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Resting state functional connectivity reflects abnormal task-activated patterns in a developmental object agnosic

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ABSTRACT

Even in the absence of stimulation or task, the cerebral cortex shows an incessant pattern of ultra slow fluctuations which are coherent across brain regions. In the healthy brain these coherent patterns (also termed resting state functional connectivity) often exhibit spatial similarity to the large scale organization of task-induced functional networks. However, it is not clear to what extent the resting state patterns can also reflect task-induced abnormalities in cortical activations which are often detected in various brain pathologies. Here we examined whether an abnormal visual activation pattern is recapitulated in the resting state functional connectivity. We examined LG, a sighted young adult with developmental object agnosia and no apparent cortical structural abnormality. We have previously reported that upon visual stimulation, LG's intermediate visual areas (V2, V3) are paradoxically *deactivated*. Here, examining LG's resting state functional connectivity revealed the same pattern of functional abnormality — including a strong atypical decorrelation between areas V2–V3 and the rest of the visual system. Thus, our results suggest that resting-state functional connectivity could provide a powerful tool which could complement task-specific paradigms in detecting task-related abnormalities in cortical activity without resorting to task performance.

Introduction

While human brain imaging has traditionally focused on task-related brain activations, there is a growing interest in the complementary phenomena – the study of brain activity in the absence of an explicit task or stimulus – i.e. "resting state" fMRI activity fluctuations. A consistent observation has been that during rest, the cerebral cortex enters into a mode of ultra-slow fluctuations, and these fluctuations are organized in clear and consistent networks (Biswal et al., 1995; Cordes et al., 2001). Specifically, sets of cortical regions tend to show correlated modulations of activity (termed "functional connectivity" (FC)) that appear as consistent patterns (Raichle, 2009). While the rules by which such patterns are organized are not fully understood, it is clear that at least at global scales they reflect the tendency of cortical networks to be co-activated during task performance (Mennes et al., 2010). For example, resting state functional connections have been shown to unite well known networks such as motor, visual, default mode, attention and other systems (Biswal et al., 1995; Damoiseaux et al., 2006; Fox et al., 2006; Greicius et al., 2003; Nir et al., 2006; Power et al., 2011; Yeo et al., 2011). A particularly striking illustration of the organized pattern of resting state FC is manifested in the tendency of homotopic points across the two hemispheres to be functionally connected — this effect has been extensively documented with fMRI (Biswal et al., 1995; Fair et al., 2008; Johnston et al., 2008; Nir et al., 2006; Stark et al., 2008).

More recently, resting state FC of ultra-slow activity fluctuations have been demonstrated in single neuron and intracranial recordings in humans (He et al., 2008; Nir et al., 2008), and have also been documented in other species including primates (Vincent et al., 2007) and rodents (Pawela et al., 2008).

While the relationship between task-activated and resting state networks has been amply documented in the typical brain, an important question concerns the potential for employing resting state patterns as a diagnostic tool for *abnormalities* in brain processing during task performance. This could prove particularly informative in the clinical setup and during patient examination, when task performance – if available – is not always reliable, and experimental setup is limited.

While abnormal brain activation patterns are commonly detected during task performance, a number of studies have reported abnormal

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resting state patterns in several brain pathologies (Boly et al., 2009; Calhoun et al., 2009; Castellanos et al., 2008; Dinstein et al., 2011; Greicius, 2008; Mizuno et al., 2006; Salomon et al., 2011). However the extent to which such resting state abnormalities closely reflect the specific pattern of the abnormal task-induced network activation is still unclear. Such relationship is of profound importance for the usage of resting state connectivity as an informative tool for understanding brain pathologies.

Here we examined the resting state connectivity patterns in the visual cortex of a sighted individual, LG, suffering from developmental object agnosia (Ariel and Sadeh, 1996; Gilaie-Dotan et al., 2009) and compared them to the abnormal task-induced activation patterns in his visual cortex (Ariel and Sadeh, 1996; Gilaie-Dotan et al., 2009). In that previous study (Gilaie-Dotan et al., 2009) we have demonstrated that LG shows a highly abnormal pattern of visual activation in his visual cortex, especially evident in a paradoxical cortical band of *deactivation* localized over his intermediate visual areas (V2, V3), despite no apparent structural abnormality (Gilaie-Dotan et al., 2011). Here we examined the resting state functional connectivity patterns in LG's visual cortex in the complete absence of visual stimulation, to determine whether they reflect the specific pattern of functional abnormality observed during a visual task. Our results show a striking FC abnormality in LG that anatomically matched the abnormal visual activation patterns. Our results thus indicate that the resting state patterns can be informative about abnormal brain activations revealed during task performance. Such a finding could endow the resting state patterns with a significant potential as "window" into the nature of brain pathologies.

Methods

Participants

LG was 21 years old when he participated in the resting state fMRI experiment described below, and 19 years old when he participated in the visual fMRI experiments (category localizer). All the 15 control participants had normal or corrected-to-normal vision. LG and three of the control participants (2 males, aged 35.5 ± 11.8 (S.D.)) were scanned in a 1.5 T Signa Horizon LX 8.25 GE scanner (GE Healthcare, Piscataway, NJ) at the Tel Aviv Sourasky Medical Center in Israel. The additional 12 control participants (5 males, aged 29.6 ± 4.6 (S.D.)) were scanned in a 3 T Trio Magnetom Siemens scanner, at the Weizmann Institute of Science, Rehovot, Israel. Written informed consent to participate in these experiments was obtained from each participant prior to participation, according to the Tel-Aviv Sourasky Medical Center ethics committee that approved the experimental protocol.

MRI data acquisition

Structural scans

A whole-brain spoiled gradient (3D SPGR) sequence was acquired for each participant to allow accurate cortical segmentation, reconstruction, and volume-based statistical analysis. For LG and the 1.5 T control participants these included 124 axial slices (field of view $240*240$ mm^2, matrix size: $256*256$ (LG), $256*192$ (controls), slice thickness 1.2 mm). For the 3 T control participants these included 176 axial slices (field of view $256*256$, slice thickness 1 mm). In addition, high-resolution (1.1×1.1 mm^2) T1-weighted anatomic images of the same orientation and thickness as the EPI slices (see below) were also acquired to facilitate the incorporation of the functional data into the 3D Talairach space (Talairach and Tournoux, 1988). The cortical surface was reconstructed from the 3D SPGR scan for LG and for one of the 1.5 T control participants for display purposes only. The procedure included segmentation of the white matter using a grow region function, the smooth covering of a sphere around the segmented region, and the expansion of the reconstructed white matter into the gray matter. The surface of each hemisphere was then unfolded, cut along the calcarine sulcus and additional predefined anatomical landmarks on the medial side, and flattened.

EPI functional scans

Blood oxygenation level-dependent (BOLD) contrast images were obtained using a gradient-echo echo-planar imaging (EPI) sequences. For LG and the three 1.5 T controls these were acquired with repetition time = 3000 ms, echo time = 55 ms, flip angle = 90º, field of view $24*24$ cm^2, matrix size $80*80$ (1.5 T controls) and $96*96$ (LG), slice thickness of 3 mm with 1 mm gap (LG), 4 mm with 1 mm gap (1.5 T controls), with an in-plane resolution of $3*3$ mm^2. The scanned volume included 30 nearly axial slices for LG, and 27 slices for the 1.5 T controls, in order to cover the entire cortex (via a standard head coil). For nine of the 3 T participants, the sequence was acquired with repetition time = 3000 ms, echo time = 30 ms, flip angle = 90º, field of view = $24*24$ cm^2, matrix size $80*80$, slice thickness of 3 mm with no gap with an in-plane resolution of $3*3$ mm^2. The scanned volume included 46 axial slices. Additional three 3 T control participants were scanned in same scanner, with a sequence of repetition time = 2000 ms, echo time = 30 ms, flip angle = 75º, field of view = $24*24$ cm^2, matrix size $80*80$, slice thickness of 4 mm with no gap with an in-plane resolution of $3*3$ mm^2. The scanned volume included 35 axial slices.

fMRI experiments

Resting state

This experiment is described in full elsewhere (Nir et al., 2006). Briefly, participants were required to close their eyes and rest while refraining from moving. The experiment lasted 600 s (LG, corresponding to 200 volumes), 615 s (three 1.5 T controls, corresponding to 205 volumes), 540 s (nine 3 T controls, 180 volumes), 720 s (three 3 T controls, 240 volumes).

Visual face, building, and object localizer

This visual category localizer experiment (Gilaie-Dotan et al., 2009; Hasson et al., 2003) was aimed at delineating visual activations in the visual cortex and in category selective regions of high-order visual cortex. It was run once on each control participant and twice on LG. This block-designed experiment included 4 conditions (faces, houses, objects, and patterns); each repeated seven times in pseudo-random order. Blocks lasted 9 s and were interleaved with 6 s fixation periods. The entire experiment lasted a total of 450 s. Blocks consisted of nine images of the same category, each displayed for 800 ms followed by a 200 ms blank screen. All stimuli were line drawings subtending a visual angle of $12° \times 12°$. The task was a 1-back same-different image task, and participants were instructed to respond via a button press following each stimulus. One or two consecutive repetitions of the same image occurred in each block.

fMRI data preprocessing and analysis

fMRI data were analyzed with the BrainVoyager QX 2.1 software package (R. Goebel, Brain Innovation, Maastricht, The Netherlands) plus additional in-house MATLAB software (Mathworks, Natick, MA, USA).

Preprocessing

The first two images of each functional scan were discarded. The functional images were superimposed on 2D anatomical images and incorporated into the 3D data sets (see structural MRI above) through trilinear interpolation. The complete data set was transformed into Talairach space (Talairach and Tournoux, 1988). Preprocessing of functional scans included 3D motion correction, linear trend removal, temporal high-pass filtering with a cutoff frequency of 2 cycles per