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Functional topography of the thalamo-cortical system during development and its relation to cognition

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ABSTRACT

The thalamus has complex connections with the cortex and is involved in various cognitive processes. However, little is known about the age-related changes of thalamo-cortical connections and their relation to cognitive abilities. The present study analyzed resting-state functional connectivity between the thalamus and nine cortical functional networks (default mode network (DMN), posterior DMN, left/right executive, dorsal attention, salience, motor, visual and auditory network) in a healthy human sample ($N = 95$, aged 5–25 years). Cognitive abilities, including processing speed, selective attention, and cognitive flexibility were assessed using neuropsychological tests. All nine cortical resting-state networks showed functional connections to the thalamus at rest, with no effect for sex ($p > 0.05$). For the motor, visual, auditory, DMN, posterior DMN, salience and dorsal attention network, we found mainly bilateral thalamic projections in the mediodorsal nucleus, pulvinar and in nuclei of the lateral group. For the right and left lateralized executive network, corresponding lateralized thalamic projections were found. Thalamo-cortical connectivity strength showed significant age-related changes from distinct sub-nuclei of the thalamus to different cortical networks including the visual, DMN, salience and dorsal attention network. Further, connectivity strength of thalamo-cortical networks was associated with cognitive abilities, including processing speed, selective attention and cognitive flexibility. Better cognitive abilities were associated with increased thalamo-cortical connectivity in the pulvinar, mediodorsal nucleus, intralaminar nucleus, and nuclei from the lateral group. Alterations in the integrity of the thalamo-cortical system seem to be crucial for the development of cognitive abilities during brain maturation.

1. Introduction

The thalamus is a complex structure composed of several nuclei with anatomical and functional connections to the cerebral cortex (Jones, 2007). Accumulating evidence supports a diverse role of the thalamus – not only as a sensory relay – but also in higher-order cognitive functions (Hwang et al., 2017; Mitchell et al., 2014). While the anatomical topography of the thalamo-cortical system is generally well understood, delineating thalamo-cortical patterns on a functional level is of increasing interest (Alcauter et al., 2014; Fair et al., 2010; Kim et al., 2013; Yuan et al., 2016; Zhang et al., 2010). The maturation of the thalamo-cortical system is of particular interest, as subcortical structures and their cortical interactions co-evolve during childhood and adolescence (Alcauter et al., 2014; Fair et al., 2010; Jones, 2007).

The thalamo-cortico-thalamic loop is already present during the late prenatal stages and is thought to be fundamental in regulating brain ontogeny of cortical and thalamic territories (Anton-Bolanos et al., 2018). Maturation and refinement of large-scale brain networks have been associated with maturation and establishment of cognitive abilities, such as processing speed, attention and executive functions (Grayson and Fair, 2017; Kolskar et al., 2018; Luna et al., 2015; Luna et al., 2001; Supekar et al., 2009; Uddin et al., 2011). The thalamus with its complex cortical and subcortical connections is suggested to be a critical integrative node in large-scale brain networks supporting cognitive processes (Fama and Sullivan, 2015; Halassa and Kastner, 2017; Hwang et al., 2017; Nakajima and Halassa, 2017; Saalmann, 2014).

Functional thalamo-cortical networks can be measured with resting-state functional magnetic resonance imaging (rs-fMRI), which is a task-independent method of exploring the brain's functional organization at rest (Fox et al., 2005; Greicius et al., 2003, 2009; Raichle, 2011;

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Raichle and Snyder, 2007). Rs-fMRI has gained wide appeal owing to its simple application and reliability within and between individuals (Fox and Raichle, 2007; Thomason et al., 2011). Multiple functional networks can be delineated from a single scan without the need for any task performance, which is particularly useful in pediatric and clinical populations.

Fair et al. (2010) examined resting-state thalamo-cortical connectivity in healthy children, adolescents and adults. They reported decreased connectivity strength between the thalamus and the frontal lobe in childhood compared to adulthood. Temporal lobe connections with the thalamus, however, were stronger in children and weaker in adults. In addition, premotor and somatosensory cortical subdivisions showed increased and decreased connectivity in different portions of the thalamus (Fair et al., 2010). In line with this, recent studies showed age-related changes in thalamo-cortical interactions with the insula, cingulate gyrus and the occipital cortex (Jacobs et al., 2019; Sato et al., 2015). Alcauter et al. (2014) examined thalamo-cortical connectivity in relation to visuo-spatial working memory performance in neonates and in one- and two-year-olds. Visuospatial working memory performance measured at one and two years of age was associated with thalamus–salience network connectivity.

These studies illustrate the utility of resting-state fMRI techniques to map age-related changes in thalamo-cortical connectivity. Yet, the characteristics of thalamo-cortical connectivity during the highly plastic but vulnerable developmental period between childhood and early adulthood are still largely unknown and knowledge about the relationship between thalamo-cortical connectivity and cognitive functions is scarce. Further, the rough classification of cortical subdivisions (Fair et al., 2010) may neglect detailed mapping within each lobe and simplify the underlying cortical organization of the thalamo-cortical relationships.

The functional organization of the cortex is subdivided into a set of networks with spatially distinct regions that are not necessarily bounded by lobes (Yuan et al., 2016). Innovative work on adults by Yuan and colleagues adopted a data-driven approach, performing spatial independent component analysis (ICA) on a series of correlation maps, using each thalamic voxel as a seed. With this approach, they identified independent patterns of the thalamo-cortical connectivity and illustrated that sub-nuclei of the thalamus have functional overlaps with multiple resting-state networks in adults (Yuan et al., 2016). However, whether such features are potentially already present in childhood and early adulthood still remains unknown.

Consequently, we aimed to investigate thalamo-cortical connectivity and its relation with age and cognitive functions (processing speed, attention, executive function) in healthy humans aged between 5 and 25 years. Building on the earlier findings presented above, we hypothesized that 1) there are age-related effects in thalamo-cortical connectivity, and that 2) there is a significant association between the strength of thalamo-cortical connectivity and cognitive abilities. In particular, we hypothesized that processing speed, selective attention, and executive function are associated with thalamo-cortical connectivity changes in networks known to be involved in cognitive functions.

2. Materials and methods

2.1. Participants

This study included 107 healthy participants, which were enrolled as controls in two different clinical studies (for more detail see Benzing et al., 2018; Kornfeld et al., 2018). They were recruited through flyers distributed in the hospital and its neighbourhood, and via siblings of the patient samples. All participants met the following inclusion criteria: absence of neurological disease or psychiatric disorders, no cognitive deficit (IQ > 85), and no contraindications for MRI (metal braces, metallic implants). Both studies were approved by the local ethics committee of the Canton of Bern and the ethics committee of the Children's University Hospital. All children and adolescents (and for subjects younger than 14 years, the legal guardian) signed written informed consent prior to enrollment. Participants were compensated for their participation (with a movie voucher or book voucher).

Twelve participants were excluded from data analysis for the following reasons: incidental findings (n = 2), retainer artefacts (n = 2), error in T1-weighted anatomical or functional image (n = 2), and motion artefacts (n = 6), which left a total of 95 subjects for the present study.

2.2. Cognitive measures

Standardized neuropsychological tests were used to assess cognitive functions and were conducted by trained psychologists or, under supervision, by study assistants and postgraduates. Neuropsychological assessments took place in the Division of Neuropediatrics, Development and Rehabilitation at the University Hospital in Bern, Switzerland, and were performed within the same week as the MRI visit at the Institute of Diagnostic and Interventional Neuroradiology, University Hospital in Bern, Switzerland. IQ was assessed to ensure comparable intellectual abilities across age in our study group. IQ was measured using a nonverbal intelligence test (Test of Nonverbal Intelligence Fourth Edition, TONI-4; Brown et al., 2010). Furthermore, different cognitive domains were assessed: 1) processing speed; 2) selective attention and 3) cognitive flexibility (the ability to flexibly switch between tasks), which is a core dimension of executive functions (Buttelmann and Karbach, 2017). These different cognitive domains were assessed with the following tests: 1) Processing speed was measured with the symbol search subtest of the Wechsler Intelligence Scale for Children (WISC-IV, Petermann and Petermann, 2012) and the Wechsler Adult Intelligence Scale (WAIS-IV). The symbol search task requires the participant to determine whether a target symbol appears among the symbols shown in a search group. Better performance is expressed by more completed items and therefore by a higher performance value. 2) Selective attention was assessed with the cancelation subtest of the WISC-IV (Petermann and Petermann, 2012). Children scan a two-page spread of relatively small colorful pictures. The pictures include animals and objects and the participant's task is to mark pictures that match the target animal. Better performance is expressed by more completed items and therefore by a higher score. This task primarily requires the participant's visual selective attention. Additionally, the task requires the neurocognitive processes of visual scanning, working memory and vigilance. 3) Cognitive flexibility was measured using the color word interference test of the Delis Kaplan Executive Function System (D-KEFS, Delis et al., 2004). This test was conducted only with participants from 8 years of age (N = 91). The task includes four conditions where participants are required to name colored squares (condition 1), read words indicating colors printed in black ink (condition 2), name the incongruous ink color of printed color words (condition 3), and switch between naming the ink color and reading the color words (condition 4). This study only contains the results from condition 4 (inhibition and switching), which requires participants to inhibit an overlearned response (i.e., naming color of the words while ignoring their semantic content) and demonstrate flexibility by set shifting. Better performance is expressed by faster completion time and therefore by lower values.

2.3. Statistical analyses of participants' characteristics and cognitive measures

Analyses of cognitive data were carried out using MATLAB 9.2 (MathWorks, Sherborn, MA, USA). To calculate IQ, raw scores of the TONI-4 were converted into age-normed scores according to the test (manual for one participant (aged 5 years) no normative data was available) (Brown et al., 2010). For the cognitive domains (processing speed, selective attention and cognitive flexibility), raw scores were used for all analyses. Associations between age and cognitive variables were an-

alyzed by Spearman's rank correlations. Each test score was converted to a Z-score.

2.4. Image acquisition and preprocessing

MRI data was acquired on a 3T Magnetom Verio or a Prisma Siemens scanner (Siemens, Erlangen, Germany). Scanner type was controlled in all analyses as covariate. The structural images were collected using a three-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) T1-weighted sequence (repetition time (TR)=2530 ms, echo time (TE)=2.96 ms, inversion time (TI)=1100 ms), and a flip angle (FA)=7°, field of view (FOV) 256 × 256 mm^2, matrix dimension 256 × 256, leading to an isovoxel resolution of 1 × 1 × 1 mm^3, acquisition time (TA)=5.05 min). Functional imaging was acquired using the T2*-weighted multi-band, simultaneous excitation echo planar imaging (mb-EPI) sequence (TR=300 ms, TE=30 ms, FA=30°, FOV 230 × 230 mm^2, matrix dimension 64 × 64, 32 axial slices positioned along the anterior commissure and the posterior commissure with a slice thickness of 3.6 mm, gap 0 mm, leading to an isovoxel resolution of 3.6 × 3.6 × 3.6 mm^3). Each scan consisted of 1000 image volumes and acquisition time was (TA)=5.06 min. To minimize head motion, a head support system consisting of two pillows positioned on either side of the head was used. Earplugs reduced the scanner noise. Participants were instructed to stay awake with their eyes closed and to remain as motionless as possible during scanning.

Preprocessing of fMRI data was performed using FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk; (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). fMRI time series of each subject was pre-processed as follows (pipeline recommended by Power et al. (2014); Power et al. (2015) and Pruim et al. (2015)): 1) rigid body realignment; 2) within-subject intensity normalization. In this step, the intensity across all voxels is scaled to a norm value of 1000. This implies that the BOLD signal afterwards is represented in a mode 1000 scale (10 units = 1% BOLD); 3) coregistration of fMRI data to each individual anatomical MP-RAGE scans. During this step, all fMRI data are resampled to a isovoxel space with 3 mm × 3 mm × 3 mm spatial resolution. 4) the functional images were then transformed to the standard Montreal Neurological Institute (MNI) template.

Contrary to the pre-processing steps described in Power et al. (2014), we did not apply the slice-time correction to the raw fMRI time series. As we had a multi-band, simultaneous excitation EPI sequence with TR=300 ms in which multiple slices are acquired at the same time, the effect of interpolation to temporally align each slice to the start of each volume is negligible.

2.4.1. Identification and treatment of subjects' motion by censoring fMRI time series

In the present study, we followed the recommendations of Power et al. (2014) and Power et al. (2015) to potentially identify and eventually remove subjects' motion caused during fMRI acquisition. Head motion could be a source that influences the computation of correlations in resting-state functional connectivity fMRI. We used the measure of framewise displacement (FD) to monitor the absolute amount of motion during acquisition and the relative measure expressed as root mean square value of the differentiated BOLD time series (by backwards differences, DVARS). This DVARS measure captures the change in signal intensity from one volume to the adjacent previous volume.

These two measure were used to censor (e.g. scrubbing) volumes for the fMRI time series. In the present analysis, we used the following criteria to identify and quantify "artifact-affected volumes": FD>0.2 and DVARS>0.38, i.e. a "geometrical" and a "physiological" surrogate of motion-related signal component. The exact procedure of censoring volumes and its effect on the quality of the data of each subject (supplement Figs. S1–S6) are described in more detail in the supplement material.

2.4.2. Nuisance regressors

During the realignment step, a set of 6 motion estimates (R = [x,y,z, pitch, yaw, roll]) are stored for each subject. These motion estimates are the basis for the computation of four additional motion-related indices such as: their derivatives (R′), their squares (R^2), (R_{t-1}) and ($R^2{}_{t-1}$), where t and $t-1$ refer to the current and immediately preceding time point of the fMRI time serie.

Altogether, these 24 motion-related indices are further used as nuisance regressors in the multiple regressions. Additionally, tissue-based signals from average signal across voxels within a ventricular mask for the CSF signal and white matter mask for the WM signal were used as nuisance regressors.

Lastly, in the present study we included global signal regression (GSR) (Fox et al., 2009; Murphy et al., 2009) as an effective procedure to remove motion-related artefacts (Power et al., 2014).

In summary, a total set of 27 nuisance regressors were included in the multiple regressions.

2.5. Processing of neuroimaging data and statistical analyses

2.5.1. The thalamus mask

We adopted the Harvard–Oxford cortical and subcortical structural atlases (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) to define a mask for the thalamus (Region 10 and 49; left and right thalamus). A total of 672 voxels were included in the final thalamus mask, which was downsampled into matching 3 × 3 × 3 mm^3 in MNI space.

2.5.2. Identifying thalamic connectivity patterns

To identify thalamic connectivity patterns, we adopted the same analyses strategy as Yuan et al. (2016). Each time series from each voxel of the thalamus was correlated to all voxels of the rest of the brain using Pearson's correlation coefficient. This procedure resulted in 672 seed-based correlation maps (connectivity maps) for each subject. All correlation maps were then Fisher-transformed to Z-scores ($Z = 0.5 * \ln(1 + r/1 - r)$). Z-score maps from all subjects were concatenated into a single 4D dataset with the dimensions of 61 × 73 × 61 × 63,840 voxels (a single volume has 61 × 73 × 61 voxels; 672 vol for each of the 95 subjects). We calculated the ICA on the resulting seed-based correlation maps using FSL's MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) (Beckmann, 2005) to identify spatially distinct connectivity maps. The resulting 4D data set was decomposed into 20 spatially independent components (ICs), representing large-scale patterns of functional connectivity of the thalamus to the whole brain (Yuan et al., 2016). From this set of ICs, we were able to identify nine well-known brain networks for further analysis.

2.5.3. Thalamo-cortical connectivity

To quantify the functional connectivity between each thalamic voxel and brain network, we first determined the contributions of each IC network with the individual thalamic connectivity maps (subject level). These individual thalamic correlation maps and the IC network maps were then transformed into vectors, and linear regression was used to quantify functional connectivity for each voxel across all individuals. In particular, linear regression was used to measure the contribution from each IC to the voxel's seed-based correlation map (for each given voxel in the thalamus). The regression analysis was performed for all of the 672 voxels in the thalamus, and nine beta values were obtained for each voxel. A voxel-wise, one sample t-test was performed on every network's thalamic beta map across subjects to find all significant clusters in the thalamus for each network separately.

In order to correct for multiple testing, we applied false discovery rate (FDR) adjusted p-values for multiple comparisons. An FDR-adjusted $p < 0.05$ was considered statistically significant in all models

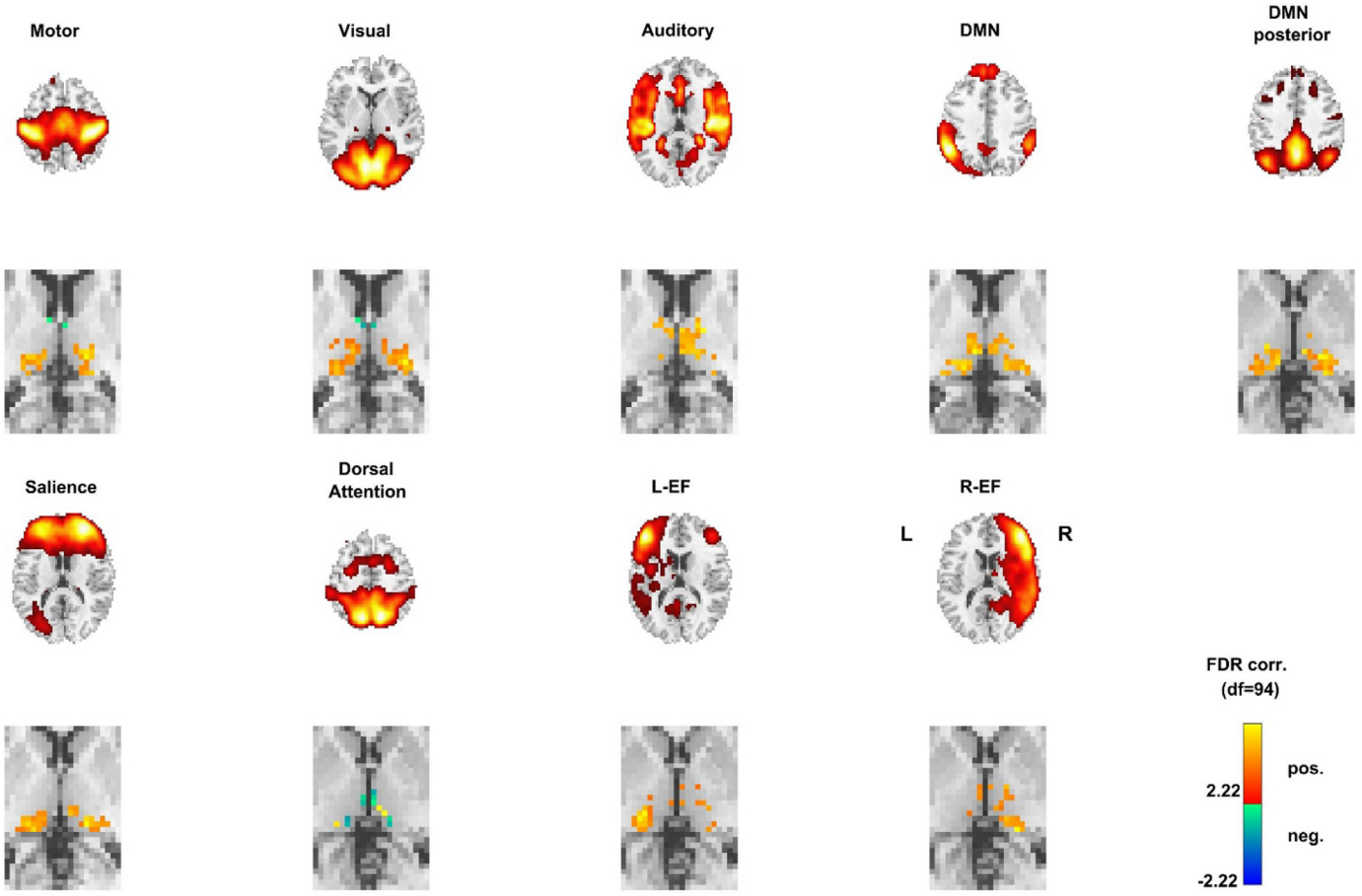

Fig. 1. Thalamo-cortical networks. Nine cortical networks from group level ICA (first and third row) and thalamic projections for each resting-sate network (second and fourth row).
Notes. DMN, default mode network; L-EF, left executive network; R-EF, right executive network. The right side of the brain is on the right side of the image. All sub-regions of the thalamus are thresholded at FDR corrected $p = 0.05$. Only FDR corrected voxels are depicted in the figure. All reported results are significant after FDR correction.

that we used. This analysis pipeline is similar to the procedure used in Yuan et al. (2016) in an adult population.

2.5.4. Association of thalamo-cortical connectivity, age, sex and cognitive abilities

To explore a potential effect of sex, two sample *t*-tests were conducted for thalamo-cortical connectivity for each network separately. The relationship between thalamo-cortical connectivity strength and age and cognition was investigated with multivariate linear regressions. Thalamo-cortical connectivity strength values were extracted from all identified significant clusters in the thalamus, for each network separately. 1) To investigate the effect of age on thalamo-cortical connectivity, we adopted multivariate linear regressions, where age was integrated as independent variable and connectivity strength values as dependent variables, with sex, scanner type and motion (mean FD) as covariates. 2) To investigate the effect of cognitive abilities (processing speed, selective attention, and cognitive flexibility) on thalamo-cortical connectivity strength, we adopted multivariate linear regressions, where cognitive variables were integrated as independent variables and connectivity strength values as dependent variables, with age, sex, scanner type and motion (mean FD) as covariates.

The significant clusters in the thalamus were identified and labeled according to the thalamus atlas by Morel and Krauth (Krauth et al., 2010; Morel et al., 1997). This atlas is built in MNI space and includes 40 small thalamic nuclei. Correction for multiple comparisons were made using false discovery rate (FDR). Analyses were carried out using MATLAB 9.2 (MathWorks, Sherborn, MA, USA).

3. Results

3.1. Descriptive and cognitive measures

The final sample consisted of 95 healthy participants, with 46 males (median 14.06 years; SD 4.6; range 5.08–25.92) and 49 females (median 12.91 years; SD 3.9; range 6.08–24.75). Using age-dependent normative values, there were no effects of age on IQ (age: r=−0.17, $p = 0.1$), nor a significant effect of sex on IQ (z=−0.47; $p = 0.641$). Using raw scores of cognitive subtests, age was significantly correlated with processing speed ($r = 0.71$, $p = 0.000$), selective attention ($r = 0.61$, $p = 0.000$) and cognitive flexibility (r=−0.67, $p = 0.000$).

3.2. Thalamo-cortical networks

3.2.1. Group level ICA of thalamic correlation maps

Nine networks involved in cognition, sensory and motor related processing were identified and were comparable to the networks that have generally been observed in resting-state fMRI studies (Alcauter et al., 2014; Fox and Raichle, 2007; Thomason et al., 2011; Yuan et al., 2016). These nine networks corresponded to the default mode (DMN), the posterior DMN, left and right executive, auditory, dorsal attention, motor, salience and visual network (Fig. 1).

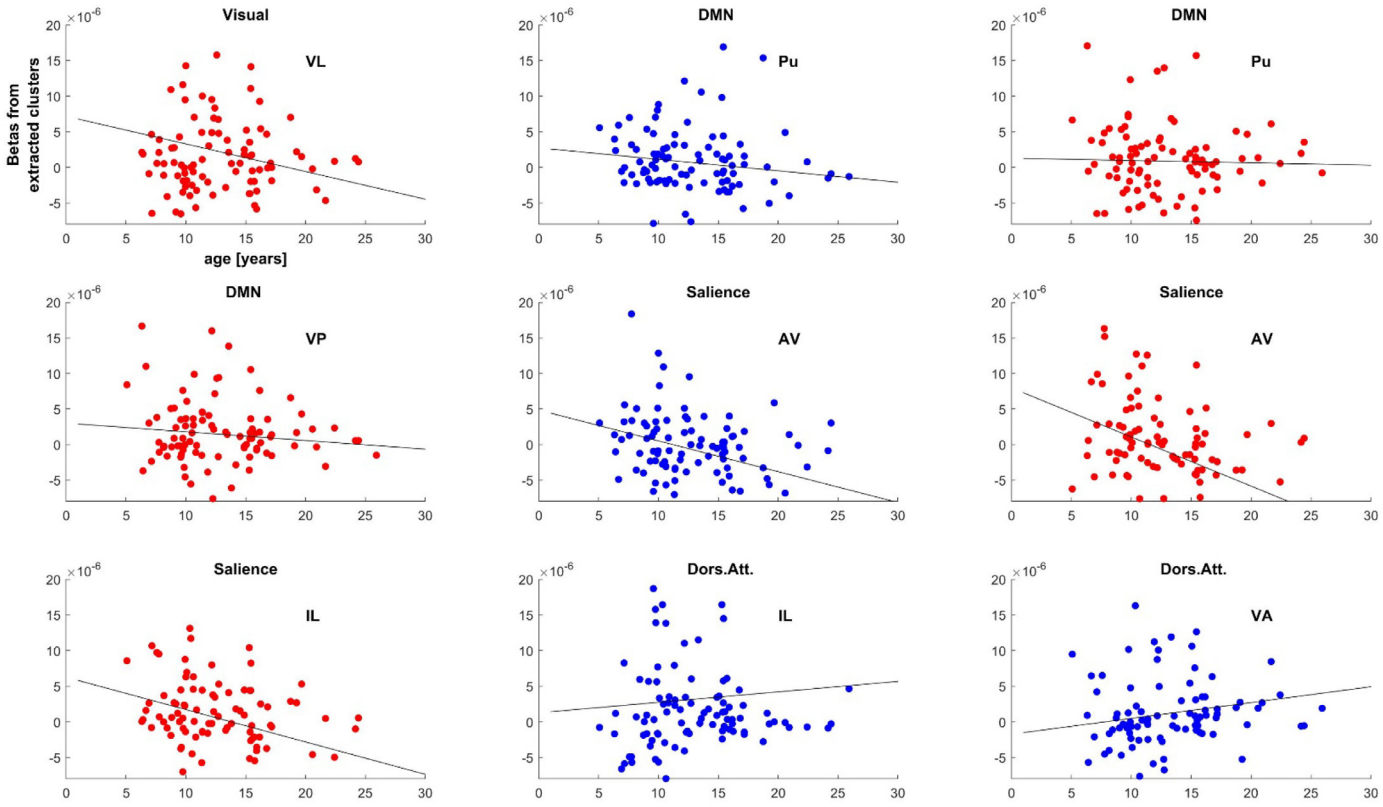

Fig. 2. Age-related decrease of thalamo-cortical connectivity strength. *Notes.* Y axis displays connectivity strength (beta values) extracted from significant thalamo-cortical clusters. X axis displays age in years. Blue dots are for clusters extracted from the left thalamus, red dots are for clusters extracted from the right thalamus. DMN, default mode network; AV, anteroventral; IL, intralaminar; Pu, pulvinar; VA, ventral anterior; VL, ventral lateral; VP, ventral posterior. All reported results are significant after FDR correction.

3.2.2. *Thalamic mapping of corresponding brain networks*

Fig. 1 shows thalamic sub-regions associated with each of the nine resting-state networks. The motor network is mainly associated with the pulvinar, ventral lateral and intralaminar nucleus. The visual network encompasses almost all lateral, medial and posterior sub-thalamic nuclei, including the pulvinar, ventral lateral nucleus, ventral posterior lateral nucleus, mediodorsal nucleus and lateral posterior nucleus. Regions associated with the auditory network are located mainly in the anterior and medial thalamic nuclei, including the anteroventral, lateral dorsal and mediodorsal nuclei. The DMN-related sub-regions encompass almost all nuclei of the thalamus, including the pulvinar, the posterior, the ventral lateral, the mediodorsal as well as the anteroventral nuclei. The posterior DMN network encompasses the pulvinar, the ventral lateral and the posterior nuclei. The thalamic sub-regions corresponding to the salience network are found mostly in the pulvinar, the mediodorsal nucleus, a small portion also at the anterior part of the thalamus and the lateral posterior nucleus. The dorsal attention network showed only small clusters in the thalamus, including the pulvinar, lateral posterior nucleus, mediodorsal nucleus and lateral dorsal nucleus. The left and the right executive networks presented lateralized connectivity patterns in the thalamus, covering the major parts of the mediodorsal nucleus, the pulvinar and the ventral lateral nucleus. Analyses revealed no effect of sex on thalamo-cortical networks ($p > 0.05$).

3.3. *Age-related changes in thalamo-cortical connectivity*

Fig. 2 and Table 1 summarize age-related changes in thalamo-cortical connectivity between different sub-nuclei of the thalamus and cortical networks. Analyses revealed significant age-related changes of thalamo-cortical connectivity in the visual, DMN, salience and dorsal attention network. For the visual network, we found an age-related decrease in connectivity in the right ventral lateral nucleus. For the DMN, we found a decrease in functional connectivity in the right ventral posterior nucleus and the bilateral pulvinar. For the salience network, age-related decreases were observed in the bilateral anteroventral and right intralaminar nucleus. In the dorsal attention network, age-related increases were found in the right intralaminar and ventral anterior nucleus. All reported results are significant after FDR correction. Voxels and t values are listed in Table 1.

Table 1
Significant associations between thalamo-cortical connectivity and age. Significant clusters in different sub-nuclei of the thalamus to various cortical networks are listed.

Network	side	nuclei	*t*	*p*	voxel
Visual	R	VL	−2.38	0.019	7
DMN	R	VP	−2.55	0.012	8
DMN	L	Pu	−2.23	0.028	3
DMN	R	Pu	−2.46	0.016	13
Salience	L	AV	−3.24	0.002	4
Salience	R	AV	−2.74	0.007	5
Salience	R	IL	−2.91	0.005	10
Dorsal Attention	R	IL	−2.44	0.017	3
Dorsal Attention	R	VA	−3.35	0.001	5

Notes. L, left; R, right; DMN, default mode network; AV, anteroventral; IL, intralaminar; Pu, pulvinar; VA, ventral anterior; VL, ventral lateral; VP, ventral posterior. All reported results are significant after FDR correction.

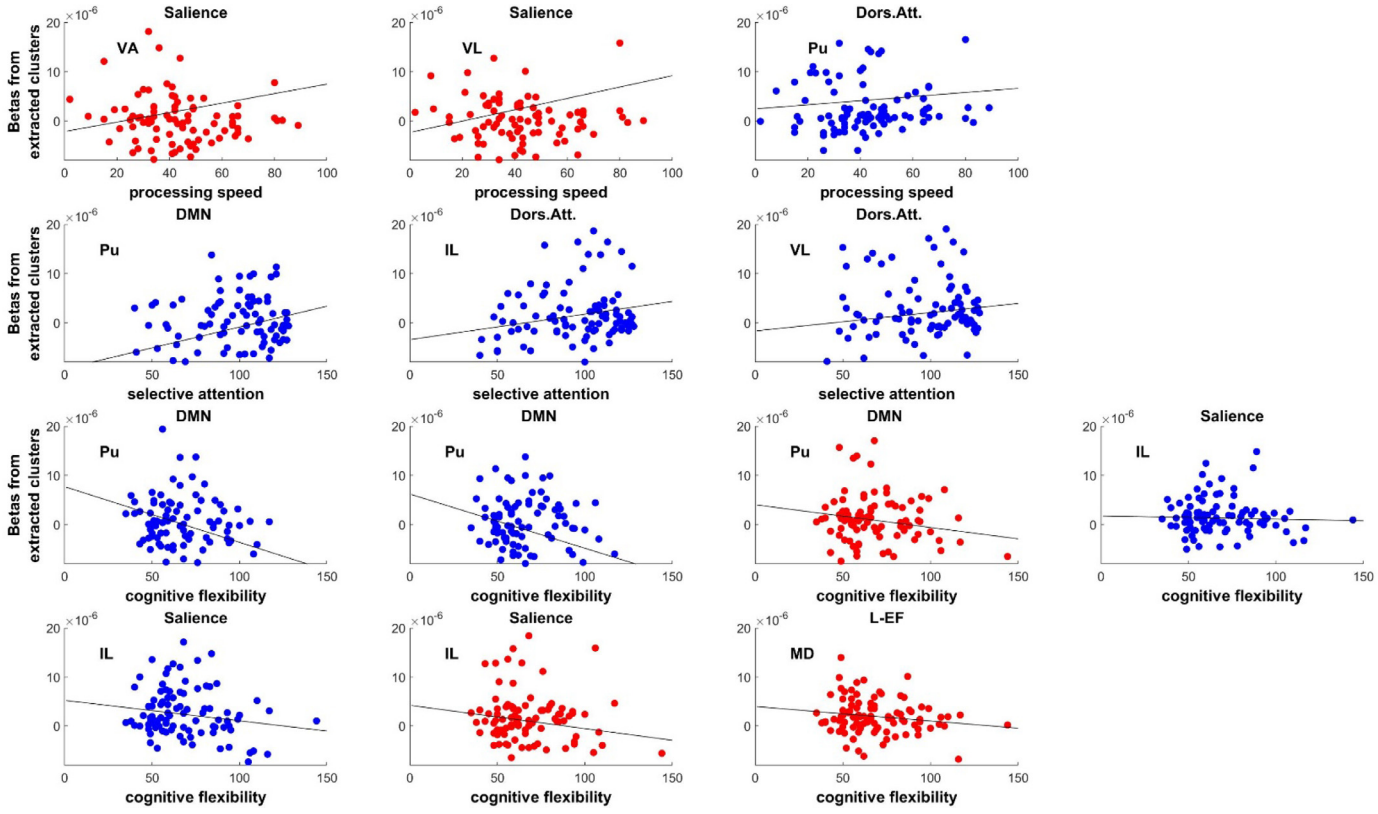

Fig. 3. Relationship between thalamo-cortical connectivity strength and cognitive abilities.
Notes. Y axis displays connectivity strength (beta values) extracted from significant thalamo-cortical clusters. *X* axis displays processing speed (first row), selective attention (second row), and cognitive flexibility (third and fourth rows). Blue dots are for clusters extracted from the left thalamus, red dots are for clusters extracted from the right thalamus. DMN, default mode network; L-EF, left executive network; AV, anteroventral; IL, intralaminar; MD, mediodorsal; Pu, pulvinar; VA, ventral anterior; VL, ventral lateral; LD, lateral dorsal. All reported results are significant after FDR correction.

3.4. Thalamo-cortical connections and cognition

Analyses revealed significant associations between cognitive abilities (processing speed, selective attention, cognitive flexibility) and the strength of thalamo-cortical connectivity (Fig. 3). We found significant positive associations between processing speed (where higher values mean better performance) and thalamo-cortical connectivity for the salience and dorsal attention network in the pulvinar, ventral anterior and ventral lateral nucleus. Further, we found significant positive associations between selective attention (where higher values mean better performance) and thalamo-cortical connectivity for the DMN and dorsal attention network in the pulvinar, intralaminar and ventral lateral nucleus. In line with this, lower completion time in the cognitive flexibility task (where lower values mean better performance) was associated with higher thalamo-cortical connectivity for the DMN, salience, and left executive network in the pulvinar, intralaminar and mediodorsal nucleus. For the remaining networks, no significant association was found between cognitive tasks and thalamo-cortical connectivity. All reported results are significant after FDR correction. For a detailed description of the association between thalamo-cortical connectivity and cognition, see Table 2.

Table 2
Significant associations between thalamo-cortical connectivity and processing speed, attention and cognitive flexibility. Significant clusters in different sub-nuclei of the thalamus to various cortical networks are listed.

Network	side	nuclei	*t*	*p*	voxel
Processing speed					
Salience	R	VA	2.30	0.024	6
Salience	R	VL	2.72	0.008	3
Dorsal Attention	L	Pu	2.90	0.005	10
Selective attention					
DMN	L	Pu	2.74	0.007	3
Dorsal Attention	L	IL	2.55	0.012	3
Dorsal Attention	L	VL	2.36	0.021	3
Cognitive flexibility					
DMN	L	Pu	−2.91	0.005	4
DMN	L	Pu	−2.32	0.001	4
DMN	R	Pu	−3.36	0.021	13
Salience	L	IL	−2.36	0.021	4
Salience	L	IL	−2.35	0.021	9
Salience	R	IL	−2.35	0.021	4
L-EF	R	MD	−2.49	0.015	7

Notes. L, left; R, right; DMN, default mode network; L-EF, left executive network; IL, intralaminar; MD, mediodorsal; Pu, pulvinar; VA, ventral anterior; VL, ventral lateral. All reported results are significant after FDR correction.

4. Discussion

In the present study, we investigated functional connectivity of the thalamo-cortical system and its relation to age and cognitive functions in healthy humans (5–25 years of age). The current study demonstrated that the thalamus has extensive functional connectivity to nine resting-state networks. According to our primary hypothesis, thalamo-cortical connections showed significant age-related changes from distinct sub-nuclei of the thalamus to different cortical networks involved in visual and cognitive processing. In addition, we provide evidence that thalamo-cortical networks, including the DMN, salience, dorsal attention and executive network are associated with processing speed, selective attention and cognitive flexibility.

4.1. Thalamo-cortical networks

The thalamus is divided into individual nuclei, each of which is reciprocally connected to a unique set of cortical regions (Nakajima and Halassa, 2017). These individual nuclei are subdivided into three major nuclear regions: the anterior, ventral, and medial nuclei. In addition, the pulvinar attaches to these larger regions caudally and the internal medullary lamina proceeds between the major thalamic nuclei, consisting of small intralaminar nuclei. In the current study, various sub-nuclei of the thalamus were associated with multiple resting-state networks, a finding that has been reported previously in adults (Yuan et al., 2016). The fact that there are functional overlaps of thalamic sub-nuclei with multiple resting-state networks supports the adopted data-driven approach, where each thalamic voxel is used as a seed for thalamo-cortical analyses with the cortex.

The thalamic sub-regions corresponding to the motor, visual, DMN and salience network encompassed mainly the lateral, medial and posterior nuclei, including the pulvinar, ventral lateral, ventral posterior, mediodorsal and lateral posterior nucleus. Regions associated with the auditory network were mainly located in the anterior and medial nuclei, including the anteroventral, lateral dorsal and mediodorsal nuclei. These thalamic sub-regions correspond with results from previous studies in adults (Jones, 2007; Yuan et al., 2016). However, compared to adults, the thalamic clusters seem to be more diffuse and widespread during brain maturation, highlighting that the clusters may become functionally specialized at a later age. For the dorsal attention network, this assumption is further strengthened, as we found very small, but widespread clusters across the thalamus (including the pulvinar, mediodorsal, ventral lateral, and lateral dorsal nucleus). For the right and left lateralized executive network, we found corresponding lateralized thalamic connectivity patterns, mainly in the mediodorsal nucleus, pulvinar and in the lateral group. In line with this finding, Yuan et al. (2016) demonstrated in adults, that the left and right lateralized executive network displayed lateralized projection in the thalamus mainly in the mediodorsal nucleus and the pulvinar.

4.2. Age-related changes in thalamo-cortical networks

We observed significant age-related changes of functional thalamo-cortical connectivity in all three major nuclear regions, as well as the pulvinar and the intralaminar nuclei with cortical resting-state networks. Decreased functional connectivity was observed for the visual, DMN and salience network, whereas increased functional connecitivty was observed for the dorsal attention network. The change of thalamo-cortical connectivity from childhood to young adulthood points towards an ongoing refinement of specific thalamo-cortical interactions over development. To some degree, changes in thalamo-cortical connectivity rely on changes of anatomical pathways (Betzel et al., 2014). Axonal retraction and the elimination of axon collaterals continue throughout development and aging (Luo and O'Leary, 2005). Early in development, there is a proliferation of synapses followed by a period of synaptic pruning that reaches adult levels in the late second decade of life. These regressive processes are highly selective, reduce connectivity between specific regions, and occur in both cortical and subcortical structures (Jones, 2007; Luo and O'Leary, 2005). Moreover, through the maturation of the myelin sheath, signal propagation between different regions increases until young adulthood, which might explain increases in functional connectivity observed for the attention network.

However, it is known that the connectivity signal measured with resting-state fMRI is not a pure representation of anatomical connectivity (Hagmann et al., 2008; Zhang et al., 2008). Thus, other explanations must be considered. The circuitry of the thalamus is complex and its function is determined not only by the structural anatomy to the cortex, but also by other modulating factors, including interneurons, subcortical input from other structures and neurotransmitter systems. Many properties related to modulatory factors continue to develop postnatally, and thus, it is likely that changes in thalamo-cortical connectivity observed in our analyses are influenced by maturation of modulatory systems (Jones, 2007). In line with this, previous studies showed age-related thalamo-cortical changes over development (Alcauter et al., 2014; Fair et al., 2010; Jacobs et al., 2019).

Contrary to previous findings, our data does not provide evidence for increased age-related thalamo-cortical connectivity with frontal structures, which has been shown before (Fair et al., 2010). Potential reasons for this inconsistency might be differences in the analyses method. We did not investigate pre-defined regions (ROI) in the cortex (e.g. frontal structures) such as the study of Fair et al. (2010), but rather applied a data-driven approach where resting state networks were obtained by ICA (where multiple structures of the cortex are integrated in a network).

4.3. Thalamo-cortical networks and cognition

Our secondary aim was to gain insight into the relationship between thalamo-cortical connectivity and cognition. Cognitive abilities (processing speed, selective attention, and cognitive flexibility) were associated with functional connectivity between several thalamic nuclei and networks involved in cognitive functions. Significant associations between thalamo-cortical connections and cognitive abilities were observed for the DMN, salience, dorsal attention and executive network. For the remaining networks, no significant association was found between cognitive tasks and thalamo-cortical connectivity.

Our finding of significant positive correlations between cognitive tasks and thalamo-cortical connectivity within the DMN, salience, dorsal attention and executive network provides further evidence that the interaction between the thalamus and these networks may be crucial for core cognitive processes. The salience network - including the fronto-insular cortex and anterior cingulate cortex - is involved in attention, salience detection, working memory and conflict monitoring (Alcauter et al., 2014; Menon and Uddin, 2010; Seeley et al., 2007; Smith et al., 2009), all of which are essential skills for the achievement of cognitive maturation across childhood and adolescence. The dorsal attention network - including mainly the superior parietal cortex and parts of the occipital cortex - is known to be important for cognitive tasks that require externally focused visuospatial attention (Dixon et al., 2017) and goal-directed, top-down processing (Farrant and Uddin, 2015). The fronto-parietal executive network – including the dorsolateral prefrontal cortex and posterior parietal cortex - is related to maintenance and manipulation of information and decision making in the context of goal-directed behavior (Uddin et al., 2011), all processes involved in the cognitive tasks used in our study.

Nuclei that showed higher connections with cognitive networks included the mediodorsal, intralaminar, pulvinar, and nuclei from the lateral and anterior group. The intralaminar and mediodorsal nuclei are part of the higher-order thalamus, which receives little sensory input, and instead forms extensive cortico-thalamo-cortical pathways. The mediodorsal nucleus has reciprocal connections to the prefrontal cortex and anterior cingulate cortices (Golden et al., 2016; Watanabe and Funahashi, 2012), whereas the intralaminar nuclei connects with fronto-parietal cortices (Saalmann, 2014). The intralaminar and mediodorsal nucleus are involved in a variety of cognitive abilities, such as attention and executive functions (Saalmann, 2014; Watanabe and Funahashi, 2012). The pulvinar is the largest thalamic nucleus and is often discussed in the context of visuo-spatial attention processing, given its widespread reciprocal connectivity with distributed areas, including regions in occipital, temporal, parietal and frontal cortex (Halassa and Kastner, 2017; Wilke et al., 2010). The ventral lateral nuclei receive afferent signals from lower motor centers and relays sensory information to the primary somatosensory cortex, supplementary motor area, and premotor cortex. Specifically, indirect inputs from the cerebellum and basal ganglia are linked to the somatosensory cortex through the ventral lateral nucleus (Bosch-Bouju et al., 2013). Our data provides further

evidence that the interaction between different sub-nuclei and multiple cortical structures is crucial for core cognitive processes.

A deepened understanding of the thalamo-cortical system is essential to elucidate how its alteration may contribute to cognitive dysfunction in psychiatric and neurological conditions. For instance, it has been shown that abnormalities of thalamo-cortical connections contribute to cognitive deficits in patients with schizophrenia. Reduced prefrontal-thalamic connectivity in patients with schizophrenia correlated with impaired working memory (Giraldo-Chica et al., 2018), whereas lesions of the mediodorsal nucleus have been reported to entail cognitive dysfunctions that are reminiscent of those observed following prefrontal lesions (Watanabe and Funahashi, 2012). Further, studies investigating aging in adults showed that the integrity of the thalamo-frontal connections is an important factor in age-associated cognitive decline (including processing speed and executive functions) (Staffaroni et al., 2019; Van der Werf et al., 2003).

4.4. Limitations

The findings of the present study should be viewed in light of some limitations. Due to the different sizes and locations of thalamic nuclei and the spatial resolution constraint of the whole-brain fMRI data, it is difficult to precisely locate each thalamic nucleus using the standardized template. Moreover, the thalamus atlas used as a reference was constructed from histological data on adults (Morel et al., 1997) and then reconstructed in the MNI space (Krauth et al., 2010). Therefore, an inherent mismatch is expected in the overlap maps. To minimize identification errors, we focused mainly on the largest of the 40 nuclei present in the Morel atlas, such as the mediodorsal and pulvinar nuclei, without differentiating finer subdivisions of these nuclei (which would not be possible in the younger age groups). Secondly, resting-state fMRI analyses - in particular in pediatric populations - are likely affected by physiological noise and head motion. However, with the adopted processing pipeline most of these nuisance signals should have been removed. Further, cross-sectional study designs provide information at a given time point. However, as the development of functional networks varies between time points, longitudinal study designs are the gold standard for gaining a deeper understanding of the temporal evolution of developmental processes in thalamo-cortical networks and its possible relation to cognitive maturation (Hart et al., 2018).

4.5. Conclusion and implication

Using a data-driven approach, we were able to provide evidence that thalamic nuclei are functionally associated with well-known resting-state cortical networks. Moreover, to the best of our knowledge, this is the first set of results showing a relationship between thalamo-cortical functional connectivity and cognitive abilities in the dynamic age range between 5 and 25 years. Our findings have important implications for functional thalamo-cortical connections that may be targeted in future studies investigating neurodevelopmental disorders involving the thalamus. Neuropsychological models of brain disruption during development should be based on a detailed understanding of the interaction between large-scale brain network maturation and cognitive development in healthy individuals.

Credit author statement

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Declarations of Competing Interest

None.

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Supplementary materials

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