

A Conceptual Framework in the Study of Neuropsychological Development in Epidemiological Studies

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Key Words

Cognitive assessment · Cohort studies · Epidemiological studies · Neuropsychological assessment

Abstract

Background: A wide range of neuropsychological development outcomes in children are currently measured in a large number of birth cohort and child cohort studies. **Methods:** We summarized neuropsychological development assessment protocols from a number of birth cohort studies, reviews and specific books on child neuropsychology into a unifying conceptual framework. **Results:** We suggest that neuropsychological development can be differentiated into two levels, i.e. functional and clinical. The functional level includes the skills, abilities, capacities and knowledge acquired during maturation of the brain as a result of the development of neural networks. It can be further divided into cognitive, psychomotor and social-emotional development subdomains. The clinical level includes the assessment of neurodevelopmental disorders or the presence of symptoms (subclinical symptomatology) of these disorders in

populations under investigation in environmental epidemiology studies. **Conclusions:** Through explicit recognition of these levels of outcomes, and in using this framework, epidemiologists will be better able to design research through the informed selection of individual levels of outcomes. The framework also serves to standardize disparate terminologies across this field and allows for pooling of epidemiological data on neuropsychological endpoints where essentially similar levels of outcomes have been analyzed using different tests.

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Introduction

The developing human brain is extremely sensitive to some environmental factors such as certain industrial chemicals, tobacco smoke, alcohol and certain drugs, as well as low socioeconomic status, elevated maternal stress, negative parenting behaviors or family violence [1]. This vulnerability is particularly important during early development, but it extends through infancy and child-

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hood [2]. Both the prenatal period and the first year of life represent critical phases in the early development of neural networks and their associated cognitive and psychomotor functions. During the postnatal period, the brain requires a particularly large complement of nutrients due to its high metabolic activity, especially for the development of certain areas of the cortex [3]. The susceptibility of infants and children to many exogenous compounds is accounted for by their low capacity to detoxify them [2, 4]. For these reasons, the developing central nervous system represents the bodily system most commonly disrupted by environmental teratogenic agents [5]. However, the developing brain is not only exposed to environmental agents but is also affected by a number of social factors that play a crucial role in the neuropsychological development process. These social influences chiefly comprise parental characteristics, such as cognitive capacities, social class or mental health. Such parental and social characteristics influence some important aspects of child development, such as quality of nutrition, health care, housing and the provision of a cognitively stimulating environment [6, 7].

The developing brain is a highly complex organ, and its development is a genetically driven process modulated by social and environmental factors [8]. Successful brain development requires that each area first be formed and then be correctly interrelated with the others [9]. Thus, a highly structured and complex approach is needed to accurately measure this process. An optimal assessment of the neuropsychological development process is crucial to the detection of subtle or more obvious effects of the environment on this process because the integrity of the whole system may be compromised if a sole specific domain is affected. The long-term consequences of these alterations may be important at the individual and population levels. For this reason, it is important to understand normal brain development to identify any abnormal differences.

The first attempts at studying associations between exposure to chemical agents and child neuropsychological development were reported in the 1970s [10, 11]. Since that time, research in environmental epidemiology has increasingly turned its attention towards the developing human brain. As a result, a wide range of neuropsychological development outcomes in children are now measured in many birth and child cohort studies. The aim of this work was to synthesize information on neuropsychological assessment protocols from a number of environmental epidemiological studies into a single practical and conceptual framework.

Methods

Firstly, as part of the Environmental Health Risks in European Birth Cohorts (ENRIECO) Project (www.enrieco.org), we reviewed the assessment protocols for neuropsychological development in all of the European longitudinal birth cohorts involved in this project that currently collect data on environmental exposures and child health. Twenty-five cohorts were identified which assess child neuropsychological development prospectively from birth to later adolescence (depending on the starting point of each cohort). These European birth cohorts were not designed according to a common protocol, and therefore the ages of assessment and the neuropsychological developmental areas evaluated differ among cohorts. However, in all cohorts children were assessed at least once in the first 2 years of life, in the preschool period and before adolescence. The most commonly used tests in the ENRIECO cohorts at these different ages were the Bayley Scales of Infant Development [12], the McCarthy Scales of Children's Abilities [13]/Wechsler Preschool and Primary Scale of Intelligence [14] and the Wechsler Intelligence Scale for Children [15]. All of them are tests assessing general neuropsychological development, albeit covering different neuropsychological domains.

Secondly, we reviewed the neuropsychological development assessment protocol of the National Children's Study from the USA [16–20]. This protocol was elaborated by a panel of experts in this area and was designed to assess the children once every year between the ages of 6 months and 20 years. Thirdly, we reviewed relevant reviews of the neuropsychological developmental literature within the epidemiological field. We used several electronic databases [PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), PsycINFO (<http://www.apa.org/pubs/databases/psycinfo/index.aspx>) and Web of Knowledge (<http://apps.isiknowledge.com>)] to conduct the initial literature search. Using a combination of the keywords 'birth cohort studies' and one of either 'neuropsychology', 'child development', 'cognitive assessment', 'neurodevelopmental' or 'neurobehavioral', we then selected relevant reviews that summarized the whole or some specific areas of neuropsychological development [3, 21–28]. Lastly, we reviewed some recently published books dedicated to child neuropsychological development [9, 29, 30].

Results

Figure 1 represents the conceptual framework of child neuropsychological development that we assembled as a result of our review. Two levels of outcomes can be differentiated, i.e. functional and clinical (table 1). The functional level refers to the skills, abilities, capacities and/or knowledge acquisition acquired during maturation of the brain and its interaction with the social and educational environment. These abilities increase their complexity over time as a result of the development of neural networks in the cortex, which allow the individual to adapt to the increasing demands of the environment. There are three domains at this functional level, i.e. cognitive, psy-

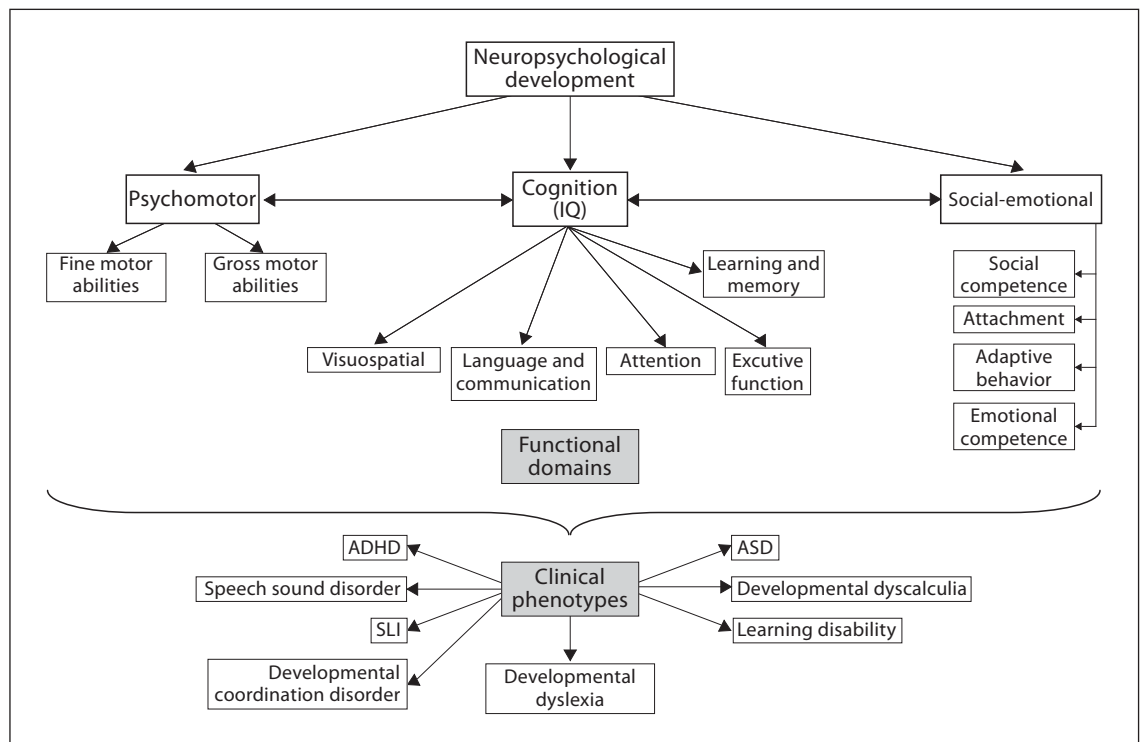


Fig. 1. Conceptual framework of the neuropsychological developmental process. SLI = Specific language impairment; ADHD = attention deficit hyperactivity disorder; ASD = autistic spectrum disorder.

chomotor and social-emotional. These three domains are highly overlapped and interrelated. Their development is dependent on one another, and a nonoptimal (or pathological) development of one of them may have implications for the rest of the domains.

Cognitive function can be conceptualized as a hierarchic model, where specific cognitive domains such as attention, language and executive functions, among others, are posited beneath the overarching domain of general cognition (table 1). Such cognitive domains should be assessed by trained neuropsychologists through the use of age-appropriate standardized neuropsychological tests. A trained neuropsychologist is also required to accurately interpret child neuropsychological assessment data. Each one of these cognitive domains can also be divided into several subdomains. This is especially critical in the case of executive functions because they are understood as a set of cognitive skills that are responsible for the planning, initiation, sequencing and monitoring of complex goal-directed behavior. The psychomotor domain can be divided into fine and gross motor skills; these are usually assessed by neuropsychological tests or by way of questionnaires. The social-emotional domain refers to the

ability to regulate emotions appropriately and to relate to others. This level has typically received the least attention, even though it encompasses several aspects of adaptive behavioral development; we argue that this area merits considerably more attention in birth cohorts because of the potential long-term consequences of poor social development in terms of unemployment, mental health issues, marital difficulties, unadaptive behaviors, delinquency or violence. The social-emotional domain is typically assessed using psychological questionnaires filled in through interviews with parents or teachers, which provide information on various characteristics of child behavior that occur in the ecological environment in which the child is developing (i.e. at home and at school).

Clinical phenotypes refer to some neurodevelopmental disorders or the presence of symptoms of these disorders in the population scrutinized in environmental epidemiology studies (subclinical symptomatology). The term neurodevelopmental disorder is usually used in one of two ways, describing either those conditions affecting neuropsychological development in children with a known genetic etiology (e.g. fragile X syndrome) or those conditions ascribed to presumed multifactorial etiologies

Table 1. Definition of different subphenotypes

Outcome	Sublevel	Specific domain	Definition	Reference	
Functional	cognitive	attention	'This domain encompasses several processes including the capacity to focus on and attend to stimuli over a period of time and the capacity to take in and report back stimuli immediately after presentation.'	White et al. [19]	
		language	'This domain includes basic linguistic abilities such as the capacity to produce phonemes, lexical development, production of words and language structure development (grammar), speech comprehension and linguistic aspects of writing and reading. Language skills are often divided into expressive and receptive components.'	White et al. [19]	
		executive function	'Metacognitive capacities that allow an individual to perceive stimuli from his or her environment, respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated or common-sense way, utilizing all these capacities to serve a common purposive goal.'	Baron [29]	
		learning and memory	'Memory terms are classified in a number of ways. Among these are reference to whether there is conscious awareness of recall (explicit or declarative memory vs. implicit or procedural memory); central stages or features (encoding, consolidation, storage, retrieval); consideration of a time-interval span (immediate, short-term, or long-term, the latter including recent and remote memory); specific memory impairment (anterograde amnesia, retrograde amnesia); or by characteristics related to the recall (prospective memory, source memory).'	Baron [29]	
		visuospatial abilities	'These non-verbal abilities generally invoke the processing and manipulation of visual designs, the spatial or physical aspects of environmental objects or constructional skills.'	White et al. [19]	
	psychomotor		'Psychomotor functions cover a broad range of morphologically and functionally different phenomena. Functions range from highly automatised gross motor activities like walking to highly skilled fine motor skills like knitting or running a computer program by highly skilled, precisely located mouse clicks.'	Kallus et al. [33]	
	social-emotional	social competence		'Effectiveness in developmentally appropriate social interactions.'	Denham et al. [16]
		attachment		'Attachment begins as the deep and enduring connection established between a child and his/her caregiver in the first several years of life.'	Denham et al. [16]
		adaptive behavior		'The development of the adaptive behavior involves the regulation of the other behaviors to the social rules and to the demands of the context surrounding the child.'	Saarni [34]
		emotional competence		'The multifaceted ability strategically to be aware of one's own and others' emotions and to act on this awareness, to negotiate interpersonal exchanges and regulate emotional experience.'	Denham et al. [16]
Clinical	ADHD		'ADHD is defined by problems with inattention and/or hyperactivity/impulsivity, with onset before the age of 7 years and resultant impairment in two or more settings.'	McClellan et al. [18]	
	speech sound disorder		'Children with SSD are delayed in the acquisition of developmentally appropriate speech sounds, resulting in reduced speech intelligibility. Idiopathic SSD is not due to known etiological factors such as cleft palate or hearing loss and is limited to disorders of speech sound production (i.e. not stuttering).'	Raitano et al. [35]	
	SLI		'Selective failure to develop language at a normal rate in the absence of frank neurological and psychiatric disease and adequate educational opportunity.'	Tranel and de Haan [36]	
	developmental coordination disorder		'Is characterized by motor impairment that interferes with the child's activities of daily living and academic achievement.'	Dewey and Wilson [37]	
	developmental dyslexia		'Developmental dyslexia, or specific reading disability, is defined as an unexpected, specific, and persistent failure to acquire efficient reading skills despite conventional instruction, adequate intelligence, and sociocultural opportunity.'	Démonet et al. [38]	
	intellectual disability/ learning disability		'This can be both a "symptom of a known disorder, and a non-syndromal condition of unknown etiology". Furthermore, in the UK, the term "learning disability" is used to refer to intellectual disability, whereas elsewhere "learning disability" is used for specific difficulties in a child of normal IQ.'	Bishop [32]	
	developmental dyscalculia		'Is defined by difficulty in learning and remembering arithmetic facts and in executing calculation procedures, with immature problem solving strategies, long solution times and high error rates.'	Geary [39]	
	ASD		'Autism spectrum disorders (ASDs) encompass the diagnoses of autism disorder, PDD-NOS and Asperger's syndrome. Children with these disorders often have life-long difficulties with their ability to communicate and socially relate to others.'	McClellan et al. [18]	

SSD = Speech sound disorder; SLI = specific language impairment; ADHD = attention deficit hyperactivity disorder; ASD = autistic spectrum disorder; PDD-NOS = pervasive developmental disorder not otherwise specified.

in which certain domains of neuropsychological development are selectively impaired [e.g. attention deficit hyperactivity disorder (ADHD)] [31]. The process of selecting disorders for inclusion in figure 1 was not straightforward. Based on publication rates, the most extensively studied neurodevelopmental disorders are ADHD and autistic spectrum disorders. However, it is misleading to focus only on certain disorders. In figure 1 we include the eight most prevalent neurodevelopmental disorders as reported by Bishop [32]. In order of decreasing prevalence, these disorders are: speech sound disorder, specific language impairment, developmental coordination disorder, developmental dyslexia, intellectual and learning disability, ADHD, developmental dyscalculia and autistic spectrum disorders. Environmental epidemiology has the potential to shed light on many such high-prevalence neurodevelopmental disorders in the general population which currently garner little attention. These disorders may have associated consequences such as low achievement in school, behavioral adaptation (school, professional and personal), diminished economic productivity and possibly an increased risk of antisocial and criminal behavior. As such, they may contribute to the so-called 'silent pandemic' proposed by Grandjean and Landrigan [2]. Neurodevelopmental disorders are usually assessed not only by psychological tests based on diagnostic criteria of mental disorders but also by structured interviews and questionnaires. However, in environmental epidemiology, it would be preferable to assess the continuum of symptoms (subclinical symptomatology) associated with such disorders rather than assessing the presence of these diagnoses as defined by clinical cutoffs.

Discussion

This framework serves as a starting point for the standardization of the relevant terminology and thereby facilitates the choice of phenotypes in future epidemiological studies. The lack of a common framework for the study of neuropsychological development in environmental epidemiology studies, and a concomitant lack of consistency in the associated terminology, currently hinders research collaboration and the setting of targets. We have summarized the work carried out so far in this increasingly relevant area in order to meet several objectives. This framework will allow epidemiologists with little expertise in this topic to better understand the area of neuropsychological development assessed in a specific study. Moreover, it will enable better design of future re-

search and foster better informed selection of the outcomes of interest. The development of this conceptual framework may also serve as a starting point towards standardizing the terminology used in the neuropsychological development field and for specific outcomes encountered in environmental epidemiology literature.

It is notable that very few neuropsychologists work in the field of environmental epidemiology. The presence of these professionals with a background in both neurodevelopment and neuropsychological development is critical to the elaboration and application of assessment protocols (based on their knowledge of brain development and neuropsychological testing), to quality control in data collection and analysis and to the interpretation of study findings. Their inclusion in multidisciplinary research teams may improve the quality of research in this important field.

The conceptual framework presented herein also provides a theoretical justification for the conduct of pooled or meta-analyses of cohort studies that use different tests in assessing the same phenotypes. The majority of functional domains may be divided into a set of specific subdomains. Clearly, a cautious and robust approach is needed in order to combine the data in a meaningful way, particularly in pooled analyses, where an a priori theoretical background and statistical modelling are employed. Sensible combination of data originating from different neuropsychological tests is highly dependent on the specificity of the effects of particular environmental agents on neuropsychological development. Again, the importance of involving neuropsychologists is paramount since it is only with their understanding of the relevant tests and cognitive functions that we may advance in this field.

The publication of this framework marks a synthesis of the highly complex processes of neuropsychological development in a unified practical and conceptual framework.

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Disclosure Statement

The authors declare that they have no competing interests.

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