Interaction of the Salience Network, Ventral Attention Network, Dorsal Attention Network and Default Mode Network in Neonates and Early Development of the Bottom-up Attention System.

Valeria Onofrj (valeria.onofrj@policlinicogemelli.it)
University Hospital Agostino Gemelli: Fondazione Policlinico Universitario Agostino Gemelli IRCCS
https://orcid.org/0000-0003-1170-7282

Antonio Maria Chiarelli
Gabriele d'Annunzio University of Chieti and Pescara: Universita degli Studi Gabriele d'Annunzio Chieti Pescara

Richard Wise
Gabriele d'Annunzio University of Chieti and Pescara: Universita degli Studi Gabriele d'Annunzio Chieti Pescara

Cesare Colosimo
University Hospital Agostino Gemelli: Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Massimo Caulo
Gabriele d'Annunzio University of Chieti and Pescara: Universita degli Studi Gabriele d'Annunzio Chieti Pescara

Research Article

Keywords: Salience Network, Ventral Attention Network, Dorsal Attention Network, Default Mode Network, data-driven analysis, mediation analysis, bottom-up salience detection

Posted Date: September 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-465657/v1

Version of Record: A version of this preprint was published at Brain Structure and Function on March 14th, 2022. See the published version at https://doi.org/10.1007/s00429-022-02477-y.

Abstract

The Salience Network (SN), Ventral Attention Network (VAN), Dorsal Attention Network (DAN) and Default Mode Network (DMN) have shown significant interactions and overlapping functions in bottom-up and top-down mechanisms of attention. In the present study we tested if the SN, VAN, DAN and DMN connectivity can infer the gestational age (GA) at birth in a study group of 88 healthy neonates with GA at birth ranging from 28 to 40 weeks. We also ascertained whether the connectivity within each of the SN, VAN, DAN and DMN is able to infer the average functional connectivity of the others. The ability to infer GA at birth or another network's connectivity was evaluated using a multi-variate data-driven framework. A mediation analysis was performed in order to estimate the transmittance of change of a network's functional connectivity (FC) over another mediated by the GA.

The VAN, DAN and the DMN infer the GA at birth ($p<0.05$). The SN, DMN and VAN were able to infer the average connectivity over the other networks ($p<0.05$). Mediation analysis between VAN's and DAN's inference on GA found reciprocal transmittance of change of VAN's and DAN's connectivity ($p<0.05$).

Our findings suggest that the VAN has a prominent role in the bottom-up salience detection in early infancy and that the role of the VAN and the SN may overlap in the bottom-up control of attention.

1. Introduction

In order to survive the changes and challenges of the external world we need the ability to focus on the multiple sources of stimuli that constantly compete for our attention, the so called "saliency detection". Saliency detection is a complex mechanism that requires a bottom-up mechanism for filtering stimuli standing out from a stream of sensory inputs and a higher order mechanism for the automatic attraction and consequent maintenance of attention on a specific task (Parr and Friston 2019). The Salience Network (SN) plays a dominant role in the detection of salient stimuli across multiple modalities (Crottaz-Herbette and Menon 2006). The role of reality filter is specifically attributed to the insula, which together with the anterior cingulate cortex, constitutes the main anatomical structures to which the SN is anchored (Menon and Uddin 2010). Saliency detection is also involved in the dynamic interaction of sensory and cognitive influences that control attention(Menon and Uddin 2010). Attention is controlled by two partially segregated networks: the ventral attention network (VAN) and dorsal attention network (DAN), forming a twofold attentional control system (V. S, JJ, and GR 2014; S. D et al. 2007). The VAN includes the temporoparietal junction (TPJ) and ventral frontal cortex (VFC), is dominant in the right hemisphere and is generally activated when an unexpected event occurs and breaks one's attention from the current task (bottom-up processing). The DAN includes the intraparietal sulcus (IPS) and the frontal eye fields (FEF) of each hemisphere and shows sustained activation when focusing attention on an object and is thought to be responsible for goal-directed, top-down processing of attention (Corbetta and Shulman 2002). The complex interaction of bottom-up and top-down attention mechanism also requires the ability to disengage from the constant stream of our self-referential thoughts (the so called "mind wondering"), a cognitive process attributed to the DMN (Raichle 2015; RL, JR, and DL 2008). This postulate is supported

by the evidence that performance of a goal-directed, non-self-referential task is accompanied by a decrease in activity in the DMN and a corresponding increase in activity in the DAN (JS et al. 2011; Esposito et al. 2018).

A number of fMRI studies have demonstrated that infants and even preterm newborns possess immature forms of many of the networks described in the adult (Doria et al. 2010; CD et al. 2010; H et al. 2015; Stoecklein et al. 2020). These studies show that higher order networks may be present, even if in a fragmented, immature form, even before term, as opposed to the previous concept by which the networks develop in parallel with the cognitive competences associated with stimulus-dependent thought.

Recent studies adopting machine learning methods, have shown that the functional connectivity data (expressed by different metrics) and volume data are able to predict prematurity both in cohorts of newborns (Smyser et al. 2016; G et al. 2016; Chiarelli et al. 2021) and adults (Shang et al. 2019) and to classify age in infants aged between 6 and 12 months (Pruett et al. 2015).These studies support the view that a functional architecture of the brain exists before birth and constantly evolves, especially during the first year of life. Changes in functional connectivity of prematurity also manifest in adults, which supports the hypothesis that neurocognitive disorders associated with preterm birth might represent a disease of brain connectivity (J et al. 2011).

Most studies based on the functional connectivity of newborns and infants have been based on a global analysis of brain networks. Few studies, however, have so far attempted to focus on the functional connectivity of high-order networks, whose structure and function is assumed to be immature in early life. The present study seeks to analyze the maturation of functional connectivity of the networks involved in the complex interaction of bottom-up and top-down attention systems and how they influence the functional connectivity of each other. We based our assumption on the evidence that the development of the insula begins early in the fetal period. This leads us to hypothesize that the salience system starts developing very early, probably interacting with the immature forms of the other networks that combine in the complex mechanism of attention.

First we explored the association with GA at birth and the resting-state Functional Connectivity (rs-FC) extracted from the SN, the VAN, the DAN and the DMN. Consequently, we examined the ability of each network to infer the mean FC of each other. Given the observation that the SN and the VAN have a different, but complementary activity of salience detection (Farrant and Uddin, 2015), we hypothesize that the SN and the VAN influence each other. Both the SN and the VAN may influence the DMN by decreasing its activity and functional connections. Finally, we employed mediation analysis in order to estimate if the influence of the FC of a network over GA could be mediated by the FC of each other network.

Our study was based on the same data-set of the recent study from Chiarelli et al. (Chiarelli et al. 2021) and adopted the same Machine Learning multi-variate data-driven framework which allows to consider all the connections within the predicting network at once without any a-priori assumptions. However, we focused on pre-selected higher order networks rather than on exploring the effect on prematurity of different functional connectivity metrics extracted from a set of regions of interest (ROIs) covering the

whole brain (Shi et al. 2011). We also further explored the ability of each network to infer the connectivity of each other.

2. Materials And Methods

2.1 Participants

The present study included a total of 88 healthy neonates with GA at birth from 28 weeks to 40 weeks (mean= 33 weeks, SD= 3.7 weeks). 43/88 patients were female and 15/88 were born at term (>37 weeks of GA at birth)(Table 1). Informed consent was obtained from the parents of all participants, and the experimental protocols were approved by the Institutional Review Committee. The Neonates underwent standard clinical MRI examination within the 40^{th} week of post menstrual age (PMA, mean=40.4; SD=0.27).

Neonates born before 37 weeks of GA, were selected based on the following exclusion criteria:

1. Chromosomal abnormality or suspected or proven congenital infection (e.g., HIV, sepsis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus).

2. Neurological abnormalities, including grade III–IV intraventricular hemorrhage, cystic periventricular leukomalacia, moderate–severe cerebellar hemorrhage or lesions in the deep or cortical gray matter.

3. Absent functional MRI.

The inclusion of premature neonates in the study aims at testing if the FC of the networks depends on the degree of maturation that the brain reaches before birth.

Neonates born within or after 37 weeks of GA, were selected from a group of consecutive neonates without asphyxia. The neonates did not present signal abnormalities at standard MR sequences and had normal neurologic status at a 12-month clinical follow-up.

Table 1

Demographic and clinical information.

All Newborns (N=88)			GA at Birth (Weeks)		
GA at Birth (Weeks) - Mean (SD)	33 (3.75)	**Association with GA at Birth**	**25-32 (N=46)**	**33-36 (N=25)**	**37-40 (N=17)**
PMA at Scan (Weeks) - Mean (SD)	40 (0)	-	40 (0)	40 (0)	40 (0)
Female - n (%)	43 (49)	t= 0.34; p= n.s.	24 (52)	12 (48)	7 (41)
Multiple Gestations - n (%)	37 (42)	t= 2.74; p< 0.01	22 (48)	15 (60)	0 (0)
Birth Weight at Birth (g) - Mean (SD)	1821 (693)	r= 0.88; p< 10^{-3}	1460 (328)	1938 (482)	3210 (423)
APGAR Score at Birth - Mean (SD)	6.4 (2.0)	r= 0.14; p= n.s.	6.3 (2.1)	7.4 (1.4)	5.3 (2.3)
Number of fMRI Volume Deemed as Outliers	7 (5)	r=0.04; p= n.s.	7 (5)	6 (4)	7 (5)

2.2 Data acquisition

MR imaging was performed with a 3 T whole-body system (Achieva 3.0 T X-Series) from Philips Healthcare (Best, Netherlands) using an 8-channel head-only receiver coil. In accordance with several previous fMRI studies in neonates (G et al. 2016; Stoecklein et al. 2020), participants were fed and then sedated with 0.05 mg oral Midazolam per kilogram of body weight immediately prior to clinical scans to minimize motion artefacts. Neonates were laid in the scanner in a supine position and swaddled in blankets. Molded foam was placed around the body to minimize head movement. Hearing protection was used through commercially available neonatal earmuffs (MiniMuffs; Natus Medical, San Carlos, California) and adapted ear-canal plugs. Heart rate and oxygen saturation were monitored during the MR imaging session by an intensive care neonatologist. Structural images used in this study were collected using the T1-weighted Turbo Field Echo (TFE) sagittal sequence (Flip Angle: 8°; TR: 9 ms; TE: 4.2 ms; voxel size: 1×1×1 mm3; FOV: 200×200×150 mm3) with a whole-body SAR below 0.2 W/Kg. At the end of standard clinical MRI sequences, whole-brain functional images were additionally acquired using a T2*-weighted, echo-planar imaging (EPI), FFE axial sequence (Flip Angle: 90°; TR: 1555 ms; TE: 30 ms; voxel size: 2.5×2.5×3mm3; FOV: 180×180×75 mm3; slice gap: 0 mm) with a whole-body SAR within 0.8 W/kg. The functional scan duration was 4 minutes and 15 seconds (255 seconds).

2.3 Preprocessing

The MR image pre-processing workflow is reported in Figure 1.

BOLD connectivity was evaluated among 90 subcortical and cortical ROIs defined by the University of North Carolina (UNC) Infant Atlas (Shi et al. 2011).

To facilitate registration with the UNC atlas, an intermediate in-house brain template, built by averaging the infants T1-weighted anatomical images (Avants et al. 2010, 2011) and by segmenting the brain of the average template by hand, was firstly registered to the atlas (Youskechevich et al. 2006). The T1 in house template was constructed by using the Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/) with default settings (BB et al. 2011; 2010). After warping each subject's anatomical image to the in-house template, inverse transformations into the in-house template and into each structural image were applied on the UNC Infant Atlas to successfully identify the ROIs in the original subject anatomical space.

EPI T2*-weighted BOLD images, acquired at rest, were pre-processed according to a standard pipeline (E 2010), using AFNI (RW 1996) and FSL (M et al. 2012). The pipeline included: i. slice time and motion correction using the 3dTshift and 3dvolreg functions; ii. marking of motion outliers with the fsl_motion_outliers tool using DVARS metric and default setting for the definition of outliers (M et al. 2012; Pruett et al. 2015) iii. 4D image scaling using fslmaths iv. linear and quadratic temporal detrending using 3dDetrer (Churchill et al. 2012). The motion parameters (3 translations, 3 rotations and motion outliers) were finally regressed out (without scrubbing) from the raw BOLD time series, employing the tool 3dREMLfit (Bright, Tench, and Murphy 2017). Finally, the pre-processed BOLD images were co-registered into anatomical images and inverse transformations were applied to anatomical images to extract the average BOLD signals (expressed as relative signal change with time) from each ROI identified in the native BOLD spaces. Of note, all registrations were performed using the diffeomorphic registration method and the mutual information metric from ANTs (BB et al. 2011; 2010). Registered images were visually inspected by an expert neuroradiologist.

Resting state functional connectivity (rsFC) matrices were built by evaluating pairwise associations of BOLD signals in the 90 ROIs considered also accounting for a global signal contribution. In particular, each normalized (z-scored) ROI's BOLD timecourse was regressed on each other normalized ROI's BOLD timecourse using the normalized average (among the 90 ROIs) BOLD signal as an additional independent variable within a general linear model (GLM) framework (M. K and MD 2017). In order to evaluate undirected connections for further analysis, the average between the lower and the upper diagonal portions of the connectivity matrices was computed.

2.4 ROIs selection within the Networks of Interest

We selected the ROIs for a given network based on previous research studies and SN-DMN-VAN-DAN were extracted from the compete rsFC matrix. For the SN we selected the insula, anterior cingulate gyrus, amygdala and thalamus, both left and right for each region (V 2011; Menon and Uddin 2010). For the DMN we selected the medial orbital cortex (as medial prefrontal cortex), the posterior cingulate gyrus, the pre-cuneus and the angular gyrus, both left and right for each region (Buckner and Di Nicola 2019). For

the VAN we selected the medial frontal gyrus, inferior frontal gyrus, inferior parietal lobule, and superior temporal gyrus bilaterally. We selected these regions available on the neonatal brain atlas in use, in order to include the ventral frontal cortex (VFC) and the temporo-parietal junction (TPJ), which are both recognized as nodes of the VAN (Corbetta and Shulman 2002; V. S, JJ, and GR 2014). For the DAN we selected the supplementary motor area and the superior parietal gyrus bilaterally. We selected these regions available on the neonatal brain atlas in use, in order to include the frontal eye filed (FEF) within the SMA and the intraparietal sulcus (IPS), which are both recognized as nodes of the DAN (Corbetta and Shulman 2002; V. S, JJ, and GR 2014).

2.5 Statistics

2.5.1 Inference of Gestational Age (GA) at Birth

A multivariate analysis framework was implemented to regress GA at birth from rsFC within different networks (Figure 2).

The number of independent connections were 28 for SN, DMN and VAN and 6 for DAN. To account for collinearity among ROI connections (“Two-Way Analysis of High-Dimensional Collinear Data | Proceedings of the 2009th European Conference on Machine Learning and Knowledge Discovery in Databases - Volume Part I” n.d.), a partial least square (PLS) regression was used (Wold et al. 2006), which reduces the predictors to a smaller set of uncorrelated components maximally associated with the dependent feature/s (Abdi, Williams, and Valentin 2013) . Of note, the learning process (fitting) of the PLS algorithm provides regression loadings that can be used to retrieve the weights (β-weights) of the original independent variables. In order to optimize the hyperparameter of the PLS (number of uncorrelated components) and to concurrently evaluate the out-of-training-sample performance of the algorithm (generalization)(“Pattern Recognition and Machine Learning | Christopher Bishop | Springer” n.d.), a 10-fold nested cross validation (nCV) was employed(Filzmoser, Liebmann, and Varmuza 2009). During the 10-fold nCV, the number of components allowed during the hyperparameter optimization were constrained between a minimum of 1 and a maximum of 6. The expected β-weights of the PLS were finally computed by running a single analysis on the complete dataset using the rounded average number of components (i.e. the optimal number) delivered by the inner loops of the 10-fold nCV analysis. β-weights were transformed into z scores by dividing them by their expected standard deviation, which was computed relying on repeating the analysis on random shuffled outputs 10^6 times. As a control for possible effects of motion on the functional connectivity and activity results, the multivariate nCV regression was also performed on the variance of motion signals.

2.5.3 Inference of mean connectivity

The same multivariate analysis presented in the previous paragraph was implemented to test if each network could infer the average connectivity of the other three networks.

2.5.4 Mediation analysis of VAN on DMN

In the last set of statistical analysis we conducted a mediation analysis that was performed in order to determine whether the cross-validated inference on GA at birth using VAN acted as a mediator on the cross-validated inference on GA at Birth using DMN. The rationale for the mediation analysis was to examine if the development of the VAN, assumed from the evidence of cross-validate inference on GA, can mediate the development of the DMN, assumed from the evidence of cross-validated inference on GA.

A second mediation analysis was performed in order to determine whether the cross-validated inference on GA at birth using VAN acted as a mediator on the cross-validated inference on GA at Birth using DAN. The rational was, again, to examine if the development of the VAN can mediate the development of the DAN.

A third mediation analysis was performed in order to determine whether the cross-validated inference on GA at birth using DAN acted as a mediator on the cross-validated inference on GA at Birth using VAN. This analysis was performed using the Sobel test (“Interactive Mediation Tests” n.d.).

3. Results

3.1 Data quality and motion artifacts

Thanks to sedation, a small average number of 7 volumes per subject (SD of 5 volumes) was deemed as outliers by the algorithm (refer to Table 1)(Ciric et al. 2017). The number of motion outliers and the variance of the 6 motion DVARS signals showed no significant correlation with GA at birth (all r’s<0.1, all p’s n.s.).

3.2 Inference of Gestational Age at Birth

Figure 3 reports the results of the multivariate framework in inferring GA at birth relying on connectivities within different networks.

The SN was not able to infer GA at birth using the multivariate framework implemented ($p>0.05$) .

The DMN was able to significantly infer GA at birth ($r=0.26$; $df=86$, $p=0.01$, 2 PLS components). By looking at the statistical relevance (z-score) of the β-weights, the strongest effects on the GA predictability was found for the connectivity of the right medial prefrontal cortex-right pre-cuneus, left medial

prefrontal cortex-right pre-cuneus, right posterior cingulate-right angular gyrus, right posterior cingulate-left angular gyrus, left posterior cingulate-right angular gyrus.

The VAN could infer GA at birth (r=0.29; df=86, $p=7\bullet10^{-2}$) with an optimal number of PLS components of 5. The strongest effects on the GA predictability, were negative effects (anti-correlation) found for the left medial frontal gyrus-inferior parietal lobule, right medial frontal gyrus-left inferior parietal lobule, right inferior frontal gyrus and left superior temporal gyrus.

The DAN could infer GA at birth (r=0.25; df=86, p=0.017) with an optimal number of PLS components of 2. The strongest effects on the GA predictability, were found for the left and right superior parietal lobules.

3.3 Prediction of mean connectivity

3.3.1 Salience Network

Results are displayed in Fig.4a.

The SN was found to significantly infer the average connectivity of the VAN (r=0.24; df=86, p= 0.026, 2 PLS components). The strongest effect on the predictability of the VAN's mean connectivity, as shown on the beta-weight matrix, was found for the left insula-right insula connectivity. A negative effect was found for the right insula-right thalamus connectivity.

The SN also inferred the average connectivity of the DAN (r=0.29; df=86, $p=6\bullet10^{-3}$, 6 PLS components). The strongest positive effect on the predictability of the DAN's mean connectivity, as shown on the beta-weight matrix, was found for the right anterior cingulum-right thalamus connectivity; the strongest negative effect was found for the left anterior cingulum-left thalamus connectivity).

All the regions of the SN did not predict the average connectivity of the DMN (p>0.05).

3.3.2 Default Mode Network

Results are displayed in Fig.4b.

The DMN was found to significantly infer the average connectivity of the SN (r=0.29; df=86, p: $p=7\bullet10^{-3}$, 6 PLS components). The strongest effects on the predictability of the SN's mean connectivity, as shown on the beta-weight matrix, were negative effects found in the left angular gyrus-right pre-cuneus and right angular gyrus-left pre-cuneus.

DMN connections did not correctly infer the average connectivity of the VAN (p>0.05).

The DMN was found to strongly infer the average connectivity of the DAN (r=0.48; $p<10^{-3}$, 4 PLS components). The strongest positive effects on the predictability of the DAN's mean connectivity were found for the left and right angular gyri. The strongest negative effects were found for the left posterior cingulate gyrus – left prefrontal cortex and in the right posterior cingulate gyrus – right pre-cuneus.

3.3.3 Ventral Attention Network

Results are displayed in Fig.5a.

The VAN was found to significantly infer the average connectivity of the SN (r= 0.34; df=86, $p=10^{-3}$, 1 PLS component). The strongest positive effects on the predictability of the SN's mean connectivity were found for the connectivity of the medial frontal gyrus with the inferior parietal lobule of the contralateral side, bilaterally.

The VAN was found to significantly infer the average connectivity of the DMN (r= 0.22; df=86, p= 0.044,2 PLS components). The strongest positive effect on the predictability of the DMN's mean connectivity was found for the connectivity of the right inferior frontal gyrus with the right inferior parietal lobule.

The VAN strongly inferred the average connectivity of the DAN (r=0.47; $p=4.8\bullet10^{-6}$, 1 PLS component). The strongest positive effect on the predictability of the DAN's mean connectivity was found for the connectivity of the left and right inferior parietal lobule. The strongest negative effect was found for the connectivity of the left inferior frontal gyrus and left inferior parietal lobule.

3.3.4 Dorsal Attention Network

Results are displayed in Fig.5b.

The DAN did not predict the average connectivity of the SN (p>0.05) of the DMN (p>0.05) and of the VAN (p>0.05).

3.4 Mediation Analysis

Figure 6 reports the outcome of the mediation analyses when the mediation delivered significant results.

The mediation analysis between VAN's and DAN's inference on GA found that VAN's connectivity significantly modify the transmittance of change of the DAN's connectivity assumed form evidence of cross-validated inference on GA (VAN mediates DAN: Sobel Test t=1.969, p=0.048).

The mediation analysis between DAN's and VAN's inference on GA found that DAN's connectivity significantly modify the transmittance of change of the VAN's connectivity assumed form evidence of cross-validated inference on GA (DAN mediates VAN: Sobel Test t=1.910. p=0.049).

4. Discussion

Salience detection is a fundamental component of attention(Parr and Friston 2019). Attention is a complex function that requires top-down sensitivity control and a bottom-up mechanism for filtering stimuli(Parr and Friston 2017). The top-down sensitivity control is a process that regulates the relative signal strengths of the different information channels that compete for access to working memory (HE and S 1997). The bottom-up mechanism for filtering stimuli is composed of a “reality filter” played by the SN, a large scale network of the heteromodal cortex involved in detecting and filtering salient stimuli and by a second network involved in the detection of unexpected task-relevant stimuli to trigger attentional shifts in stimulus-driven attention (Corbetta and Shulman 2002; V. S, JJ, and GR 2014): the VAN.

The SN contributes to a variety of brain functions including social behavior and self-awareness through the interaction of sensory, emotional and cognitive information(Menon and Uddin 2010; V 2011). A major function of the anterior insula (AI) node of the SN is the detection of behaviorally relevant stimuli (Crottaz-Herbette and Menon 2006; Eckert et al. 2009; Sridharan, Levitin, and Menon 2008; P and A 2010), while the anterior cingulate cortex (ACC) send strong motor output. The subcortical nodes of the SN provide preferential context-specific access to affective and reward cues(Lindquist et al. 2012).

The VAN is composed of the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC) and is thought to be lateralized to the right hemisphere of the brain (Corbetta and Shulman 2002; Corbetta, Patel, and Shulman 2008). However, several studies have observed bilateral TPJ activation in tasks tapping attentional reorienting and the processing of rare deviant stimuli(Downar et al. 2000; Geng and Mangun 2011; Serences et al. 2005; Vossel et al. 2009). The VAN and the DAN, a bilateral network comprising the intraparietal sulcus (IPS) and the frontal eye fields (FEF) of each hemisphere involved in top-down voluntary allocation of goal-driven attention(V. S, JJ, and GR 2014), form a twofold attentional control system.

The study of salience detection and attention requires to focus on the activity of the DMN, a large-scale brain network primarily composed of the medial prefrontal cortex, posterior cingulate cortex/precuneus and angular gyrus(Raichle 2015; RL, JR, and DL 2008), identified with the stream of self-referential thoughts, the so called “resting state” (JR et al. 2010; Raichle 2015). The mental state of stimulus-independent thoughts counteracts attention. This finding is supported by the evidence that the DMN is anticorrelated with the DAN(Fair et al. 2007). Moreover, in a previous study adopting causality stochastic methods of analysis, the SN has shown to play a crucial role switching between the DMN and the Central Executive Network (CEN) in a previous study adopting causality stochastic methods of analysis(N et al. 2014). The present study tries to focus on the bottom-up and top-down attention systems. Adding the CEN to the data would have largely complicated the interpretation of the results, especially considering the degree of immaturity of the CEN in neonates. Nevertheless, the study of connectivity between the CEN and attention networks shall be the focus of our future studies.

A number of fMRI studies have demonstrated that infants and even preterm newborns possess immature forms of many of the networks described in the adult (Doria et al. 2010; CD et al. 2010; Smyser et al.

2016; Stoecklein et al. 2020; H et al. 2015). These studies show that higher order networks may be present, even if in a fragmented, immature form, even before term, as opposed to the previous concept by which the networks develop in parallel with the cognitive competences associated with stimulus-dependent thought.

The rapid expansion in the use of machine learning techniques to analyze neuroimaging data has led to employ these methods to model functional connectivity in newborn brains. Ball et al.(G et al. 2016) have combined high dimensional independent component analysis (ICA) with multivariate machine learning techniques to test the hypothesis that preterm birth results in specific alterations to functional connectivity by term-equivalent age. Their study demonstrates that functional connectivity of the basal ganglia and higher-level frontal regions are significantly altered in in preterm infants by term-equivalent age.

Smyser et al.(Smyser et al. 2016) have applied a Support Vector Machine (SVM) – multivariate pattern analysis (MVPA) classification method to infants' resting state fMRI (rs-fMRI) data and developed a model to estimate an infant's GA at birth based upon rs-fMRI data collected at term equivalent PMA. The SVM identified widespread intra- and interhemispheric connections within and between the rs networks able to categorize term-born infants from preterm infants, thus enabling quantitative prediction of GA at birth in individual subjects. By adopting the same SVM method Pruett et al.(Pruett et al. 2015) were able to classify, above chance, 6 versus 12 months old infants on FC data.

Shang et al.(Shang et al. 2019) used multivariate machine learning methods to classify young adults born prematurely when compared to full-term on the basis of volumetric data and by measuring the amplitude of low frequency fluctuations (ALIFF) within a repeated and nested cross-validation design. The authors compared the structural and functional preterm features, validated them by assessing the clinical history and assessed their contribution to the prediction of IQ. This study shows that volumetric imaging related to subcortical brain damage present in infancy also appears in early adulthood and that these abnormalities are interconnected with a pattern of predominantly decreased AFF in adults born preterm. Additionally the ALFF appeared to be able to predict among other clinical features, performance IQ. Moreover, the prediction of general IQ was improved by the addition of the ALIFF decision score.

In a recent study by Chiarelli et al.(Chiarelli et al. 2021) the authors examined the effect of prematurity on measures of rs-FC, resting state functional connectivity nodal strength (rs-FCNS), fractional amplitude of low frequency fluctuations (fALFF) and regional volume in 90 ROIs covering the whole brain by performing region-based univariate analysis of each metric to explore the association with GA at birth and the spatial consistency across metrics. To this aim they implemented a Machine learning framework using partial least square regression (PLS). The study demonstrated that prematurity is associated with a complex pattern of bidirectional alterations of FC metrics and regional brain volume and, to a lesser extent, with modifications of fALFF.

We analyzed the same data-set of the recent study from Chiarelli et al.(Chiarelli et al. 2021) and adopted the same Machine Learning multi-variate data-driven framework using partial least square regression

(PLS), which allows to consider all the connections within the predicting network at once without any a-priori assumptions. However, the goal of our study was fairly different from that of Chiarelli et al.. First, we focused our attention on a group of specific networks known to be involved in the mechanisms of salience detection and attention. Second, we analyzed how the functional connectivity of each network influences each other network.

In the present study the SN connectivity was found unable to infer the GA at birth. It has long been observed that the insula is the first cortex to differentiate, beginning from 6 weeks after conception, providing the structural basis for its hub role even before term(Gao et al. 2011). Subregional segregation of the insula into an anterior insular cortex, mainly connected with the anterior cingular cortex, the frontal cortex and the posterior insular cortex, densely connected with somatosensory, temporal and parietal cortex, is always present at birth(Alcauter et al. 2015). These findings may suggest that because the insula development starts early in fetal life, its connectivity, under the influence of early external stimulation, matures faster and earlier than other networks(Afif A et al. 2007). The connectivity of the SN after birth might therefore be found at a stage that is too late to infer the GA at birth. In other words, the functional connectivity of the insula after birth might be too mature to variate accordingly with the gestational age.

The VAN was found to significantly infer the GA at birth. The strongest effects on the GA predictability were negative effects (anti-correlation) found for the left medial frontal gyrus-inferior parietal lobule. A possible explanation for this finding might be that the VAN goes under early lateralization during infancy, although the process might be still incomplete in early life(V. S, JJ, and GR 2014). Further studies are needed in order to assess the timing of lateralization of the VAN. The DAN is able to infer the GA at birth. This finding supports the evidence by which the VAN operates with the Dorsal Attention Network (DAN) forming a twofold largely interconnected attentional control system(Corbetta and Shulman 2002; Corbetta, Patel, and Shulman 2008; V. S, JJ, and GR 2014).

The DMN was found to significantly infer the GA at birth, with the strongest effects on the GA predictability found for the connectivity of the right medial prefrontal cortex-right pre-cuneus. These findings are in line with previous studies showing that the DMN is present, even if in a fragmented, immature form, even before term(Doria et al. 2010). More specifically, the cortical hubs in infants seem to be less present in the prefrontal cortex and in the precuneus than in adults. The connectivity of these cortical hubs might therefore reflect the GA.

The SN connections were found to significantly infer the average connectivity of the VAN ($p = 0.026$). Interestingly, also the VAN was found to strongly infer the mean functional connectivity of the SN ($p = 10^{-3}$). These findings seem to be in agreement with previous studies showing that the function of the VAN overlaps with that of the SN in salience detection(Dosenbach et al. 2008; LQ 2015; F. K and LQ 2015). Uddin and Farrant proposed that the VAN and the SN have overlapping nodes in the region surrounding the VFC and anterior insula. They also speculated that in children, these two networks may be less segregated than in adults, and that bottom-up salience processes and attention to environmental stimuli

may be over-represented in the child's brain(F. K and LQ 2015). The strongest positive effects on the predictability of the SN's mean connectivity by the VAN were found for the connectivity of the medial frontal gyrus with the inferior parietal lobule of the contralateral side, bilaterally. The SN connections also inferred the average connectivity of the DAN ($p = 6 \bullet 10^{-3}$), supporting the theory by which the SN and VAN have overlapping roles.

All the connections of SN did not correctly infer the average connectivity of the DMN ($p > 0.05$). The DMN, on the contrary, was found to significantly infer the average connectivity of the SN ($p = 7 \bullet 10^{-3}$). This finding seems to oppose to the role of the SN in modulating the background activity of the DMN in order to elicit detection of salient stimuli and facilitate goal directed behavior. However, since the function of the CEN is likely reduced in infancy, this finding might also indicate that the SN function in switching attention to goal directed behavior matures with the development of the executive functions(Teffer and Semendeferi 2012).

The VAN was found to significantly infer the average connectivity of the DMN ($p = 0.044$). We believe this is the first evidence of the influence of the VAN over the DMN in neonates subjects. This finding might be explained by the overlap of function of the SN and VAN and by the over representation of bottom-up saliency detection seen in children (F. K and LQ 2015). The VAN was able to strongly infer the average connectivity of the DAN ($p = 4.8 \bullet 10^{-6}$). On the contrary, the DAN did not infer correctly average connectivity of any of the other networks, suggesting that it might be too early for the DAN to properly interact with other networks. A number of studies have shown that VAN and DAN are in competition during visual and verbal tasks (Anticevic A et al. 2010; Todd, Thaler, and Dijkstra n.d.; M. D et al. 2010; M. S et al. 2012). Specifically, the higher the load of the task, the higher the activation of the DAN and the higher the deactivation of the VAN. In other words, there seems to be a trade-off between the two attention networks, when the recruitment of task-related attention is high stimulus attention is deactivated allowing for successful task performance. Our finding lead us to hypothesize a conjoint development of the VAN and DAN with a prominent role of the VAN and, therefore, the bottom-up attention system during fetal life and early infancy. The two networks form an immature twofold attention system that matures with the growing ability of the top-down attention system to counteract the bottom-up system. Our hypothesis is further supported by a recent study by Suo et al.(Suo et al. 2021), underpinning the stable and reliable anatomical connections of the DAN and the VAN via functional connectors, demonstrating that the functional interaction of the VAN and the DAN is supported by a solid anatomical structure.

The mediation analysis of the VAN's inference over the DAN, mediated by the GA found that VAN's connectivity significantly modify the transmittance of change of the DAN's connectivity assumed form evidence of cross-validated inference on GA (VAN mediates DAN: Sobel Test $t = 2.14$, $p = 0.032$). A specular analysis of the DAN's inference over the VAN found that DAN's connectivity significantly modify the transmittance of change on the VAN's connectivity, assumed from evidence of cross-validated inference on GA (DAN mediates VAN: Sobel Test $t = 1.969$ $p = 0.048$). This finding further supports the theory of a twofold, largely interconnected attentional control system(Corbetta and Shulman 2002;

Corbetta, Patel, and Shulman 2008; V. S, JJ, and GR 2014) and suggests that the interaction between the bottom-up and top-down attention system influence the development of each other. This twofold relationship among VAN and DAN is mediated by the GA; this led us to hypothesize that maturation is crucial for the development of attention networks and prematurity may, therefore, substantially affect their architecture and function.

This is the first study performed on a cohort oh neonates to show that the VAN may influence the connectivity of the SN, the DMN and the DAN. Interestingly the SN influenced the VAN and the DAN, but not the DMN. We believe our findings suggest a prominent role of the VAN in the bottom-up salience detection in early infancy and that the VAN and the SN may overlap in their roles of bottom-up control of attention. Although a small number of studies have adopted machine learning methods to assess if FC metrics were able to predict the GA at birth, this is the first study to focus on a small group of networks of higher order. The evidence that the SN is not able to predict GA at birth, as opposed to the other higher order networks we analyzed, is a novel finding that we thought to be the result of the early development of the insula, which goes under a complex process of maturation between the 13th and the 28th week of gestation(Afif A et al. 2007). Such an early pattern of maturation would be less impaired by the effect of prematurity.

Our studies has some limitations. First, the atlas we used to select the seed regions for each network only identifies coarse regions. However, this limitation is provided by the absence of efficient brain anatomy segmentation tool in newborns. Second the number of subjects was not very large considering that we studied 4 different networks using a multivariate analysis framework. A short BOLD acquisition time (4min), driven by the limited time available for conducting a relatively non-clinical evaluation in a clinical environment. In order to reduce motion artifacts and maximize the efficacy of the standard clinical evaluation, newborns were also mildly sedated using Midazolam. Although Midazolam might have altered brain activity and hemodynamics, an effect of Midazolam should be observed in all subjects and should therefore not affect regression analyses that exploit subject-specific alterations. Another limitation of the present retrospective study is the minimally essential clinical information available. Although infants with evident alterations at standard radiological assessment were excluded from the analysis and no relationship was found between the main available clinical variable, the APGAR score soon after birth, and the extent of prematurity, the presence of subtle clinical confounders cannot be definitely ruled out. Future studies should replicate the present study with a larger cohort of patient with larger sets of clinical data available. Moreover, longer acquisition time should be taken into consideration together with a no sedation approach. Manual segmentations of ROI should be also performed for a more precise delineation of brain regions in neonates.

5. Conclusions

This is the first study performed with a on a cohort oh neonates with a multi-variate data-driven framework (i.e. Machine Learning framework) to suggest a prominent role of the VAN in the bottom-up salience detection in early infancy and that the VAN and the SN may overlap in their roles of bottom-up

control of attention. We also found reciprocal influence of VAN and DAN on the development of each other network.

The SN was the only network in our analysis unable to infer the gestational age at birth.

This finding may indicate that the stage of maturation of the SN at birth might be too advanced to infer the GA.

Declarations

Funding:

The authors received no financial support for the research, authorship, and publication of this article.

Conflicts of interest/Competing interests

The authors have no conflict of interest to declare

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author (VO). The data are not publicly available due to privacy and consent reasons.

Code availability

The custom code is available on request from the corresponding author (VO).

Ethics approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its amendments or comparable ethical standards.

Consent to participate

Informed consent for participation to the present study was obtained by the legal guardian of each one of the children enrolled in the study.

Consent for publication

Consent for publication was obtained by the legal guardian of each one of the children enrolled in the study.

References

1. Afif A, Bouvier R, Buenerd A, Trouillas J, and Mertens P (2007) Development of the Human Fetal Insular Cortex: Study of the Gyration from 13 to 28 Gestational Weeks. Brain Structure Function 212(3–4):335–346. https://doi.org/10.1007/S00429-007-0161-1
2. Anticevic A, Repovs G, Shulman GL, Barch DM (2010) When Less Is More: TPJ and Default Network Deactivation during Encoding Predicts Working Memory Performance. NeuroImage 49(3):2638–2648. https://doi.org/10.1016/J.NEUROIMAGE.2009.11.008
3. Abdi H, Williams LJ, and Domininique Valentin (2013) “Multiple Factor Analysis: Principal Component Analysis for Multitable and Multiblock Data Sets.” Wiley Interdisciplinary Reviews: Computational Statistics 5 (2): 149–179. https://doi.org/10.1002/WICS.1246
4. Alcauter S, Lin W, Keith Smith J, Gilmore JH, and Wei Gao (2015) Consistent Anterior–Posterior Segregation of the Insula During the First 2 Years of Life. Cereb Cortex 25(5):1176. https://doi.org/10.1093/CERCOR/BHT312
5. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2011) A Reproducible Evaluation of ANTs Similarity Metric Performance in Brain Image Registration. NeuroImage 54(3):2033–2044. https://doi.org/10.1016/J.NEUROIMAGE.2010.09.025
6. Avants BB, Yushkevich P, Pluta J, Minkoff D, Korczykowski M, Detre J, Gee JC (2010) The Optimal Template Effect in Hippocampus Studies of Diseased Populations. NeuroImage 49(3):2457–2466. https://doi.org/10.1016/J.NEUROIMAGE.2009.09.062
7. Bright MG, Christopher R, Tench, and Kevin Murphy (2017) “Potential Pitfalls When Denoising Resting State FMRI Data Using Nuisance Regression.” *NeuroImage* 154 (July): 159–68. https://doi.org/10.1016/J.NEUROIMAGE.2016.12.027
8. Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, Neil JJ (2010) “Longitudinal Analysis of Neural Network Development in Preterm Infants.” *Cerebral Cortex (New York, N.Y.: 1991)* 20 (12): 2852–62. https://doi.org/10.1093/CERCOR/BHQ035
9. Chiarelli AM, Sestieri C, Navarra R, Wise RG, and Massimo Caulo (2021) Distinct Effects of Prematurity on MRI Metrics of Brain Functional Connectivity, Activity, and Structure: Univariate and Multivariate Analyses. Hum Brain Mapp 42(11):3593–3607. https://doi.org/10.1002/HBM.25456
10. Churchill NW, Yourganov G, Oder A, Tam F, Graham SJ, and Stephen C. Strother (2012) “Optimizing Preprocessing and Analysis Pipelines for Single-Subject FMRI: 2. Interactions with ICA, PCA, Task Contrast and Inter-Subject Heterogeneity.” PLoS ONE 7 (2). https://doi.org/10.1371/JOURNAL.PONE.0031147
11. Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT et al (2017) “Benchmarking of Participant-Level Confound Regression Strategies for the Control of Motion Artifact in Studies of

Functional Connectivity." *NeuroImage* 154 (July): 174–87. https://doi.org/10.1016/J.NEUROIMAGE.2017.03.020

12. Corbetta M, Patel G, and Gordon L. Shulman (2008) The Reorienting System of the Human Brain: From Environment to Theory of Mind. Neuron 58(3):306. https://doi.org/10.1016/J.NEURON.2008.04.017
13. Corbetta M, Shulman GL (2002) "Control of Goal-Directed and Stimulus-Driven Attention in the Brain." *Nature Reviews Neuroscience 2002 3:3* 3 (3): 201–15. https://doi.org/10.1038/nrn755
14. Crottaz-Herbette S, and V Menon (2006) Where and When the Anterior Cingulate Cortex Modulates Attentional Response: Combined FMRI and ERP Evidence. J Cogn Neurosci 18(5):766–780. https://doi.org/10.1162/jocn.2006.18.5.766
15. Matsuyoshi D, Ikeda T, Sawamoto N, Kakigi R, Fukuyama H, and Osaka N (2010) Task-Irrelevant Memory Load Induces Inattentional Blindness without Temporo-Parietal Suppression. Neuropsychologia 48(10):3094–3101. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2010.06.021
16. Sridharan D, Levitin DJ, Chafe CH, Berger J, and Menon V (2007) Neural Dynamics of Event Segmentation in Music: Converging Evidence for Dissociable Ventral and Dorsal Networks. Neuron 55(3):521–532. https://doi.org/10.1016/J.NEURON.2007.07.003
17. Doria V, Beckmann CF, Arichi T, Merchant N, Groppo M, Turkheimer FE, Counsell SJ et al (2010) Emergence of Resting State Networks in the Preterm Human Brain. Proc Natl Acad Sci USA 107(46):20015–20020. https://doi.org/10.1073/PNAS.1007921107
18. Dosenbach NUF, Damien A, Fair AL, Cohen BL, Schlaggar, Petersen SE (2008) A Dual-Networks Architecture of Top-down Control. Trends in Cognitive Sciences 12(3):99. https://doi.org/10.1016/J.TICS.2008.01.001
19. Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) "A Multimodal Cortical Network for the Detection of Changes in the Sensory Environment." *Nature Neuroscience 2000 3:3* 3 (3): 277–83. https://doi.org/10.1038/72991
20. E, Dolgin (2010) This Is Your Brain Online: The Functional Connectomes Project. Nat Med 16(4):351. https://doi.org/10.1038/NM0410-351B
21. Eckert MA, Menon V, Walczak A, Ahlstrom J, Denslow S, Horwitz A, Dubno JR (2009) At the Heart of the Ventral Attention System: The Right Anterior Insula. Hum Brain Mapp 30(8):2530. https://doi.org/10.1002/HBM.20688
22. Esposito R, Cieri F, Chiacchiaretta P, Cera N, Lauriola M, Giannantonio MD, Tartaro A, and Antonio Ferretti (2018) Modifications in Resting State Functional Anticorrelation between Default Mode Network and Dorsal Attention Network: Comparison among Young Adults, Healthy Elders and Mild Cognitive Impairment Patients. Brain Imaging Behavior 12(1):127–141. https://doi.org/10.1007/S11682-017-9686-Y
23. Fair DA, Nico UF, Dosenbach JA, Church AL, Cohen S, Brahmbhatt FM, Miezin DM, Barch ME, Raichle SE, Petersen, Schlaggar BL (2007) Development of Distinct Control Networks through Segregation

and Integration. Proc Natl Acad Sci USA 104(33):13507–13512. https://doi.org/10.1073/PNAS.0705843104

24. Filzmoser P, Liebmann B, and Kurt Varmuza (2009) Repeated Double Cross Validation. J Chemom 23(4):160–171. https://doi.org/10.1002/CEM.1225
25. Ball G, Aljabar P, Arichi T, Tusor N, Cox D, Merchant N, Nongena P, Hajnal JV, Edwards AD, Counsell SJ (2016) "Machine-Learning to Characterise Neonatal Functional Connectivity in the Preterm Brain." *NeuroImage* 124 (Pt A): 267–75. https://doi.org/10.1016/J.NEUROIMAGE.2015.08.055
26. Gao W, Gilmore JH, Giovanello KS, Smith JK, Shen D, Zhu H, and Weili Lin (2011) Temporal and Spatial Evolution of Brain Network Topology during the First Two Years of Life. PLOS ONE 6(9):e25278. https://doi.org/10.1371/JOURNAL.PONE.0025278
27. Geng JJ, Mangun GR (2011) Right Temporoparietal Junction Activation by a Salient Contextual Cue Facilitates Target Discrimination. NeuroImage 54(1):594. https://doi.org/10.1016/J.NEUROIMAGE.2010.08.025
28. Toulmin H, Beckmann CF, O'Muircheartaigh J, Ball G, Nongena P, Makropoulos A, Ederies A et al (2015) Specialization and Integration of Functional Thalamocortical Connectivity in the Human Infant. Proc Natl Acad Sci USA 112(20):6485–6490. https://doi.org/10.1073/PNAS.1422638112
29. Egeth HE, and Yantis S (1997) Visual Attention: Control, Representation, and Time Course. Annu Rev Psychol 48:269–297. https://doi.org/10.1146/ANNUREV.PSYCH.48.1.269
30. "Interactive Mediation Tests." n.d. Accessed August 9 (2021) http://quantpsy.org/sobel/sobel.htm
31. Lubsen J, Vohr B, Myers E, Hampson M, Lacadie C, Schneider KC, Katz KH, Constable RT, Ment LR (2011) Microstructural and Functional Connectivity in the Developing Preterm Brain. Semin Perinatol 35(1):34–43. https://doi.org/10.1053/J.SEMPERI.2010.10.006
32. Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL (2010) Evidence for the Default Network's Role in Spontaneous Cognition. J Neurophysiol 104(1):322–335. https://doi.org/10.1152/JN.00830.2009
33. Anderson JS, Ferguson MA, Lopez-Larson M, Yurgelun-Todd D (2011) Connectivity Gradients between the Default Mode and Attention Control Networks. Brain Connect 1(2):147–157. https://doi.org/10.1089/BRAIN.2011.0007
34. Farrant K, Uddin LQ (2015) Asymmetric Development of Dorsal and Ventral Attention Networks in the Human Brain. Dev Cogn Neurosci 12:165–174. https://doi.org/10.1016/J.DCN.2015.02.001
35. Murphy K, and Fox MD (2017) "Towards a Consensus Regarding Global Signal Regression for Resting State Functional Connectivity MRI." *NeuroImage* 154 (July): 169–73. https://doi.org/10.1016/J.NEUROIMAGE.2016.11.052
36. Lindquist KA, Tor D, Wager H, Kober E, Bliss-Moreau, Lisa FB (2012) The Brain Basis of Emotion: A Meta-Analytic Review. The Behavioral Brain Sciences 35(3):121. https://doi.org/10.1017/S0140525X11000446
37. LQ U (2015) Salience Processing and Insular Cortical Function and Dysfunction. Nature Reviews Neuroscience 16(1):55–61. https://doi.org/10.1038/NRN3857

38. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) “FSL” *NeuroImage* 62(2):782–790. https://doi.org/10.1016/J.NEUROIMAGE.2011.09.015
39. Menon V, Uddin LQ (2010) Saliency, Switching, Attention and Control: A Network Model of Insula Function. Brain Structure Function 214(5–6):655. https://doi.org/10.1007/S00429-010-0262-0
40. Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, McNulty JP, and Mullins PG (2014) “The Salience Network Is Responsible for Switching between the Default Mode Network and the Central Executive Network: Replication from DCM.” *NeuroImage* 99 (October): 180–90. https://doi.org/10.1016/J.NEUROIMAGE.2014.05.052
41. Sterzer P, and Kleinschmidt A (2010) Anterior Insula Activations in Perceptual Paradigms: Often Observed but Barely Understood. Brain Structure Function 214(5–6):611–622. https://doi.org/10.1007/S00429-010-0252-2
42. Parr T, and Karl J. Friston (2019) Attention or Salience? Current Opinion in Psychology 29(October):1–5. https://doi.org/10.1016/J.COPSYC.2018.10.006
43. Parr T, Karl JF (2017) “Working Memory, Attention, and Salience in Active Inference.” *Scientific Reports 2017 7:1* 7 (1): 1–21. https://doi.org/10.1038/s41598-017-15249-0
44. “Pattern Recognition and Machine Learning | Christopher Bishop | Springer.” n.d. Accessed August 9 (2021) https://www.springer.com/gp/book/9780387310732
45. Pruett JR Jr, Kandala S, Hoertel S, Snyder AZ, Jed T, Elison T, Nishino et al (2015) Accurate Age Classification of 6 and 12 Month-Old Infants Based on Resting-State Functional Connectivity Magnetic Resonance Imaging Data. Dev Cogn Neurosci 12:123. https://doi.org/10.1016/J.DCN.2015.01.003
46. Raichle ME (2015) “The Brain’s Default Mode Network.” *Http://Dx.Doi.Org/10.1146/Annurev-Neuro-071013-014030* 38 (July): 433–47. https://doi.org/10.1146/ANNUREV-NEURO-071013-014030
47. Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The Brain’s Default Network: Anatomy, Function, and Relevance to Disease. Ann N Y Acad Sci 1124(March):1–38. https://doi.org/10.1196/ANNALS.1440.011
48. RW, Cox (1996) AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. Computers Biomedical Research an International Journal 29(3):162–173. https://doi.org/10.1006/CBMR.1996.0014
49. Majerus S, Attout L, D’Argembeau A, Degueldre C, Fias W, Maquet P, Martinez Perez T et al (2012) “Attention Supports Verbal Short-Term Memory via Competition between Dorsal and Ventral Attention Networks.” *Cerebral Cortex (New York, N.Y.: 1991)* 22 (5): 1086–97. https://doi.org/10.1093/CERCOR/BHR174
50. Vossel S, Geng JJ, Fink GR (2014) Dorsal and Ventral Attention Systems: Distinct Neural Circuits but Collaborative Roles. The Neuroscientist: A Review Journal Bringing Neurobiology Neurology Psychiatry 20(2):150–159. https://doi.org/10.1177/1073858413494269
51. Serences JT, Shomstein S, Leber AB, Golay X, Egeth HE, and Steven Yantis (2005) Coordination of Voluntary and Stimulus-Driven Attentional Control in Human Cortex. Psychol Sci 16(2):114–122.

https://doi.org/10.1111/J.0956-7976.2005.00791.X

52. Shang J, Fisher P, Bäuml JG, Daamen M, Baumann N, Zimmer C, Bartmann P et al (2019) A Machine Learning Investigation of Volumetric and Functional MRI Abnormalities in Adults Born Preterm. Hum Brain Mapp 40(14):4239–4252. https://doi.org/10.1002/HBM.24698
53. Shi F, Yap P-T, Wu G, Jia H, Gilmore JH, Lin W, and Dinggang Shen (2011) Infant Brain Atlases from Neonates to 1- and 2-Year-Olds. PLOS ONE 6(4):e18746. https://doi.org/10.1371/JOURNAL.PONE.0018746
54. Smyser CD, Nico UF, Dosenbach TA, Smyser, Abraham Z, Snyder CE, Rogers TE, Inder BL, Schlaggar, and Jeffrey J. Neil (2016) "Prediction of Brain Maturity in Infants Using Machine-Learning Algorithms." NeuroImage 136 (August): 1. https://doi.org/10.1016/J.NEUROIMAGE.2016.05.029
55. Sridharan D, Levitin DJ, and Vinod Menon (2008) "A Critical Role for the Right Fronto-Insular Cortex in Switching between Central-Executive and Default-Mode Networks." *Proceedings of the National Academy of Sciences* 105 (34): 12569–74. https://doi.org/10.1073/PNAS.0800005105
56. Stoecklein S, Hilgendorff A, Li M, Förster K, Flemmer AW, Galiè F, Wunderlich S et al (2020) "Variable Functional Connectivity Architecture of the Preterm Human Brain: Impact of Developmental Cortical Expansion and Maturation." *Proceedings of the National Academy of Sciences* 117 (2): 1201–6. https://doi.org/10.1073/PNAS.1907892117
57. Suo X, Ding H, Li X, Zhang Y, Liang M, Zhang Y, Chunshui Yu, and Wen Qin (2021) Anatomical and Functional Coupling between the Dorsal and Ventral Attention Networks. NeuroImage 232(May):117868. https://doi.org/10.1016/J.NEUROIMAGE.2021.117868
58. Teffer K, and Katerina Semendeferi (2012) Human Prefrontal Cortex: Evolution, Development, and Pathology. Prog Brain Res 195(January):191–218. https://doi.org/10.1016/B978-0-444-53860-4.00009-X
59. Todd JT, Lore Thaler, Tjeerd MH Dijkstra. n.d. "The Effects of Field of View on the Perception of 3D Slant from Texture." Accessed August 9 (2021) https://doi.org/10.1016/j.visres.2005.01.003
60. "Two-Way Analysis of High-Dimensional Collinear Data | Proceedings of the 2009th European Conference on Machine Learning and Knowledge Discovery in Databases - Volume Part I." n.d. Accessed August 9 (2021) https://dl.acm.org/doi/10.5555/3121576.3121597
61. V M (2011) Large-Scale Brain Networks and Psychopathology: A Unifying Triple Network Model. Trends in Cognitive Sciences 15(10):483–506. https://doi.org/10.1016/J.TICS.2011.08.003
62. Vossel S, Weidner R, Thiel CM, Fink GR (2009) What Is 'Odd' in Posner's Location-Cueing Paradigm? Neural Responses to Unexpected Location and Feature Changes Compared. J Cogn Neurosci 21(1):30–41. https://doi.org/10.1162/JOCN.2009.21003
63. Wold S, Ruhe A, Wold H, Dunn IIIWJ (2006) "The Collinearity Problem in Linear Regression. The Partial Least Squares (PLS) Approach to Generalized Inverses." *Http://Dx.Doi.Org/10.1137/0905052* 5 (3): 735–43. https://doi.org/10.1137/0905052

Figures

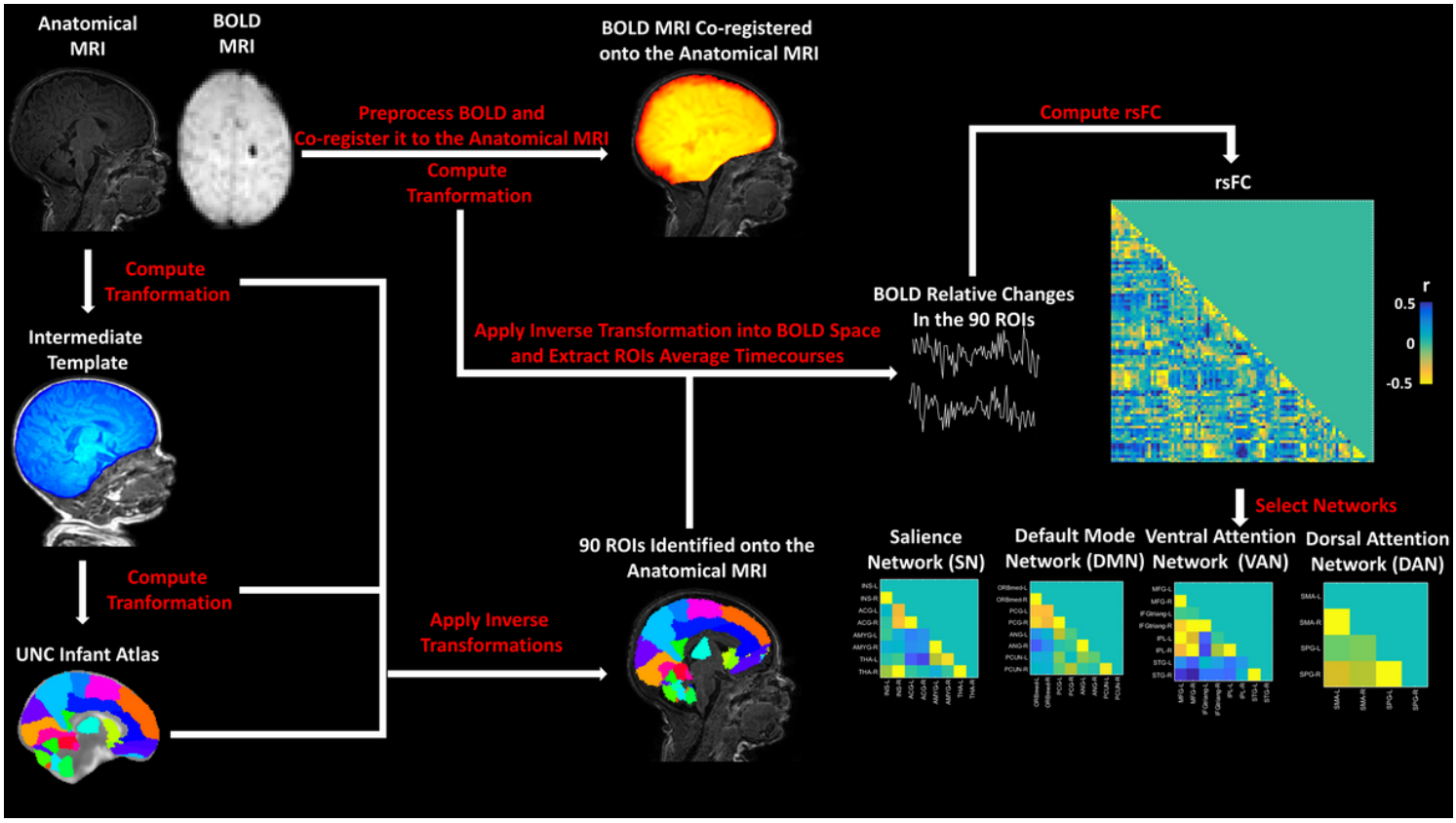

Figure 1

Workflow of Anatomical and BOLD MR Images Preprocessing, rsFC computation in the 90 ROIs identified based on the UNC Infant Atlas (Shi et al., 2011) and identification of the networks of interest. Connectivity matrices reported are from an exemplar subject.

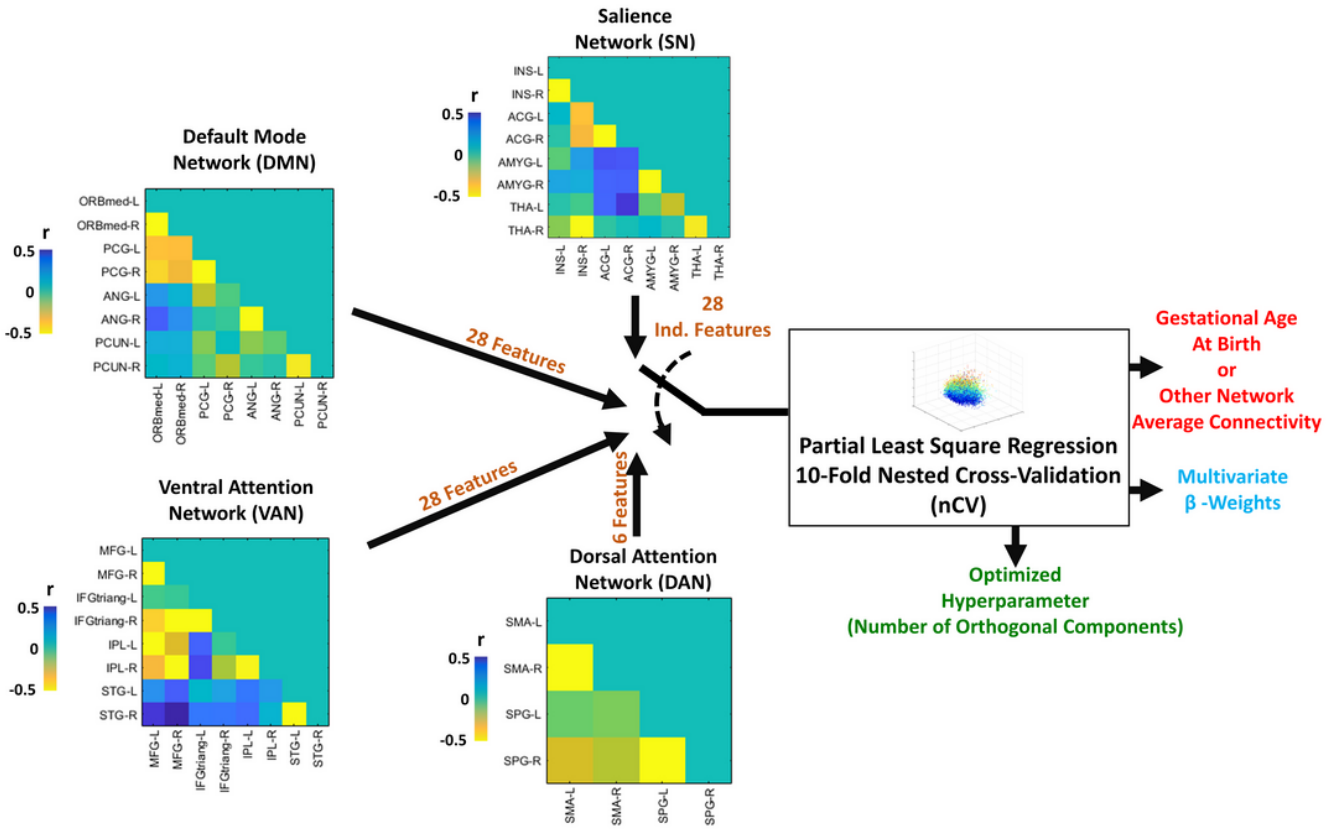

Figure 2

Multivariate PLS analysis implemented to infer GA at birth or other networks average connectivity. The optimal number of PLS components, the multivariate β-weights and the inference performances were estimated through a 10-fold nested Cross-Validation scheme. Connectivity matrices reported are from an exemplar subject.

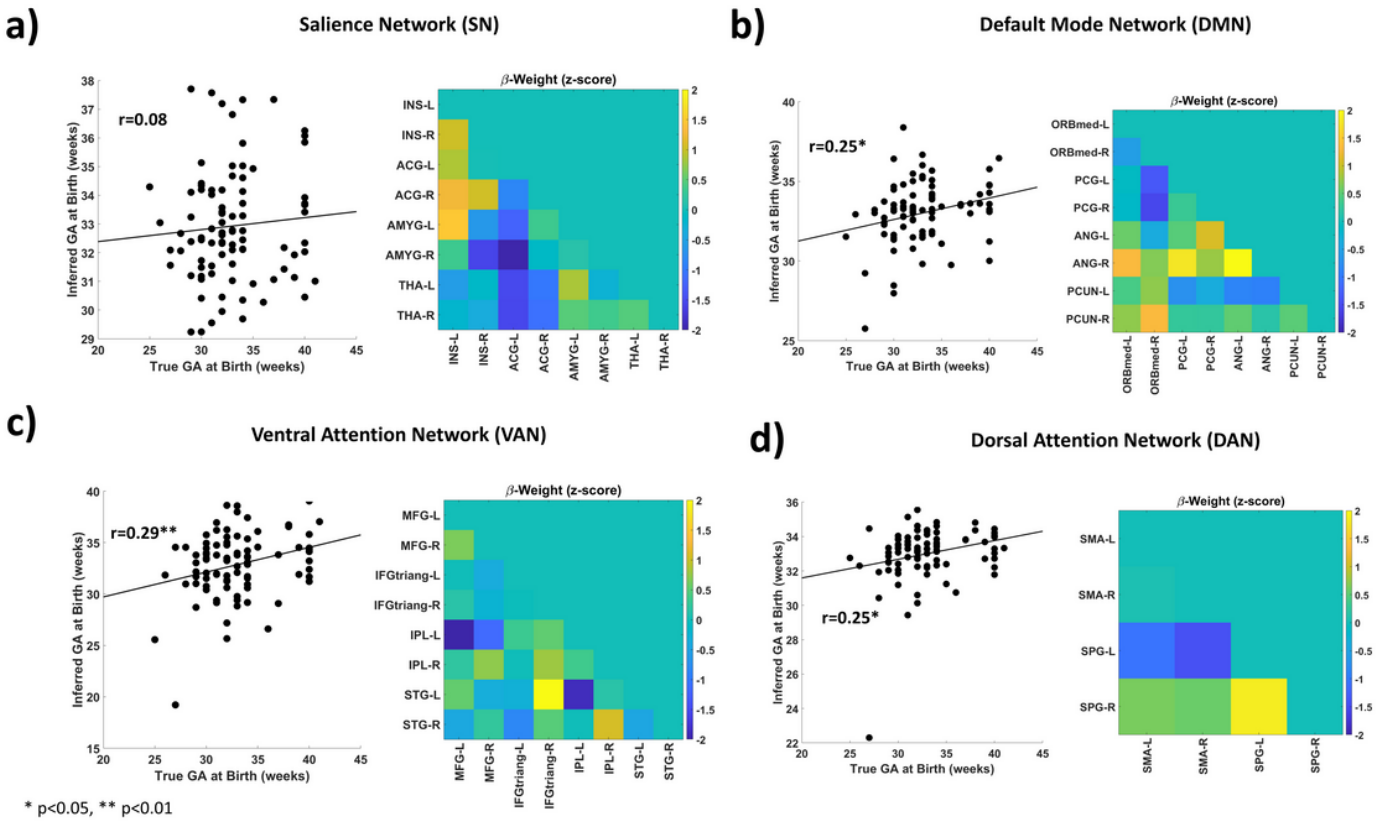

Figure 3

Results of the multivariate framework to infer GA at Birth based on connectivities within a) Salience Network (SN) , b) Default Mode Network (DMN), c) Ventral Attention Network (VAN) and d) Dorsal Attention Network (DMN). For each predicting network, both the association between the true and the inferred GA at Birth and the normalized (z-score) beta-weights of the multivariate analysis are reported.

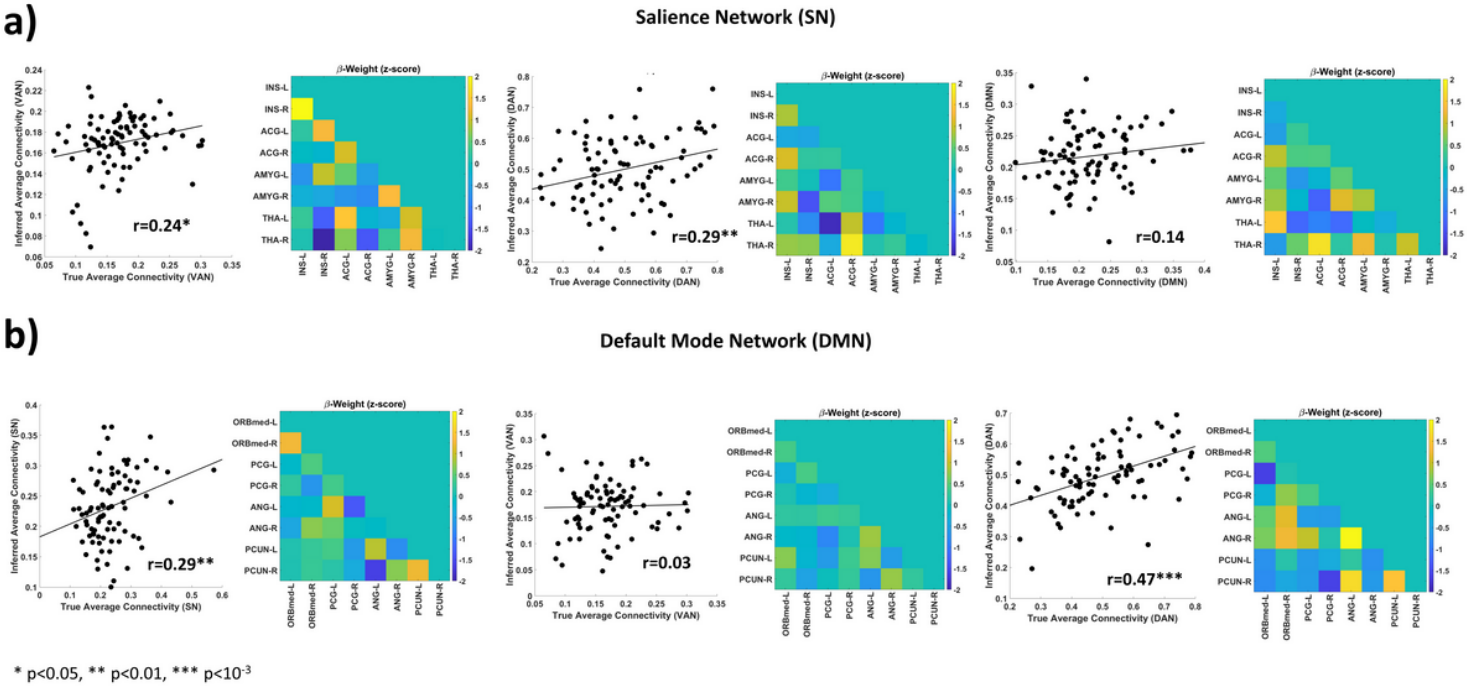

Figure 4

Results of the multivariate framework to other network based on connectivities within different networks.

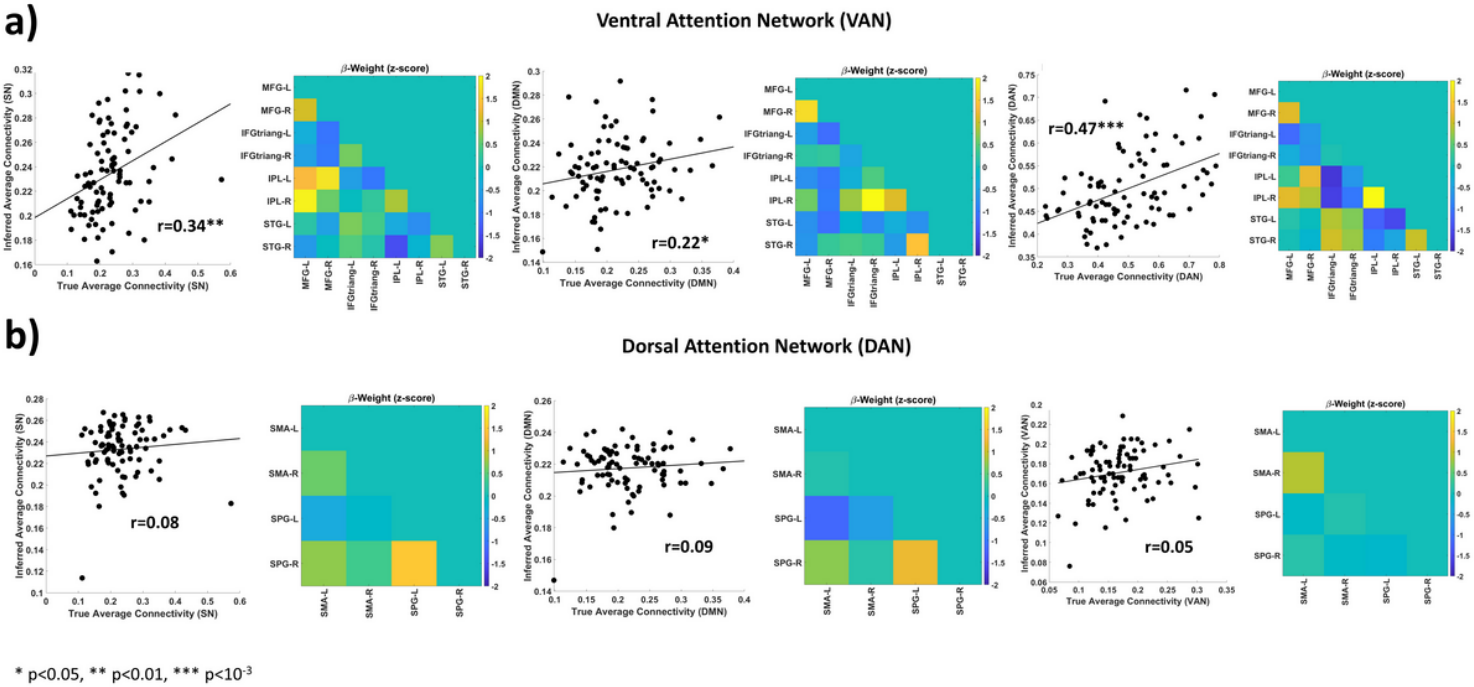

Figure 5

Results of the multivariate framework to infer average connectivities of another network based on (a) Ventral Attention Network (VAN), (b) Dorsal Attention Network (DAN)

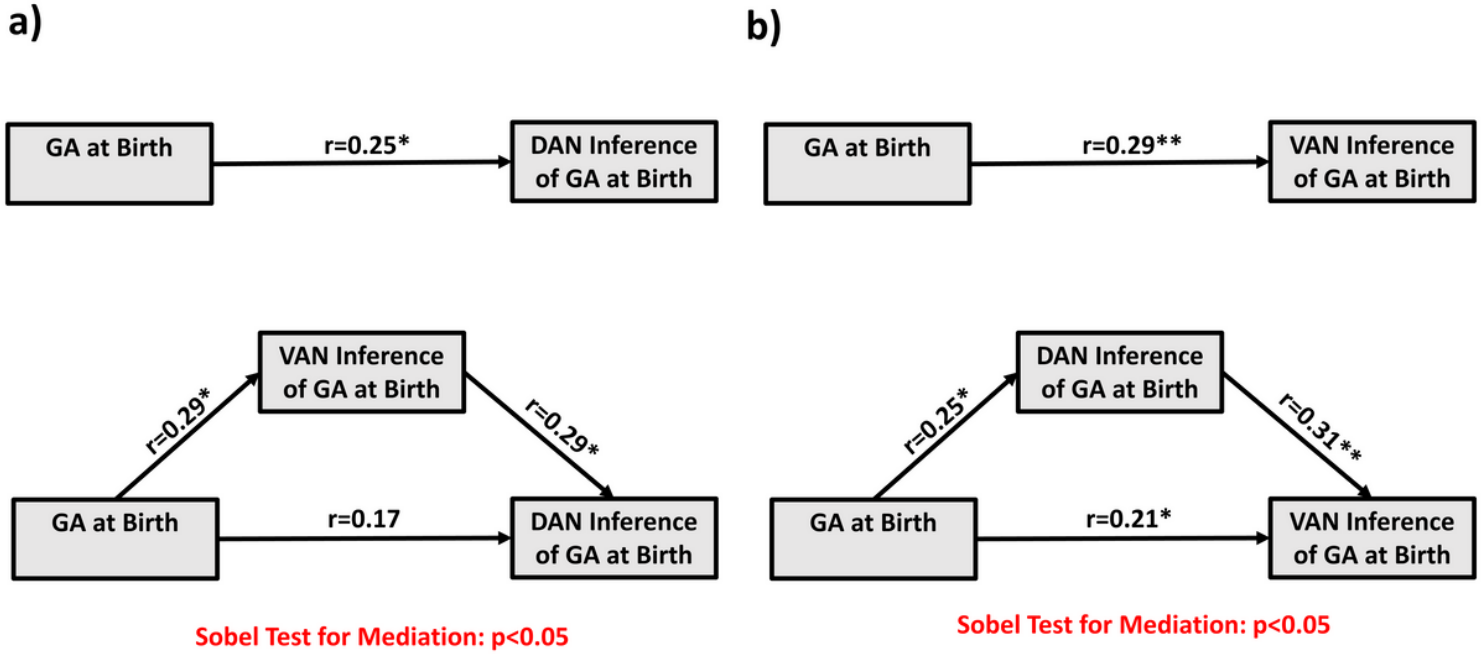

Figure 6

Mediation Analyses. a) VAN mediating the relation between GA at Birth and DAN; b) DAN mediating the relation between GA at Birth and VAN.