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Opportunities and limitations of intrinsic functional connectivity MRI

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Intrinsic functional connectivity magnetic resonance imaging (fcMRI) has emerged as a powerful tool for mapping large-scale networks in the human brain. Robust and reliable functionally coupled networks can be detected in individuals that echo many known features of anatomical organization. Features of brain organization have been discovered, including descriptions of distributed large-scale networks interwoven throughout association cortex, interactions (including anticorrelations) between brain networks and insights into the topography of subcortical structures. But interpreting fcMRI is complicated by several factors. Functional coupling changes dynamically, suggesting that it is constrained by, but not fully dictated by, anatomic connectivity. Critically to study of between-group differences, fcMRI is sensitive to head motion and to differences in the mental states of participants during the scans. We discuss the potential of fcMRI in the context of its limitations.

Soon after the development of functional MRI, Ogawa and colleagues noted that functional MRI signals display reproducible oscillatory dynamics that might provide a basis for mapping connections between brain areas[1]. Biswal *et al.*[2] demonstrated the method's feasibility by showing that spontaneous fluctuations in the motor cortex measured at rest are correlated with fluctuations in other regions of the motor system (**Fig. 1**). As similar results accumulated for other brain systems[3–9], the possibility emerged that fcMRI could be used as a general mapping tool to explore brain organization. The appeal of the technique lies in its simplicity. A brief MRI data set acquired in resting subjects is sufficient to explore diverse brain systems. Over 500 fcMRI studies have been reported including studies of individual differences, development and mental dysfunction[10,11]. But resting state functional connectivity is not a direct proxy for anatomic connectivity and is susceptible to several forms of technical artifact that confound interpretation. Here we take a critical look at what fcMRI measures can tell us about brain organization.

Functional connectivity is a powerful but ambiguous mapping tool

The basis of fcMRI is the slow (<1 Hz) intrinsic fluctuations in hemodynamics that can be measured with functional MRI (**Fig. 1**). Lending support to the possibility that anatomic connectivity constrains intrinsic fluctuations, coupled fluctuations are observed between many regions that possess monosynaptic or polysynaptic anatomic connections. For example, intrinsic fluctuations in the cerebral hand motor region show coupling to the midline motor structures[2] and to the primary and secondary hand representations in the contralateral cerebellum[12]. Focal pontine lesions disrupt functional coupling between the cerebrum and contralateral cerebellum[13], and corpus callosum lesions disrupt homotopic functional coupling, suggesting that intact anatomy is necessary for functional coupling[14]. fcMRI results also partially correlate with estimates of structural connectivity measured by diffusion tractography[15–17], and tract tracing results demonstrate reasonable correspondence with fcMRI in the monkey[18–20].

Going beyond known cortical organization, fcMRI has revealed networks of functionally coupled regions distributed across less well understood territories of the human brain (**Fig. 2**). fcMRI results have been particularly useful for understanding how distributed networks involving association cortex are organized (**Supplementary Video 1**). Human association cortex is vastly expanded relative to the monkey[21], and it is unclear how putatively cognitive systems are situated in relation to each other and to limbic systems. One landmark observation was that a distributed network of association regions, often referred to as the default network, behaves as a functionally coupled system[3]. Another important observation was that distinct networks converge on nearby regions of the insular cortex, with a specific zone preferentially coupled to limbic structures putatively involved in assigning salience to incoming stimuli[7]. An innovative study targeting the cingulate similarly mapped adjacent subdivisions to sensorimotor, cognitive and limbic systems[8].

But there are also observations that make clear functional connectivity is not a simple proxy for static anatomic connectivity. For example, there are functional correlations between regions that do not possess direct connections, such as between the left and right central primary visual cortex (V1) (central V1 callosal connections are not present in Old World primates). Coupling between homotopic cortical regions is preserved in some cases of developmental callosal agenesis, suggesting that correlated dynamics can arise from common subcortical inputs or still poorly understood indirect anatomic pathways that support cortical synchronization[22]. Functional coupling is modulated by the current task[23] and recent experience[24] and is dynamic within a person over time[25], although it is unclear whether such fluctuations reflect transient neuronal reconfigurations[26].

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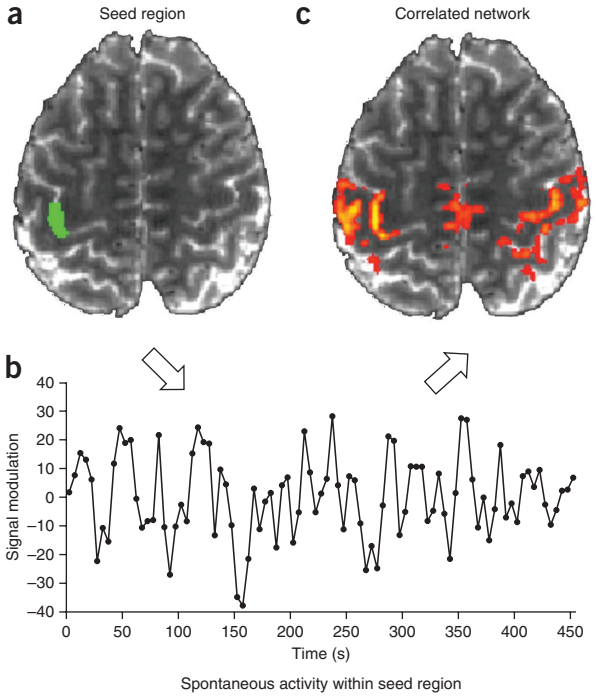

Figure 1 The basic strategy of intrinsic functional connectivity MRI (fcMRI). The basis of fcMRI is that spontaneous activity fluctuations measured at rest are correlated between regions. Inferences can be made about the organization of the brain by measuring correlations among brain regions. (**a**) An example seed region in the motor cortex (green). Activity in this region is measured indirectly through the blood oxygenation level–dependent MRI signal. (**b**) The time course of intrinsic activity fluctuations for the seed region for a period of 7 min. The general strategy of functional connectivity is to determine the network of brain regions that show correlated activity fluctuations over time with the seed region. (**c**) In this example, many cortical regions in the motor system are correlated with the seed region. These data come from a single subject imaged at near 1-mm resolution on a 7-tesla MRI scanner. Image courtesy K. Van Dijk (Massachusetts General Hospital).

fcMRI measures are also sensitive to confounding factors that include head motion[27,28] and physiological artifacts linked to respiratory and cardiac rhythms[29]. Methods for dealing with these factors are being explored by many laboratories, but a concern is that many published results pertaining to individual and group differences are artifacts of either head motion or actual neural events associated with motion and breathing. In a frank and thoughtful discussion of the issue, one laboratory reanalyzed data that had been initially used to support a reorganization of brain networks during development. They discovered that head motion, which was differentially present in the younger children, mimicked the interpreted effects[28].

In many ways, these complications are expected, as functional connectivity is a functionally based measure that depends on indirect measurement of neuronal activity in the context of a technique that is sensitive to subject motion and other confounding factors. They are nonetheless essential to consider when interpreting the functional connectivity networks and group differences that are now commonly referenced in the human neuroscience literature.

'Rest' is a task state with potential performance differences

Functional connectivity estimates are frequently made while subjects passively rest in an MRI scanner with their eyes open or closed, or while doing a minimal task, such as staring at a fixation point. The absence of complex task requirements is a benefit of the method because data can be acquired in children and in those who are impaired. However, a particularly murky area emerges when functional connectivity from data collected during rest is interpreted to provide a privileged and unbiased view of underlying brain organization. One hypothesis is that networks defined from the resting state capture fundamental units of organization that are then recruited and combined to perform tasks[30].

Our perspective is that any acquisition state used to derive functional connectivity estimates—passive fixation, eyes-open rest, a continuous active task—is an arbitrary state with a portion of its coupling pattern arising from invariant constraints that include anatomic connectivity and another portion arising from dynamic properties encouraged by the task state (**Fig. 3** and **Supplementary Video 2**). The hypothesis that rest should be considered as just another arbitrary task state is based on three findings. First, behavioral analyses of rest states suggest that they are accompanied by specific cognitive operations[31]. Second, the functional regions active during rest parallel those regions active during tasks that require subjects to engage in internally directed mental operations[32]. Thus, rest states may involve task-dependent coactivation of regions, much like any other experimentally controlled task. Finally, although functional connectivity patterns derived from rest are good predictors of the organization of task-based patterns[33], they are not better predictors than other functional connectivity patterns derived from task states (B.T.T.Y., unpublished data).

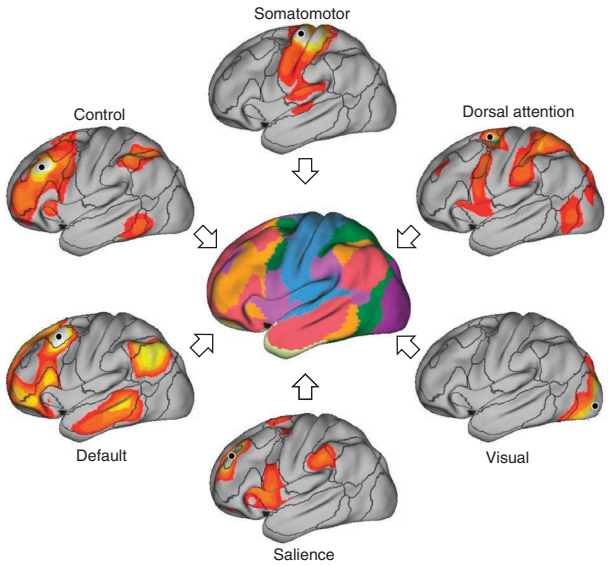

Figure 2 Large-scale cerebral networks identified by intrinsic functional connectivity. Studies using functional connectivity have consistently revealed that the human brain possesses several large-scale distributed networks. Outer maps: examples of networks displayed by showing the functional connectivity map for a single seed region (black circle) placed in a different cortical region. Each functional connectivity map is computed from 1,000 subjects whose data have been aligned and projected to the cortical surface. The labels correspond to common names given to the networks in the human neuroimaging literature, but they should not be taken to reflect absolute functional designations. More detailed analyses of certain networks have revealed that they can be fractionated further. Center map: a colored map shows a composite estimate of the networks using an analytical approach to parcellate regions of cortex into their most dominant network. The color of each vertex is assigned to its best-fit network. The black lines in the outer maps show the borders between the colored networks depicted in the center map. Data adapted from ref. 37.

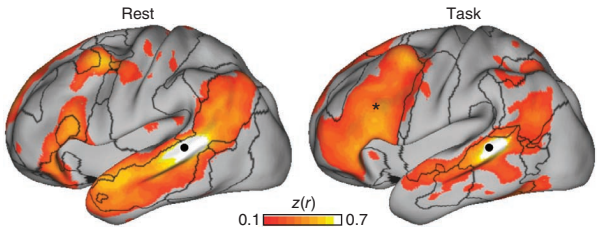

Figure 3 Functional connectivity is sensitive to the task performed during data acquisition. fcMRI maps and gradients are sensitive to the task used to acquire the data. An extreme example is displayed. Functional connectivity is displayed for a seed region (black circle) for data acquired during rest (left) and during the continuous, self-paced performance of a semantic classification task (right). The asterisk demarcates a region of prefrontal cortex that changes its coupling pattern. Whereas many results of fcMRI analyses are stable across rest and task states, other features and estimated network configurations change. Such data suggest that fcMRI estimates reflect a combination of stable anatomically constrained and state-dependent signal components. $z(r)$ indicates Fisher's r-to-z transformed correlation values.

The possibility that resting-state estimates include state-dependent coupling patterns has direct implications for interpreting differences among individuals. Although performance is not typically measured during rest, it seems prudent to consider that mental activity or unmeasured aspects of behavior (eye movements) systematically differ among groups with neuropsychiatric disorders or individuals at different developmental ages. For example, active psychosis is linked to disorganized thought patterns[34]. Mild forms of anxiety or low mood may be associated with systematic differences in spontaneous mental events[35]. An anecdotal observation is that adults with autism can sometimes comply more vigilantly with instructions to fixate and hold still than typical adults. Although the implications of this observation are unclear, it is a reminder to leave open the possibility that observed differences in functional connectivity may be related to individual differences in transient task- or state-dependent factors, in addition to underlying differences in stable features of brain organization.

Interpreting cortical organization from functional connectivity

As noted above, a major application of functional connectivity has been to define distinct regions of cortex and coupled networks of regions. Transitions in coupling patterns between adjacent regions are readily observed with fcMRI[36]. A clear way to visualize these transitions is to animate functional coupling patterns for a small seed region moved smoothly across the cortical surface[37] (**Supplementary Video 1**). The transitions are often sharp, with widely distributed regions of cortex showing patterns that parallel one another (for example, parietal and prefrontal association cortices show mirrored transitions). Various analytical techniques have been harnessed to parcellate the cortex using information provided by the connectivity patterns (for example, **Fig. 2**). Details differ across parcellations depending on the exact methodological choices, but certain regional distinctions emerge across methods, laboratories and task states (for example, contrast refs. 37 and 38). The challenge has been how to interpret the regional organization that emerges.

By most contemporary models, the cerebral cortex is proposed to possess a mosaic of areas across its surface differing in function, architectonics, connectivity and topography[39]. One possibility is that transitions in fcMRI coupling patterns reflect the borders between brain areas[40]. Considered at the level of areas, nearby areas distinguish themselves by different patterns of cortical-cortical connectivity or 'anatomical fingerprints'[39,41,42]. For example, area V1 in the macaque has weaker connections to VIP than does area V2 (ref. 41). However, these descriptions at the level of the whole area obscure another well-established feature of anatomic connectivity that is critical to interpreting regional borders that emerge from fcMRI: gradients often change within an area as much (or more) than they do between areas.

The canonical example of within-area anatomical connectivity gradients is found in retinotopic visual cortex. The portion of V1 representing a certain visual eccentricity projects to the same part of the visual field in V2 and V3 (ref. 41). Transitions in projection patterns within V1 reflect eccentricity. Thus local anatomic connectivity gradients do not straightforwardly demarcate areal borders between V1 and V2 even though the global connectivity fingerprints between the two areas may be distinct. fcMRI boundaries that are constrained by anatomic connectivity would be expected to split each early visual area and lump portions of multiple areas together into eccentricity-based regions. fcMRI networks follow this expectation[37]. We suspect that anatomic connectivity gradients in association cortex will present similar complexities.

Fuzzy transitions between areas[43] and patchy projections[41] might be real features of cortical organization and not simply a consequence of inadequate methods or criteria. This might be particularly true of evolutionarily newer cortex. For instance, whereas borders of primary sensory areas are determined by strong evolutionary and developmental constraints[44], brain regions that were later to evolve and develop may not be subject to the same rigorous molecular specification. A recent study of individual differences demonstrated that association regions display the greatest variation in fcMRI coupling patterns[45].

One intriguing possibility is that the global view of connectivity provided by fcMRI may be pointing us to important underappreciated features of cortical organization. For example, recent comprehensive estimates of the organization of the full cerebral cortex suggest that association cortex is a patchwork of interwoven distributed networks that repeatedly juxtapose similar networks across the cortex[37,38]. Unlike sensory and motor hierarchies that are hallmarked by dense local connectivity to nearby areas, association networks are defined by connectivity between widely distributed regions. Furthermore, nearby regions within association cortex often have markedly different connectivity profiles. Goldman-Rakic[46] noted a precedent for such an organization in association cortex of the macaque monkey. The recent fcMRI results reveal that most of the human cerebral mantle comprises this form of distributed association network including regions that have undergone the greatest evolutionary expansion in hominins[21]. It is unclear whether the pattern of networks observed in association cortex is best conceptualized as distinct networks of brain areas following the traditional definition of a brain area or, rather, reflects an organization arising from large repeating topographical arrangements of projections that span cerebral association cortex without strict adherence to histologically identifiable brain areas. Other methods, higher resolution, and fcMRI-guided analyses of anatomic connectivity will be required to disambiguate these alternatives.

An evolving perspective on functional connectivity for mapping

fcMRI is a powerful tool for providing information about large-scale networks in the human brain, as illustrated by recent insights into the organization of distributed association networks. However, when used in isolation, it is not possible to determine whether fcMRI observed networks reflect stable anatomical circuits or transient coupling configurations of the active brain. How can such a potent but ambiguous technique best be applied? The technique's usefulness lies in its ability

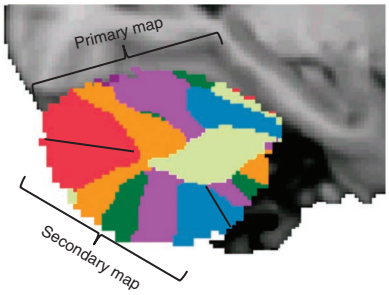

Figure 4 The organization of the human cerebellum. Functional connectivity between the cerebral cortex and the cerebellum suggests a relatively simple global organization of cerebrocerebellar circuits. The cerebellum possesses two large, roughly homotopic maps of the cerebral cortex. The colors of the sagittal map show the regions of the cerebellum that are linked to the cerebral networks as plotted in the center panel of **Figure 2**. The first cerebellar map begins in the anterior lobe (right) with a topographical somatomotor map (blue). The map continues posteriorally by mapping premotor cortex (purple) and then progressively higher order association cortices (orange, red). The map ends near the boundary of crus I and crus II (black line, left). A second, mirror-image map then progresses backwards from association networks to premotor cortex and then motor cortex. The long-recognized anterior and posterior lobe motor representations thus appear to be the tail ends of two large, near complete maps of the cerebral cortex. There is a putative third representation that is mirrored (black line, lower right) with respect to the second map. Nearly two-thirds of the human cerebellum is linked to association networks. Adapted from ref. 12.

to generate hypotheses that can then be explored by other methods to resolve uncertainties. To further illustrate this perspective, we describe two discoveries made using fcMRI that took advantage of its distinct properties but now require convergent exploration from alternative methods.

Cerebellar topography. The cerebellum participates in diverse functional domains owing to its broad connectivity. However, there is little agreement about the organization of the cerebellum beyond sensorimotor zones[47]. A specific challenge arises because there are no monosynaptic projections between the cerebrum and the cerebellum. Traditional tract tracing methods reveal only monosynaptic projections. A breakthrough came when polysynaptic viral tracing techniques demonstrated that extensive portions of crus I and crus II of the monkey cerebellum project to cerebral association cortex[48]. But what is the arrangement of these projections, and how is the human cerebellum organized in light of vastly expanded association networks? Here fcMRI has a unique role[12,49,50]. Like viral tracing techniques, fcMRI can detect information that spans polysynaptic circuits. Unlike other polysynaptic techniques, it can comprehensively survey organization across the entire brain simultaneously.

By allowing visualization of the full cerebellum, fcMRI results have revealed a simple mapping principle that may account for the global organization of cerebrocerebellar circuits[12]. The cerebellum possesses two representations of body space: one inverted representation in the anterior lobe and a second, upright, representation in the posterior lobe[47]. The human fcMRI data detect the double motor map representation and further reveal that the territory between the two motor maps comprises a double, inverted representation of cerebral association networks. The specific ordering of the association networks suggests that both the nonmotor and motor representations of the cerebellum form two continuous maps of the cerebral cortex that are mirror images (**Fig. 4**). Thus, the motor representations of the cerebellum may be the tail ends of two roughly homotopic maps of the cerebral cortex. The remaining two-thirds of the human cerebellum possesses an orderly representation of association cortex.

But there are critical ambiguities inherent in the fcMRI data of the cerebellum, such as whether prefrontal and parietal regions project differentially to the two maps and whether the emergent maps reflect anatomic connectivity or task-dependent configurations of cerebrocerebellar circuits. More extensive analyses with fcMRI data will likely provide little further insight. The critical point here is that the hypothesized organization can be tested using convergent approaches. For example, as barriers for double-labeled viral tracing techniques are surmounted, it should be possible to confirm or disconfirm the double map hypothesis in the monkey.

Interactions and anticorrelations between networks. Many of the large-scale, distributed networks detected by fcMRI in the human have precedent in monkey anatomy. For example, a robust human network involves a visual region at or near MT+, a region near the inferior parietal sulcus and a frontal region that is likely the human frontal eye field (**Fig. 2**). This network is commonly called the dorsal attention system[4] and is almost certainly related to the anatomically

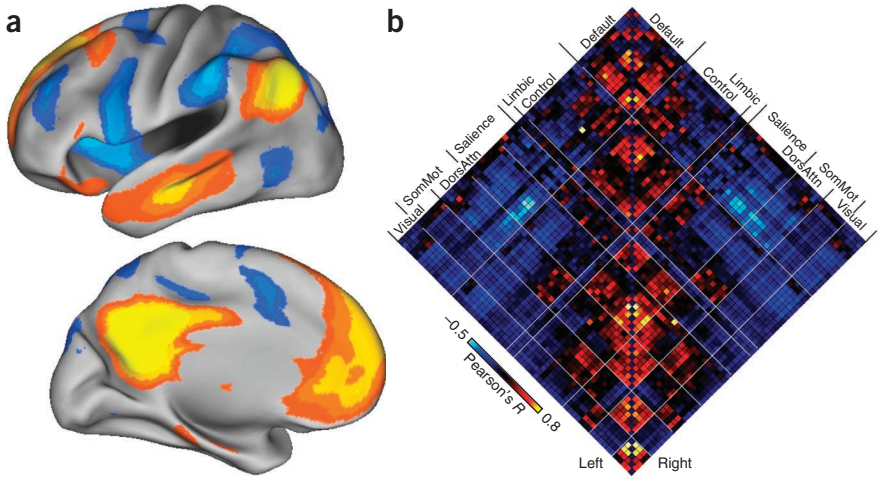

Figure 5 Network interactions. Functional coupling provides information about between-network interactions. (**a**) Functional connectivity suggests that the default network is negatively coupled (anticorrelated) to brain networks that are used for focused external visual attention[50,51]. Anticorrelated networks are displayed by plotting those regions that negatively correlate with the default network in blue in addition to positive correlations in yellow–orange. (**b**) A correlation matrix shows the complete coupling architecture of the full cerebral cortex measured at rest. Regions fall in the networks labeled in **Figure 2**, as well as a limbic network from ref. 37. SomMot, somatomotor; DorsAttn, dorsal attention. Between-network correlations are characterized by both positive and negative relations, with strong anticorrelation notable between the default and salience/dorsal attention networks (in bright blue). Methodological confounding factors have raised concerns about whether the strength and direction of correlation can be interpreted (see main text). Direct physiological methods will now be required to confirm and expand on the network interactions identified by fcMRI. Data adapted from ref. 37.

connected cortical visuomotor circuit established in the monkey[41]. fcMRI has also detected other association networks that are less well studied in the monkey, such as the so-called default network (**Fig. 2**), which also may reflect an anatomically constrained circuit[51]. What study of static anatomy leaves uncharted are the functional relations between networks.

Functional connectivity, because of its sensitivity to coupling dynamics and ability to broadly survey the cortex, provides information about relations between networks. Taking advantage of this property, two studies in 2005 reported that spontaneous fluctuations in the dorsal attention system are strongly anticorrelated with those of the default network[52,53]. As normalized functional MRI signals increase in the dorsal attention system, they decrease in the default network (**Fig. 5**). This discovery may mark a fundamental feature of brain organization that had not been appreciated by earlier techniques. The dorsal attention system is associated with processing information from external sensory channels; the default network is characterized by processing of internally focused information, such as during remembering or mentally imagining the future. The observation of anticorrelation suggests that these two systems may be functionally competing brain systems. Recent evidence further suggests that anticorrelation might have special importance for understanding brain dysfunction in mental illness[54].

However, the interpretation of anticorrelations has met with criticism. The problem with interpreting anticorrelations arises because fcMRI is a relative measure. It depends on signal change estimates that are extracted after processing and denoising steps have been applied. Owing to the way fcMRI data are typically normalized, it is difficult to surmise how to interpret the meaning of the correlation strength and whether the sign of correlation should be interpreted at all[55]. New strategies for processing fcMRI data may mitigate the specific issue of normalization[56]. But the ambiguity speaks directly to a broader limitation of fcMRI: fcMRI is difficult to interpret because it is an indirect, relative measure of neural activity fluctuations. As a result, observations such as anticorrelations are ambiguous without more insight into their mechanisms. Thus, while fcMRI was the essential tool for detecting the phenomenon of anticorrelations, physiological data from other sources will now be required to confirm and interpret the finding[57,58].

Conclusions

Intrinsic functional connectivity provides a powerful and, at present, unique tool to provide insight into human brain organization. However, fcMRI is based on an inherently ambiguous measure that reflects constraints both from static anatomical connectivity and from poorly understood functional coupling changes that are dynamic. For this reason, fcMRI is best used as a tool for generating hypotheses about brain organization that will require further study with external methods.

Note: Supplementary information is available in the online version of the paper.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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