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Abnormal functional connectivity density in children with anisometropic amblyopia at resting-state

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ABSTRACT

Amblyopia is a developmental disorder resulting from anomalous binocular visual input in early life. Task-based neuroimaging studies have widely investigated cortical functional impairments in amblyopia, but changes in spontaneous neuronal functional activities in amblyopia remain largely unknown. In the present study, functional connectivity density (FCD) mapping, an ultrafast data-driven method based on fMRI, was applied for the first time to investigate changes in cortical functional connectivities in amblyopia during the resting-state. We quantified and compared both short- and long-range FCD in both the brains of children with anisometropic amblyopia (AAC) and normal sighted children (NSC). In contrast to the NSC, the AAC showed significantly decreased short-range FCD in the inferior temporal/fusiform gyri, parieto-occipital and rostrolateral prefrontal cortices, as well as decreased long-range FCD in the premotor cortex, dorsal inferior parietal lobule, frontal-insular and dorsal prefrontal cortices. Furthermore, most regions with reduced long-range FCD in the AAC showed decreased functional connectivity with occipital and posterior parietal cortices in the AAC. The results suggest that chronically poor visual input in amblyopia not only impairs the brain's short-range functional connections in visual pathways and in the frontal cortex, which is important for cognitive control, but also affects long-range functional connections among the visual areas, posterior parietal and frontal cortices that subserve visuomotor and visual-guided actions, visuospatial attention

Abbreviations: AAC, children with anisometropic amblyopia; ACC, anterior cingulate cortex; aIPS, anterior intraparietal sulcus; Cal, calcarine; Cuns, cuneus; dPFC, dorsal prefrontal cortex; dIPL, dorsal inferior parietal lobule; DLPFC, dorsolateral prefrontal cortex; dPOC, dorsal parieto-occipital cortex; dPPC, dorsal posterior parietal cortex; FG, fusiform gyrus; FIC, frontal-insular cortex; FCD, functional connectivity density; ITG, inferior temporal gyrus; LPC, lateral parietal cortex; LG, lingual gyrus; MPFC, medial prefrontal cortex; NSC, normal sighted children; PCC, posterior cingulate cortex; PMC, premotor cortex; rlPFC, rostrolateral prefrontal cortex; Ins/RO, posterior insula/rolandic operculum; rsFC, resting-state functional connectivity

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modulation and the integration of salient information. This study provides evidence for abnormal spontaneous brain activities in amblyopia.

1. Introduction

Amblyopia is a developmental disorder characterized by a loss of visual acuity that cannot be improved by refractive correction and that has no detectable organic cause (Roper-Hall, 2007). Although it is commonly associated with an abnormal visual experience (i.e., anisometropia or strabismus) early in life (Kiorpes and McKee, 1999), the neural mechanisms underlying amblyopia are still under investigation (Greenwood et al., 2012; Li et al., 2007).

Previous studies have shown that the physiological basis for amblyopia is mainly located at the level of the brain, instead of the retina (Hess, 2001; Hess et al., 2009). Consistently, no matter whether functional or structural imaging is used, abnormalities in visual cortical regions have been detected by previous neuroimaging studies on amblyopia (Barnes et al., 2001; Conner et al., 2007; Hess, 2001; H. Li et al., 2013; Q. Li et al., 2013; Lv et al., 2008; Mendola et al., 2005; Muckli et al., 2006; Thompson et al., 2012). More recently, impairments in some other regions, such as the parietal and ventral temporal cortices important for higher-cortical visual pathways have also reported to be related to deficits in spatial vision and object recognition (Anderson and Swettenham, 2006; H. Li et al., 2013; Q. Li et al., 2013; Mendola et al., 2005). However, far more defects have been found in patients with amblyopia. In addition to deficits in primary visual detection or discrimination (Eggers and Blakemore, 1978; Greenwood et al., 2012; McKee et al., 2003) or mid-level visual tasks involving local feature and contour integration (Chandna et al., 2001; Hess et al., 2001) and motion perception (Knox et al., 2013; Simmers et al., 2003, 2005), individuals with amblyopia also show higher-level impairments in visuomotor and visually guided movements (Niechwiej-Szwedo et al., 2010, 2011, 2012a, 2012b; Secen et al., 2011; Suttle et al., 2011; Webber et al., 2008), visual decision-marking (Farzin and Norcia, 2011), visual attention (Popple and Levi, 2008; Thiel and Sireteanu, 2009) and number processing (Mohr et al., 2010). As such, the underlying neural mechanism of amblyopia may be more comprehensive than what has previously been reported, and these mechanisms most likely involve additional neural connections and functional systems across the brain.

However, most current fMRI studies of amblyopia have been designed to detect changes in local brain activity when performing a specific visual task. Resting-state fMRI (rs-fMRI), which requires no stimulation or response, is an effective platform for exploring spontaneous neuronal activity and connectivity across the brain, and it has been applied in some investigations of amblyopia. Studies using this technique have reported alterations in regional homogeneity (ReHo) of spontaneous neuronal activity in the parietal and frontal cortices as well as alterations in the resting-state functional connectivity (rsFC) pattern of the primary visual area in amblyopic patients (Ding et al., 2013; Lin et al., 2012). It should be noted that ReHo is typically used for evaluating regional functional connections, and hypothesis-driven rsFC analysis may be biased by the selection of predefined seed regions. To obtain more comprehensive and objective knowledge of spontaneous neuronal activity and connectivity, functional connectivity density (FCD) mapping (Tomasi and Volkow, 2010, 2011), an ultrafast data-driven graph theory approach, was adopted in this study. This approach measures the numbers of both local and global functional connections of each voxel in the whole brain, for computing short-range (intraregional) and long-range (interregional) FCD maps of the brain. It has been used to investigate the neural mechanisms of aging (Tomasi and Volkow, 2011) and ADHD (Tomasi and Volkow, 2012), and it may be suitable for investigating changes in cortical functional connectivity in amblyopia.

In this paper, FCD mapping was applied to investigate changes in cortical functional connectivity in children with anisometropic amblyopia (AAC) during the resting-state. First, short- and long-range FCD maps were compared between the AAC and normal sighted children (NSC), respectively. Subsequently, to identify the distribution of altered long-range rsFCs in the AAC, we compared their rsFC maps with seed regions with an altered long-range FCD to the NSC. In addition, within the AAC group, partial correlation analysis was conducted for evaluating the correlationship between distance visual acuity and the short- and long-range FCD and rsFC of the obtained abnormal regions. The results revealed abnormalities in both short- and long-range functional connectivity across the brains of the AAC in contrast with the NSC.

2. Results

2.1. Demographic and clinical data

The demographic and clinical characteristics of the 14 AAC (11 males, 3 females; age: 9.6±2.9 years, 5–15 years,) are summarized in Table 1. The nine right-handed NSC (6 males, 3 females; age: 11.3±2.9 years, 5–15 years) were well matched with the AAC group in age ($P=0.19$, two-sample two-tailed t-test) and gender ($P=0.36$, two-sided Chi-squared test).

2.2. Spatial distribution of short- and long-range FCD

The spatial distribution maps of the mean short- and long-range FCD in the AAC group and NSC group, respectively, were identified (Fig. 1). The AAC and NSC showed similar distributions of their short-range FCD hub regions, including the bilateral posterior cingulate cortices (PCC), precuneus, posterior parietal cortices, occipital and dorsolateral prefrontal cortices. Their long-range FCD hubs were also bilaterally