would be differences between females and males in the maturation of brain networks (Riley et al., 2018), as well as alterations associated with information flow for control networks as these nodes are central to a range of disorders (Cortese, Kelly, & Di Martino, 2012; Eisenberg & Berman, 2010; Francx et al., 2015; Geiger et al., 2016; Li et al., 2017; Zhao, Swati, Metmer, Sang, & Lu, 2019).

Methods

Study samples

The HBN is a project organized by the Child Mind Institute (Alexander et al., 2017) and is a resource targeting novel insight into the critical time period when psychiatric and mental disorders emerge. The HBN consortium aims to include 10,000 individuals in the age range of 5-21 years from the New York area, where participants are included by use of announcements that are distributed to community members, educators, local care providers with the addition of sending information via email lists and events to parents, encouraging participation of children with clinical concerns to this study (Alexander et al., 2017). Data on these individuals include a package consisting of MRI scanning, genetics, electroencephalography (EEG), eye-tracking, as well as biological testing and a neuropsychological battery consisting of cognitive, lifestyle indices, behavioral and psychiatric domains in addition to actigraphy and voice and video interviews (Alexander et al., 2017). Exclusion criteria include serious neurological disorders, neurodegenerative disorders, acute encephalopathy, hearing or visual impairment, lifetime

substance abuse that necessitated chemical replacement therapy/acute intoxication at time of study, recent diagnosis of a severe mental disorder or manic/psychotic episode within the last 6 months without ongoing treatment, in addition to the onset of suicidality/homicidality where there is no current, ongoing treatment (Alexander et al., 2017). All participants over the age of 18 years provided signed informed consent, while legal guardians signed informed consent for participants under the age of 18, in addition to participants giving a written assent (Alexander et al., 2017). The Chesapeake Institutional Review Board approved the study (https://www.chesapeakeirb.com/).

MRI acquisition and preprocessing

MR data was collected by the study team of HBN, where we included MRI data from the following sites; Rutgers University Brain Imaging Center (RUBIC), Citigroup Biomedical Imaging Center (CBIC) and a mobile scanner located in Staten Island. MRI data was collected using one scanner at each site, giving a total of 3 scanners comprising our sample. Rutgers applied a Siemens 3T Trim Tio scanner, while CBIC utilized a Siemens 3T Prisma, and both sites applied the same MRI parameters, where resting- state blood-oxygen-level-dependent (BOLD) fMRI data was collected for each subject using a T2*-weighted BOLD echo-planar imaging (EPI) sequence with a repetition time (TR) of 800ms, echo time (TE) of 30ms, 60 number of slices with the rsfMRI session consisting of 375 volumes and with voxel size= 2.4×2.4×2.4 mm. The third mobile scanner located in Staten Island used a 1.5T Siemens Avanto system equipped with 45 mT/m gradients (Alexander et al., 2017), where the following parameters were implemented; TR= 1.45s, TE=40ms, number of volumes=420, slices= 54, resolution in mm= 2.5×2.5×2.5 mm (for more information about the MRI parameters, see http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/MRI%20Protocol.html).

Raw imaging data was downloaded from the HBN database (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/sharing_neuro.html#Direct%20Down), and analyzed on the secure data storage and computing facilities (TSD, https://www.uio.no/tjenester/it/forskning/sensitiv) at University of Oslo. Image processing tools, based largely on Smith et al. (2013), were used for the functional data while T1-weighted data, which was applied as an intermediate in the registration, was processed using FreeSurfer 5.3 (http://freesurfer.net), including removal of non-brain tissue.

As part of the HBN MRI protocol, multiple T1weighted sequences were acquired for each subject, and we used MRIQC for automated quality assessment (N=2427, CUNY scanning site was included for the MRIQC stage, yet this site was dropped at a later stage due the low sample size, N=22). From this, T1 weighted images with the best image quality metrics were used as input for registration, while structural scans that were flagged (N=160) were manually checked and excluded (N=117) if they were of low quality. In addition, 22 subjects had errors when they were run through FreeSurfer and after manually inspecting these datasets, these were also omitted due to motion artefacts and/or having MRI findings disrupting the segmentation pipeline in FreeSurfer. We also made a global mask of the T1 data where we manually checked subjects that had low coverage, excluding another 95 subjects leaving a total of 2171 datasets that had a usable T1w sequence for registration.

Two of the MRI sites, RUBIC and CBIC, had two resting-state scans acquired as part of the same MRI session. As such, we merged these scans together to leverage all available resting-state data and to optimize the data for the DGM method that benefits from more time points. Furthermore, the first four volumes for the fMRI dataset were discarded. We preprocessed fMRI data using FSL 6.0.3 (http://fsl.fmrib.ox.ac.uk), including motion correction and brain extraction. FSL's FEAT (Woolrich, Ripley, Brady, & Smith, 2001) included spatial smoothing with a Gaussian kernel FWHM of 6 mm and a high-pass temporal filter equivalent

188 to 100s. FMRIB's Nonlinear Image Registration tool (FNIRT) was used to register fMRI
189 volumes to standard space (MNI-152) with the T1w volumes as intermediates.

190 We also implemented a cleaning step for fMRI data, where we made a global mask for
191 the fMRI datasets (which indicated data coverage across participants), and from this we
192 excluded 45 of 1813 datasets with poor coverage. To reduce the influence of noise in the data,
193 we removed artefacts by use of ICA-AROMA, which is a classifier that identifies and removes
194 motion specific noise in fMRI data (Pruim, Mennes, Buitelaar, & Beckmann, 2015; Pruim,
195 Mennes, van Rooij, et al., 2015). In addition, FSL's FIX (FMRIB's ICA-based X-noisiefier,
196 (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014)) was used with the recommended
197 threshold of 20 to remove remaining motion confounds and other artefacts in the data. Next,
198 data was temporally demeaned and variance normalized (Beckmann & Smith, 2004), and the
199 quality controlled fMRI dataset (N=1678) was submitted to a group ICA, utilizing FSL's
200 Multivariate Exploratory Linear Optimized Decomposition into Independent Components
201 (MELODIC) tool (Beckmann & Smith, 2004; Hyvärinen, 1999), where 30 components were
202 extracted from the ICA and used for further analysis. Dual regression was applied to estimate
203 individual spatial maps and corresponding time series from the group ICA (Beckmann & Smith,
204 2004; Filippini et al., 2009), which were used as input for the DGM analysis.
205
206 Mental and cognitive measures
207 From the HBN data release, N=1768 participants were included after quality assessment. Out
208 of these, information on age was missing for N=332, age at MR for N=3, sex for N=46, and
209 cognitive/clinical information for 740. The participants were 5-22 years (mean: 11.4, years, sd:
210 3.55 years) and 36.3% were females. This data was used to study group-level patterns of dFC
211 (average connectivity matrix). For the subsequent associations with age, sex, cognition and
212 mental health, we had to restrict the analysis to a subset based on data availability. Thus, the

final sample for the association analyses comprised N=979 individuals aged 6-17 years (mean: 10.6, years, sd: 2.68 years, 37.6% females). A large proportion of this sample had a diagnosis (N=865), while N=93 did not have a diagnosis, N=20 dropped out before a diagnosis could be determined, and N=1 was missing information for clinical consensus diagnosis data and had as such not received a diagnosis. Broadly, the majority of patients included in our analysis had disorders in the following categories (where comorbidities are included): Neurodevelopmental disorders (N=1306), anxiety disorders (N=464), disruptive, impulsive control and conduct disorders (N=145), elimination disorders (N=94), and depressive disorders (N=92), see SI; SFig. 1-2 for further details.

We used the full-scale intelligence quotient (FSIQ) from the Wechsler Intelligence Scale for Children (WISC-V) taken for participants aged 6-17 years as a proxy for cognitive ability. This composite score includes the following domains; visual spatial, verbal comprehension, fluid reasoning, working memory, and processing speed (Wechsler, 2003). Mental health was measured on a continuum including both healthy subjects and patients as it is difficult to uncover robust findings for psychiatric diagnosis that constitutes heterogeneous disorders, showing a wide range in symptoms, severity, duration and prognosis, and as patients often have more than one diagnosis. Such heterogeneity is also reflected in the brain, making the search for biological markers a complex task. As such, for mental health, we performed a principal component analysis (PCA) on The Extended Strengths and Weaknesses Assessment of Normal Behavior (E-SWAN), which has been shown to be a valid psychometric assessment tool for investigating behavior underlying DSM disorders (Alexander, Salum, Swanson, & Milham, 2020). E-SWAN domains include depression, social anxiety, disruptive mood dysregulation disorder (DMDD), and panic disorder. We excluded 3 of the items relating to panic disorder from the questionnaire that had a high degree (>90%) of missing values, giving a total of 62 items for the PCA analysis. The remaining items had available data for 1993

participants with no missing values. We performed PCA using the "prcomp" function in R, where the first PC, often denoted as the p-factor or pF (Caspi et al., 2013), explained 44.0% of the variance (Figure 1). From the loadings from the PCA, this component was associated with items related to self-control and depression/anxiety (Figure 1). In accordance with other studies showing more than one factor being of importance (Alnaes et al., 2018; Mallard et al., 2019), we also included the second principal component referred to as pF_2 which was associated with items relating to mood dysregulation. This component explained 11.2% of the variance.

Figure 1: Principal component analysis performed on the ESWAN questionnaire taken as part of the HBN protocol. For visualization purpose, only the components included in our analysis are shown. We used the first two principal components as proxies of psychopathology, referred to as "pF" and "pF2".

Network analysis

We chose ten resting networks from the model order of 30 for inclusion in the dFC analysis. These networks were chosen based on spatial correlation and manually ensuring overlapping ICs with the ten RSNs reported by Smith et al. (2009). The ten networks comprised the default mode (DMN), cerebellar (Cer), visual occipital (VO), visual medial (VM), visual lateral (VL), right frontoparietal (FPR), left frontoparietal (FPL), sensorimotor (SM), auditory (Au), and executive control (Ex) network. These networks were also used in previous DGM studies (Lund et al., 2020; Schwab et al., 2018) and including the same nodes allowed us to compare results with prior findings and to integrate the current results obtained from a childhood and adolescent sample with previous adult studies. The included timeseries for each node were mean centered before estimating dFC from individual level RSN time series using the DGM package v1.7.2 in R (for details on the DGM method, see Schwab et al. (2018) or description in the methods section of Lund et al. (2020)).

Statistical analysis

We included all available rsfMRI scans for the group ICA, as a higher number of subjects is beneficial for yielding more robust ICs, while restricting the association analyses to the subset that had all covariates available. We performed the same analysis as previously reported in an adult sample (Lund et al., 2020), examining dFC on the edge- and node-level. Edge-level analysis deployed logistic regression for every connection of the directed network using

directed connectivity as the response variable and testing for associations with age, age-orthogonalized age squared (age², using the poly function in R), sex, cognitive abilities, mental health, tSNR, motion and scanning site (as data was acquired at multiple scanners). These covariates were included into one model (see SI; SFig.3, for additional analyses examining potential multicollinearity for covariates included in the model). P-values were Bonferroni corrected for a number of 90 analyses on the edge-level (alpha level of 0.05). In addition, we performed node-level analysis to examine which networks overall send and receive information to each other (Lund et al., 2020). We calculated the number of output connections or outgoing edges (referred to as out-degree) and the number of input connections or incoming edges (referred to as in-degree) for a given node. We performed linear regression using in-degree and out-degree as dependent variables and the same independent variables as used in the logistic regression on edge-level. P-values were Bonferroni corrected for a number of 10 analysis on the node-level (alpha level of 0.05).

Results

Figure 2 depicts the average directed functional connectivity matrix across all individuals. While many connections indicated bi-directionality in information flow, we found that most edges of the SM network were more often receivers than senders of information. For example, the DMN node sends information to the SM in 79.6% of cases whereas the DMN receiving from the SM was only present in 25.4% of cases. The edge most present across all individuals was SM receiving input from the Au (95.9%). However, this connection was also strongly expressed in the other direction (83.3%). It is also worth noting that we replicated the bi-directionality in dFC between the VM-VL networks that we previously found in adults (Lund et al., 2020), yet in this neurodevelopmental sample we did not observe that Cer and Au networks were mostly receivers, as found for adults (Lund et al., 2020; Schwab et al., 2018).

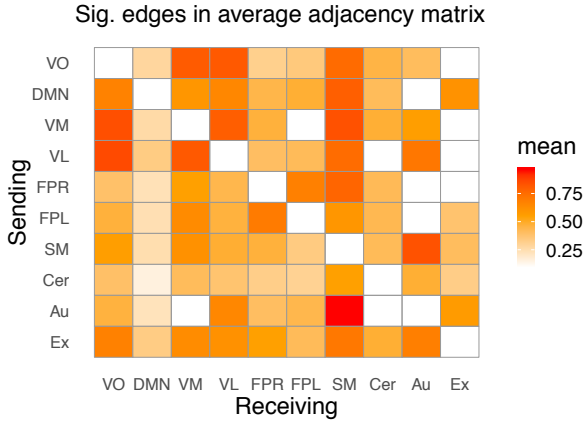

Figure 2: Average directed connectivity matrices across HBN subjects showing the significant proportions of edges (binomial test, 5% FDR threshold, hypothesized probability p0 = .52). The legend shows the 10 RSNs included in the analysis; VO, visual occipital; DMN, default mode; VM, visual medial; VL, visual lateral; FPR, frontoparietal right; FPL, frontoparietal left; SM, sensorimotor; Cer, cerebellum; Au, auditory; Ex, executive control network, where the y-axis indicates the sender node, and the x-axis refers to the same nodes but here they are receivers.

Age effect on directionality and in-degree

Edge-level analysis of dFC showed significant effects of age, in line with our hypothesis of age being associated with the functional networks' maturation processes occurring in childhood and adolescence (Figure 3; SI Tables 1-5 show z-scores and p- values and SFig.3-4 show effects of scanner). We observed a positive association with age and dFC from the VO, DMN and SM to the Ex network. Also, the FPR and Ex send more information with higher age to the SM node.

On the node-level, we assessed similar phenotypic associations for the out-degree and in-degree of the networks. Confirming edge-level results, we found that age was significantly associated with the in-degree of SM and Ex (fig.4b), indicating that the SM and Ex nodes overall receive more information with increasing age. Additionally, there was significant confound effects of scanning site (SFig.3-4) and tSNR on edge-level and network in- and out-

317 degree, and of motion for network in-degree and edge-level.

318 Based on prior studies, we expected that mental health and cognitive abilities would be
319 associated with information flow for control networks, however, this was not observed. We
320 also expected sex-related differences in the maturation of brain networks, but this was not
321 found.

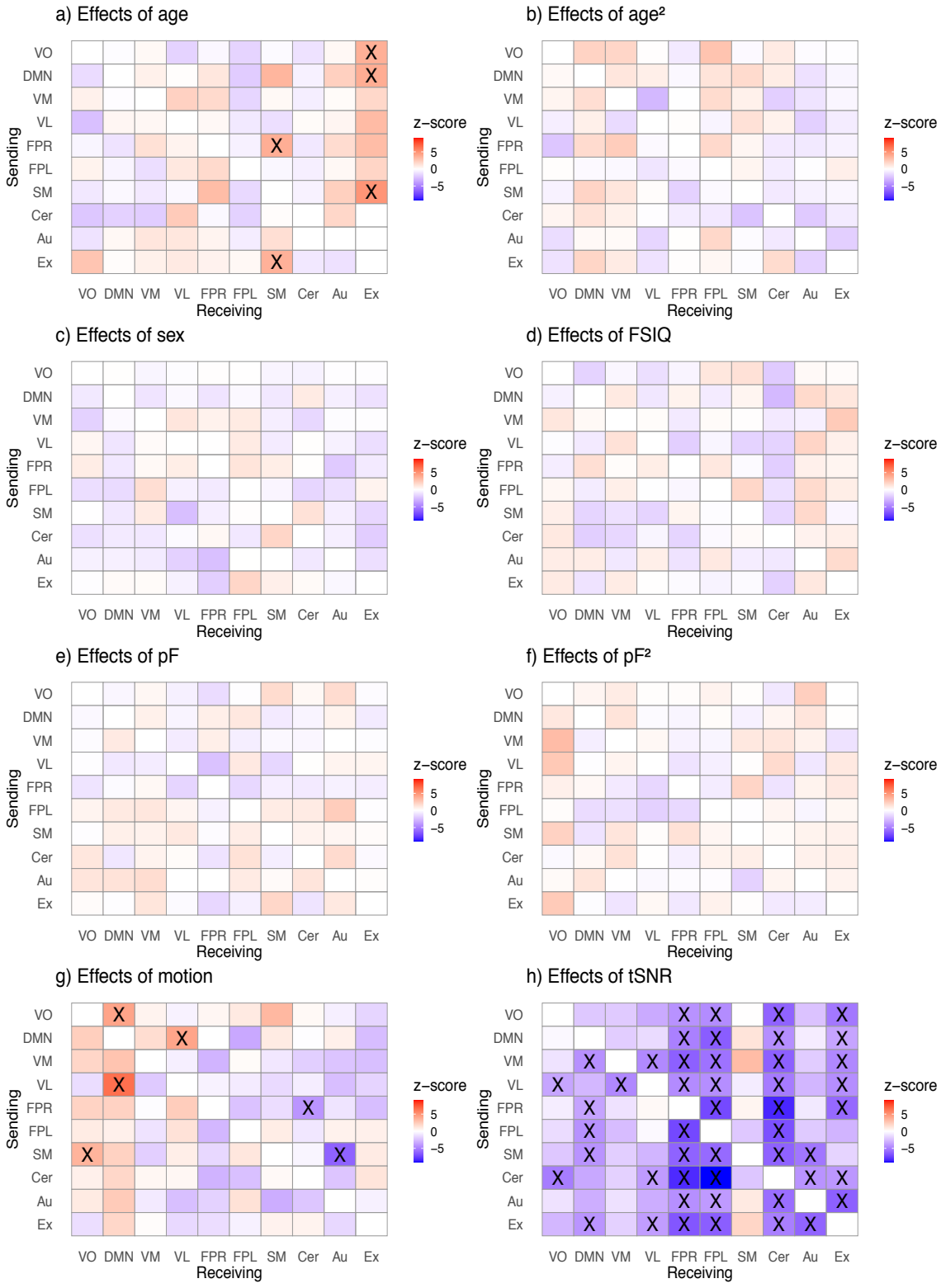

Figure 3: Matrices showing the effects of age (a), age2 (b), sex (c), intellectual abilities (FSIQ) (d), mental health (pF and pF²) (e,f), motion (g), and tSNR (h) on directed connectivity. The analysis was performed in HBN data that had no missing values (N = 979, 6–17 years, df =

968). Significant edges following Bonferroni correction are marked as X. The legend shows the 10 RSNs included in the analysis; VO, visual occipital; DMN, default mode; VM, visual medial; VL, visual lateral; FPR, frontoparietal right; FPL, frontoparietal left; SM, sensorimotor; Cer, cerebellum; Au, auditory; Ex, executive control network. The y-axis indicates the sender node, while the x-axis refers to the receiving node. The colors reflect the z-value for the corresponding effects where red indicates a positive association and blue a negative association.

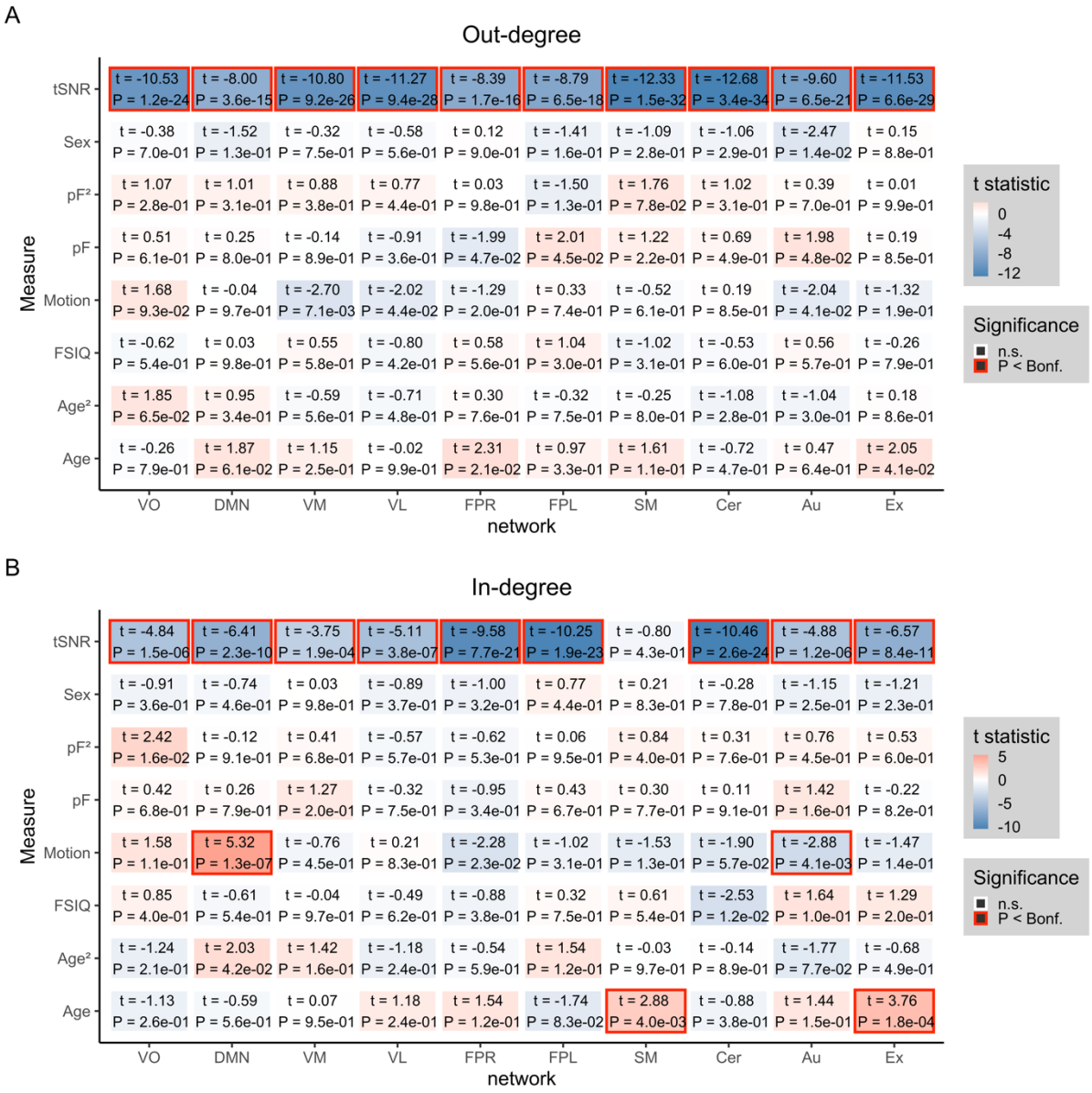

Figure 4: Associations on the node level (N=979, 6-17 years, df= 968). a) Out-degree matrix with corresponding effects of covariates age, age^2, sex, cognition (FSIQ), mental health (pF and pF^2), tSNR, and motion in HBN data. B) In-degree matrix with corresponding effects for the same covariates as in panel a). The colors reflect the t-value for the corresponding effect where numbers inside the boxes indicate t-statistic and p-value, and significant effects are marked with a red border following Bonferroni correction (p < .0.05).

Discussion

Our analysis revealed dFC patterns of the visual networks, specifically a reciprocal information flow between the VM and VL networks in a sample of children and adolescence. This seems to be in alignment with findings in adult samples (Lund et al., 2020), However, we did not find that the cerebellum or auditory networks are mostly receivers of information as observed in adults (Lund et al., 2020; Schwab et al., 2018). In contrast, our results implicated the SM network as the network that was receiving most information from other networks.

We observed significant associations between age and directed connectivity both at edge and node-level. Specifically, at the edge-level, with increasing age the VO, DMN and SM had higher information flow to the Ex network, and the FPR and Ex send more information to the SM node. Likewise, on the node-level, the SM and Ex node received more information with increasing age. These results support sensitivity of dFC to age within the investigated age range of this developmental sample, especially for SM and Ex.

Of note, studies on functional connectivity have implied the SM and Ex network in abnormal brain development (Berman et al., 2016; Cortese et al., 2012; Kaufmann et al., 2017; Zhang et al., 2020) and adults with psychiatric disorders (Birur, Kraguljac, Shelton, & Lahti, 2017; Cortese et al., 2012; Kaufmann et al., 2015; Lee, Doucet, Leibu, & Frangou, 2018; Soros et al., 2019).

Moreover, it has been reported that the cerebellar network is mostly a receiver of information from other attention and memory related regions in children with ADHD when estimating directed connectivity in rsfMRI using a seed-based approach (Zhao et al., 2017), although we did not find this in our sample.

For cognition, FSIQ was not significantly associated with information flow. Here we used a normed cognitive composite test score as a proxy for cognition. However, this may not be an optimal approach as test norms could have limitations when it comes to representativeness and number of subjects included in the normative sample making it less sensitive for clinical populations and for the lowest scoring percentile.

Symptoms pertaining to inattention and cognitive control in participants from 8-17 years old with ADHD has been linked to modifications in effective connectivity between control networks in task-fMRI (Cai, Griffiths, Korgaonkar, Williams, & Menon, 2019). In addition, cognitive flexibility in healthy adults has been associated with strong within-system connectivity in higher order systems and from these nodes to primary-sensory motor nodes (Chen et al., 2019). Here we estimated information flow between networks with different functions rather than within-system connectivity (with the exception of the visual networks), which may elucidate the lack of associations with cognition.

We did not observe significant associations between dFC and mental health for any of the networks. Our dimensional approach of estimating PCA on symptom data represents both healthy subjects and individuals with a psychiatric disorder on symptom continuum rather than as cases and control. Such a dimensional approach may better capture intermediate phenotypes which map to brain biology and the neuronal mechanisms underlying the symptoms, compared to diagnostic categories (Hengartner & Lehmann, 2017; Krueger & Bezdjian, 2009). While the lack of significant associations in our study indicates that

between-network dFC in large-scale brain networks is not sensitive to mental health in this sample, future research will need to investigate dFC in distinct subnetworks.

Finally, we expected to find differences between sexes in relation to directed connectivity as this has been found previously in adolescence (Riley et al., 2018) using task-fMRI, and when examining dFC in adults (Lund et al., 2020). However, we did not find any significant sex differences in dFC on edge- or node-level in rsfMRI. This may partly relate to sample characteristics such as the uneven sex distribution and the inclusion of patients in our sample.

Limitations

As with any MRI study, participant motion during scanning may confound the results, especially as it is known that both young individuals and those with a psychiatric diagnosis on average move more (Satterthwaite et al., 2012). We therefore implemented a stringent correction pipeline, where we implemented several steps of ICA and machine learning based cleaning (FIX and AROMA), and also included the mean relative motion measure from FSL as a covariate in our analysis step. Another relevant confound effect that could potentially bias our results and the comparison to previous work is variability in the ICA decompositions. We here performed ICA in the study sample sample and selected components based on similarity to (Smith et al., 2009). While this approach yielded overall good comparison to previous work, subtle differences between decompositions may retain and might impact the derived dFC patterns. As our results call for follow-up analysis in more fine-grained networks, different ways to parcellate the brain could be tested in such a framework.

The majority of the individuals in the sample were patients. Medication may have had an effect on our results, as participants were asked to discontinue stimulant medication but were

still enrolled if they choose not to discontinue due to personal reasons or if recommended by their physician.

On a methodological note, DGM reflects instantaneous relationships and does not only look at lagged relationships, however sensitivity of DGM drops depending on the total offset between a node pair and can as such influence the estimation of these interactions (Schwab et al., 2018). Further, DGM estimates binary connections, which may have reduced the sensitivity of the association analyses.

Lastly, whether these differences in findings are of methodological origin, such as differences in preprocessing pipelines or network definitions, or can be explained by differences in dynamic connectivity between children and adults remains to be further investigated.

Conclusions

To conclude, using a sample of children and adolescents, we showed that the sensorimotor network receives information from other large-scale brain networks and found that direction of the information flow was age dependent in the sensorimotor and executive networks. These findings contribute to the existing knowledge in the brain development field, and warrant further studies for replication in healthy samples as well as other clinical populations.

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Data and code availability

The data incorporated in this work were gathered from the open access Healthy Brain Network resource. Software needed to estimate directed connectivity is available at https://github.com/schw4b/DGM.

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