Neuropsychologia 48 (2010) 2041–2050

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Children's executive functions: Are they poorer after very early brain insult

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ARTICLE INFO

Article history:
Received 1 October 2009
Received in revised form 17 March 2010
Accepted 25 March 2010
Available online 1 April 2010

Keywords:
Brain injury
Plasticity
Neuropsychological outcome
Language
Executive function
Memory

ABSTRACT

Traditionally early brain insult (EBI) has been considered to have better outcome than later injury, consistent with the notion that the young brain is flexible and able to reorganize. Recent research findings question this view, suggesting that EBI might lead to poorer outcome than brain insult at any other age. Exploring this early vulnerability perspective, we investigated whether skills developing later in childhood, for example, executive functions (EF), would be at greater risk of disruption from EBI. The aim of this study was to investigate EF in children sustaining EBI at different developmental stages. We expected that brain insult during gestation and infancy, before the emergence of EF, would lead to global EF deficits. In contrast, we predicted that brain injury in late childhood would have fewer consequences. Using a cross-sectional, retrospective, group design we compared six groups of children (Total $N = 164$), with a history of brain insult and documented focal brain pathology, aged 10–16 years on a range of measures of EF. Groups were based on age of EBI: (1) *Congenital*; (2) *Peri-natal*; (3) *Infancy*; (4) *Preschool*; (5) *Middle Childhood*; and (6) *Late Childhood*. Children with EBI were at increased risk for impairment across all aspects of EF. Presence of seizures and/or frontal pathology were not predictive of outcome, but age at insult was. Children sustaining EBI before age 3 recorded more global and severe EF deficits, while children with later EBI performed closer to normal expectations. With the exception of attentional control, skills emerging at time of insult were found to be more vulnerable to disruption than those previously established, supporting the 'early vulnerability' model for EBI.

1. Introduction

While, traditionally, the young brain has been thought to possess a high level of '*plasticity*' with a greater capacity for regeneration and recovery than that of the older child or adult brain, the relative advantage that this provides, if any, is unclear (Ballantyne, Spilkin, & Trauner, 2007; Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Giza & Prins, 2006; Hebb, 1942, 1949; Huttenlocher & Dabholkar, 1997; Johnston, 2009; Kennard, 1936, 1940). In fact, recent research suggests that the young brain may be uniquely '*vulnerable*' to insult, and that, if damaged at a critical stage of development, cognitive skills dependent on that region may be irreversibly impaired (Anderson & Moore, 1995; Anderson et al., 1997; Bittigau, Sifringer, Felderhoff-Meuser, & Ikonomidou, 2004; Luciana, 2003).

Plasticity perspectives are underpinned by the assumption that the young brain is less functionally committed than that of the older child or adult brain, and so skills thought to be subsumed by damaged brain regions may be more easily transferred or reorganized as a result. This view derives from early animal and human studies, which documented better recovery from brain insult in infants than adults (Kennard, 1936, 1940; Lenneberg, 1967; Woods, 1980). In contrast, early vulnerability theories see this lack of specialization as a disadvantage, suggesting that the young injured brain may recover in ways not specified by the normal developmental blueprint, thus leading to anomalous results (Giza & Prins, 2006; Hebb, 1942, 1949). In addition, reduced healthy brain tissue may well lead to a 'crowding effect, which acts to depress all functional abilities (Lansdell, 1969; Satz, Strauss, Hunter, & Wada, 1994).

Outcome studies from both animal and clinical domains have investigated these two conflicting perspectives (Anderson & Moore, 1995; Anderson, Morse, Catroppa, Haritou, & Rosenfeld, 2004; Aram & Eisele, 1994; Bates et al., 2001; Giza & Prins, 2006; Jacobs, Harvey, & Anderson, 2007; Kolb, Pellis, & Robinson, 2004; Pavlovic et al., 2006; Stiles et al., 2008). Findings suggest that, while extent and location of injury are likely to predict severity of residual impairments, the timing of early brain insult (EBI) will determine

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doi:10.1016/j.neuropsychologia.2010.03.025

Table 1
Demographics of sample.

	Congenital	Peri-natal	Infancy	Preschool	Mid childhood	Late childhood	Total group
N	38	33	23	19	31	20	164
Gender *n* (%) males	19 (50.0)	23 (69.7)	13 (56.5)	12 (63.2)	16 (51.6)	9 (45.0)	92 (56.1)
SES *M* (SD)	4.40 (1.4)	4.07 (0.84)	4.04 (1.06)	4.09 (1.13)	4.21 (1.29)	4.25 (1.11)	4.20 (1.06)
Age at testing (years) *M* (SD)	12.97 (1.86)	13.24 (1.98)	12.48 (1.97)	12.57 (1.72)	12.90 (1.72)	14.45 (1.46)	13.07 (1.86)
Age at insult (years) *M* (SD)	N/A	N/A	1.35 (0.93)	4.80 (1.07)	8.30 (0.80)	11.85 (1.60)	N/A
Time since insult (years) *M* (SD)	N/A	N/A	11.10 (2.19)	7.78 (1.98)	4.59 (2.10)	2.50 (1.30)	N/A
Age at diagnosis (years) *M* (SD)**	3.56 (3.91)	1.96 (2.19)	1.60 (1.23)	4.95 (1.03)	8.47 (1.05)	11.91 (1.59)	5.20 (4.27)
Time from diagnosis *M* (SD)**	9.40 (3.68)	10.97 (3.68)	10.79 (1.85)	7.68 (1.99)	4.30 (2.05)	2.54 (1.28)	7.79 (4.14)
History of seizures* *n* (%)	24 (63.1)	16 (48.5)	14 (60.9)	5 (26.3)	11 (35.5)	5 (25.0)	75 (46.9)
Full Scale IQ** *M* (SD)	79.05 (16.10)	81.00 (18.40)	79.91 (17.53)	93.79 (13.67)	94.41 (19.99)	94.53 (17.08)	87.93 (20.10)

* $p < .01$.
** $p < .001$.

the nature of these impairments, with skills already established being relatively spared, but those emerging or partially developed at risk of disruption, which may lead to either transient or more persisting sequelae (Dennis, 1989; Johnson, 2005; Thomas & Johnson, 2008). While there is little empirical evidence available, it would be expected that very early brain insult, for example, during the first trimester when processes such as cell differentiation are occurring, would have the most global and dramatic effects on functional development, Such early insults would potentially lead to disruption of cell characteristics and neural and network connections, as well as functional organization (Johnson, 2001, 2005; Thomas & Johnson, 2008). To study the impact of age at insult, it is necessary to compare outcomes associated with brain insults sustained at different time points while the brain is in a rapid state of development, for skills which demonstrate developmental trajectories across this timeframe. Executive functions, which demonstrate protracted development from infancy to late adolescence provide such a model, and are the focus of this paper.

Executive functions (EF) are skills necessary for purposeful, goal directed activity. Components of cognitive aspects of EF include attentional control, cognitive flexibility/working memory, goal setting and processing speed (Anderson, Anderson, & Garth, 2001; Fuster, 1993; Stuss & Benson, 1986), while behavioral aspects include emotional control, self-monitoring, initiative and insight (Stuss & Anderson, 2004). Deficits in EF may interfere with the child's capacity to develop normally and interact effectively with the environment, leading to ongoing cognitive, academic, behavioral and social disturbance (Anderson & Catroppa, 2005; De Luca et al., 2003; Dennis, 1989; Levin & Hanten, 2005). Adult literature demonstrates that EFs are largely mediated by the frontal and prefrontal cortices of the brain (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994: Stuss & Alexander, 2000), which are relatively immature during childhood, with development continuing into adolescence (Casey, Giedd, & Thomas, 2000; Giedd et al., 1999; Gogtay et al., 2004; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Sowell et al., 2003). Whether the same relationship between frontal regions and EF exists in the context of EBI is less clearly defined. Recent evidence suggests that executive deficits are present following EBI, regardless of lesion location (Anderson, Jacobs, & Harvey, 2005; Chilosi et al., 2005; Duchowny et al., 1996; Hertz-Pannier et al., 2002; Jacobs & Anderson, 2002), likely reflecting the lack of functional specificity in the developing brain. This lack of location specificity is best established in the behavioral domain, where impairments have been reported regardless of site of lesion or timing of insult (Anderson et al., 2009; Max et al., 2004). Of note, findings from these studies should be interpreted with caution, as most employed quite a wide age range, are unable to comment whether the reported lack of location specificity is stable or changes through childhood depending on age at insult.

Parallels between ongoing maturation of the frontal lobes and executive capacities have been reported in a number of studies. Attentional control, incorporating the ability to inhibit prepotent responses, or to suppress impulsive responses, is the earliest EF domain to emerge, with the capacity to inhibit responses apparent by 7–12 months (Diamond, 2002; McKay, Halperin, Schwartz, & Sharma, 1994; Ruff & Rothbart, 1996). By age three children can inhibit instinctive behaviors (Diamond, 2002, Espy, 1997), and improvements in impulse control continue until around age nine (Anderson, 1998). Cognitive flexibility and working memory relate to the capacity to hold information in mind and shift attention from one aspect of a stimulus to another in a flexible, efficient manner. Working memory skills begin to emerge in infancy, and consolidate in middle to late childhood (Anderson, Anderson, & Lajoie, 1996; Anderson, Anderson, & Garth, 2001; De Luca et al., 2003; Luciana, 2003), while cognitive flexibility begins to come on line at around age three (Espy, 1997, 2004; Jacques & Zelazo, 2001; Zelazo, Craik, & Booth, 2004; Smidt, Jacobs, & Anderson, 2004; Stuss & Anderson, 2004). The capacity for mental flexibility is established by around eight years (Anderson, 2002; Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Jacobs et al., 2001). Goal setting skills, the ability to plan, organize and think strategically, emerge later, but show continued maturation from middle childhood through late adolescence (Anderson, Anderson, & Lajoie, 1996; Anderson, Anderson, & Garth, 2001; De Luca et al., 2003; Krikorian et al., 1994; Welsh, Pennington, & Groisser, 1991), while processing speed shows gradual increments through childhood (Kail, 1988). These varying EF developmental trajectories provide an opportunity to examine the impact of brain insult, when both brain and cognition are rapidly developing.

We addressed the '*plasticity-vulnerability*' debate by posing the following main hypothesis: Neurobehavioral recovery following EBI is not consistent with early plasticity views. We predicted that: (1) EBI would have long-term implications for EF; (2) in contrast to adult findings, as described above, location of lesion (that is, frontal or extrafrontal) would not be directly associated with poorer EF function, reflecting lack of functional specificity in the developing brain; and (3) age at brain insult would have long-term implications for EF. We expected that for cognitive aspects of EF, profiles would differ according to both age at insult and level of EF development, with younger age at insult and less established EF linked to poorer long-term outcomes. Specifically: (a) *attentional control*, which emerges during early childhood and is established in middle childhood, would be poorest in children with early insult (≤ age 3 years), and intact for those with later insults (≥7 years); (b) *cognitive flexibility*, *working memory*, developing rapidly between preschool and middle childhood (3–8 years), would be poorest for those sustaining insults prior to age 3, and best for those with lesions after age 9 years; (c) *goal setting*, emerging in late childhood, would be poor across all early insult groups with the exception of those with insults after age 10 years; (d) *processing speed*, which improves gradually through childhood, would be impaired across all age groups, but with a trend for better results with older age at