Large-Scale functional network overlap is a general property of brain functional organization: Reconciling inconsistent fMRI findings from general-linear-model-based analyses

Jiansong Xu^{1*}, Marc N. Potenza^{1, 2, 3, 4, 5}, Vince D. Calhoun^{1, 6, 7}, Rubin Zhang¹, Sarah W. Yip^{1, 4}, John T. Wall⁸, Godfrey D. Pearlson^{1, 3, 9}, Patrick D. Worhunsky¹, Kathleen A. Garrison¹, Joseph M. Moran¹⁰

*** Corresponding Author:** Jiansong Xu, 1 Church St., Room 729, New Haven, CT 06519, USA; E-mail: Jiansong.xu@yale.edu, Tel: 203-785-5306.

¹ Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06510, United States

² Child Study Center, Yale University School of Medicine, New Haven, CT 06510, United States

³ Department of Neuroscience, Yale University School of Medicine, New Haven, CT 06510, United States

⁴ CASAColumbia, Yale University School of Medicine, New Haven, CT 06510, United States

⁵ The Connecticut Mental Health Center, New Haven, CT 06519, United States

⁶ The Mind Research Network & LBERI, Albuquerque, NM 87131, United States

⁷ Dept of ECE, The University of New Mexico, Albuquerque, NM, 87131,
United States

⁸ Department of Neurosciences, University of Toledo, Toledo, OH, 43614,
United States

⁹ Olin Neuropsychiatry Research Center, Institute of Living, Hartford,
Connecticut, CT 06106, United States

¹⁰ The Center for Brain Sciences, Harvard University, Cambridge, MA,
United States; U.S. Army Natick Soldier Research, Development, and
Engineering Center, United States.

Abstract

Functional magnetic resonance imaging (fMRI) studies regularly use univariate general-linear-model-based analyses (GLM). Their findings are often inconsistent across different studies, perhaps because of several fundamental brain properties including functional heterogeneity, balanced excitation and inhibition (E/I), and sparseness of neuronal activities. These properties stipulate heterogeneous neuronal activities in the same voxels and likely limit the sensitivity and specificity of GLM. This paper selectively reviews findings of histological and electrophysiological studies and fMRI spatial independent component analysis (sICA) and reports new findings by applying sICA to two existing datasets. The extant and new findings consistently demonstrate several novel features of brain functional organization not revealed by GLM. They include overlap of large-scale functional networks (FNs) and their concurrent opposite modulations, and no significant modulations in activity of most FNs across the whole brain during any task conditions. These novel features of brain functional organization are highly consistent with the brain's properties of functional heterogeneity, balanced E/I, and sparseness of neuronal activity, and may help reconcile inconsistent GLM findings.

Keywords: fMRI, GLM, ICA, functional network overlap, default mode network, balanced excitation and inhibition, sparseness of neuronal activity

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1. Introduction

1.1. Overview

Functional magnetic resonance imaging (fMRI) studies regularly use univariate general-linear-model-based analyses (GLM) to interrogate blood-oxygenation-level-dependent (BOLD) signal from each voxel separately (Pernet, 2014; Poline and Brett, 2012; Xu et al., 2015). This GLM approach and its findings are in general consistent with a modular view of brain functional organization that different mental processes operate in different brain regions (Donoso et al., 2014; Kanwisher, 2010; Pessoa, 2014; Rowland and Moser, 2014; Szentagothai, 1983). However, some findings from different studies appear highly inconsistent and may generate confusion for the field. The present paper continues our recent efforts for addressing inconsistent GLM findings and for better understanding brain functional organization (Xu, 2015; Xu et al., 2015; Xu et al., 2013b). The manuscript consists of two parts. The first part reviews histological, electrophysiological, and fMRI findings supporting extensive functional network (FN) overlaps that contrast with a modular functional organization of the brain. The second part uses spatial independent component analysis (sICA) to generate new evidence for further support of our hypothesis that large-scale FN overlap is a general property of brain functional organization,

and that analytical approaches capable of revealing this property might reconcile previously inconsistent findings generated by GLM. The following sections of the introduction will present examples of inconsistent fMRI findings, discuss why GLM may generate inconsistencies, review evidence for FN overlap, and introduce findings from a new study that further support our theory.

1.2. Examples of inconsistent fMRI findings

One example is related to the so-called default mode network (DMN) (Fox et al., 2005; Mazoyer et al., 2001; Raichle et al., 2001; Sonuga-Barke and Castellanos, 2007). Around the year of 2000, Raichle and colleagues found that several brain regions often exhibited reduced activities during cognitive tasks relative to rest condition (Gusnard and Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). For example, Gusnard et al used fMRI and GLM to assess brain activity in healthy participants while they viewed pictures selected from the International Affective Picture System (IAPS) (Lane et al., 1997) under two different task conditions (Gusnard and Raichle, 2001). For the internally cued condition (ICC), participants were instructed to respond to their feeling (i.e., pleasant, unpleasant, or neutral) induced by the pictures. In the externally cued condition (ECC), participants responded to the scene depicted by the picture (i.e., indoors, outdoors, or uncertain). Both ICC- and ECC-induced activity decreases in the ventral medial prefrontal cortex (MPFC) relative to a condition of passive visual fixation, and ECC induced a greater deactivation relative to ICC. Based on these findings, these investigators proposed that the brain regions with a greater activity during rest condition formed a default mode network (DMN).

Furthermore, a later study from the same group analyzed correlations of BOLD signal timecourse in different brain regions during a resting condition (Fox et al., 2005). Three seeds (i.e., ROI, region of interest) were selected in the brain regions often showing increased activity during cognitive tasks (i.e., task-positive regions), and another three seeds were selected in the brain regions often showing decreased activity (i.e., DMN). They found that BOLD signals in the task-positive regions positively correlated with each other and formed a so-called task-positive network, that BOLD signals in the DMN positively correlated with each other and formed a so-called task-negative network, and that the BOLD signal in the two networks negatively correlated with each other. Their findings received extensive support from other fMRI studies using GLM (Buckner et al., 2008; Kelly et al., 2008; McKiernan et al., 2003; Raichle, 2015). These GLM studies together demonstrated that the brain consists of a lateral task-positive network and a medial task-negative network or DMN with anti-correlated functional activities between them, and that the task-positive network responds to external goal-directed tasks while the task-negative network relates to mentalizing (i.e., theory of mind), spontaneous mind-wandering, and internally oriented self-related mental processes (Fox et al., 2005; Gusnard et al., 2001; Mason et al., 2007; Raichle, 2015; Sonuga-Barke and Castellanos, 2007).

However, not all findings from GLM studies support the DMN concept. For example, Gilbert et al studied task-related changes in BOLD signal while healthy participants performed stimulus-oriented tasks by monitoring stimuli on the screen and stimulus-independent tasks by monitoring internally generated

information (e.g., adding 7 repeatedly) (Gilbert et al., 2012; Gilbert et al., 2006). The rostral MPFC, a main region of the DMN, showed reduced BOLD signal in the stimulus-independent tasks relative to stimulus-oriented tasks. In another study, healthy participants performed a working memory tasks with parametric task loads of social information (Meyer et al., 2012). For each trial of this task, participants started to remember (i.e., encoding phase) 2-4 names of friends on the screen for 4 s. Then a word for personality trait (e.g., funny) appeared for 1.5 s after the names disappeared from the screen. Participants were instructed to remember the names and rank these friends based on the given trait for 6 s (i.e., delay phase), and finally to press a button to respond to a probe that appeared on the screen (i.e., retrieving phase). During both the delay and retrieving periods, participants showed a task-load dependent increases in BOLD signal not only in the so-called task-positive network such as the dorsal lateral prefrontal cortex and superior parietal lobule, but also in the task-negative network or DMN including the dorsal and ventral MPFC, precuneus/posterior cingulate, and temporal parietal junction (Meyer et al., 2012). Several other studies further investigated the above-discussed finding of anti-correlations of task-positive and task-negative networks during rest condition by analyzing simulated and real fMRI data acquired during a resting condition (Anderson et al., 2011; Murphy et al., 2009). These studies did not find anti-correlations between BOLD signals from the two networks if they did not perform global signal regression during data preprocessing, and found such anti-correlations only after global signal regression. The authors of these studies proposed that the previous

reported anti-correlations were largely artifacts relating to global signal regression (Anderson et al., 2011; Murphy et al., 2009). Furthermore, multiple studies report that the external goal-directed tasks activate not only the lateral regions (i.e., the task-positive network), but also the medial regions (i.e., the task-negative network), and that mind-wandering and self-related mental processes also activate both the medial and lateral regions (Anderson et al., 2011; Chai et al., 2012; Fox et al., 2015; Murphy et al., 2009; Spreng et al., 2014; Spreng et al., 2009; Spreng et al., 2010).

A second example is related to reported hyper-activity and hypo-activity in older relative to younger adults during cognitive tasks. Some studies found a greater task-related activity in older relative to younger adults during cognitive tasks such as memory encoding and retrieving. For example, younger and older adults were instructed in one study to view (i.e., encode) color photographs and were tested whether they could recognize viewed pictures about 10 minutes later (Gutchess et al., 2005). Relative to the younger adults, the older adults showed a greater activation in the prefrontal and parietal cortices but a smaller activation in the parahippocampal gyrus for remembered relative to forgotten pictures during the encoding phase. Another study assessed task-related brain activity while younger and older adults viewed words and judged their living/nonliving categorization (Kennedy et al., 2015). During easy trials of unambiguous words relative to fixation baseline, the older adults showed a greater increase in BOLD signal in the right middle frontal gyrus and the bilateral parietal cortices, but no smaller increases in any regions relative to the younger adults. The task-related

hyper-activation in the older relative to the younger adults has been hypothesized to reflect a compensation of reduced functional efficiency in the aging brain (Reuter-Lorenz and Park, 2014; Turner and Spreng, 2015).

However, several other studies reported that older adults exhibited a smaller task-related brain activity relative to younger adults during cognitive tasks. For example, one study assessed task-related brain activity in younger and older adults while they viewed a list of words and decided whether the words were abstract or concrete in meaning (Stebbins et al., 2002). Relative to the young adults, the older adults showed a smaller task-related increase in activity in the left superior, middle, and inferior frontal gyri. In a series of studies, younger and older adults performed a Sternberg working memory task with two task loads (Rypma and D'Esposito, 2000; Rypma et al., 2001). They needed to remember two and six letters during the low- and high-load conditions, respectively. The older and younger groups did not show significant difference in task-related activity in any brain regions during the low-load condition, but the older showed a smaller task-related activity in the dorsal prefrontal cortex during the high-load condition. In a more recent study, younger and older adults were instructed to read and remember lists of word pairs, and their recollections were tested about 15 minutes after reading (de Chastelaine et al., 2016). For remembered relative to forgotten word pairs, older adults relative to younger adults exhibited a smaller task-related activity in the anterior cingulate cortex. The task-related hypo-activation in older adults has been hypothesized to reflect impaired brain function (Kaup et al., 2014; Li et al., 2015; Nagel et al., 2011; Sala-Llonch et al., 2015).

Furthermore, similar inconsistencies in task-related hyper- versus hypo-activation have been reported in almost all neuropsychiatric disorders in fMRI studies using GLM, including depression, schizophrenia, and substance-use disorders (Balodis and Potenza, 2014; Hommer et al., 2011; Limbrick-Oldfield et al., 2013; Mayberg, 2014; Parens and Johnston, 2014; Whalley et al., 2012; Xu, 2015a).

1.3. Limited sensitivity and specificity of GLM

Multiple factors, such as task context, sample size, individual variability, and the spatial and temporal resolutions of fMRI may contribute to inconsistent fMRI findings (Mayberg, 2014; Parens and Johnston, 2014; Xu, 2015). In addition, we propose that the limited sensitivity and specificity of GLM in detecting neuronal activity is a critical factor. GLM is typically a univariate approach, analyzes BOLD signal from each voxel separately, and reports significant or no significant changes in the signal under different task conditions at different time points (Poline and Brett, 2012). GLM studies regularly interpret signal increases as increased neuronal activities in the voxel, signal decreases as reduced neuronal activities, and no signal change as no changes in neuronal activity. This practice implicitly follows the afore-mentioned modular view of brain functional organization and assumes that BOLD signal increases and decreases in different voxels reflect activation and deactivation of neurons related to different mental processes, respectively. However, as discussed below, it oversimplifies the relationship between changes in BOLD signal and heterogeneous activities of neuronal populations in a voxel and neglects several fundamental brain properties including functional heterogeneity, balanced

excitation and inhibition (E/I), and sparseness of neuronal activity (Logothetis, 2008; Serences and Saproo, 2012; Xu, 2015).

Histological studies report extensive convergent and divergent fiber projections among cortical regions and between cortical and subcortical structures (Boucsein et al., 2011; Cappe et al., 2009; Dancause et al., 2006; Driver and Noesselt, 2008; Padberg et al., 2009; Schnepel et al., 2015; Stepniewska et al., 2015). These data indicate that intermixed neurons in the same cortical regions receive inputs from and send outputs to extensive cortical and subcortical areas. Consistent with these histological findings, electrophysiological studies report that intermixed neurons respond to different afferents and exhibit highly heterogeneous functional activities (Funahashi, 2013; Fuster, 2009; Swindale, 1998). These findings do not support the modular theory of brain functional organization. Instead, they indicate that functional heterogeneity of intermixed cortical neurons within the same region is a fundamental property of the cortex (Fuster and Bressler, 2015; Harris and Mrsic-Flogel, 2013; Hermansen et al., 2007; Perin et al., 2011). A typical fMRI voxel in the cortex with 3-5 mm in each dimension contains at least hundreds of thousands of neurons (Druga, 2009; Logothetis, 2008; Roth and Dicke, 2012). Therefore, the BOLD signal from each voxel reflects a highly heterogeneous mixture of functional activities of the entire neuronal population in a voxel, and analyzing this heterogeneous nature of BOLD signal from each voxel is not a strength of the standard univariate GLM.

Furthermore, about 15~20% of cortical neurons are GABAergic inhibitory

interneurons and 80-85% excitatory pyramidal neurons (Druga, 2009). These inhibitory and excitatory neurons form feedforward and feedback inhibitory circuits, the building blocks in the cortex (Fig. 1) (Haider et al., 2013; Isaacson and Scanziani, 2011; Okun and Lampl, 2008; Ren et al., 2007; Silberberg and Markram, 2007). Even though inhibitory neurons are fewer than excitatory neurons in the cortex, they form extensive synapses onto adjacent pyramidal neurons, as if to exert a 'blanket of inhibition' (Fino et al., 2013; Fino and Yuste, 2011; Inan et al., 2013; Karnani et al., 2014; Markram et al., 2004; Packer and Yuste, 2011). The inhibitory and excitatory neurons maintain a balanced E/I in the cortex; i.e., increased activity in some neurons relates to reduced activity in adjacent neurons, and neurons in the same voxels may show concurrent, co-localized activation and deactivation (CCAD) (Logothetis, 2008; Xu, 2015). Closely related to the property of balanced E/I is sparseness of neuronal activities, another fundamental property in the brain (Barth and Poulet, 2012; Wolfe et al., 2010). This property indicates that only a fraction of cortical neurons in the same regions may fire action potentials at any instant, while most neurons are silent (Barth and Poulet, 2012; Crochet et al., 2011; Tolhurst et al., 2009). Again, GLM cannot differentiate concurrent increase, decrease, and no changes in activity from intermixed neurons in a voxel.

If increases and decreases in neuronal activities indeed induce BOLD signal increase and decrease, respectively, as reported in many studies (Goense et al., 2012; Logothetis, 2008; Mullinger et al., 2013, 2014; Shmuel et al., 2006), BOLD signals related to opposite changes in neural activities in the same voxels

may cancel each other. Therefore, BOLD signal changes in each voxel probably reflect changes in differences (or ratios) between CCAD, not in activation or deactivation alone (Logothetis, 2008; Xu, 2015). A voxel may not show any BOLD signal change if its difference in CCAD does not change, even though individual neurons may change activity significantly. It may express a greater BOLD signal if its neuronal population reduces total deactivation without an increase in activation (Logothetis, 2008; Xu, 2015). Therefore, increases or decreases in BOLD signal do not reliably indicate a greater activation or smaller deactivation, and this uncertainty may contribute to inconsistent findings from fMRI studies using GLM (Logothetis, 2008; Xu, 2015).

1.4. Functional network overlap

The convergent and divergent axonal projections in the brain and heterogeneous activities of intermixed neurons in the same brain region demonstrate that cortical microcircuits are not independent and segregated in space, but they rather overlap and interdigitate with each other (Harris and Mrsic-Flogel, 2013; Hermansen et al., 2007; Perin et al., 2011). Based on these findings, some investigators have explicitly proposed extensive overlap of large-scale FNs in the brain (Fuster, 2009; Fuster and Bressler, 2015; Hermansen et al., 2007; Swindale, 1998). Supporting this proposal, multiple fMRI studies from our and other groups demonstrate extensive FN overlap by using sICA or analytical techniques other than GLM.

Independent component analysis (ICA) is a computational technique for extracting hidden signals from observed signal mixtures (Beckmann, 2012;

Calhoun and Adali, 2012; Calhoun et al., 2009; Comon, 1994; McKeown et al., 1998b). Different from univariate GLM, sICA is multivariate and treats BOLD signal from each voxel as a signal mixture of different source signals, and separates it into spatially independent components (ICs) by using higher-order statistics (Calhoun and Adali, 2012; Calhoun et al., 2002; Calhoun et al., 2009; McKeown et al., 1998a; McKeown et al., 1998b; McKeown and Sejnowski, 1998). This advantage of sICA was one of the reasons for introducing sICA to fMRI (McKeown et al., 1998b). In an early sICA study, both sICA and GLM were used to extract simulated signals from a synthetic dataset (McKeown et al., 1998b). Synthetic fMRI data were generated by adding simulated signals with known timecourses to acquired real BOLD data in arbitrarily selected brain regions. SICA generated an IC with a timecourse consistent with the simulated signals and a spatial map consistent with the selected brain regions, and another IC with a timecourse consistent with the actual task-related activity. However, GLM recovered only a small proportion of voxels with the simulated signal. Findings from this study indicated that sICA had a greater sensitivity and specificity than GLM in detecting brain regions of simulated signal (McKeown et al., 1998b).

SICA groups all voxels with synchronized source signals into one temporally coherent FN and is a popular method for studying large-scale FNs in fMRI (Beckmann, 2012; Calhoun and Adali, 2012; Calhoun et al., 2009; Comon, 1994; McKeown et al., 1998b). Because of its unique capacity of separating signal mixture from each voxel into source signals, investigators have used sICA to de-noise fMRI data by separating artifacts from signals (Aron and Poldrack,

2006; Beckmann, 2012; Brooks et al., 2013; Du et al., 2016; Griffanti et al., 2014; Tohka et al., 2008; Yakunina et al., 2013). Furthermore, some fMRI sICA studies have described spatial overlap of two or more FNs, indicating that sICA can separate BOLD signal mixtures from individual voxels into two or more FNs in the overlapping regions (Calhoun et al., 2008; Domagalik et al., 2012; Kim et al., 2009a; Kim et al., 2009b; Menz et al., 2009; St Jacques et al., 2011; van Wageringen et al., 2009; Wu et al., 2009; Zhang and Li, 2012). Very recently, we and at least three other groups systematically described FN overlap generated by sICA (Beldzik et al., 2013; Braga et al., 2013; Geranmayeh et al., 2014; Leech et al., 2012; Xu et al., 2014a; Xu et al., 2013a; Xu et al., 2013b; Yeo et al., 2013).

For example, a recent study used sICA to extract FNs from fMRI datasets related to speech (Speech), counting (Count), and decision-making (Decision) tasks (Geranmayeh et al., 2014). SICA generated one FN at the left frontal-temporal-parietal (FTP) and another FN at the right FTP mirroring the left one. The two FNs overlapped with each other at the left parietal and frontal cortices. The left FN showed a task-related activity increase during Speech but an activity decrease during Count and Decision. However, the right FN showed opposite changes in task-related activity; i.e., reduced activity during Speech and increased activity during Count and Decision. Furthermore, a third FN extensively overlapped with the FN at the left FTP and showed reduced activation during Speech and Count. Therefore, three overlapping FNs showed task-related, concurrent, opposite modulations during Speech and Count (Geranmayeh et al., 2014). These findings demonstrate that the BOLD signal from the same brain

regions may consist of heterogeneous source signals each with independent unique task-related modulations.

In another study, both GLM and sICA were used to interrogate fMRI data acquired during pro-saccadic (PS) and anti-saccadic (AS) tasks (Beldzik et al., 2013; Domagalik et al., 2012). sICA extracted 11 FNs which showed extensive overlap at multiple brain regions including the intraparietal sulcus, frontal eye field, precuneus and posterior cingulate (PCC). Some of these overlapping FNs showed synergistic changes in task-related activity; i.e., increased activity during AS relative to PS. The overlapping regions of synergistic FNs also exhibited increased activity as revealed by GLM. However, the FNs overlapping at the PCC showed opposite changes in task-related activity during AS relative to PS; i.e., increased in some FNs but decreased in others. These opposite changes in activity in the PCC appeared to cancel each other because GLM did not detect significant changes in activity in these brain regions.

Over the last several years, we have applied both GLM and sICA to five task-related datasets acquired from different participants at four different institutes (Xu, 2015; Xu et al., 2014a; Xu et al., 2014b; Xu et al., 2015; Xu et al., 2013a; Xu et al., 2013b). These tasks involve visual attention, working memory, interference inhibition, mentalizing, and monetary motivation and rewards. Consistent with data from other GLM studies (Fox et al., 2005; Gusnard et al., 2001; Mason et al., 2007; Raichle, 2015; Sonuga-Barke and Castellanos, 2007), our GLM application revealed that the visual attention and working memory tasks activated the lateral task-positive network and deactivated the medial task-

negative network, and that the mentalizing task activated the task-negative network. Different from GLM findings, sICA consistently demonstrated that: 1) FNs overlapped with each other extensively at both medial and lateral brain regions, 2) overlapping FNs may show concurrent task-related increases and decreases in activity in both medial and lateral brain regions, 3) FNs did not show task-related changes in activity (i.e., task-neutral FNs) occupied most or all brain volumes and overlapped with FNs showing increases or decreases in activity, 4) brain regions exhibiting task-related increases in activity as revealed by GLM may involve overlapping FNs exhibiting concurrent task-related increases and decrease in activity as revealed by sICA, with the increases dominating over the decreases, 5) brain regions exhibiting task-related decreases in activity as revealed by GLM may involve overlapping FNs exhibiting concurrent task-related increases and decrease in activity as revealed by sICA, with the decreases dominating over the increases, and 6) brain regions that did not exhibit task-related changes in activity as revealed by GLM may show overlapping FNs with concurrent opposite changes in activity, indicating these opposite changes in activity may have cancelled each other in GLM.

Consistent with these sICA findings, multiple studies using several other multivariate analytic methods also reported extensive FN overlap either during resting state or task performance. These methods include temporal ICA (Smith et al., 2012), Connected Iterative Scan (CIS) (Yan et al., 2011), Link Cluster (Madhyastha et al., 2013), Latent Dirichlet Allocation (LDA) (Yeo et al., 2013), Sparse Coding And Dictionary Learning (Lv et al., 2015), Stable Overlapping

Replicator Dynamics (SORD) (Yoldemir et al., 2015), and Innovation-Driven Co-Activation Patterns (iCAPs) (Karahanoğlu and Van De Ville, 2015). These consistent findings from different approaches indicate that extensive FN overlap is a general property of large-scale brain functional organization, not a unique feature of specific cognitive tasks or specific population. We proposed that overlapping FNs with simultaneous but different task-related modulations probably reflect the fundamental properties of functional heterogeneity, balanced E/I, and sparseness of neuronal activity in the brain (Xu, 2015; Xu et al., 2015).

1.5. Reconciling inconsistent GLM findings

The sICA findings of extensive FN overlap may help reconcile some inconsistent GLM finding from a novel theoretical viewpoint (Xu, 2015). For example, some studies proposed that the finding of anti-correlated task-positive and task-negative FNs was an artifact introduced by removing global signals during data preprocessing, because it could not be found in studies without this preprocessing procedure (Anderson et al., 2011; Carbonell et al., 2011; Raichle, 2015). On the other hand, other investigators suggested that removing global signals could remove signals common to all brain regions and thus reveal the anti-correlation hidden in mixed raw signals (Anderson et al., 2011; Carbonell et al., 2011; Raichle, 2015). As reviewed in the sections above, FNs generated by sICA overlap extensively in both medial and lateral brain regions, and they may show task-related concurrent synergistic or opposite modulations. This finding indicates that both correlated and anti-correlated signals exist in the same brain regions, regardless of medial or lateral locations, and between different brain

regions (e.g., medial relative to lateral). This interpretation of sICA findings is supported by the brain's property of balanced E/I, which stipulates that both correlated and anti-correlated activities exist among adjacent neurons in the same brain regions. Therefore, FN overlap revealed by sICA may help reconcile conflicting findings related to the anti-correlations between activities in the medial and lateral brain regions.

Using sICA to separate overlapping FNs may also help reconcile inconsistent GLM findings of hyper- vs. hypo-activity in older adults and psychiatric patients. There is strong evidence that glutamatergic excitation, GABAergic inhibition and balanced E/I are altered in older adults and psychiatric patients relative to younger adults and healthy controls (HCs), respectively, and that unbalanced E/I contributes to impaired cognitive functioning (Brady et al., 2013; Caspary et al., 2008; Edden et al., 2012; El Idrissi et al., 2013; Ende et al., 2016; Gonzalez-Burgos et al., 2015; Legon et al., 2015; Luscher and Fuchs, 2015; Murray et al., 2014; Nelson and Valakh, 2015; Pehrson and Sanchez, 2015; Purkayastha et al., 2015; Riese et al., 2015; Robertson et al., 2016; Roux and Buzsaki, 2015; Schmidt and Mirnics, 2015; Stebbings et al., 2016; Tse et al., 2015). This pathophysiological mechanism may contribute importantly to inconsistent GLM findings because they may lead to BOLD signal decrease, increase, or no change in different brain regions in older adults and patients, depending on the relative extent of changes in excitation and inhibition in each region. sICA's unique capacity of separating overlapping FNs enables sICA to reduce the cancellation of opposite signals by separately measuring concurrent

increases and decreases in source signals from the same voxels; sICA may also avoid confusion relating to the potential conflation of reduced deactivation and increased activation. Thus, sICA may help reconcile inconsistent GLM findings of hyper- vs. hypo-activity.

The remaining sections of this paper will report findings by applying sICA to two fMRI datasets downloaded from public databases. These findings will provide further support to our hypothesis that extensive overlap of large-scale FNs is a general property of brain functional organization, and that using sICA to separate overlapping FNs may help reconcile inconsistent GLM findings of hyper- versus hypo-activation in older relative to younger adults. The two datasets were acquired from younger and older adults during an audiovisual speech perception task (AVSPT) and a false-belief task (FBT). The AVSPT was a typical external goal-directed task and required participants to identify external targets by pressing a button. The FBT involved mentalizing and required participants to answer question regarding the mental state of characters described in stories. We made the following predictions regarding sICA findings based on recent sICA data and the fundamental brain properties discussed above. 1) FNs generated by sICA would overlap extensively at both the lateral and medial parts of the brain, because of the functional heterogeneity property of the brain. 2) Overlapping FNs may show different, or even opposite (i.e., up versus down), task-related modulations in timecourses, because of the balanced E/I property. 3) FNs not showing task-related modulations over time may occupy most or the whole brain volume and extensively overlap with FNs exhibiting

significant modulations, because of the sparseness of neuronal activity property.

4) Older participants would show smaller, but not greater, modulations in FN timecourse relative to the younger adults at selected contrasts of task conditions, because of altered excitation and inhibition and impaired cognitive function in older relative to younger adults. Findings from sICA would demonstrate that reduced task-related suppression of FNs contributed to the GLM finding of hyper-activation in older relative to younger adults. For qualitative comparison of the findings from sICA and GLM, we also applied a GLM to the two datasets and present the GLM findings in the supplementary materials.

2. Materials and Methods

2.1. Participants and fMRI tasks

Two fMRI datasets were downloaded from public repositories. The first dataset related to manual responses to auditory stimuli and the second to a false-belief task (FBT). Previous GLM findings indicate that tasks used in the first and second dataset should activate the lateral (i.e., task-positive network) and the medial (i.e., default mode network (DMN) or task-negative network) part of the brain, respectively (Fox et al., 2005; Mason et al., 2007; Raichle, 2015). We selected the two tasks that should activate different brain regions to demonstrate extensive overlap of large-scale FNs representing a general property of brain functional organization.

Audiovisual speech perception task (AVSPT). This dataset was downloaded from figshare (<http://dx.doi.org/10.6084/m9.figshare.1181943>)

(Baum and Beauchamp, 2014), and was acquired from 14 younger (20–39 years, 6 female, mean age 26.1 years) and 19 older adults (53–70 years, 12 female, mean age 63.0 years) during performance of an AVSPT. The task used a rapid event-related design, and consisted of McGurk (auditory “pa” + visual “ka”, auditory “ba” + visual “ga”), non-McGurk congruent (“ba”, “ga”, “da”, “pa”, “ka” and “ta”), non-McGurk incongruent (auditory “ka” + visual “pa”, auditory “ga” + visual “ba”), target (audiovisual “ma” in younger subjects or “press” in older adults), and fixation (fixing on crosshairs) trials. Participants were required to press a button as a response to the targets and do nothing in response to other stimuli. Behavioral data were missing for two younger subjects. Available data indicated that the accuracy was near ceiling (10/12 younger adults at 100% accuracy, 18/19 older adults at 100% accuracy, with no significant difference between groups, $t_{29} = 0.6$, $p = 0.57$), and that all participants were alert in the scanner. The duration for each stimulus varied from 1.7 to 1.8 seconds followed by fixation crosshairs for the remainder of the trial. Each participant had two functional runs. The duration for each run was 456 ~ 596 seconds and consisted of 10 ~ 20 target trials, 25 ~ 55 McGurk trials, and 40 ~ 75 non-McGurk trials. Please see (Baum and Beauchamp, 2014) for a more detailed description of participant characteristics, task conditions, and task performance.

False-belief task (FBT). This dataset was downloaded from <https://openfmri.org> (ds000109) (Moran et al., 2012) and was acquired from healthy younger and older participants. The younger group includes 21 subjects (mean age = 22.7 years, range: 18-37; female = 15) while the older group

includes 12 subjects (mean age = 72 years; range: 65 ~ 88; female = 5). The participants performed a FBT using a block design. The task required the participants read a short story, remember the content, and answer questions about the mental status of a character described in the story (Moran et al., 2012). The duration for each story-reading and question-answering block was 10 and 6 seconds, respectively. There was a variable delay of 0-6 seconds between the two blocks. The crucial test in the FBT was for participants to answer the question from the perspective of the story character and not from their own perspective. The control condition, i.e., false photograph stories task (FPT), was isomorphic to the FBT in that participants again read stories describing a state of the world and answered questions about that content after a variable delay. The critical difference between conditions was that the FPT contained an incorrect *physical* description of the world rather than a false belief (or mental state) about the world. During scanning, participants answered questions more accurately for the FPT relative to the FBT, and the older group showed a trend reflecting worse performance on the FBT relative to the younger group, but not on the FPT. Please see (Moran et al., 2012) for a more detailed description of task conditions, participant characteristics, and task performance. In addition, some sICA findings from this dataset have been reported (Xu, 2015). However, the data reported in the current paper were not described in the previous publication.

2.2. Imaging data acquisition

AVSPT. The imaging data were acquired using a 3T scanner (Phillips Medical Systems). A T2* weighed gradient echo-planar imaging sequence (TR=

2000 ms, TE = 30 ms, flip angle = 90°, in plane resolution: 2.75 x 2.75 mm²) was used to acquire blood-oxygenation level dependent (BOLD) signal. Each participant performed two functional runs in the scanner. T1-weighted MP-RAGE high-resolution images were also acquired.

FBT. The imaging data were acquired using a 3T Trio scanner (Siemens). BOLD signals were acquired using a gradient echo-planar sequence (TR=2000 ms, TE = 35 ms, in plane resolution: 3 x 3 mm², slice thickness: 3 mm with 0.54 mm skip, and 36 slice). Each participant had two runs and each run acquired 179 volumes.

2.3. ICA procedures

SPM12 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) was used to preprocess imaging data. Each BOLD timeseries in each dataset was motion-corrected, normalized to the MNI (Montreal Neurological Institute) template, and smoothed with a 6-mm Gaussian kernel. The group ICA algorithm (GIFT, <http://mialab.mrn.org/software/gift>, version 1.3h) was used to extract spatially independent components (ICs) from the preprocessed fMRI timeseries of each dataset (Calhoun et al., 2001; Calhoun et al., 2009). Data from all participants of each dataset were concatenated into a single dataset and reduced using two stages of principal component analysis (PCA) (Calhoun et al., 2001). We extracted 75 ICs from each dataset by using the Infomax algorithm (Bell and Sejnowski, 1995). This high-model-order ICA generated refined components consistent with known anatomical and functional segmentations of the brain (Abou-Elseoud et al., 2010; Allen et al., 2011;

Balsters et al., 2013; Ciccarelli et al., 2009; Kiviniemi et al., 2009; Smith et al., 2009; Ystad et al., 2010). The Infomax algorithm generated a spatial map and a timecourse of the source signal changes for each IC. For each dataset, this analysis was repeated 50 times using ICASSO for assessing the repeatability of ICs (Supplemental Fig. 1) (Himberg et al., 2004), and the most representative run was selected for further analysis. Finally, subject-specific IC timecourses and spatial maps were back-reconstructed using the GICA3 method (Calhoun et al., 2001; Erhardt et al., 2011; Meda et al., 2009). GICA3 derives subject-specific timecourses and spatial maps directly from the PCA and ICA. The product of PCA and ICA is used to predict the subject data to the accuracy of information retained from the PCA. The aggregate spatial map is the sum of the subject-specific spatial maps, analogous to a random effects model where the subject-specific effects are zero-mean distributed deviations from the group mean effect. GICA3 provides a natural interpretation for the subject-specific timecourses and spatial maps (Allen et al., 2011; Erhardt et al., 2011). The detailed algorithms of GICA3 were presented in a previous paper (Erhardt et al., 2011).

Each IC was visually inspected for separating artifacts from functional networks (FNs). Our diagnostic criteria for artifacts were consistent with the criteria used previously (Allen et al., 2011). ICs with peak voxels in white matter and/or cerebrospinal fluid (CSF) were diagnosed as artifacts. A small dynamic range of power spectra and/or small ratio of the integral of spectral power below 0.10 Hz to the integral of power between 0.15 and 0.25 Hz were used as indicators of artifacts (Allen et al., 2011; Robinson et al., 2009). For defining brain

regions associated with each IC, we used the GIFT one-sample t-test tool to create a group-level t-map for each IC. The significance threshold was set at voxel height $p < 0.001$, false-discovery-rate (FDR)-corrected for multiple comparisons of voxel-wise whole-brain analysis.

2.4. Assessing FN overlap

Since each IC has a positive and a negative element, the above-described t-map of each IC contains significant clusters with positive and negative t values. In this paper, we call the positive and negative clusters in the t-map as positive and negative sub-networks, respectively, and each sub-network represents one FN. In the following text of this paper, the term IC refers to a component extracted by sICA, and each IC includes both positive and negative sub-networks. In contrast, FN refers to either the positive or negative sub-network of each IC. We converted each sub-network into a binary mask. Only significant voxels in each sub-network surviving the statistical threshold described above were converted into voxels with a value of one in the output mask, while all other voxels were converted into voxels with values of zero. Two masks were generated for each t-map: one for positive clusters and one for negative clusters. We added these masks together for assessing FN overlap in each dataset. Within the output map, any voxels with a value of two or higher indicated that two or more FNs overlapped at this voxel.

2.5. Assessing task-related modulation over timecourses

For sICA temporal sorting, SPM12 was used to create a design matrix for each subject. The design matrix represents the onset of each trial or task block

during fMRI. For the AVSPT, McGurk, non-McGurk, and target trials were modeled explicitly as different event-related trials, and fixations were modeled implicitly as baseline. For the FBT, blocks related to reading FBT and FPT were explicitly modeled as different task blocks, as were the blocks for answering related questions, while the resting blocks were implicitly modeled as baseline conditions. The temporal sorting function from GIFT was used to perform a multiple regression analysis between the IC timecourse and the design matrix for each participant. For each IC, this regression generated a beta-weight value for each trial type or block of each functional run. These beta-weight values represent the correlations between IC timecourses and the canonical hemodynamic response model of task conditions, and index the engagement of ICs during specific task conditions (Meda et al., 2009). An increase or decrease in beta-weight values in one task condition relative to another indicates an increase or decrease in task-related activity in the IC.

The beta-weights of each IC for each task condition across multiple runs for each subject were averaged to generate mean beta-weights for each participant, which were used to calculate the group means for each task condition. We used SPSS (v. 21, IBM SPSS) GLM for repeated measure to assess the main effect of task condition and group (i.e., younger vs. older group), and the two-way interaction effect of group-by-task condition. In this study, we assessed beta-weight changes between McGurk vs. target trials for the AVSPT, and FBT blocks versus FPT blocks for the FBT. The significance threshold was $p < 0.05$, using FDR algorithm for correction of multiple comparisons due to

multiple ICs. A significant increase in beta-weight indicates a task-related up-modulation of the timecourse or an increase in activity of the positive sub-network of the IC during a specific task condition relative to another task condition. Therefore, the positive sub-network of this IC was designated as a positive FN, and the negative sub-network as a negative FN. A significant decrease in beta-weight indicates a task-related down-modulation of the timecourse or a decrease in activity of the positive sub-network of the IC. Therefore, the positive sub-network of this IC was designated as a negative FN, and the negative sub-network as a positive FN. If the beta-weight was not significantly different between the two task conditions after correction for multiple comparisons, then the IC is a neutral IC and both of its sub-networks are neutral FNs. For assessing the volume of all positive FNs, we grouped all positive FNs into one brain space, and the total number of voxels covered by any positive FN represented the total volume of all positive FNs. A similar method was used to calculate the total volume of negative FNs and neutral FNs.

3. Results

3.1. Audiovisual speech perception task (AVSPT)

We analyzed task-related modulations of 36 ICs after excluding ICs diagnosed as artifacts and ICs mainly involving the cerebellum. The reason for excluding cerebellum ICs was to reduce the number of comparisons. Sixteen of the ICs (IC1, 4, 8, 17, 25, 27, 32, 33, 36, 39, 41, 42, 44, 45, 50, and 51) showed a significant main effect of task (please see Supplemental Fig. 2 and Table 2 for detailed spatial maps and statistics). All ICs, except IC44, exhibited up-modulation in timecourses for target vs. McGurk trials (Fig. 2A, B & Fig. 3). Therefore, they were task-positive ICs as defined in the current study, and their positive and negative sub-networks were task-positive and task-negative FNs, respectively. IC44 showed significant down-modulation at target versus McGurk trials (Fig. 2C). Therefore, it was a task-negative IC and its positive and negative sub-networks were task-negative and task-positive FNs, respectively.

One task-positive IC (i.e., IC27) showed a significant main effect of group and two-way interaction effect of task-by-group (Fig. 3 & Supplemental Table 2). The effects were mainly due to a greater task-related up-modulation of its timecourse in the younger relative to the older group at target versus McGurk trials (Fig. 3). Therefore, its positive and negative sub-network showed a greater increase and decrease, respectively, in BOLD signal in the younger relative to the older group at target versus McGurk trials. The positive sub-network of this IC mainly involved the anterior insula and adjacent ventrolateral PFC, medial PFC, temporoparietal junction (TPJ), and caudate heads, bilaterally, while its negative

sub-network mainly involved the bilateral superior frontal sulcus. The remaining 20 of the 36 ICs were task-neutral ICs; i.e., they did not show significant task-related modulations. Therefore, their positive and negative sub-networks were task-neutral FNs.

All task-positive FNs combined together covered about 64.9% of all brain volume analyzed in this study and included both medial and lateral parts of each cortical lobe and subcortical regions such as the thalamus, basal ganglia, and midbrain (Fig. 4A & Table 1). Furthermore, two or more task-positive FNs overlapped extensively at multiple cortical and subcortical regions including the dorsomedial PFC, precuneus/posterior cingulate (PCC), insula, and TPJ, bilaterally. These regions probably represent the interaction areas of synergistic FNs related to different mental processes for successful task performance.

Task-negative FNs were less extensive than the task-positive FNs. They covered about 29.7% of the studied brain volume and involved all major divisions of the brain, including the medial, lateral, dorsal, and ventral cortical regions (Fig. 4B & Table 1). Similar to the task-positive FNs, two or more task-negative FNs may overlap at the same locations. In addition, task-negative and task-positive FNs overlapped at multiple regions including the medial PFC, frontal eye fields, PCC/precuneus, ventrolateral PFC, and posterior insula (Fig. 4A, B). This finding indicates that these regions probably represent interaction areas of FNs involved in different functions.

Relative to the task-positive and task-negative FNs, the task-neutral FNs occupied the most extensive brain regions (i.e., ~78.0% of all analyzed brain

volume), including most cortical and subcortical regions (Fig. 4C & Table 1). Many of them overlapped with each other extensively at multiple cortical and subcortical locations, including the intraparietal sulcus, medial frontoparietal cortex, and dorsolateral PFC. Furthermore, the task-neutral, task-positive, and task-negative FNs overlapped at several brain regions including the medial and ventrolateral PFC, frontal eye fields, and PCC, as revealed by visual inspection of Fig. 4A, B, and C and indicated in Table 1.

3.2. False-belief task (FBT)

We analyzed task-related modulations of 40 ICs after exclusion of ICs diagnosed as artifacts and ICs mainly involving the cerebellum. Five (IC 25, 42, 52, 57, and 60) of the 40 ICs showed a significant main effect of task (please see Supplemental Fig. 3 and Table 2 for spatial maps and statistics). They exhibited up-modulation in their timecourses during FBT versus FPT blocks and therefore were task-positive ICs (Fig. 5). The remaining 35 of the 40 ICs did not show significant task-related modulations and therefore were task-neutral ICs.

Three task-neutral ICs (IC12, 62, and 66) showed a significant effect of group (please see Supplemental Fig. 3 and Table 2 for spatial maps and statistics). Two of them (IC12 and 62) exhibited a greater up-modulation in the younger relative to the older group during both FBT and FPT blocks (Fig. 6A, B). The positive sub-network of IC12 mainly involves the medial visual cortex. The positive sub-network of IC62 mainly involves the left temporal cortex and bilateral dorsolateral PFC, while its negative sub-network is the right TPJ. The remaining

IC (IC66) showed a greater down-modulation in the younger relative to the older group during both task blocks (Fig. 6C). The positive sub-network of this IC mainly involves the TPJ and lateral PFC, while its negative sub-network mainly involves the precuneus and medial PFC. No ICs showed a significant two-way interaction of task-by-group.

All task-positive FNs combined together covered about 33.3% of the studied brain volumes (Table 1), and they covered more posterior portions of the brain such as the parietal and temporal cortices than the anterior part of the brain such as the PFC (Fig. 7A). Consistent with the findings from the AVSPT, sICA showed extensive overlap of task-positive FNs at multiple cortical and subcortical regions including the precuneus and TPJ, bilaterally, indicating interaction of synergistic FNs. Task-negative FNs covered about 16.7% of the studied brain volume including frontal, parietal, and temporal cortices (Fig. 7B & Table 1). Consistent with findings from the first task, some task-negative FNs overlapped with each other, and overlapped with task-positive FNs at multiple regions including the precuneus/PCC and parietal and temporal cortices (Fig. 7A, B). Relative to the task-positive and task-negative FNs, the task-neutral FNs occupied the most extensive brain regions (i.e., ~98.2% of all studied brain volume), including almost all cortical and subcortical volumes (Fig. 7C & Table 1). They showed extensive overlap with each other, and overlap with task-positive and task-negative FNs.

4. Discussion

4.1. Main findings. The main findings revealed by sICA are highly consistent with our predictions and they include: 1) extensive overlap of task-positive, task-negative, and task-neutral FNs, 2) extensive task-neutral FNs covering most of the analyzed brain volumes, and 3) smaller task-related modulation of FNs in the older relative to the younger group.

4.2. FN overlap. Two lines of data are regularly cited to support the modular theory of brain functional organization. The first is related to cortical columns; i.e., cortical neurons in a vertical cluster often respond to the same attributes of peripheral stimulation (Horton and Adams, 2005; Mountcastle, 1997; Szentagothai, 1983). The second is related to topographic maps of peripheral receptive fields in the sensory cortex, such as the retinotopic map in the primary visual cortex (Hubel and Wiesel, 1968). However, many studies find that dense horizontal connections exist between cortical columns, that intermixed neurons in the same columns respond to different attributes of peripheral stimulation, and that multiple microcircuits occupy the same space and interlace with each other (Boucsein et al., 2011; Harris and Mrsic-Flogel, 2013; Hermansen et al., 2007; Horton and Adams, 2005; Perin et al., 2011). Therefore, both histological and electrophysiological studies indicate that neurons in the same cortical columns are heterogeneous in functional activities and may join in different microcircuits. Furthermore, the same sensory cortex may contain multiple topographic maps representing different attributes of external inputs. For example, topographic maps for space, color, ocular dominance, motion orientation, and spatial

frequency superimpose on each other in the primary visual cortex (Swindale, 1998, 2000). These data strongly indicate that large-scale FNs overlap with each other, instead of being isolated from each other (Fuster, 2009; Fuster and Bressler, 2015; Swindale, 1998, 2000). Consistent with these histological and electrophysiological findings, extensive overlap of large-scale FNs has been reported by recent fMRI studies using sICA and several other multivariate analytical approaches capable of separating intermixed signals as reviewed in the introduction (Beldzik et al., 2013; Geranmayeh et al., 2014; Xu et al., 2015; Xu et al., 2013b). The extensive FN overlap revealed in the current studies provide further support to our hypothesis that large-scale FN overlap is a general property of brain functional organization.

The current and previous sICA studies find that more FNs overlap in the higher-order association cortex relative to the primary sensory cortex (Beldzik et al., 2013; Geranmayeh et al., 2014; Xu et al., 2015; Xu et al., 2013b). These brain regions often exhibit more “edges” (i.e., functional connectivity) with more diverse brain regions relative to the primary sensory cortex in functional connectivity studies using seed-based approaches (Crossley et al., 2014; van den Heuvel and Sporns, 2013). It has been proposed that these brain regions represent “cores or hubs” of brain FNs, and that they may play central roles in brain communication and neuropsychiatric disorders (Crossley et al., 2014; Rubinov and Bullmore, 2013). The co-localization of FN overlap and “cores or hubs” indicates that common neural substrates may underlie these different findings using different analytical methods. Relative to the primary sensory

cortex, the association cortex contains more heterogeneous neurons, receiving inputs from and sending outputs to more diverse brain regions (Augustine, 1996; Cavanna and Trimble, 2006; Katsuki and Constantinidis, 2012; Petrides, 2005). We propose that the highly heterogeneous neurons and their divergent and convergent inputs and outputs in the association cortex probably underlie more FN overlap as revealed by sICA and more functional connectivity (i.e., edges) as revealed by seed-based functional connectivity analyses. However, we acknowledge that the exact relations between brain microcircuits and large-scale FNs generated by fMRI are not clear, in part related to an incomplete understanding of neurovascular coupling.

FN overlap suggests that local connections, not just long-rang projections, contribute to functional connectivity among different FNs. Local fibers are much denser than long-range fibers and may play a greater role in FN connectivity than long-rang fibers (Buzsaki et al., 2004; Levy and Reyes, 2012; Watkins et al., 2014). Therefore, changes in functional and anatomical connectivity measured using BOLD signal and diffusion MRI (dMRI), respectively, may demonstrate different patterns in patients with neuropsychiatric disorders (Fornito and Bullmore, 2015), because BOLD signal correlations probably reflect both local and long-range connectivity, but dMRI may preferentially reflect long-range (i.e., white-matter) fiber tracts (Alexander et al., 2007; Mori et al., 2009).

4.3. FN modulation. Overlapping FNs may show modulations in the same direction; e.g., up-modulations at target trials relative to McGurk trials. In this scenario, a GLM may detect task-related changes in BOLD within the

overlapping regions, and thus the two approaches may reveal consistent findings. On the other hand, overlapping FNs may show opposite modulations during the same task conditions. This finding is novel relative to most fMRI studies using GLM but consistent with the properties of balanced E/I and functional heterogeneity in the brain (Isaacson and Scanziani, 2011; Swindale, 1998). These task-related concurrent co-localized opposite changes may cancel each other, and thus a GLM may not show significant changes in BOLD signal in the overlapping regions. Therefore, sICA may reveal functional activities hidden from GLM.

Previous fMRI studies using GLM have repeatedly reported task-related opposite modulations of BOLD signal in different brain regions; e.g., in the default mode vs. task-positive networks (Fox et al., 2006; Raichle, 2015). However, sICA findings indicate that opposite-modulated FNs do not need to be separated in space, and they actually overlap at both medial and lateral brain regions extensively. We posit that this sICA finding is more consistent with the known brain anatomy relative to the GLM findings of segregated FNs. For example, most cortical inhibitory neurons are local interneurons and do not project to other brain regions (Isaacson and Scanziani, 2011; Okun and Lampl, 2008). The inhibitory interactions among different cortical regions are mainly performed by excitatory pyramidal neurons. It is logical to predict that, for one cortical region to exert inhibitory effect on another region, it sends long-range axons to activate local inhibitory interneurons in the target brain region, and the activation of the inhibitory neurons in turn suppresses the activity of adjacent pyramidal neurons

in the target brain regions. Therefore, excitation and inhibition among adjacent cortical neurons should correlate with each other as stipulated by balanced E/I (Isaacson and Scanziani, 2011; Okun and Lampl, 2008). The task-related BOLD signal reduction in a region should be interpreted as a decrease in the total activities of its neuronal populations; however, some neurons in the region (e.g., the inhibitory interneurons) may increase activity. Therefore, overlapping FNs with different task-related modulations as revealed by sICA probably more accurately reflect functional activities in the brain relative to segregated FNs as revealed by GLM, and this knowledge may help reconcile conflicting GLM findings related to anti-correlation between activities in the lateral vs. medial frontoparietal cortex as reviewed in the introduction.

4.4. Neutral FNs. SICA found that most FNs were task-neutral and did not show significant task-related modulations. These task-neutral FNs covered most of the brain and overlapped with task-positive and task-negative FNs. This finding is different from typical GLM findings of brain regions exhibiting no task-related activity as being restricted and separated from brain regions showing task-related activity, but is consistent with the property of sparseness of neuronal responses in the brain. This brain property indicates that only a small percentage (<10%) of the entire neuronal population in any brain region may be able to fire action potentials at any moment (Barth and Poulet, 2012; Crochet et al., 2011; Tolhurst et al., 2009). Therefore, most large-scale FNs may not show task-related changes in timecourses during any task.

4.5. Older vs. younger groups. As reviewed in the introduction, fMRI studies using GLM have reported both greater and smaller task-related activities in older relative to younger adults, and have interpreted the two opposite findings as compensation of impaired functional efficiency and impaired function, respectively (Reuter-Lorenz and Cappell, 2008; Toepper et al., 2014). However, most of these studies did not consider the possibility of balanced E/I in the same voxels and that increased BOLD signal may relate to reduced deactivation. In the current study, the GLM found that, relative to the younger group, the older group exhibited a smaller deactivation or greater activation during different task conditions (please see supplementary result and Fig. 4 and 5). These findings are consistent with the interpretation of functional compensation in the older adults. GLM also found a smaller task-related increase in activation in the older relative to the younger adults (please see supplementary result and Fig. 4 and 5), consistent with the interpretation of impaired function in older adults. However, sICA found reduced activation and deactivation, not increased activation and deactivation, in the older relative to the younger group at all task conditions. The findings from applying sICA to both tasks are highly consistent, suggest impaired function in older relative to younger adults, and do not support the functional compensation theory, while GLM revealed findings suggesting both impaired function and functional compensation. Therefore, the consistent findings from sICA may help reconcile inconsistent findings from GLM. We acknowledge that comparing findings from sICA and GLM alone may not determine whether sICA

or GLM findings more accurately reflect real events in the brain, and this issue should be further investigated in future studies.

4.6. Methodological considerations. Most fMRI studies have used GLM since the invention of fMRI about 25 years ago, and multiple studies have assessed the test-retest reliability of GLM. The overall conclusion is that GLM findings at the group level are highly reliable (Brandt et al., 2013; Caceres et al., 2009; Gountouna et al., 2010; Plichta et al., 2012; Upadhyay et al., 2015). While sICA is less frequently employed relative to GLM, group sICA is one of the two most popular methods (the other is seed-based approach) for studying large-scale brain functional networks in fMRI (Erhardt et al., 2011; Franco et al., 2013). Multiple studies have consistently reported high test-retest reliability of spatial maps and related timecourses generated by sICA (Franco et al., 2013; Moodie et al., 2014; Poppe et al., 2013; Wisner et al., 2013; Zuo et al., 2010; Zuo and Xing, 2014). Therefore, both GLM and sICA are reliable analytical approaches for fMRI studies. However, they have different assumptions on relationships between BOLD signal and neuronal activities from the same voxels. GLM treats each voxel as a single unit and assumes the increases and decreases in BOLD signal reflect increases and decreases in neuronal activity, respectively. Therefore, it is not particularly sensitive to functional heterogeneity, balanced E/I, and sparseness of responses in a voxel. In contrast, sICA assumes that the BOLD signal from each voxel represents a linear mixture of different source signals in the voxel, and separates the source signals into maximally independent components using higher-order statistics (Calhoun et al., 2002; McKeown et al.,

1998b), and generates overlapping FNs with different timecourses. However, the exact relationship between this sICA finding and heterogeneous neuronal activities and balanced E/I in the same brain regions has not been validated and should be investigated further in future studies.

sICA is arguably more popular than temporal ICA (tICA), perhaps in part because fMRI has many more voxels than time points, and ICA needs a large number of samples for optimal performance (Calhoun and Adali, 2012; Smith et al., 2012). sICA enforces spatial independence and has several limitations. The first is that the optimal number of ICs existing in each dataset is not known and different participants may have different optimal number of ICs. However, several studies indicated that a small change (5-10) in the number of ICs does not appear to change the pattern of each IC, and that ICA can extract physiologically interpretable ICs across a wide range of decomposing dimensions (Abou-Elseoud et al., 2010; Calhoun et al., 2008; Kiviniemi et al., 2009; Smith et al., 2009). While the number of ICs may influence the extent of FN overlap, the proposed framework should be supported if we used a smaller number of ICs because extensive FN overlaps were demonstrated in previous studies using a lower dimension of sICA (Beldzik et al., 2013; Geranmayeh et al., 2014; Xu et al., 2015; Xu et al., 2013b). The second is the uncertainty of an optimal statistical threshold for defining task-positive, task-negative, and task-neutral FNs. Using a strict threshold for positive and negative FNs may lead to a liberal threshold for neutral FNs and vice versa. Therefore, the number of FNs in each category may change depending on the selection of different thresholds. However, the final

conclusion of extensive overlap of different FNs still holds at different thresholds. The third is that sICA may not always detect significant changes in BOLD signal revealed by a GLM, because sICA may split the synergistic changes into several ICs and make them less detectable. Therefore, GLM and sICA each appear to have advantages and disadvantages relative to the other in detecting different aspects of brain functional activity. Findings from the two approaches may complement each other and provide a more complete and consistent picture regarding brain functional organization than either method alone. In addition to the limitation of sICA, the findings of this study were limited by the small sample size of the younger group in the AVSPT dataset and the older group in the FBT dataset. Therefore, these findings should be verified in larger samples in future studies.

5. Summary

This study provides further evidence supporting our hypothesis that sICA may reconcile inconsistent GLM findings on the anti-correlations of functional activities at the medial and lateral brain regions, and that large-scale FN overlap is a general property of brain functional organization. This property does not support the traditional modular view of brain functional organization, but is compatible with several fundamental properties in the brain including functional heterogeneity, balanced E/I, and sparseness of neuronal responses. Furthermore, this is the first study to demonstrate that sICA may reconcile inconsistent GLM findings on task-related hyper- vs. hypo-activation in older

relative to the young adults. By separating concurrent co-localized opposite signal, sICA revealed a novel framework for brain functional organization. It indicated more extensive brain regions and more complicated neuronal events (e.g., CCAD) in each region underlying cognitive functions relative to the picture provided by GLM. However, we acknowledge that the relationships between FN overlap, balanced E/I and functional heterogeneity are hypothetical at present. Since these brain properties have been defined based on functional activity in microcircuits, their relationships with large-scale networks as defined by fMRI should be further investigated in future studies.

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Figure Legends

Fig. 1. Schematic demonstration of feedforward and feedback inhibition circuits. Feedforward inhibition circuit: Excitatory inputs from the thalamus activate both pyramidal neurons and inhibitory interneurons, with the latter in turn suppressing activated pyramidal neurons. Feedback inhibition circuit: Activated pyramidal neurons excite inhibitory interneurons, which in turn suppress pyramidal neurons. The inhibitory interneurons form extensive synapses onto adjacent pyramidal neurons, as if to exert a 'blanket of inhibition'. They inhibit not only the activated neurons, but also other neurons. Please note that different colors of pyramidal neurons indicate potential heterogeneous functional properties.

Fig. 2. Examples of ICs exhibiting significant modulations during AVSPT performance. Each of rows A, B, & C presents an IC exhibiting significant task-related modulations at Target relative to McGurk trials. The first column shows the spatial pattern of each labeled IC, the second column shows the mean and SE of beta weights at McGurk and Target trials, and the third column shows the mean timecourses of BOLD signals within 15 seconds after the onset of McGurk or Target trials.

Fig. 3. An IC showing different modulations between the younger and older groups during AVSPT performance. A presents the spatial pattern of the labeled

IC. B shows the mean and SE of beta weights at McGurk and Target trials. C shows the mean timecourses of BOLD signals within 15 seconds after the onset of McGurk or Target trials.

Fig. 4. Spatial distributions of task-positive, task-negative, and task-neutral functional networks (FNs). A, B, and C. The color on the brain images shows regions covered by task-positive, task-negative, and task-neutral FNs, respectively. The color bar indicates the number of overlapping FNs.

Fig. 5. Examples of ICs exhibiting significant modulations during FBT performance. Each of the rows A, B, & C presents an IC exhibiting significant task-related modulations during FBT relative to FPT blocks. The first column shows the spatial pattern of each labeled IC, the second column the mean and SE of beta weights during FBT and FPT blocks, and the third column the mean timecourses of BOLD signals within 30 seconds after the onset of FBT or FPT blocks.

Fig. 6. ICs showing different modulations between the younger and older groups during FBT. A, B, and C each presents an IC showing a significant difference in task-related modulations during FBT and FPT blocks. Please see the legend for Fig. 5 for more details.

Fig. 7. Spatial distribution of task-positive, task-negative, and task-neutral functional networks (FNs). A, B, and C. The color on the brain images shows regions covered by task-positive, task-negative, and task-neutral FNs, respectively. The color bar above row A indicates the number of overlapping FNs for task-positive and task-negative FNs, and the color bar beneath row C indicates the number of overlapping task-neutral FNs.

Table 1: Volumes of different FNs and their overlaps (cm³)

Tasks*	Positive FNs	Negative FNs	Neutral FNs	Posi & Nega	Posi & Neut	Nega & Neut	PNN
AVSPT (%)	985.9 (64.9)	451.3 (29.7)	1184.5 (78.0)	275.5 (18.1)	699.9 (46.1)	340.1 (22.4)	212.5 (14.0)
FBT (%)	552.6 (33.3)	277.1 (16.7)	1628.9 (98.2)	139.8 (8.4)	528.4 (31.9)	268.1 (16.2)	135.1 (8.1)

*For AVSPT and FBT, the total brain volumes occupied by all selected ICs (i.e., 36 for AVSPT and 40 for FBT) are 1518.8 cm³ and 1658.6 cm³, respectively. Number in each pair of parenthesis indicates the % of total brain volumes of all selected ICs of each dataset. Abbreviations: Nega & Neut: overlap of negative and neutral FNs; Posi & Nega: overlap of positive and negative FNs; Posi & Neut: overlap of positive and neutral FNs; PNN: overlap of positive, negative, and neutral FNs.

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