Functional Connectivity Parcellation of the Human Thalamus by Independent Component Analysis

Sheng Zhang¹ and Chiang-Shan R. Li¹–⁴

Abstract

As a key structure to relay and integrate information, the thalamus supports multiple cognitive and affective functions through the connectivity between its subnuclei and cortical and subcortical regions. Although extant studies have largely described thalamic regional functions in anatomical terms, evidence accumulates to suggest a more complex picture of subareal activities and connectivities of the thalamus. In this study, we aimed to parcellate the thalamus and examine whole-brain connectivity of its functional clusters. With resting state functional magnetic resonance imaging data from 96 adults, we used independent component analysis (ICA) to parcellate the thalamus into 10 components. On the basis of the independence assumption, ICA helps to identify how subclusters overlap spatially. Whole brain functional connectivity of each subdivision was computed for independent component’s time course (ICtc), which is a unique time series to represent an IC. For comparison, we computed seed-region-based functional connectivity using the averaged time course across all voxels within a thalamic subdivision. The results showed that, at $p < 10^{-6}$, corrected, 49% of voxels on average overlapped among subdivisions. Compared with seed-region analysis, ICtc analysis revealed patterns of connectivity that were more distinguished between thalamic clusters. ICtc analysis demonstrated thalamic connectivity to the primary motor cortex, which has eluded the analysis as well as previous studies based on averaged time series, and clarified thalamic connectivity to the hippocampus, caudate nucleus, and precuneus. The new findings elucidate functional organization of the thalamus and suggest that ICA clustering in combination with ICtc rather than seed-region analysis better distinguishes whole-brain connectivities among functional clusters of a brain region.

Keywords: independent component analysis; parcellation; resting state functional connectivity; thalamus

Introduction

The thalamus comprises many subnuclei and integrates cortical and subcortical activities to subservie cognitive and affective functions (Jones, 2007). Together with the basal ganglia, the thalamus forms part of a core circuit that supports large-scale integration of functionally diverse neural signals (Bell and Shine, 2016). Anatomically, the thalamus can be separated into the anterior nuclei (AN), medial dorsal nuclei (MD), and lateral nuclei with the latter further divided into the ventral anterior (VA), ventral lateral (VL), ventral posterior (VP) nuclei, and the pulvinar (PUL) (Herrero et al., 2002). Previous research has provided a broad description of the functions of these subnuclei.

Through connectivity with the hippocampus and cingulate cortices, the AN is involved in learning and memory (Aggleton et al., 2010; Child and Barroch, 2013; Law and Smith, 2012) as well as memory-guided attention (Leszczynski and Staudigl, 2016). The loss of episodic memory in early Alzheimer’s disease critically involves this limbic thalamic subnucleus (Aggleton et al., 2016). Connected with the prefrontal cortex and amygdala, the MD plays a role in performance monitoring, planning, and memory processing (Jueptner et al., 1997; Monchi et al., 2001; Simo et al., 2005; Squire and Moore, 1979; Wagner et al., 2006). Damage to the MD resulted in difficulty in recollection of previously learned information (Edelstyn et al., 2006; Pergola et al., 2012). Connected with the basal ganglia and premotor cortex, the VA facilitates movement initiation and interruption (Xiao and Barbas, 2004). Connected with the cerebellum, pallidum, and primary motor cortex (PMC), the VL helps coordination, planning, and learning of movement (Crosson, 1992). Lesions involving the VL led to movement disorders (Lee and Marsden, 1994), and reduction in

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noradrenaline in the VL and VA may be related to motor symptoms in patients with Parkinson’s disease (Pifl et al., 2012). Connected with the somatosensory cortex, the VP processes sensory information and supports alertness and arousal (Diamond et al., 1992; Krause et al., 2012; Nicolelis and Chapin, 1994; Patterson et al., 2002; Rinaldi et al., 1991). Connected with the parietal, occipital, and temporal cortices, the PUL links associative cortical circuits to mediate visual attention and integrate information for executive control (Coull et al., 2004; Li et al., 2006; Petersen et al., 1987). Lesions circumscribed to the PUL compromised attention to the contralosional hemisphere (Habekost and Rostrup, 2006; Kraft et al., 2015).

In contrast, there is accumulating evidence that the functions of individual thalamic subnuclei are much more complicated than this broad categorization. For instance, activations of the MD, VL, VA, and PUL were all observed during working memory (Bastin et al., 2012; de Zubicaray et al., 2001; Elliott and Dolan, 1999). Studies showed that reward processing evoked activation in the MD, AN, as well as VA (Elliott et al., 2000; Haber and Knutson, 2010; Helfenstein et al., 2013; Knutson et al., 2000, 2001). Furthermore, anatomically, neurons within a subnucleus appear to demonstrate a topography of differential connectivities. For instance, neurons in the medial part of MD project to the medial prefrontal cortex (MPFC) ventrally, whereas lateral MD neurons project dorsally (Alcaraz et al., 2016). Projections from within specific thalamic nuclei differ in density to the anterior and middle cingulate cortex (Fillinger et al., 2017). Together, these findings suggest a need to clarify thalamic functional subdivisions.

Anatomical and functional connectivity analyses are widely used to characterize subregions of a brain region. This approach parcellates brain areas on the basis that each subregion has a unique pattern of connectivities (Passingham et al., 2002). Using diffusion tensor imaging, studies have parcellated the thalamus based on the anatomical connectivity between thalamic and cortical voxels (Behrens et al., 2003; Duan et al., 2007; Johansen-Berg et al., 2005; Kumar et al., 2015; Mang et al., 2012; Wiegel et al., 2003; Ye et al., 2013; Ziyang et al., 2006). In functional connectivity analysis, investigators examined how fluctuations of low-frequency blood oxygenation level-dependent (BOLD) signals synchronize among functionally related brain regions (Biswal et al., 1995; Fair et al., 2007; Fox and Raichle, 2007) and described subareal boundaries for the thalamus on the basis of functional connectivity between thalamic voxels and all other voxels or a set of predefined regions (Fan et al., 2015; Ji et al., 2016; Zhang et al., 2008, 2010). For instance, a recent study parcellated functional subregions of the PUL by way of voxelwise patterns of coactivation (Barron et al., 2015).

Whereas most parcellation studies employed seed-region-based correlations, independent component analysis (ICA) represents another useful approach. Based on the assumption that BOLD signal from each voxel represents a linear mixture of sources, ICA separates this mixture into spatially independent sources using higher order statistics. Regions showing synchronized source signals are grouped into independent components (ICs) (Calhoun and Adali, 2006; Calhoun et al., 2001, 2009; McKeown and Sejnowski, 1998; McKeown et al., 1998b). All voxels associated with an IC can be treated as an intrinsically coherent functional network/region with a unique time course. Previous studies have employed ICA in functional clustering of the thalamus (Hale et al., 2015; Kim et al., 2013; Yuan et al., 2016) and largely replicated findings from seed-region-based correlation analyses (Zhang et al., 2008, 2010). There are a few issues to consider for these three ICA studies. First, all of them examined thalamic connectivity to a limited set of brain regions identified as functional networks or regions of interest (ROIs). Because the individual networks or ROIs may comprise functionally heterogeneous areas, as demonstrated recently (Fan et al., 2016; Finn et al., 2015; Glasser et al., 2016; Power et al., 2011; Shen et al., 2013), it is plausible that the complexity of thalamic functional connectivities may not have been fully revealed in these earlier studies. That is, it would be important to perform whole-brain voxelwise analysis to uncover detailed patterns of functional connectivity of the thalamic subdivisions. Second, two of the studies included only 21 healthy volunteers and the results need to be replicated with a larger data set.

Here, we applied ICA to parcellate the thalamus using a larger resting state data set (n = 96). We hypothesized that individual thalamic voxels may partake in multiple functional subclusters and we would observe overlapping voxels in identified thalamic subdivisions even under a very stringent threshold. Furthermore, we examined whole-brain voxelwise connectivity for each thalamic subdivision, and hypothesized that each subdivision shows distinct connectivity patterns when computed of independent component’s time course (ICtc), whereas those computed of voxel-averaged time course would yield overlapping connectivity patterns.

**Materials and Methods**

**Data set**

The data set comprised a convenience sample of magnetic resonance imaging (MRI) scans collected over the last few years. Resting-state functional magnetic resonance imaging (fMRI) scans of 96 healthy volunteers were obtained on a 3-Tesla Siemens Trio scanner at Yale University (20–55 years of age; 44 men, 1 scan per participant; duration: 10 min; repetition time [TR] = 2 sec; eyes closed). Individual subjects’ images were viewed one by one to ensure that the whole brain was covered.

**Imaging protocol**

Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the anterior commissure-posterior commissure (AC–PC) line with repetition time (TR) = 300 msec, echo time (TE) = 2.5 msec, bandwidth = 300 Hz/pixel, flip angle = 60°, field of view = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4 mm, and no gap. Functional, BOLD signals were then acquired with a single-shot gradient echo echoplanar imaging sequence. Thirty-two axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 2000 msec, TE = 25 msec, bandwidth = 2004 Hz/pixel, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm, and no gap.

**Imaging data processing**

Brain imaging data were preprocessed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging
Neuroscience, University College London, London, United Kingdom). Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation. Standard image preprocessing was performed. Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were coregistered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at full width at half maximum.

**Independent component analysis**

ICA was applied to parcellate the whole thalamus. A thalamus mask (698 voxels, voxel size = 3×3×3 mm³) was obtained from the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Preprocessed time series of voxels within the thalamus were analyzed with a group ICA algorithm⁴ to identify ICs (Calhoun et al., 2001, 2009). ICA identifies distinct groups of brain regions with the same temporal pattern of hemodynamic signal change.

The data of 96 individuals were concatenated into a single data set and reduced through 2 stages of principal component analysis (first reduced to 50 components and then reduced to the target) (Calhoun et al., 2001) and separated into 10 maximally ICs with an infomax algorithm (Bell and Sejnowski, 1995). The dimensionality was determined based on a recent study (Hale et al., 2015), wherein the authors parcellated the whole thalamus into 10 and 20 components using ICA and found that the results of 10 and 20 components were largely similar. We thus focused on 10 components in this study. This analysis was repeated 20 times with ICASSO (both “Randini” and “Bootstrap” options with 2 and 10 as minimum and maximum cluster size) to assess the repeatability of ICs (Himberg et al., 2004). Finally, component time courses and spatial maps, which captured individual differences in the expression of the ICA-derived component, were obtained through back reconstruction for each participant (Calhoun et al., 2001; Meda et al., 2009). GICA3 method was applied in back reconstruction because it could provide the most robust and accurate estimated spatial maps and time courses as suggested by a previous study (Erhardt et al., 2011).

We normalized back-reconstructed spatial maps of each IC into z-scores (Beckmann et al., 2005). A one-sample t test was applied to the “z maps” across all participants to define significant thalamic voxels associated with each IC.

**Head motion**

As extensively investigated in Van Dijk et al. (2012), microhead motion (>0.1 mm) is an important source of spurious correlations in resting state functional connectivity analysis (Van Dijk et al., 2012). Therefore, we applied a “scrubbing” method proposed by Power et al. (2012) and successfully applied in previous studies (Power et al., 2012; Szymser et al., 2010; Tomasi and Volkow, 2014) to remove time points affected by head motions. In brief, for every time point t, we computed the framewise displacement given by $FD(t) = |Δd_x(t)| + |Δd_y(t)| + |Δd_z(t)| + r|x(t)| + r|β(t)| + r|γ(t)|$, where $(d_x, d_y, d_z)$ and $(x, β, γ)$ are the translational and rotational movements, respectively, and r (=50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transform rotations into displacements (Power et al., 2012). The second head movement metric was the root mean square variance (DVARS) of the differences in percentage BOLD intensity I(t) between consecutive time points across brain voxels, computed as follows: $DVARS(t) = \sqrt{\langle (I(t) - I(t-1))^2 \rangle}$, where the brackets indicate the mean across brain voxels. Finally, to compute each subject’s correlation map, we removed every time point that exceeded the head motion limit $FD(t) > 0.5$ mm or DVARS(t) > 0.5% (Power et al., 2012; Tomasi and Volkov, 2014). On average, 1% of the time points were removed across subjects. None of the 96 individuals had >9% of the time series removed.

**Functional connectivity of ICs**

ICtc was used to compute the functional connectivity maps. For individual subjects, we computed the correlation coefficient between the ICtc and the time courses of voxels of the whole brain. Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Rombouts et al., 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular, and white matter signals were also included in the regression. It is worth noting that such artifacts were removed when generating ICtc through ICA, thus, we only need to apply this additional preprocessing for voxel time courses. Furthermore, Cordes et al. (2001) suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations. Thus, we applied a temporal band-pass filter (0.009 Hz < f < 0.08 Hz) to both component and voxel time courses to obtain low-frequency fluctuations, as in previous studies (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Lowe et al., 1998). To assess and compare the resting state functional connectivity, we converted these image maps, which were not normally distributed, to z score maps by Fisher’s z transform (Berry and Mielke, 2000; Jenkins and Watts, 1968): $z = 0.5 \log_e \left[ \frac{1 + z}{1 - z} \right]$. The z maps were used in group random effect analyses. Group-level one sample t test was applied on these z maps to obtain t statistic connectivity maps for these ICs in SPM 8.

We also followed conventional methods and computed seed-region-based functional connectivity for each IC for comparison. In brief, a thalamic subdivision was extracted for each IC at a specified threshold (see Results) using MarsBaR.⁵ Following additional preprocessing as described earlier, the BOLD time

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⁴Group ICA of tMRI Toolbox (GIFT); http://icatb.sourceforge.net, version 1.3i

⁵http://marsbar.sourceforge.net
courses were averaged spatially across all voxels in that subdivision. Finally, instead of using ICtc, we computed the correlation coefficient between this averaged BOLD time course and the time courses of all other brain voxels.

**Results**

**Thalamic functional subclusters by ICA**

We ran group ICA 20 times using ICASSO and employed cluster quality index ($I_q$) of the selected components to assess the repeatability of ICA components (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/brain). We identified 10 ICs for the whole thalamus, each depicting a distinct group of voxels with the same pattern of hemodynamic change over time (Fig. 1A). With $p<0.05$ and $p<10^{-6}$, corrected for family-wise error (FWE) of multiple comparisons, these 10 thalamic subdivisions overlapped in voxel composition each with an averaged overlap rate of 51% and 49% (Table 1). Overlap rate was computed by rate = $\frac{\text{# of overlapping voxels of IC}_i \text{ and } \text{IC}_j}{\text{total # of voxels of } \text{IC}_i} \%$ ($i=1–10; \ j=1–10, \ i \neq j$). That is, even with a very stringent threshold to define and separate the ICs for the group, there were still ~50% of voxels showing representation in multiple ICs. We used the ICs defined by $p<10^{-6}$ for the analyses described hereunder. Further, we reran the analysis for 5 components and 20 components. The results did not appear to demonstrate additional or new functional connectivity patterns (Supplementary Results).

**ICtc-based and seed-region-based functional connectivity**

Figure 2 shows the $t$ statistic connectivity maps of the 10 ICs obtained with ICtc at $p<0.05$ corrected for FWE. In comparison, we formed seed regions on the basis of these 10 ICs and computed seed-region-based correlation maps (Fig. 3). The results showed that seed-region-based connectivity maps are highly overlapped with a mean ± standard deviation overlap rate = 84% ± 6%, whereas ICtc-based connectivity maps are more distinguished with a mean overlap rate = 13% ± 16%. The overlap rate was computed based on voxels surviving $p<0.05$ corrected for FWE with the afore-described formula.

**FIG. 1.** (A) Ten thalamic subdivisions identified from ICA. Regions shown are thresholded at $p<10^{-6}$ ($n=96$), corrected for FWE of multiple comparisons. (B) Nonoverlapping ROIs created by assigning each thalamic voxel to an IC depending on which IC showed the highest $z$ score for that voxel. FWE, family-wise error; IC, independent component; ICA, independent component analysis; ROIs, regions of interest. Color images available online at www.liebertpub.com/brain
Table 1. Pairwise Overlapping Rate (%) Among the 10 Independent Components at $p < 10^{-6}$, Corrected for Family-Wise Error of Multiple Comparisons

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Overlapping rate was computed by: $\text{rate} = 100 \times \frac{\# \text{ of overlapping voxels of IC}_i \text{ and } \text{ IC}_j}{\# \text{ of total voxels of } \text{ IC}_i} (i = 1–10; j = 1–10, i \neq j)$.

IC, independent component.

FIG. 2. Group results of ICtc-based functional connectivity of each of the 10 thalamic subdivisions. Positive (warm color) and negative (cold color) correlations were superimposed on axial slices at $z$ from −35 to 65 mm (10 mm sections) of a structural image. $p < 0.05$, Corrected for FWE of multiple comparisons. Color scales reflect $t$ values of one-sample $t$ test. ICtc, independent component’s time course. Color images available online at www.liebertpub.com/brain.
Because the ROIs extracted are highly overlapped in voxel composition even at \( p < 10^{-6} \) FWE corrected, we examined whether this resulted in greater overlaps of seed-region-based connectivity maps. To this end, we created nonoverlapping thalamic subdivisions by assigning each thalamic voxel to an IC with the highest \( z \) score for that voxel (Fig. 1B) and reran seed-region-based correlation analysis. The results showed connectivity maps with a mean overlap rate of 48% ± 19% for voxels at \( p < 0.05 \) corrected for FWE (Fig. 4). Thus, voxel overlap of thalamic subregions alone could not account for overlap in whole-brain connectivity of these subregions.

Hierarchical clustering of ICs according to functional connectivity patterns

To examine how functional connectivity patterns of these 10 ICs “resemble” one another, we performed hierarchical clustering analysis on these patterns, using the Statistics and Machine Learning Toolbox in MATLAB. The clustering algorithms successively merged pairs of ICs until all ICs were merged into a single cluster, based on the similarity of the functional pattern of ICs (Hartigan, 1975; Rokach and Maimon, 2005). Thus, represented as a dendrogram, the result of hierarchical clustering demonstrated nested groupings of ICs and similarity levels at which grouping changed. The height in the dendrogram represented the dissimilarity value: the lower the values, the higher the similarity between two ICs’ functional connectivity patterns. We used correlation as a similarity measure in the analysis. The results showed that these 10 ICs could be roughly separated into 2 groups according to their functional connectivity patterns (Fig. 5A). Specifically, IC 8 and IC 10 as well as IC 5 and IC 6 were grouped together at a very low height, suggesting high similarity in the connectivity patterns.

ICA MAPPING FOR THALAMUS

FIG. 3. Group results of seed-region-based functional connectivity of each of the 10 thalamic subdivisions. Positive (warm color) and negative (cold color) correlations were superimposed on axial slices at \( z \) from –35 to 65 mm (10 mm sections) of a structural image. \( p < 0.05 \), Corrected for FWE of multiple comparisons. Color scales reflect \( t \) values of one-sample \( t \) test. Color images available online at www.liebertpub.com/brain
brain atlas that included the prefrontal gyrus, motor cortex, insular, parietal gyrus, temporal gyrus, occipital gyrus, limbic cortex, subcortex, cerebellum, and brainstem (Rosenberg et al., 2016; Shen et al., 2013), and examined the connectivity with each region with one sample t tests across the entire cohort. We showed brain regions with connectivity surviving p < 0.05 corrected for FWE of multiple comparisons (Fig. 5B). Thalamic subregions were identified by reference to the Morel atlas (Morel, 2007).

ICs 8 and 10 predominantly included VA, ventral-lateral-anterior, and ventral-lateral-posterior (VLP) nuclei. ICs 8 and 10 showed similar functional connectivity, both with positive connectivity with superior, middle, and inferior frontal gyri, anterior cingulate gyri, MPFC, angular gyrus, cerebellum, and subcortical regions, including the caudate, putamen, and pallidum. Negative connectivities were observed for both ICs with the supplementary motor area (SMA), PMC, postcentral gyrus (PCG), precuneus, cuneus, and occipital gyri. The connectivity to the prefrontal and parietal gyri was more left and right lateralized each for ICs 8 and IC 10.

IC 1 predominantly included medial pulvinar (PuM) and central lateral nucleus (CL). IC 1 showed positive connectivity with the posterior cingulate gyrus (PCingG) and precuneus and negative connectivity with the occipital gyri and cerebellum. The VLP, CL, and AN formed most of IC 2, which showed positive connectivity with the SMA, precuneus, and left middle frontal gyrus and negative connectivity with the cerebellum. VLP and lateral posterior nucleus (LP) predominated IC 3, which showed positive connectivity with the right superior and middle frontal gyri, right inferior parietal gyrus, right angular gyrus, and precuneus, and negative connectivity with the left PMC, left PCG, brainstem, and cerebellum. IC 7 included mostly AN and MD, and showed positive connectivity with the anterior, middle, and PCingG, precuneus, and the caudate, putamen, pallidum, and a small

**FIG. 4.** Group results of seed-region-based functional connectivity of each of the 10 thalamic nonoverlapping subdivisions as shown in Figure 1B. Positive (warm color) and negative (cold color) correlations were superimposed on axial slices at z from −35 to 65 mm (10 mm sections) of a structural image. p < 0.05, Corrected for FWE of multiple comparisons. Color scales reflect t values of one-sample t test. Color images available online at www.liebertpub.com/brain
area in the insula. Negative connectivities were observed in PMC, PCG, occipital gyrus, and superior parietal gyrus. MD and central median nucleus (CM) formed most of IC 4, which showed positive connectivity with the anterior and middle cingulate gyri, left insula, putamen, pallidum, cerebellum, and brainstem, and negative connectivity with the superior parietal gyrus.

ICs 5 and 6 predominantly included the PUL and ventral posterior lateral nucleus (VPL). ICs 5 and 6 showed similar functional connectivity, both with positive connectivity with the lingual gyrus, cuneus, occipital gyrus, precuneus, and hippocampus. Specifically, IC 5 positively connected with the right PCG, whereas IC 6 positively connected with the PClG. Negative connectivities were observed in the middle and inferior frontal gyri, SMA, insula, anterior and middle cingulate gyri, supramarginal gyrus, caudate, putamen, pallidum, and cerebellum. IC 9 included mostly VPL, ventral posterior medial nucleus (VPM), and VLP and showed positive connectivity with the PMC/PCG and negative connectivity with the PClG and precuneus. The results are summarized in Table 2.

Discussion

We examined functional parcellation of the thalamus using ICA. We observed that, on average, 49% of voxels overlapped among 10 thalamic subdivisions identified by ICA under \( p < 10^{-6} \), corrected for FWE of multiple comparisons. We examined functional connectivity patterns of these identified thalamic subdivisions, each based on seed-region time course correlation and component time course correlation (ICtc). The results showed that an average of 84% of voxels, with functional connectivity meeting \( p < 0.05 \) FWE, overlapped across the 10 thalamic subdivisions when averaged subdivision time course was used to compute whole-brain correlation map. In contrast, only 13% of voxels on average overlapped when ICtc was used to compute whole-brain correlation map. That is, more detailed functional connectivity patterns were captured by ICtc-based correlation analysis. These findings supported our hypothesis that, first, overlapping voxels would be observed in identified thalamic subdivisions even under a very stringent threshold, and, second, ICtc-based connectivity analysis yielded more detailed functional connectivity patterns, as compared with seed-region-based connectivity analysis.

Overlapping voxels

In a previous study, we identified task positive and negative functional networks in response to parametric loads of working memory, and showed that task-positive and task-negative networks overlapped in 86.6% and 52.4% of the total volume covered by each respective functional network (Xu et al., 2013). The current findings showed that the identified components were highly overlapped too when we applied ICA to a smaller brain area—the thalamus—which occupies only 1.2% of brain volume.

The aim of fMRI component analysis is to factor the image matrix into a product of a set of ICts and a set of spatial patterns (thalamic subdivisions) (Calhoun et al., 2001, 2009; Zhang and Li, 2012b; Zhang et al., 2015). Consider an observed series of brain images \( x = [x_1, x_2, \ldots, x_M]^T \), which can be “decomposed” by ICA as \( x = As \), where \( s = [s_1, s_2, \ldots, s_N]^T \) is a series of brain images referred to as the independent sources and \( A_{M \times N} \) is an unknown mixing matrix. ICA is to estimate a demixing matrix \( W_{N \times M} \) such that estimated brain images \( y \) given by \( y = Wx \) are a good approximation to the sources \( s \). The demixing matrix \( W_{N \times M} \) is estimated based only on the “independence” assumption so that the estimated brain images are as spatially independent as possible and each with a unique ICtc. It is important to note that the constraint of spatial independence of ICs generated by spatial ICA does not mean that different ICs do not overlap in space. Rather, spatial independence stipulates that the spatial patterns (i.e., spatial distributions in the brain) of different ICs are independent from each other (Beckmann, 2012; McKeown et al., 1998a). The spatial pattern represents voxels’ contribution to a specific IC/ICtc, with a higher value indicating greater contribution to the IC/ICtc from that voxel and vice versa. Our findings showed that even at \( p < 10^{-6} \) corrected for FWE, voxels remained extensively overlapped across ICs. For instance, 82% of the voxels within IC 8 overlapped with voxels in IC 6 and 59% of voxels within IC 6 overlapped with voxels in IC 8 (Fig. 6A). That is, more than half of the voxels in these two thalamic subdivisions contributed to both ICs. These findings suggest that in fMRI studies, one may not fully capture the specific roles of a voxel or brain region by examining
### Table 2. Summary of Functional Connectivity Findings for the Independent Components

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+, Positive connectivity; -, negative connectivity; SMA, supplementary motor area.

**FIG. 6.** (A) An example of overlaps between ICs. Eighty-two percent of voxels within IC 8 (green) overlapped with voxels in IC 6 (red) and 59% of voxels within IC 6 (red) overlapped with voxels in IC 8 (green). Yellow color represents overlapping voxels of these two thalamic subdivisions. Nonoverlapping ROIs in Figure 1B are encircled by black and blue lines each for ICs 6 and 8. (B–D) Each represents whole-brain functional connectivity computed by (B) seed-region-based analysis using overlapping ICs (Fig. 3), (C) ICtc-based analysis (Fig. 2), as well as (D) seed-region-based analysis using nonoverlapping ICs (Fig. 4). Color images available online at www.liebertpub.com/brain
the spatial patterns alone without considering the temporal property of BOLD signals.

Seed-region versus ICtc-based functional connectivity: general issues

Seed-region-based connectivity patterns of thalamic subregions are much more similar than those obtained with ICtc (Figs. 2 and 3). One possible explanation is that overlapping voxels rendered the averaged time courses close to one another. In contrast, the connectivity patterns remained quite similar even after we removed those overlapping voxels before computing averaged time course (Fig. 4). When creating nonoverlapping subdivisions, we assigned each thalamic voxel to an IC with the highest z score for that voxel. However, besides the main contribution to the assigned IC, that voxel partakes in other ICs of lesser importance. Although not as significant as the main contribution, these smaller effects add up in the computation of averaged time course, such that the averaged time course is different from ICtc. Thus, ICA separates these different contributions into ICs and the ICtc is a unique time pattern to represent the IC. The results suggested that whole-brain functional connectivity should be computed using ICtc in ICA-based parcellation.

For instance, IC 6 and IC 8 largely overlapped in voxel compositions (Fig. 6A) and both showed positive connectivity with the putamen, pallidum, insula, and anterior cingulate cortex in seed-region-based analysis (Figs. 3 and 6B). In contrast, negative connectivities for IC 6 but positive connectivities for IC 8 were each observed with these brain regions on the basis of ICtc analysis (Figs. 2 and 6C). The differences may arise because around 82% of voxels in IC 8 went into computing the averaged time course for IC 6 using the seed-region-based method, such that the averaged time course of IC 6 approximates that of IC 8 and, as a result, both share a large swath of connectivities. When we restricted the analysis to nonoverlapping subdivisions, fewer voxels showed overlapping connectivity (around 10%) (Fig. 6A).

For both ICs 8 and 10, the 10% voxels from IC 6 contributed to the averaged time course of IC 6 and positive and negative connectivity each of IC 8 and IC 6 may cancel out, resulting in nonsignificant connectivities with putamen, pallidum, insula, and anterior cingulate cortex for IC 6 (Figs. 4 and 6D).

ICtc versus seed-region-based connectivity: specific examples

Compared with seed-region analysis, ICtc analysis reveals more distinguished patterns of subregional thalamic connectivity. For instance, negative connectivities with the PMC were demonstrated for ICs 3, 7, 8, and 10 and positive connectivity for IC 9 under ICtc but not seed-region analysis. Furthermore, negative connectivities with the PCG were identified for ICs 3, 7, 8, and 10 and positive connectivity for ICs 5 and 9 under ICtc analysis, whereas only negative connectivity with a small region of the PCG was shown for IC 7 under seed-region analysis.

Anatomical studies have documented extensive structural connectivities between the PMC and thalamus (Fang et al., 2006; Hooks et al., 2013; Matelli and Luppino, 1996; Rouiller et al., 1994, 1999; Stepniewska et al., 1994). However, imaging studies employing seed-region-based approaches have failed to demonstrate these cortical thalamic connectivities (Farr et al., 2014; Tomasi and Volkow, 2011). Thus, ICtc but not seed-based analysis revealed functional connectivity between the thalamus and PMC. A possible explanation is that there were both positive and negative connectivities between thalamic voxels and PMC. Thus, whereas positive and negative functional connectivities would cancel out with averaged subdivision time course, ICA helps to separate them. In particular, an animal study examined the PMC thalamic connectivity in nonhuman primates (Kultas-Ilinsky et al., 2003). Through six injections of biotinylated dextran amine at different locatations of the PMC, the authors reported that VL, VA, centromedian, centrolateral, paracentral, mediodorsal, lateral posterior, and PM nuclei were all labeled, suggesting elaborated connectivity between PMC and thalamus. In accord, the current findings that ICs 3, 7, 8, 9, and 10 all demonstrated connectivity with the PMC support wide and strong functional link between the thalamus and motor cortex.

ICs 5 and 6 were both represented in PUL and VPL. ICs 5 and 6 were each connected with the right and left hippocampus for ICtc but not seed-based connectivity analysis. Recent studies including a meta-analysis suggested that thalamic subregions such as the PUL functionally connect with the hippocampus (Allen et al., 2007; Barron et al., 2015; Wang et al., 2014). Indeed, the current findings showed that ICs 5 and 6 mainly involved the PUL. This provides another example that ICtc analysis may reveal more detailed and perhaps veridical functional inter-regional connectivities.

Previous studies were at discrepancy with regard to thalamus caudate connectivity, with some (Barnes et al., 2010; Hacker et al., 2012; Robinson et al., 2012) but not others (Di Martino et al., 2008) showing positive connectivity and another study showing positive caudate connectivity with dorsal and medial thalamus and negative connectivity with the ventrolateral thalamus only after the caudate was parcelled into nine functional subdivisions (Jung et al., 2014). The current findings based on seed-region analysis showed negative connectivity for ICs 1, 5, and 6, and weak positive connectivity for the MD parts of ICs 2 and 7. In contrast, the ICtc analyses clearly demonstrated both positive (ICs 7, 8, and 10) and negative (ICs 5 and 6) connectivities with the caudate, capturing the details as reported in Jung et al. (2014). Another example is the connection between thalamus and prefrontal. Functional connectivity parcellation studies from our (Zhang and Li, 2012a) and others’ (Cauda et al., 2010) laboratories both showed prefrontal positively connected with PUL and mediodorsal thalamus but negatively connected with the sensory thalamic nuclei. Here, seed-region analyses showed significant positive connectivity only in a small area of prefrontal for ICs 1, 5, and 6 and weak negative connectivity for ICs 8, 9, and 10. In contrast, with ICtc-based analysis, we were able to clearly identify both positive (ICs 1, 2, 3, 5, 6, and 7) and negative (ICs 8, 9, and 10) connectivities with the prefrontal. Together, the findings suggest that ICA with ICtc-based analysis could help in revealing functional connectivities that were “buried” because of signal mixing. These new data not only shed light on the functional architecture of the thalamus but also help in integrating fMRI studies that report thalamic activities to similar contrasts but in different subregions as conventionally named.
Comparison with Morel atlas of the thalamus

The Morel atlas separated the whole thalamus into anterior, medial, posterior, and lateral groups and has been used in many studies of thalamic structure and function (Krauth et al., 2010; Morel, 2007; Niemann et al., 2000). The anterior group includes anteroventral nucleus and lateral dorsal nucleus. The medial group includes magnocellular and parvocellular parts of the mediodorsal nuclei, medioventral nucleus, CL-central medial nucleus/CM, habenular nucleus, and parafascicular nucleus. The posterior group includes PuM, lateral, and anterior pulvinar, LP, medial geniculate nucleus, suprageniculate nucleus, limitans nucleus, and posterior nucleus. The lateral group includes anterior and posterior parts of the VPL, VPM, ventral posterior inferior nucleus, ventral lateral anterior nucleus, dorsal and ventral parts of the VL posterior nuclei, magnocellular and parvocellular parts of the ventral AN, and ventral medial nucleus. For comparison, we focused on the nonoverlapping voxels for each IC (Fig. 1B). The results are shown in Table 3.

Methodological considerations

Back reconstruction is an important step in group ICA, and there are different options including GICA1, GICA2, GICA3, and spatial–temporal regression. A previous study examined the effects of these different methods and suggested that GICA3, which we used in this study, provides the most robust and accurate estimated spatial maps and time courses (Erhardt et al., 2011). Furthermore, recent studies presented a new methodological framework with group information-guided ICA (GIG-ICA) to obtain subject-specific ICs (Du and Fan, 2013; Du et al., 2015, 2016). In brief, group ICs were extracted as spatial references in a second one-unit ICA to identify subject-specific ICs. With GIG-ICA, Du et al. were able to obtain subject-specific ICs with stronger independence and better spatial correspondence than GICA1, GICA2, and GICA3. Furthermore, the authors also suggested that the GICA3 might not be reliable for some data sets. Thus, the current findings can be further confirmed by different algorithms in group ICA, including different back reconstruction methods.

Table 3. Percentage of Voxels in Each of the 10 Independent Components Belonging to Thalamus Subregional Masks in the Morel Atlas

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<th>IC 3 (%)</th>
<th>IC 4 (%)</th>
<th>IC 5 (%)</th>
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Rate was computed by: $rate = 100 \times \frac{\# \ of \ overlapping \ voxels \ of \ IC \ i \ and \ Morel \ Atlas}{\# \ of \ total \ voxels \ of \ IC \ i} (i = 1–10)$.

AV, anteroventral nucleus; CeM, central medial nucleus; CL, central lateral nucleus; CM, central median nucleus; Hb, habenular nucleus; LD, lateral dorsal nucleus; Li, limitans nucleus; LP, lateral posterior nucleus; MDmc, magnocellular part of the mediodorsal nucleus; MDpc, parvocellular part of the mediodorsal nucleus; MGN, medial geniculate nucleus; MV, mediodorsal nucleus; Pf, parafascicular nucleus; Po, posterior nucleus; PuA, anterior pulvinar; PuL, lateral pulvinar; PuM, medial pulvinar; SG, suprageniculate nucleus; VAmc, magnocellular part of the ventral anterior nucleus; VApc, parvocellular part of the ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLpd, dorsal part of the ventral lateral posterior nucleus; VLpv, ventral part of the ventral lateral posterior nucleus; VM, ventral medial nucleus; VPI, ventral posterior inferior nucleus; VPLa, anterior part of the ventral posterior lateral nucleus; VPLp, posterior part of the ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.
Previous studies suggested that the global signal regression, a common data preprocessing step in seed-based connectivity analyses, is most likely the cause of anticorrelated functional networks (Murphy et al., 2009; Weissenbacher et al., 2009). In contrast, many characteristics of anticorrelated networks, including cross-subject consistency, spatial distribution, and its presence with modified whole-brain masks and before global signal regression, suggested otherwise (Fox et al., 2009). To examine this issue, we repeated the same analysis except without performing global signal regression on the current data set. The results showed a similar pattern of functional connectivity as in the analyses with global signal regression (Supplementary Fig. S2).

Conclusions
This study demonstrates overlaps of functional thalamic subdivisions as identified by ICA. These overlapping voxels contribute specifically to each of the thalamic subdivisions by “generating” a unique ICTc to represent that subdivision. Thus, functional connectivity computed using ICTc reveals patterns that would not be available from seed-region-based analysis. Overall, parcellation using ICA together with ICTc-based connectivity analysis could provide new insights into cerebral functional organization.

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Author Disclosure Statement
No competing financial interests exist.

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ICA MAPPING FOR THALAMUS


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