CORTEX 83 (2016) 222–230

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

Uncovering cortico-striatal correlates of cognitive fatigue in pediatric acquired brain disorder: Evidence from traumatic brain injury

Nicholas P. Ryan [a,b,c,*], Miriam H. Beauchamp [d,e], Richard Beare [f], Lee Coleman [a], Michael Ditchfield [a], Michael Kean [f], Timothy J. Silk [f,g], Sila Genc [f], Cathy Catroppa [a,b,g] and Vicki A. Anderson [a,b,c,g]

[a] Australian Centre for Child Neuropsychological Studies, Murdoch Childrens Research Institute, Melbourne, Australia
[b] Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia
[c] Department of Psychology, Royal Children's Hospital, Melbourne, Australia
[d] Department of Psychology, University of Montreal, Montreal, Canada
[e] Ste-Justine Research Center, Montreal, Canada
[f] Developmental Imaging, Murdoch Childrens Research Institute, Melbourne, Australia
[g] Department of Paediatrics, University of Melbourne, Melbourne, Australia

ARTICLE INFO

Article history:
Received 27 April 2016
Reviewed 29 June 2016
Revised 4 July 2016
Accepted 22 July 2016
Action editor Lesley Fellows
Published online 16 August 2016

Keywords:
Cognitive fatigue
Pediatrics
Brain injuries
Neurobiology
Magnetic resonance imaging

ABSTRACT

Cognitive fatigue is among the most profound and disabling sequelae of pediatric acquired brain disorders, however the neural correlates of these symptoms in children remains unexplored. One hypothesis suggests that cognitive fatigue may arise from dysfunction of cortico-striatal networks (CSNs) implicated in effort output and outcome valuation. Using pediatric traumatic brain injury (TBI) as a model, this study investigated (i) the sub-acute effect of brain injury on CSN volume; and (ii) potential relationships between cognitive fatigue and sub-acute volumetric abnormalities of the CSN. 3D T1 weighted magnetic resonance imaging sequences were acquired sub-acutely in 137 children (TBI: $n = 103$; typically developing – TD children: $n = 34$). 67 of the original 137 participants (49%) completed measures of cognitive fatigue and psychological functioning at 24-months post-injury. Results showed that compared to TD controls and children with milder injuries, children with severe TBI showed volumetric reductions in the overall CSN package, as well as regional gray matter volumetric change in cortical and subcortical regions of the CSN. Significantly greater cognitive fatigue in the TBI patients was associated with volumetric reductions in the CSN and its putative hub regions, even after adjusting for injury severity, socioeconomic status (SES) and depression. In the first study to evaluate prospective neuroanatomical correlates of cognitive fatigue in pediatric acquired brain disorder, these findings suggest that post-injury cognitive fatigue is related to structural abnormalities of

Abbreviations: ANZSCO, Australian and New Zealand standard classification of occupations; CBCL, Child Behavior Check List; CSN, cortico-striatal network; CT, computed tomography; GCS, glasgow coma score; MRI, magnetic resonance imaging; PedsQL, pediatric quality of life inventory; SES, socioeconomic status; TAI, traumatic axonal injury; TBI, traumatic brain injury; TD, typically developing.

* *Corresponding author.* Child Neuropsychology, c/o Murdoch Children's Research Institute, Flemington Road, Parkville, 3052, Australia.
E-mail address: nicholas.ryan@mcri.edu.au (N.P. Ryan).

http://dx.doi.org/10.1016/j.cortex.2016.07.020

cortico-striatal brain networks implicated in effort output and outcome valuation. Morphometric magnetic resonance imaging (MRI) may have potential to unlock early prognostic markers that may assist to identify children at elevated risk for cognitive fatigue post-TBI.

1. Introduction

Cognitive fatigue is a common symptom of acquired neurological disorders and diseases of childhood, and is associated with reduced quality of life and elevated risk for depression (Crichton, Knight, Oakley, Babl, & Anderson, 2015; Jóhannsdóttir et al., 2012; Mollayeva et al., 2014; Schönberger, Herrberg, & Ponsford, 2013). Defined as, "the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (Johnson, 2008), cognitive fatigue is among the most debilitating sequelae of pediatric stroke (O'Keeffe, Ganesan, King, & Murphy, 2012), encephalitis (Fowler, Stödberg, Eriksson, & Wickström, 2008), meningitis (Sumpter, Brunklaus, McWilliam, & Dorris, 2011), brain tumor (Meeske, Katz, Palmer, Burwinkle, & Varni, 2004), and traumatic brain injury (TBI) (Gagner, Landry-Roy, Lainé, & Beauchamp, 2015), however the neural correlates of post-injury cognitive fatigue in these conditions remains unexplored.

Theoretical models of cognitive fatigue suggest that motivation to complete a difficult task depends on balance between the perception of energetic costs (effort) and benefits of the outcome (reward), such that we complete difficult tasks only when the rewards for doing so are sufficiently high (Boksem & Tops, 2008; Boksem, Meijman, & Lorist, 2006; Chaudhuri & Behan, 2000; Dobryakova, DeLuca, Genova, & Wylie, 2013; Dobryakova, Genova, DeLuca, & Wylie, 2015). Functional neuroimaging and lesion-deficit evidence suggests that balance between effort and reward is maintained by an anatomically distributed cortico-striatal network (CSN). This network involves subcortical nuclei of the striatum [putamen, caudate nucleus – CN, and nucleus accumbens – NAcc] (Botvinick & Rosen, 2009; Salamone, Correa, Mingote, & Weber, 2003)'and its projections from the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC), regions involved in effort calculation (Walton, Bannerman, Alterescu, & Rushworth, 2003) and processing subjective goal value (O'Doherty, 2011), respectively. In applying the effort-reward model to cognitive fatigue in acquired neurological injury, the effort-reward imbalance hypothesis (Boksem et al., 2006; Boksem & Tops, 2008; Dobryakova et al., 2013, 2015) suggests that cognitive fatigue might arise when damage to one or more regions of the CSN disrupts the normal balance between effort output and outcome valuation.

While studies of healthy adult and adult clinical populations have linked increased cognitive fatigue to structural and functional abnormalities of CSN circuitry (DeLuca, Genova, Hillary, & Wylie, 2008; Kohl, Wylie, Genova, Hillary, & Deluca, 2009; Roelcke et al., 1997; Tang et al., 2010, 2013), it remains unclear whether cognitive fatigue may share similar neuroanatomical correlates after traumatic injury to the developing brain. Since neuroanatomical regions of the CSN comprise many of the same brain areas commonly vulnerable to the acceleration-decelerations forces of pediatric TBI (Bigler, 2013; Wilde et al., 2007), it may be that extensive frontal-limbic damage disrupts CSN connectivity, thereby contributing to an effort-reward imbalance that is reflected in the subjective experience of cognitive fatigue.

Using pediatric TBI as a model, this study aims to (1) evaluate the sub-acute effect of brain injury on CSN volume; and (2) evaluate prospective neuroanatomical correlates of post-TBI cognitive fatigue by exploring potential relationships between volumetric abnormalities detected on sub-acute morphometric magnetic resonance imaging (MRI) and cognitive fatigue symptoms at 24-months post-injury. We had three hypotheses: (1) compared to typically developing (TD) controls and children with milder injuries; children with severe TBI would show volumetric reductions in the overall CSN package, as well as regional volumetric change in cortical and subcortical regions of the CSN; (2) children with TBI would show greater fatigue relative to TD controls and published population sample norms; (3) based on the effort-reward imbalance hypothesis (Dobryakova et al., 2013), greater cognitive fatigue would be associated with gray matter volumetric reductions of the overall CSN package and its putative hub regions, even after controlling for theoretically relevant covariates, including injury severity group membership, socioeconomic status (SES) and depression symptoms.

2. Methods and materials

2.1. Participants

This study included 137 children: 103 children and adolescents with TBI (70 males) and 34 TD children (21 males), group matched for age, sex, and SES, who underwent research MRI sub-acutely at 6-weeks post-injury ($M = 42.28$, $SD = 29.53$ days). 67 participants from the original sample (TBI: $n = 42$; TD control: $n = 25$) completed measures of cognitive fatigue and psychological functioning at 24-months post-injury.

All participants were ascertained between 2007 and 2010, and were between 5.3 and 15.4 years old at time of recruitment. Children with TBI were recruited at time of injury, and represented consecutive admissions to the emergency department (ED) of the Royal Children's Hospital (RCH) in Melbourne, Australia. TD children were recruited from the community, through local schools chosen to provide a range