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Research Article: New Research | Development

Key Brain Network Nodes Show Differential Cognitive Relevance and Developmental Trajectories during Childhood and Adolescence

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Abstract (211/250 words)

Human adolescence is a period of rapid changes in cognition and goal-directed behavior, and constitutes a major transitional phase towards adulthood. One of the mechanisms suggested to underlie the protracted maturation of functional brain networks, is the increased network integration and segregation enhancing neural efficiency. Importantly, the increasing coordinated network interplay throughout development is mediated through functional hubs, which are highly connected brain areas suggested to be pivotal nodes for the regulation of neural activity. To elucidate brain hub development during childhood and adolescence, we estimated voxel-wise eigenvector centrality (EC) using fMRI data from two different psychological contexts (resting state and a working memory task), in a large cross-sectional sample (n=754) spanning the age from 8-22 years, and decomposed the maps using independent component analysis. Our results reveal significant age-related centrality differences in cingulo-opercular, visual and sensorimotor network nodes during both rest and task performance, suggesting that common neurodevelopmental processes manifest across different mental states. Supporting the functional significance of these developmental patterns, the centrality of the cingulo-opercular node was positively associated with task performance. These findings provide evidence for protracted maturation of hub properties in specific nodes of the brain connectome during the course of childhood and adolescence, and suggest that cingulo-opercular centrality is a key factor supporting neurocognitive development.

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Significance statement (113/120 words)

Adolescence is a sensitive period during ontogeny and a maturational gateway to adulthood. A better characterization of the brain changes underpinning cognitive and emotional development occurring during this period is key to inform models of normal and abnormal adaptation. Advanced brain imaging allows for *in vivo* studies of the protracted maturation of brain network function and connectivity during childhood and adolescence. Here, we used functional brain imaging to identify neural hubs during two psychological contexts in 754 children and adolescents. Key regions of the brain network showed increasing importance through adolescence, and individual differences in working memory performance was associated with the centrality of cingulo-opercular network nodes, suggesting a hot-spot for neurocognitive development.

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Introduction (715/750 words)

The gradual transition from childhood to adulthood is characterized by profound physical, cognitive and emotional changes. Individual adaptation to the dynamic and socially expanding environment throughout this period is enabled by the large potential for neuroplasticity, e.g. reflected in a transformation of cortical gray matter by a massive synaptic downscaling (Spear, 2000), and increases in brain white matter coherence and volume (Paus, 2005; Westlye et al., 2010; Alnæs et al., 2018). These protracted neurodevelopmental changes form the structural backbone allowing efficient neural signaling, enabling functional integration and adaptation of the brain networks underlying the substantial cognitive and functional maturation seen over this age span (Casey et al., 2008). Of note, while adolescence marks the successful transition from childhood to adulthood for the majority, this is also the period where most mental disorders emerge, supporting the critical role of adolescence as a sensitive period during ontogeny (Paus et al., 2008).

Functional brain connectivity (FC) provides an intriguing window into the developing brain, and has been extensively studied using resting-state functional magnetic resonance imaging (rs-fMRI). Resting state networks (RSN) show high spatial concordance with networks associated with task activations (Smith et al., 2009), and brain connectivity and activation are highly coordinated aspects of brain functioning (Gratton et al., 2016). In a large-scale study on children and adolescents from the Philadelphia Neurodevelopmental Cohort (PNC), Satterthwaite and collagues (2014) analyzed fMRI data recorded during the performance of a cognitive task and found that a reciprocal pattern of executive-network activation and default-mode network (DMN) de-activation was associated with working memory performance. This pattern was more predictive of performance differences than activations and deactivations in isolation. Network dynamics and connectivity thus contains

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complementary information about the neural substrate supporting executive ability and its maturation (Power et al., 2010; Gu et al., 2015).

Whereas the hubs in the default mode and executive-networks are fairly established from five years of age (Hwang et al., 2013; Wu et al., 2013; Cao et al., 2014), key dynamic and functional characteristics of brain nodes display maturational alterations throughout adolescence (Grayson et al., 2014). How these changes support the marked increase in executive abilities during this period is still unclear.

One commonly used metric for investigating hub properties is centrality, which reflects the number and strength of connections of a given node to the rest of the network. Previous studies have reported a maturational increase in centrality of task positive networks like frontoparietal, cingulo-opercular and task negative default mode network (DMN) nodes (Fransson et al., 2011; Hwang et al., 2013; Cao et al., 2016). While most developmental studies on brain network connectivity have employed rs-fMRI, cognitive engagement modulates the connectivity and centrality of brain nodes (Chadick and Gazzaley, 2011; Cole et al., 2013; Alnæs et al., 2015a; Alnæs et al., 2015b; Mišić and Sporns, 2016; Kaufmann et al., 2017b). Further, higher cognitive load has been shown to increase the sensitivity for age-related differences in FC (Dørum et al. 2017), motivating investigation of brain dynamics beyond the unconstrained resting-state.

Here, to characterize age-related differences in functional connectivity in the adolescent brain, we estimated whole-brain voxelwise eigenvector centrality (EC) of fMRI data collected during resting state and a working memory task (fractal n-back) for 754 children and adolescents aged 8-22 years from the PNC (Satterthwaite et al., 2014). To allow for multiple levels of inference and to investigate the hierarchical organization of the brain network nodes, we decomposed the voxel-wise EC maps using independent component analysis (ICA) and tested for main effects of task, age, and their interactions both on the

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voxel-wise EC maps and the ICA subject weights. Based on previous studies and models of adolescent brain development, we hypothesized (1) increased centrality in task positive networks and decreased centrality in DMN, sensorimotor and visual networks in response to task engagement, (2) and that these centrality changes would be associated with task performance. Furthermore (3) we hypothesized that these effects on network centrality would parallel task-related activation through a characteristic pattern of increased activation in networks involved in task engagement and decreased activation in DMN. Lastly, we hypothesized (4) that the centrality of key nodes would show evidence of protracted maturation during the sampled age-span, with differential age-related differences across nodes and conditions, possibly indicating increasing age-dependent differentiation between the two psychological contexts for both activation and centrality.

Material and methods

Sample and exclusion criteria

The analysis was performed on the publicly available PNC (Satterthwaite et al., 2014), access permission no. 8642. All participants gave written informed consent and the study was approved by the review boards of the University of Pennsylvania and the Children's hospital of Philadelphia. After exclusion of participants with severe medical and psychiatric conditions, missing task responses, and poor normalization of fMRI data, the final sample comprised 754 individuals aged 8 to 22 years (405 males, mean age 15 years, SD 3.3 years).

MRI acquisition

MRI scans were acquired at the University of Pennsylvania on a 3T Siemens TIM Trio scanner. An anatomical scan used here for registration purposes was acquired using a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR:

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1.81 s, TE: 3.5 ms, FA: 9°, FOV: 240 × 180 mm, slice thickness: 1 mm, slices: 160). Functional images were acquired using single-shot, interleaved multislice, gradient-echo, echo planar imaging (GE-EPI) sequence (TR: 3.0 s, TE: 32 ms, FA: 90°, FOV: 192 mm^2).

fMRI task paradigm and behavior

The task has been previously described in detail (Satterthwaite et al., 2013). Briefly, we included data from two fMRI runs: One was a resting-state run (eyes open while fixating on central fixation cross), while the other was collected while participants performed a fractal-version of the n-back task. The n-back task consisted of three load levels: 0-back, 1-back and 2-back. During 0-back participants were asked to press a button every time a target fractal was presented. During 1- and 2-back participants were asked to respond whenever the presented fractal was identical to the one presented one or two trials prior, respectively. Each run consisted of three blocks per condition, and each block consisted of 20 trials of which 5 were targets and 15 were non-target fractals. We computed the total hit-rate, false-positive rate and d-prime. The latter was calculated by subtracting z-score for false positives from the z-score for hit-rate from the in-scanner responses during the n-back task (Stanislaw and Todorov, 1999).

fMRI data processing

fMRI data was processed using FMRI Expert Analysis Tool (FEAT) Version 6.00, from FMRIB's Software Library (FSL; Smith et al., 2004; Jenkinson et al., 2012), and included the following steps: correction for motion using MCFLIRT (Jenkinson et al., 2002), linear trend removal and high-pass filtering (0.01 Hz), removal of non-brain tissue using BET (Smith, 2002), spatial smoothing with a Gaussian kernel of full width at half maximum (FWHM) of 6 mm (SUSAN; Smith and Brady, 1997). We employed automated procedures for data de-

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noising, including (FIX; Salimi-Khorshidi et al., 2014) and ICA-AROMA (Pruim et al., 2015), that has been reported to reduce risk of inflating age-related effects due to higher in-scanner head-movement (Kaufmann et al., 2017a). Further, we applied nonlinear registration using FNIRT to Montreal Neurological Institute (MNI) 152 standard space using the T1-weighted scan as an intermediate.

Eigenvector centrality mapping (ECM)

Following previous studies (Alnæs et al., 2015b; Skatun et al., 2016), we first created a group mask containing common voxels across all participants and sessions (n-back and rest). To accommodate images to EC estimation, the pre-processed and normalized n-back, resting state runs and analysis mask were resampled to an isotropic voxel resolution of 3 mm, converted to the Vista image format (Pope and Lowe, 1994) using LIPSIA (Lohmann et al., 2001) and submitted to estimation of voxel-wise EC (Lohmann et al., 2010) using the absolute of the full correlation coefficients (equal weight to positive and negative correlations), yielding one EC map per run for each participant. Individual EC-maps and brain masks were converted to nifti format, resampled to 2 mm isotropic resolution and submitted to further analysis (ICA and voxel-wise statistics).

Independent component analysis (ICA) on EC maps

The 1508 EC maps were decomposed into a fixed set of 40 components, for optimal trade-off between spatial resolution of components and not over-fitting the model, using spatial ICA in MELODIC (Beckmann and Smith, 2004). To assess effects of condition on EC for each IC, the associated subject-weights from the ICA was utilized to calculate the difference in subject weights between rest and n-back runs for each IC. For visualization of the network structure, we used subject weights for both n-back and rest to form a component by component

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correlation matrix, which was submitted to hierarchical clustering using FSLNets (Smith et al., 2011). ICs covering white matter and CSF were excluded before clustering.

Dual regression

To assess the relationships between the centrality and task-related activation of the ECM-based ICs, we extracted individual time series from each of the component spatial maps from the n-back data using dual regression (Nickerson et al., 2017). GLMs were estimated for each participant and each component's time series, modeling 0-back, 1-back and 2-back as well as responses and instructions. As a measure of BOLD task effect, beta estimates for 0-back was subtracted from the average of 1-back and 2-back beta estimates.

Voxelwise analysis

For transparency, we compared our main results obtained using ICA-based decomposition of EC maps with voxel-wise effects of task and age and their interactions on EC using FSL randomise (Winkler et al., 2014). First, we computed difference maps by subtracting the individual resting-state EC maps from the n-back EC maps. We tested for main effect of condition by performing a one-sample t-test on the difference maps (n-back minus rest). We further tested for associations with age age by performing linear regression on rest, n-back and the difference maps, including sex as covariate. Statistical inference was done by permutation testing with 5000 iterations and threshold-free cluster enhancement (Smith and Nichols, 2009).

Statistical analysis

Analyses beyond the voxel- and imaging domain were performed in MATLAB 2014a® (MathWorks, Natick, MA). To test for effects of age on EC, we performed linear regressions

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with the subject weights from n-back or resting-state runs as dependent variable, and age and sex as independent variables for all ICs. To test for main effect of task on each component, we performed one-sample t-tests on the difference scores between rest and n-back weights. To test for interactions between task and age on EC, we performed linear regressions with the difference score as dependent variable and age and sex as independent variables. To test for associations between EC and task performance (hit-rate, false positives and d-prime), we used the same derived difference score as dependent variable, and hit-rate, false positives or d-prime as independent variables in separate analyses, in addition to age and sex.

In the same manner, using the beta estimates derived from dual regression on the n-back data, we tested for effect of task by performing one-sample t-tests. To test for effect of age, we performed linear regression with task effect as the dependent variable, and age and sex as independent variables.

To test for associations between task-related effects on centrality and activation for each IC, we correlated the difference EC-score (n-back minus rest) with beta estimates for task engagement. To account for multiple comparisons, we adjusted the false discovery rate (FDR, q=.05) across all tests and components (Genovese et al., 2002). For visualization of the association between centrality and activation, component-wise EC-difference-weights and beta-estimates for the n-back task was imported to R (http://www.r-project.org) and plotted with the ggplot2-package (Wickham, 2009).

Results

ICA and hierarchical clustering

ICA of EC maps yielded 31 spatial maps corresponding to cortical gray-matter components, including frontoparietal, default mode, visual networks, and nine maps corresponding to white matter and CSF (See Table 1 for an anatomical description of the 31 maps included in

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the hierarchical clustering). Figure 1-1 shows the hierarchical clustering based on the correlation between IC-weights across n-back and rest, and Figure 1-2 shows the associated spatial maps. Clustering revealed a structure coherent with known large-scale functional networks, largely reflecting visual, sensorimotor, frontoparietal, subcortical, cingulo-opercular and DMN.

[Insert Figure 1 and Table 1]

Component-wise EC task effects

Task engagement (n-back>rest) was associated with distributed differences in EC across most nodes. Figure 1-4 displays significant (FDR corrected, q=0.05) associations between EC, task engagement and task performance, and Table 2 summarizes corresponding statistics. All *frontoparietal components* displayed a significant increase in EC with task engagement, and for one of the components (IC 2) higher centrality was significantly associated with better performance. Three of the four *cingulo-opercular* nodes displayed significant increase of centrality with task engagement, and higher EC was associated with better performance (2 of 4 ICs). The *subcortical* components displayed a mixed pattern of centrality changes, thalamus decreased, but cerebellum increased with task engagement. Higher EC for both cerebellum and thalamus was associated with better performance. *DMN components* displayed both increase (2 of 5 ICs) and decrease (2 of 5 ICs) in centrality with task engagement, but no significant associations with task performance. *Sensorimotor* components displayed reduced centrality (5 of 6 ICs) with task engagement, and for two of the components, the degree of reduction was associated with task performance. *Visual* components displayed a mixed pattern with both increased (3 of 7 ICs) and decreased (3 of 7 ICs) centrality with task

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engagement, and centrality in two components showed negative correlations with task performance.

[Insert Table 2]

Component-wise activation

Significant effects (FDR corrected, q=0.05) of task engagement are displayed in the lower panel of Figure 1-5. Table 2 summarizes the corresponding statistics. The component-wise activation pattern revealed several similarities with the pattern for EC. Task engagement was associated with significantly increased activation in the *frontoparietal* (6 of 7 ICs) and *cingulo-opercular* (4 of 4 ICs) components. Among the *subcortical* components, we found increased activation in cerebellum and decreased activation in putamen. The *visual, sensorimotor and DMN* components displayed reduced activation during task.

[Insert Figure 2]

Associations between centrality and activation

Overall, we found a positive correlation between activation and EC ($r=0.64$, $p=1.11e^{-4}$); components showing increased activity with task generally also showed task-related increases in EC. Figure 3 displays the component-wise association between task-related activation and differences in EC between n-back and rest. However, the results revealed some notable exceptions. For example, whereas components in the frontoparietal cluster showed both strong task-related activation and increased centrality, and visual and sensorimotor cluster components showed deactivation and decreased centrality, DMN components showed overall task related deactivations, but a mixed pattern of increased and decreased centrality.

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316

317 *[Insert Figure 3]*

318

319 *Component-wise associations with age*

320 Figure 1-3 and 1-5 upper panel show the significant (FDR corrected, q=0.05) associations
321 between age centrality and task-related activation. Table 3 summarizes the corresponding
322 statistics. For *frontoparietal components,* we found significant positive associations between
323 centrality and age in one component during n-back and two components during rest. One of
324 the frontoparietal components displayed a significant interaction effect suggesting a stronger
325 negative age effect during rest compared to n-back. In contrast, we found significantly
326 increased activation with increasing age across all frontoparietal components, with the
327 exception of one. *Cingulo-opercular* components displayed significant age-related increases
328 in EC in two of four components, anterior cingulate and insula respectively. The increase in
329 EC was paralleled by significant increase in activation in all cingulo-opercular components.
330 Among the *subcortical components,* thalamus and cerebellum showed significant age-related
331 decreased centrality, and the latter also showed age-related increased activation. Within the
332 *DMN cluster,* one component showed significant age-related decrease in EC during n-back. In
333 contrast, all DMN-components showed significant decrease in activation with increasing age,
334 indicating stronger deactivation with higher age. *Visual and sensorimotor components*
335 displayed a highly similar pattern; age-related increases in EC during both task and rest, but
336 decreased activation with higher age. The exception was one component, showing age-related
337 increases both in centrality and activation.

338

339 *[Insert Table 3]*

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Voxelvise analysis

Figure 4 shows the results from the full-brain voxelwise analyses. Figure 4-1 displays the difference in centrality during n-back compared to rest, suggesting higher centrality in frontoparietal areas and posterior DMN and lower centrality in sensorimotor areas, mirroring the ICA-based analysis. Figure 4-2 and 4-3 show associations between centrality and age during n-back and rest, respectively. We found significant age-related increases in centrality in both conditions in visual and sensorimotor regions as well as in the anterior cingulate. During n-back, we found significant age-related differences in the frontal pole, extending to the superior frontal gyrus. Negative associations with age were found in large white matter and CSF regions. However, there was no significant age-effect in the derived difference-maps, indicating no evidence of interactions between age and condition.

[Insert Figure 4]

Discussion (1882/3000 words)

Using graph-based metrics and data-driven decomposition of fMRI data obtained during an unconstrained resting state condition and performance of an n-back task, the current study yielded three main findings. First, we demonstrated the sensitivity of eigenvector centrality to differences in task demands. Next, we revealed age-dependent alterations in the centrality of key brain networks, with increasing centrality in sensorimotor, visual and cingulo-opercular network components and decreasing centrality in thalamus, cerebellum and left temporal gyrus. Finally, the lack of condition by age interactions suggests that these age-related differences in network centrality are not strongly dependent on mental state, supporting that the maturation of the functional architecture of the brain is relatively pervasive across psychological contexts. These main findings will be discussed below.

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367 *Brain network centrality and task engagement*

368 The most prominent finding in the current study was increased centrality of frontoparietal,
369 cerebellar and cingulo-opercular components, and decreased centrality in sensorimotor and
370 thalamic components with task engagement, which align with previous investigations of EC
371 in adults (Alnæs et al., 2015b; Hearne et al., 2017). FC during task engagement is associated
372 with increased cross-network connectivity, and decreased network modularity (Di et al., 2013;
373 Cole et al., 2014; Shine et al., 2016). This dynamic shift in connectivity pattern in response to
374 task demands supports increased global effectiveness, through shortening path lengths in the
375 network, and increased efficiency of information transfer across the global network (Stanley
376 et al., 2015). These alterations in brain network dynamics enable flexible reconfiguration in
377 response to task demands, which supports executive control, including working memory
378 performance (Braun et al., 2015; Stanley et al., 2015). Among the proposed neurocognitive
379 mechanisms is an increased influence of executive nodes exerting top down control (Chadick
380 and Gazzaley, 2011), as well as suppression of task-irrelevant nodes to minimize interference
381 which may be detrimental to performance (Tomasi et al., 2013). Indeed, within-network
382 visual and sensorimotor connectivity have been reported to decrease with task demand, with
383 simultaneous increases in connectivity with frontoparietal and cerebellar nodes (Kellermann
384 et al., 2012; Spadone et al., 2015; Brissenden et al., 2016; Kwon et al., 2017), which
385 facilitates both suppression and biasing of sensory input. Thalamus plays a key role in the
386 gating of sensory input towards higher cortical network structures (Halassa and Kastner,
387 2017; Hwang et al., 2017). Interestingly, reduced connectivity between specific sub-clusters
388 of the thalamus and visual and motor cortices in response to task demands has been reported,
389 also in absence of altered FC with executive or DMN networks (Fan et al., 2015). In light of
390 these observations, our findings indicate that task engagement reduces thalamic FC with

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391 cortical areas, facilitating the suppression and filtering of sensory signal during task
392 engagement.

393 Our results align with previous findings highlighting the importance of increased
394 influence of executive and cerebellar nodes during task engagement, as higher cingulo-
395 opercular, cerebellar and frontoparietal centrality was associated with better task performance,
396 and higher centrality in visual and sensorimotor nodes was associated with lower
397 performance. Thalamus in particular was further associated with decrease in centrality during
398 task engagement reflecting a drop in global FC, and the degree of differentiation between task
399 and rest EC was positively associated with performance. Indeed, our results support both the
400 interference-hypothesis (D'Esposito et al., 1999), suggesting that performance during the n-
401 back task is supported by increased influence from frontoparietal and cingulo-opercular
402 nodes, providing top-down attentional control, as well as the sensory gating hypothesis
403 (Cromwell et al., 2008), reflected through the decreased thalamic EC, which was associated
404 with better performance.

405 Notably, to a large extent the centrality pattern observed during task engagement
406 paralleled the observed activation patterns. Studying activation and connectivity across
407 several cognitive tasks, Gratton and colleagues (Gratton et al., 2016) reported coordinated
408 changes in connectivity and activation, in which an increase in both measures were observed
409 for brain regions involved in active task control. This supports the notion of connectivity and
410 activation as coordinated aspects of brain functioning. Overall, our results comply with these
411 findings of coordinated activity and network changes for the frontoparietal and the cingulo-
412 opercular-network. However, while the DMN displayed a task-related increase in centrality, it
413 also displayed the commonly observed de-activation in response to task demands. This could
414 reflect a coordinated disengagement, as previous studies have reported task-driven increases
415 in internal DMN connectivity and coherence during cognitive engagement (Anticevic et al.,

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2012; Goparaju et al., 2014). On the other hand, recent studies using a graph theoretical approach alternatively suggest that the DMN dynamically changes its cross talk with other networks during task execution (Vatansever et al., 2015b; Vatansever et al., 2015a), and displays larger integration with the full connectome. In particular, variability in functional connectivity between executive networks and DMN during an executive task was shown to be positively associated with performance (Douw et al., 2016). Taken together, there is still a large degree of uncertainty regarding DMN-involvement during task engagement, and further studies are needed to gain a better understanding of the DMN dynamics and its implications for brain development and cognitive functioning.

Age-related differences in activation

In line with our expectations and previous activation analysis in an overlapping sample (Satterthwaite et al., 2013), our analysis revealed age-related increases in the activation of frontoparietal components and increased deactivation of visual and DMN components, suggesting increased differentiation of these networks with age in response to task demands. We also observed additional age-related effects in cingulo-opercular and subcortical components, which were not reported earlier. This discrepancy may be related to higher sensitivity for the current ICA-based approach compared to the voxel-wise analysis, allowing for higher component-wise specificity and effectively reducing number of comparisons.

Age-related differences in centrality

For the connectivity and graph-based analysis we found increasing centrality with increasing age in key cingulo-opercular components, as well as posterior cingulate, and superior frontal gyrus, reflecting increased centrality in task positive visual and sensorimotor components, along with reductions in thalamus, cerebellum and temporal gyrus during both n-back and

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441 rest. We found no significant interaction effects between task and age. Although one should
442 be cautious when interpreting null findings, the lack of significant interactions suggest that
443 age-related differences in network characteristics are not strongly dependent on cognitive
444 load. A recent large-scale developmental study demonstrated that maturation of the structure
445 and organization of the brain functional connectome is characterized by increasing
446 segregation of large-scale functional networks, along with differentiation of the various
447 networks' influence on the full connectome (Gu et al., 2015). Indeed, converging evidence
448 points towards an increasing global influence from DMN in general, and cingulo-opercular
449 network nodes during cognitive processing, as hallmarks of healthy development (Gu et al.,
450 2015; Marek et al., 2016). Specifically, Marek and colleagues (2016) reported that
451 maturational increase in inhibitory control during early adolescence is accompanied by
452 increased between-network connectivity, in particular within the sensorimotor, visual and
453 cingulo-opercular networks. Furthermore, temporal variability in cingulo-opercular
454 connectivity has been suggested to serve as a proxy for brain maturation (Sato et al., 2015b).
455 The importance of the cingulo-opercular network for cognitive functioning is further
456 supported by studies investigating both healthy adults and clinical groups. Cingulo-opercular
457 activity in healthy adults is associated with the ability to maintain sustained attention and
458 integrate feedback (Cocchi et al., 2013), and within-network efficiency measured as degree of
459 edge density has been linked to cognitive flexibility (Sheffield et al., 2016). Complementary,
460 decreased functional connectivity between cingulo-opercular, sensorimotor and DMN nodes
461 with aging has been linked to deteriorated cognitive performance (Meier et al., 2012), and
462 lesions targeting hub cingulo-opercular nodes are associated with greater cognitive
463 impairment compared to non-hub nodes (Warren et al., 2014). Indeed, structural
464 abnormalities in hubs has been found to be overrepresented across a range of brain disorders
465 (Crossley et al., 2014), and abnormalities in anterior cingulate of the cingulo-opercular

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network was proposed as one of the key brain predictors for schizophrenia. Identifying deviant hub development may show promise as a biomarker for risk of future psychopathology in the adolescent brain, as well as being a predictive marker for prognosis and the degree of symptom severity following brain insults.

Our results only displayed maturational effect in one of six frontoparietal components, and thus revealed sparse age associations with the centrality of the frontoparietal network. Recent studies suggest that maturation of task positive networks may be better reflected by dynamic rather than static measures of functional connectivity, and that development as well as aging are accompanied by changes in dynamic transitions between brain states, operationalized through temporal variability in between-network connectivity (Ryali et al., 2016; Córdova-Palomera et al., 2017; Faghiri et al., 2017). Thus, graph and centrality measures based on a static apprehension of the brain connectome may fail to capture key aspects of maturational differences in the brain temporal dynamics.

The most prominent age related reduction in centrality was seen in thalamus and cerebellum, converging with previous reports (Baker et al., 2015; Sato et al., 2015a; Petrican et al., 2017). Subcortical nodes have been reported to display enhanced connectivity with prefrontal nodes during adolescence (Ezekiel et al., 2013; Sato et al., 2015a). In conjunction, these findings suggest that subcortical networks reduce its influence throughout adolescence, through a drop in internal connectivity, shifting towards higher influence from frontal cortices and increased top-down control (Baker et al., 2015). Indeed, aberrant thalamo-cortical connectivity in adults have been linked to mental disorders (Wang et al., 2015; Skatun et al., 2017), where the suggested mechanisms include altered inhibition of sensory signalling. In line with the notion that cognitive and emotional development during childhood and adolescence is accompanied and supported by substantial tuning and specialization of brain network activation and connectivity, it was recently demonstrated that the brain connectome

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develops into a more stable and individualized pattern, and that a delay in this development is associated with increased burden of mental health issues (Kaufmann et al., 2017a).The balance between maintaining a stable and idiosyncratic connectivity pattern across contexts on one hand and brain network flexibility in response to dynamic contextual changes on the other may reflect a key characteristic of a healthy mind. Delineating the maturational trajectories of dynamic shifts in hub-properties between mental states may provide important clues for healthy and pathological brain development, as well as shed light upon adult neuronal pathology. Indeed, degree of damage to hub locations have been shown to be a key predictor of cognitive impairment (Warren et al., 2014).

Limitations

The current study employed a cross-sectional design. This limits the conclusions that can be made, as there is no measure of within-person changes, and cohort effects cannot be ruled out. To further differentiate healthy and pathological development, longitudinal studies will be of importance to better identify markers for delayed and aberrant maturation. Furthermore, the mounting evidence for misinterpreted motion-driven age-effects in previous developmental studies on FC (Power et al., 2012), calls for caution when interpreting maturational findings. Although we implemented stringent procedures for data denoising (Kaufmann et al., 2017a), it is not possible to completely rule out residual motion effects as a confounder regarding age-related findings.

Conclusion

Our study adds to the mounting evidence supporting the importance of hub development for healthy maturation during adolescence. The activation and centrality of cingulo-opercular components were associated with task engagement, task performance, as well as increasing

age. This supports the importance of the hub properties of cerebellum and cingulo-opercular network as key to healthy development of executive capacities, as well as its vulnerability to injuries and deviant development.

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Table captions:

*Table 1: A*natomical location for each IC

Table 2: Effect of task engagement on EC (n-back minus rest), and effect of EC on hit-rate, false positives, and d-prime, and effect of task on activation. Significant results are highlighted. All results are corrected for multiple comparisons (FDR), q = .05.

Table 3: Effect of age on EC in n-back, rest, and the interaction between n-back and age, and effect of age on activation. Significant results are highlighted. All results are corrected for multiple comparisons (FDR), q = .05.

Figure captions:

Figure 1: Results from the ICA-analysis, and corresponding statistics.

(1-1) The hierarchical clustering of the components, based on the partial correlations between the difference weights (n-back minus rest).

(1-2) Visualization of the IC spatial maps.

(1-3) Visualization of statistics described in Table 2, reflecting the effect of age on EC during both n-back and rest, and the interaction between age and task engagement respectively.

(1-4) The effect of task engagement on EC for the ICs, and effect of EC on hit-rate, false positives and d-prime, as described in Table 3.

(1-5) The significant effects of age on task activation, the effect of increases in task difficulty (load), as well as effects of task engagement and increase in load, on the ICs. Corresponds with values reported in Table 4.

(1-6) The IC-subject weight correlation-matrix. Correlations across both conditions are displayed below the diagonal, and was used for the hierarchical clustering displayed in A. Above the diagonal are the correlations between IC difference-weights (n-back minus rest).

*Figure 2:A*ssociations between BOLD and EC changes due to task engagement.
Abbreviations: *co*: cingulo-opercular network; *dmn*: default mode network; *fp*: frontoparietal; *sm*: sensorimotor; *sub*: subcortical; *vis*: visual

*Figure 3:*Age-effect on EC during both n-back and rest on the left panel, and activation in different network nodes on the right panel.
(3-1) Frontoparietal, (3-2) Cingulo-opercular, (3-3) DMN, (3-4) Visual, (3-5) Sensorimotor and (3-6) Subcortical. Non-significant associations are annotated.

*Figure 4:*Results from full-brain voxel-wise analysis.
(4-1) Significant changes in EC associated with differentiation between task and rest across the age-span. (4-2) Age-effect in the n-back data and (4-3) Age-effect in the rest-data. All maps were corrected for multiple comparisons using permutation testing (n=5000) and TFCE with an alpha of .05 (FWE, two-tailed).

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803 **Table 1**

Sensorimotor components	
IC	Area
7	Bilateral superior pre / postcentral gyrus
19	Right pre / postcentral gyrus, left superior cerebellum
30	Left pre / postcentral gyrus, right superior cerebellum
1	Bilateral Juxtapositional cortex, bilateral insular cortex, bilateral central opercular cortex
28	Bilateral precentral gyrus
10	Bilateral superior temporal gyrus
Visual components	
IC	Area
3	Bilateral Intracalcarine cortex, bilateral cuneal cortex, bilateral lingual gyrus
4	Bilateral lateral superior occipital cortex
15	Bilateral occipital fusiform gyrus, bilateral lingual gyrus
20	Bilateral occipital pole
11	Bilateral precuneus cortex
24	Right lateral occipital cortex
37	Left lateral occipital cortex
Task-positive network components	
Frontoparietal-associated components	
IC	Area
2	Right Superior parietal / lateral occipital cortex, right middle frontal gyrus, right paracingulate gyrus
6	Left Superior parietal / lateral occipital cortex, left middle frontal gyrus, left paracingulate gyrus
14	Left middle frontal / inferior frontal gyrus
17	Bilateral superior frontal gyrus, bilateral juxtapositional cortex
33	Bilateral superior posterior cingulate / precuneus, bilateral supramarginal gyrus
21	Bilateral superior parietal lobe / Precentral gyrus / Posterior cingulate / medial prefrontal cortex
Subcortical components	
13	Bilateral putamen
18	Bilateral thalamus
23	Cerebellum
Cingulo-opercular associated components	
16	Anterior cingulate cortex

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27	Bilateral frontal pole
32	Bilateral insula, bilateral frontal operculum
36	Right Insular cortex / frontal operculum
DMN associated components	
IC	Area
8	Bilateral superior medial prefrontal cortex
29	Bilateral inferior medial prefrontal cortex
26	Left middle temporal gyrus
9	Bilateral posterior cingulate cortex
34	Right posterior cingulate cortex, bilateral lateral occipital cortex

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817 **Table 2**

IC	Task effect		Hit-rate		False positives		d-prime		Activation	
	t	p	t	p	t	p	t	p	t	p
Sensorimotor										
7	**-7,95**	**6,7E-15**	-0,2	8,4E-01	0,99	3,2E-01	-0,26	8,0E-01	**-11,82**	**1,1E-29**
19	**-6,46**	**1,9E-10**	-1,58	1,2E-01	-0,21	8,4E-01	-1,09	2,8E-01	**-17,46**	**1,3E-57**
30	**-6,65**	**5,6E-11**	**-3,00**	**2,8E-03**	1,53	1,3E-01	**-3,48**	**5,4E-04**	**-7,10**	**2,8E-12**
1	**-9,73**	**3,6E-21**	-1,37	1,7E-01	0,88	3,8E-01	-1,92	5,5E-02	**-26,91**	**2,7E-112**
28	**-3,96**	**8,0E-05**	-0,22	8,3E-01	1,25	2,1E-01	-0,13	8,9E-01	**-15,77**	**1,3E-48**
10	**4,26**	**2,3E-05**	-1,95	5,2E-02	0,38	7,0E-01	**-2,32**	**2,1E-02**	**-16,49**	**2,2E-52**
Visual										
3	**-9,49**	**2,9E-20**	2,08	3,8E-02	-0,76	4,5E-01	1,88	6,1E-02	**-18,66**	**3,7E-64**
4	**-3,53**	**4,4E-04**	0,36	7,2E-01	-0,85	4,0E-01	1,29	2,0E-01	**-15,29**	**3,6E-46**
15	**-2,9**	**3,9E-03**	**-2,33**	**2,0E-02**	1,44	1,5E-01	-2,02	4,4E-02	**-15,35**	**1,8E-46**
20	-0,17	8,6E-	1,09	2,7E-	-0,46	6,4E-01	1,19	2,3E-	**-6,81**	**2,1E-**

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		01		01				01		**11**
11	**6,45**	**2,0E-10**	-0,12	9,0E-01	-1,24	2,1E-01	1,12	2,6E-01	**13,28**	**2,6E-36**
24	**2,36**	**1,9E-02**	-1,05	3,0E-01	0,07	9,4E-01	-0,45	6,5E-01	**-3,47**	**5,5E-04**
37	**4,37**	**1,4E-05**	**-2,45**	**1,5E-02**	1,12	2,6E-01	-1,91	5,6E-02	**-15,82**	**7,1E-49**
Frontoparietal										
2	**16,09**	**2,8E-50**	**3,63**	**3,1E-04**	-0,8	4,2E-01	2,21	2,8E-02	**29,80**	**1,7E-129**
6	**12,14**	**4,2E-31**	1,04	3,0E-01	-0,2	8,4E-01	0,33	7,4E-01	**13,19**	**6,8E-36**
14	**15,21**	**9,3E-46**	1,26	2,1E-01	-0,84	4,0E-01	0,79	4,3E-01	**26,79**	**1,4E-111**
17	**4,68**	**3,4E-06**	1,6	1,1E-01	-1,6	1,1E-01	1,36	1,7E-01	**21,79**	**5,1E-82**
33	**6,35**	**3,8E-10**	0,22	8,3E-01	-1,3	1,9E-01	0,35	7,3E-01	**-9,75**	**3,1E-21**
21	**6,58**	**8,5E-11**	-1,36	1,7E-01	-0,69	4,9E-01	-1,47	1,4E-01	**28,01**	**7,8E-119**
Subcortical										
13	-1,21	2,3E-01	-0,22	8,2E-01	-1,37	1,7E-01	0,81	4,2E-01	**-14,82**	**8,7E-44**
18	**-8,51**	**9,4E-17**	0,75	4,5E-01	**-2,76**	**6,0E-03**	**2,4**	**1,7E-02**	-1,81	7,0E-02
23	**6,74**	**3,2E-**	**2,69**	**7,3E-**	-1,96	5,0E-02	**3,7**	**2,3E-**	**25,37**	**3,9E-**

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		11		**03**				**04**		**103**
Cingulo-opercular										
16	**2,78**	**5,6E-03**	2,19	2,9E-02	**-2,36**	**1,8E-02**	**2,32**	**2,1E-02**	**9,57**	**1,6E-20**
27	**3,33**	**9,1E-04**	**2,64**	**8,5E-03**	0,4	6,9E-01	1,91	5,6E-02	**19,83**	**9,6E-71**
32	**3,11**	**1,9E-03**	1,29	2,0E-01	-1,53	1,3E-01	0,97	3,3E-01	**9,35**	**9,9E-20**
36	1,99	4,7E-02	0,73	4,6E-01	-0,96	3,4E-01	0,58	5,7E-01	**9,15**	**5,4E-19**
DMN										
8	1,73	8,4E-02	-0,7	4,8E-01	-0,28	7,8E-01	-0,46	6,5E-01	**-27,31**	**1,2E-114**
29	**-3,37**	**7,8E-04**	-0,18	8,6E-01	1,42	1,6E-01	-0,89	3,8E-01	**-33,81**	**3,6E-153**
26	**-4,03**	**6,1E-05**	-1,38	1,7E-01	1,77	7,7E-02	-1,53	1,3E-01	**-22,76**	**1,2E-87**
9	**9,03**	**1,4E-18**	0,74	4,6E-01	-1,71	8,7E-02	1,11	2,7E-01	**-21,41**	**8,6E-80**
34	**6,51**	**1,3E-10**	-1,09	2,8E-01	-0,1	9,2E-01	-1,26	2,1E-01	**-23,77**	**1,3E-93**

Table 3

IC	Age n-back	Age rest	Task x age	Activation age

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	t	p	t	p	t	p	t	p
Sensorimotor								
7	**4,71**	**2,90E-06**	**4,48**	**8,50E-06**	-0,05	9,60E-01	**-2,89**	**4,0E-03**
19	**6,12**	**1,50E-09**	**5,46**	**6,40E-08**	0,77	4,40E-01	-1,02	3,1E-01
30	**6,15**	**1,30E-09**	**7,00**	**5,70E-12**	-0,59	5,60E-01	0,51	6,1E-01
1	**4,98**	**8,10E-07**	**7,58**	**1,00E-13**	-0,96	3,40E-01	**-5,34**	**1,2E-07**
28	**7,14**	**2,20E-12**	**6,14**	**1,40E-09**	0,42	6,70E-01	**-3,54**	**4,2E-04**
10	**8,49**	**1,10E-16**	**5,8**	**9,90E-09**	2,17	3,00E-02	**-5,22**	**2,3E-07**
Visual								
3	**8,49**	**1,10E-16**	**6,39**	**2,80E-10**	1,68	9,20E-02	-0,19	8,5E-01
4	**6,74**	**3,10E-11**	**5,15**	**3,30E-07**	1,28	2,00E-01	**-2,56**	**1,1E-02**
15	**3,4**	**7,20E-04**	**3,52**	**4,60E-04**	-0,05	9,60E-01	-0,39	7,0E-01
20	**2,93**	**3,50E-03**	**3,31**	**9,80E-04**	0,11	9,10E-01	1,58	1,1E-01
11	**6,48**	**1,70E-10**	**6,39**	**2,90E-10**	0,07	9,40E-01	1,73	8,4E-02
24	**6,3**	**4,90E-10**	**5,29**	**1,60E-07**	0,02	9,80E-01	0,08	9,4E-01
37	**4,3**	**1,90E-05**	1,93	5,40E-02	1,79	7,40E-02	-1,05	2,9E-01
Frontoparietal								
2	1,25	2,10E-01	0,42	6,70E-01	0,88	3,80E-01	**4,62**	**4,6E-06**

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6	-1,45	1,50E-01	0,67	5,00E-01	-1,67	9,60E-02	1,09	2,8E-01
14	-0,09	9,30E-01	-0,9	3,70E-01	0,6	5,50E-01	**5,73**	**1,5E-08**
17	**5,53**	**4,30E-08**	**3,61**	**3,20E-04**	1,26	2,10E-01	**6,40**	**2,7E-10**
33	1,9	5,80E-02	**2,64**	**8,40E-03**	-0,69	4,90E-01	**-2,55**	**1,1E-02**
21	-1,61	1,10E-01	1,46	1,50E-01	**-2,36**	**1,90E-02**	**5,44**	**7,2E-08**
Subcortical								
13	-0,77	4,40E-01	-1,88	6,10E-02	0,95	3,40E-01	-2,33	2,0E-02
18	**-3,65**	**2,80E-04**	**-4,57**	**5,70E-06**	0,99	3,20E-01	-0,37	7,1E-01
23	0,06	9,60E-01	**-2,49**	**1,30E-02**	2,26	2,40E-02	**4,15**	**3,6E-05**
Cingulo-opercular								
16	**5,14**	**3,50E-07**	**3,81**	**1,50E-04**	1,08	2,80E-01	**3,38**	**7,6E-04**
27	-0,38	7,10E-01	1,44	1,50E-01	-1,38	1,70E-01	**3,34**	**8,8E-04**
32	**2,4**	**1,70E-02**	**3,8**	**1,60E-04**	-0,92	3,60E-01	1,27	2,0E-01
36	1,04	3,00E-01	1,43	1,50E-01	-0,32	7,50E-01	1,82	6,9E-02
DMN								
8	2,24	2,50E-02	0,6	5,50E-01	1,26	2,10E-01	**-4,73**	**2,7E-06**
29	-1,83	6,70E-02	-0,22	8,20E-01	-1,23	2,20E-01	**-5,62**	**2,7E-08**
26	**-5,36**	**1,10E-07**	**-2,1**	**3,60E-02**	-2,23	2,60E-02	**-4,65**	**4,0E-06**

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9	0,03	9,70E-01	-0,87	3,80E-01	0,65	5,10E-01	**-4,50**	**7,8E-06**
34	1,1	2,70E-01	-0,01	9,90E-01	0,82	4,10E-01	**-4,34**	**1,6E-05**

820

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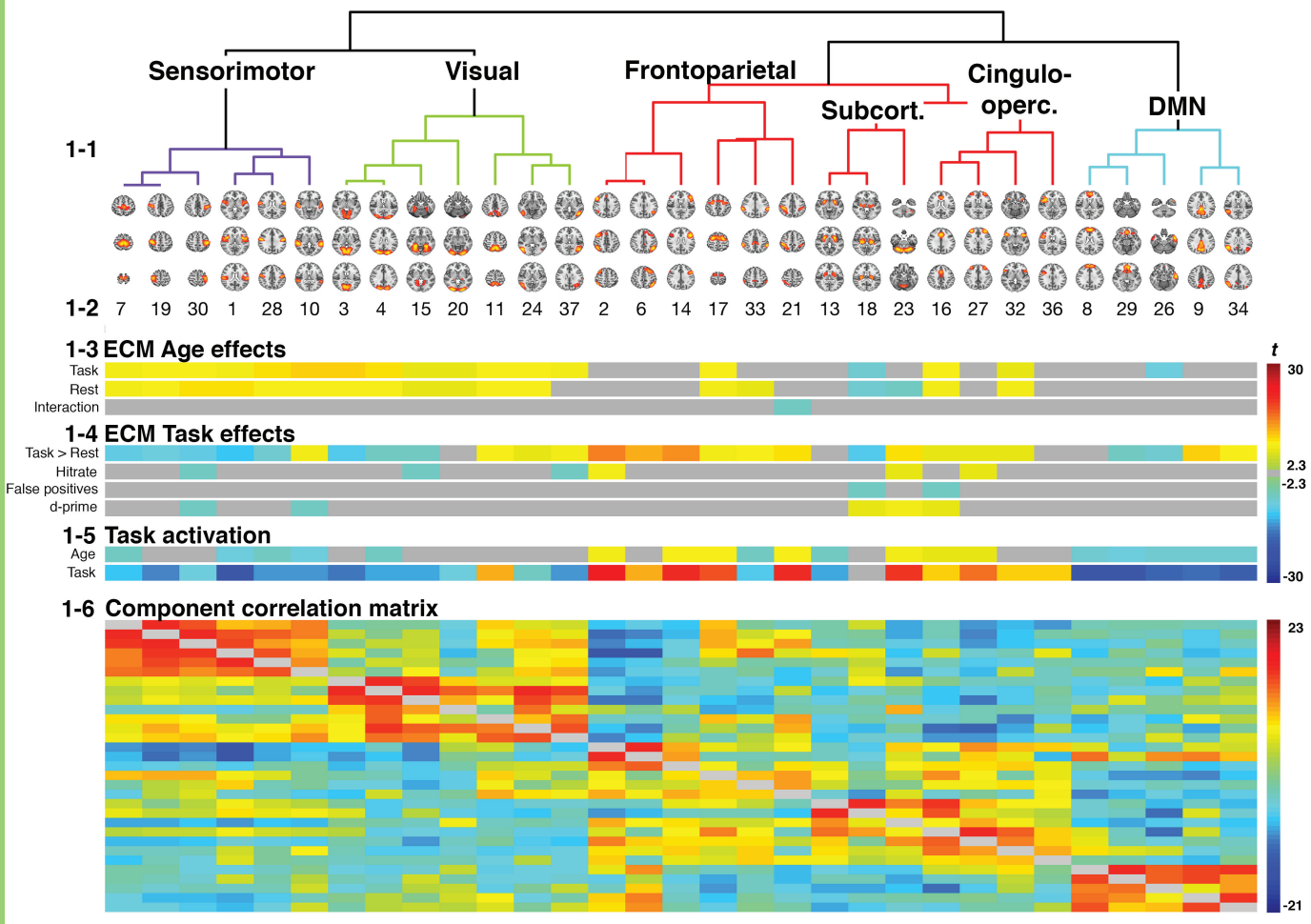

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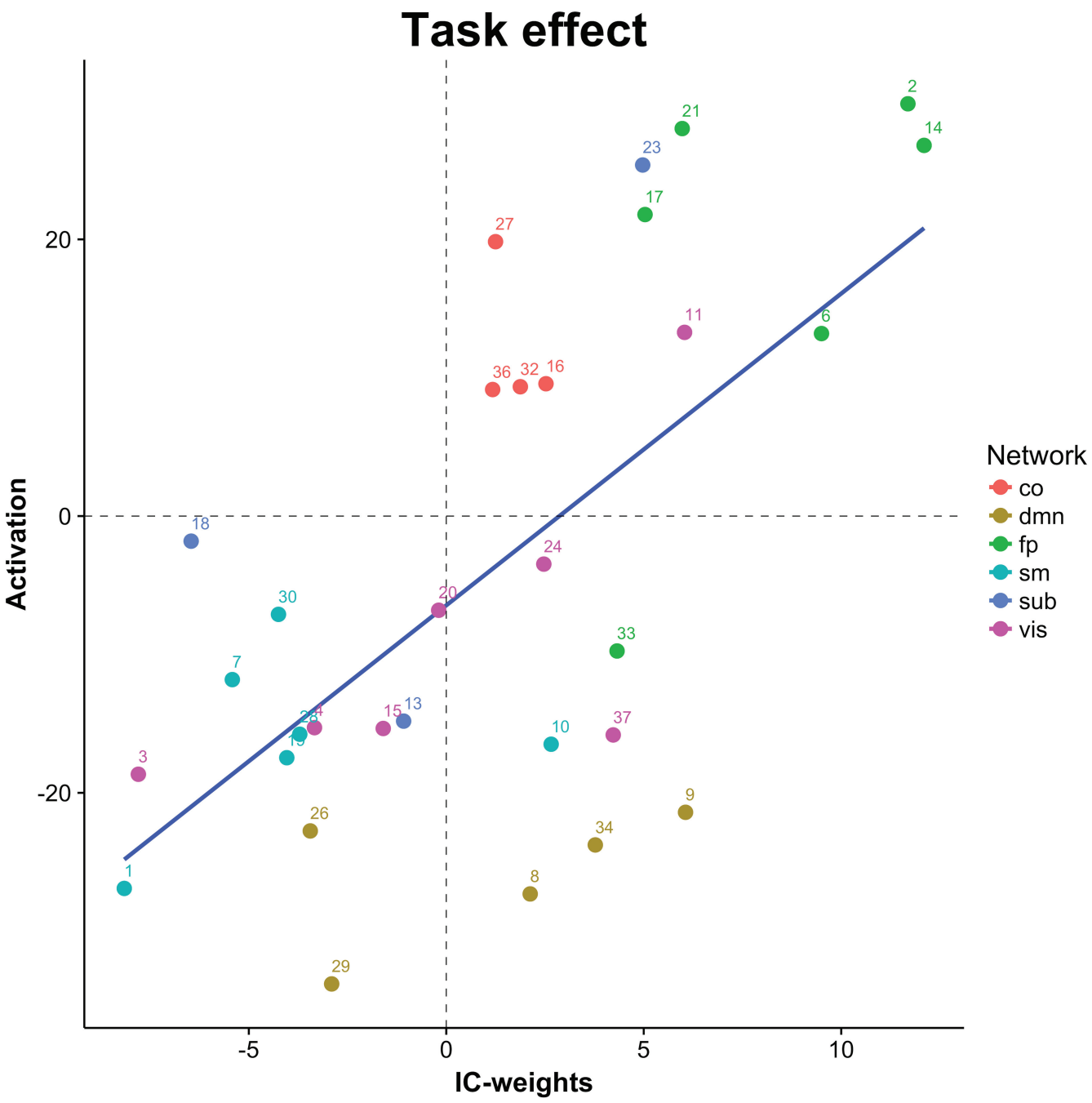

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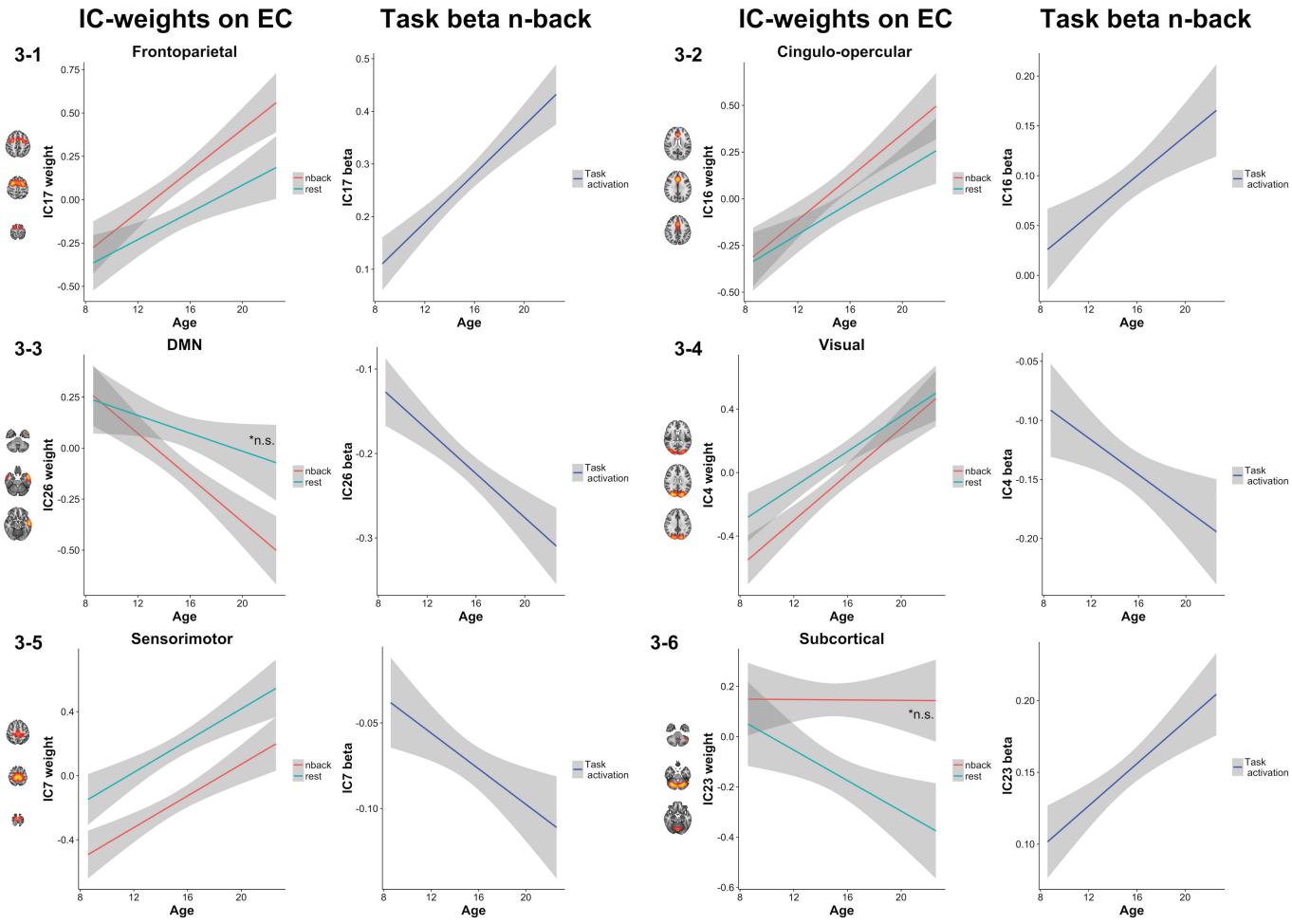

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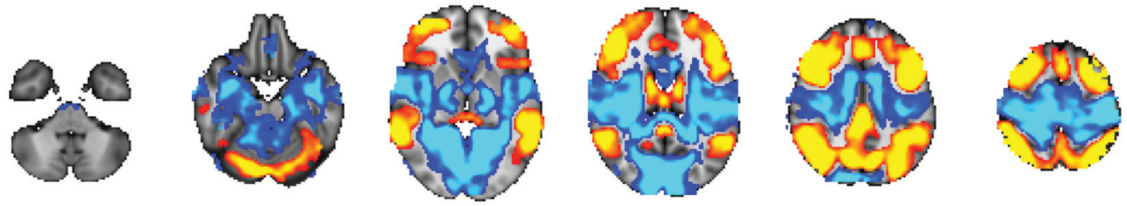

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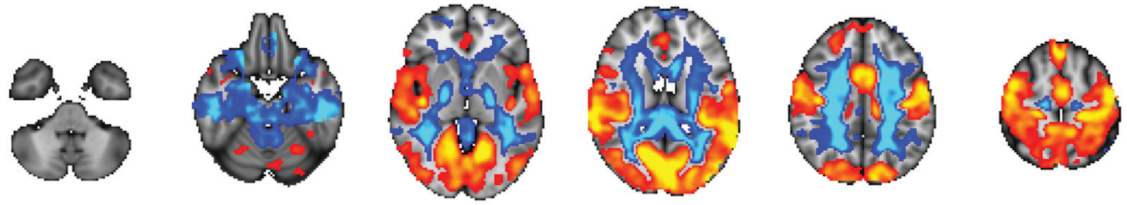
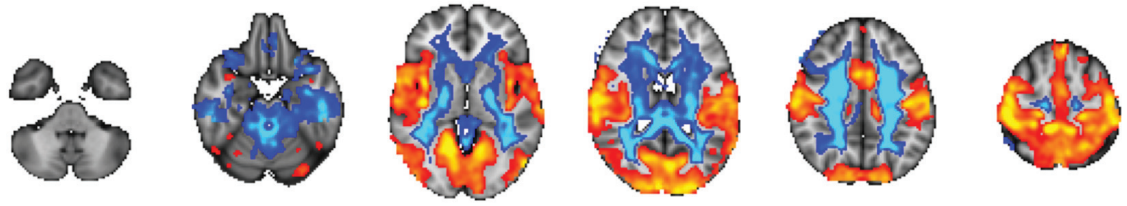
4-3