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Resting-state connectivity and executive functions after pediatric arterial ischemic stroke

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ABSTRACT

Background: The aim of this study was to compare the relationship between core executive functions and frontoparietal network connections at rest between children who had suffered an arterial ischemic stroke and typically developing peers.
Methods: Children diagnosed with arterial ischemic stroke more than two years previously and typically developing controls were included. Executive function (EF) measures comprised inhibition (Go-NoGo task), fluency (category fluency task), processing speed (processing speed tasks), divided attention, working memory (letter-number sequencing), conceptual reasoning (matrices) and EF in everyday life (questionnaire). High-resolution T1-weighted magnetic resonance (MR) structural images and resting-state functional MR imaging were acquired. Independent component analysis was used to identify the frontoparietal network. Functional connections were obtained through correlation matrices; associations between cognitive measures and functional connections through Pearson's correlations.
Results: Twenty participants after stroke (7 females; mean age 16.0 years) and 22 controls (13 females; mean age 14.8 years) were examined. Patients and controls performed within the normal range in all executive tasks. Patients who had had a stroke performed significantly less well in tests of fluency, processing speed and conceptual reasoning than controls. Resting-state functional connectivity between the left and right inferior parietal lobe was significantly reduced in patients after pediatric stroke. Fluency, processing speed and perceptual reasoning correlated positively with the interhemispheric inferior parietal lobe connection in patients and controls.
Conclusion: Decreased interhemispheric connections after stroke in childhood may indicate a disruption of typical interhemispheric interactions relating to executive functions. The present results emphasize the relationship between functional organization of the brain at rest and cognitive processes.

1. Introduction

Pediatric arterial ischemic stroke (AIS) has an incidence of 2.1:100,000 children per year (Steinlin et al., 2005) and impacts on the lives of affected children (Christerson and Strömberg, 2010; Kornfeld et al., 2017). As two-thirds of affected children suffer from lifelong cognitive or neurological problems (Christerson and Strömberg, 2010; Everts et al., 2008; Hajek et al., 2014; Kolk et al., 2011; Kornfeld et al., 2017; Studer et al., 2014), prediction of recovery and adaptation of interventions are important. This requires knowledge about both structural and functional recovery mechanisms after stroke.

After AIS, children often exhibit problems in executive domains, e.g. working memory and processing speed (Studer et al., 2014). Executive functions (EF) encompass diverse higher-order cognitive skills (Alvarez and Emory, 2006). According to Anderson (2002), EF comprise attention, information processing, cognitive flexibility and goal setting. These core processing skills are important for planning, problem solving and decision-making (Alvarez and Emory, 2006), and develop

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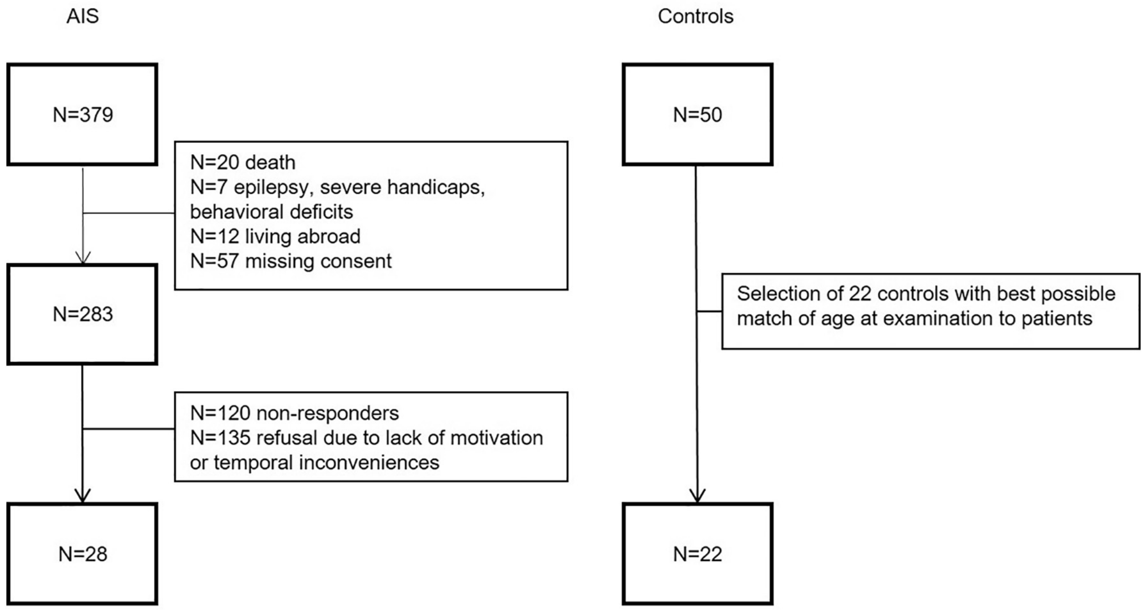

Fig. 1. Study population flowchart.
AIS = patients with arterial ischemic stroke; N = number of participants.

throughout childhood in parallel with maturation of prefrontal and parietal brain structures (Anderson, 2002).

AIS causes structural brain damage in circumscribed cerebral regions within the supply area of a specific artery. A brain lesion may affect functions that are not directly related to the damaged brain structure. This points to a complex system underlying functional brain organization, consisting of broader functional networks rather than simple structure–function relationships (Corbetta, 2012; Fornito et al., 2015; McIntosh, 2000).

Resting-state functional MRI (rsfMRI) is used to investigate functional networks based on synchronous oscillations in the blood-oxygen level dependent (BOLD) signal between structurally separated brain regions (Biswal et al., 1995; Fair et al., 2007) and has the advantage of independence from the compliance and performance level (Dinomais et al., 2012). Resting-state fMRI measures BOLD signals in the frequency range below 0.1 Hz, and allows the correlation between the BOLD-response and various cognitive functions, as no specific task is performed during MRI acquisition. It is particularly well-suited for detecting subtle alterations in the hemodynamic response to brain lesions (Biswal et al., 1995; Dinomais et al., 2012; Fair et al., 2007; Stevens and Spreng, 2014).

Findings in adults reveal associations between resting-state fluctuations and individual differences in language, memory and conceptual knowledge (Stevens and Spreng, 2014). In adult patients after acute stroke, a reduction in interhemispheric resting-state connectivity was found to be associated with reduced attention (Carter et al., 2010; He et al., 2007). These findings suggest that cognitive performance after stroke is related to the strength of corresponding functional resting-state network connections. Function-specific processes in the resting brain also exist in children (Thomason et al., 2011). Thomason et al. (2011) defined an “executive network” in healthy children, consisting of frontoparietal brain regions. Based on the network perspective, it is assumed that a lesion at any level of the neural systems within the executive network might lead to cognitive problems (Anderson, 2002). Very little is known about resting-state network properties and their influence on cognitive outcome after pediatric stroke although in a study on a mixed sample of 17 patients after perinatal AIS and periventricular venous infarction, an increase in default mode network connectivity and lower cognitive functions was reported (Ilves et al., 2016).

Based on this finding and previous literature reporting of executive post-stroke deficits, the present study investigated the frontoparietal network (FPN) in children who had experienced AIS more than two years previously and in typically developing controls. It was hypothesized that children who have experienced AIS would show lower EF than controls, and that resting-state FPN properties would differ between patients after pediatric AIS and controls. Finally, it was assumed that FPN connections at rest would correlate with EF in both groups. The findings of the present study aim to contribute to the knowledge about EF characteristics and executive resting-state networks after a focal brain lesion in childhood, and provide new insights into the underlying mechanisms of recovery following pediatric stroke.

2. Materials and methods

2.1. Participants

All participants were part of a clinical study investigating cortical reorganization after pediatric stroke, the HERO (Hemispheric Reorganization)-Study (Kornfeld et al., 2015). Children and adolescents who had an AIS before the age of 16 years were recruited from the population-based Swiss Neuropaediatric Stroke Registry (SNPSR) (Steinlin et al., 2005; Studer et al., 2014). The criteria for inclusion of patients in this study were: (1) diagnosis of AIS (confirmed by MRI or computed tomography), defined as a focal or generalized neurological deficit with acute onset showing infarction in a localization consistent with neurological symptoms (Steinlin et al., 2005), (2) AIS at chronic stage, namely that the acute stroke event had happened at least two years prior to the study, (3) age ≤ 16 years at the time of AIS, and (4) at least five years old at the time of assessment due to the MR-compatibility. Exclusion criteria were ferrous implants, active epilepsy, claustrophobia, additional neurological disorder not attributable to stroke (e.g. trisomy 21) and behavioral problems that would make assessments impossible. Details of the patient and control recruitment process are presented in Fig. 1. Of 379 patients from the SNPSR who met the criteria, 96 were not contacted due to the following reasons: death ($n = 20$), trisomy 21, epilepsy, other severe handicaps or heavy behavioral problems ($n = 7$), living abroad ($n = 12$), missing consent for SNPSR or follow-up studies ($n = 57$). All 283 remaining patients were contacted by letter post and additionally by phone two weeks later if no