PS PUBLIC SERVICE REVIEW
european union 21

A shift in focus on brain disorders

Should we start from the beginning?

Cover inspired by

UNIVERSITY OF HELSINKI

www.publicservice.co.uk

PS
analysis•opinion•debate
An Independent Review

Protecting the child's brain

Urging a strategy that could greatly improve life quality…

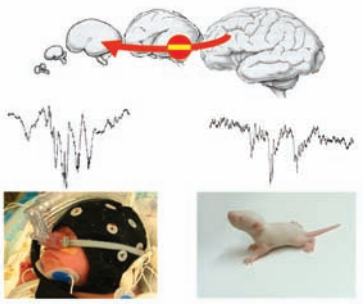
Brain disorders are a major cause of human suffering and disability. In the member states of the EU and in other wealthy countries, brain diseases impose a tremendous direct economical burden on public healthcare and, indirectly, an even higher burden on the society as a whole. In Finland, for example, with its population of five million, the estimated annual total costs attributable to brain disorders are more than €4bn. The current steep increase in human life span will lead to a parallel increase in the number of people afflicted by major neurodegenerative diseases, such as Alzheimer's and Parkinson's, with a consequent increase in the societal and economic disease burden. Hence, it is not surprising that most of the academic research on brain diseases is currently focused on disorders that are most prevalent in the aged brain. This emphasis is further enhanced by the business prospects for pharmaceutical companies, leading to massive investments into development of drugs aimed at alleviating the symptoms or slowing down the progress of neurodegenerative diseases.

In contrast, funding agencies in Europe and elsewhere do not provide significant support for studies on brain disorders that have their origins in early childhood. The situation is made worse by the fact that there are numerous reasons why pharmaceutical companies have little interest in developing novel drugs for the treatment of diseases in newborn babies (neonatal diseases) and infants (paediatric diseases), even those that are highly prevalent. Yet, it is clear that therapeutic effects achieved at early stages of development will have lifelong benefits. Although human suffering cannot be estimated in economic terms, it should be obvious that the development of early therapeutic interventions and novel drugs for neonatal and paediatric brain disorders will not only improve the quality of life of countless individuals, but will also dramatically reduce the societal costs of brain disorders. Because of the lack of market-driven economical support, basic and clinical research of the newborn and infant brain must obtain its main funding from public sources.

Brain disorders of newborns and infants

The most common causes of brain disorders that have their onset at birth are related to prematurity. The birth of a human baby takes place, normally, after about 40 weeks of gestation. The development of intensive-care techniques to support respiratory and circulatory functions in preterm babies now give a rapidly increasing number of very small babies, born around the 24th week, a good chance of survival. However, the majority of them (more than 85%) develop debilitating dysfunctions of the brain, ranging from cerebral palsy and defects in hearing and vision to various disturbances of cognitive functions. Another major birth related cause of lifelong brain disorders is asphyxia, which implies a temporary but serious lack of oxygen and related metabolic disturbances. Severe birth asphyxia can have devastating consequences, such as lifelong epilepsy and/or major permanent brain damage.

Many of the newborn babies' brain disorders arise during the time spent in the neonatal intensive care unit (NICU). Hence, the time period in the NICU provides an effective window of opportunity for novel, early therapeutic interventions. Novel techniques, based on close cooperation between basic and clinical research, are urgently needed in the NICU.



The Neonatal Gap. Neuronal signalling undergoes major qualitative changes during brain development, prohibiting direct extrapolations from the adult to the immature brain. Using relevant animal models makes it possible to bridge the 'Neonatal Gap'. The EEG of a preterm baby and a rat pup is dominated by long-lasting, high-amplitude events, which disappear in healthy babies at the time of normal birth. Animal models permit an in-depth analysis of these events, from molecular and cellular mechanisms to the unique properties of immature neuronal networks

Monitoring the activity of the newborn's brain

The quality of human life depends on the health of the brain and the nervous system as a whole. A long-standing paradox is that, while the lungs and the circulatory system are under close scrutiny in NICUs worldwide, adequate monitoring of the activity of the brain is often practically non-existent. This paradox gains further irony from the obvious fact that a major goal for supporting respiratory and circulatory functions in the NICU is, ultimately, to support the functions of the baby's brain.

Novel electroencephalography (EEG) techniques designed for monitoring the unique characteristics of the newborn's EEG should become standard in all NICUs. In the absence of brain

monitoring, many types of early dysfunctions of the brain go unnoticed. For instance, recent EEG studies have shown that birth asphyxia very often leads to the emergence of epileptic seizures and poor neurological outcome. It is also becoming obvious that the majority of babies who have epileptic seizures receive medication that is ineffective or even harmful. All these grave problems – absence of adequate monitoring and medication of the diseased newborn brain – reflect one simple fact: there is a profound lack of knowledge of the basic neurobiology of the immature human brain.

> '...early interventions have a potential that is not easily surpassed by any other strategy aimed at improving human life quality.'

The 'Neonatal Gap'

Extensive animal studies have shown that the maturation of the brain is not simply based on an increase in the complexity of its 'wiring'. While changes in both macroscopic and microscopic structures do take place, a highly significant general observation is that the molecular and cellular signalling mechanisms show radical, qualitative differences between the immature and mature brain. Nerve cells communicate with each other by means of transmitter substances, some of which have an excitatory action on their target cells, while others are inhibitory. A well-known example of the qualitative differences between the immature and mature brain is the action of gamma-aminobutyric acid (GABA), which is the main inhibitory transmitter in the adult brain. However, in the immature brain, signals mediated by GABA can be excitatory. Such fundamental, age-dependent differences in the functional properties of neuronal communication have direct implications for drug actions. Most of the antiepileptic compounds used to prevent seizures in adult epilepsy patients are drugs that potentiate the actions of GABA. One of these drugs, phenobarbital, is also the most common medication still given to babies with epileptic seizures. Keeping in mind the developmental change in the properties of GABA signalling, it is perhaps not surprising that phenobarbital is largely ineffective in babies and may, in fact, have harmful side effects.

The qualitative, age-dependent differences in the actions of GABA are just one small facet of a large spectrum of fundamental differences in the molecular and cellular machinery of the brains of babies and of adult human beings. A major conclusion is that much of the basic neurobiological, clinical and pharmacological knowledge that stems from research and clinical experience on the adult brain cannot be extrapolated to the newborn. This problem manifests itself as a 'Neonatal Gap', which can be overcome only by basic research on suitable animal models. Fortunately, standard laboratory animals such as rats and mice provide good models for research on early brain development. They are born at a very immature stage, and the maturity of their brain (strictly speaking, the cortex) corresponds to that of a human foetus at the beginning of the last trimester of gestation and hence, to that of a very small preterm baby.

Convergence of basic and clinical science

For reasons unknown, clinical neurology of the newborn human brain lost contact with basic neurobiological research several decades ago. However, there is no realm in science, whether basic or applied, that can thrive in isolation. In order to re-establish the lost connection, major efforts have to be made so that basic and clinical research of the newborn brain will converge. This kind of multidisciplinary research is urgently needed for accurate diagnosis and rational therapies of diseases of the child's brain. Recent research done in parallel on preterm babies and rat pups has revealed a striking similarity between the basic characteristics of their EEG activity, which consists of large, spontaneous discharges generated by immature neuronal networks. This type of activity has little in common with the adult EEG, which, again, underscores the fundamental differences in immature and mature brain functions. Understanding the developmental differences in the human EEG and other systems-level functions requires concerted research efforts by basic scientists and clinicians.

Summary and prospects

In order to alleviate the extremely high burden of brain diseases at the individual, societal and economic levels, a rational approach is to broaden the focus on brain diseases to encompass early development. It should be clear that efforts to achieve lifelong improvement in brain health by early interventions have a potential that is not easily surpassed by any other strategy aimed at improving human life quality. The time is ripe for reconsidering standard schemes in European funding of research on brain diseases to bring in a new focus on the newborn brain. In addition, interdisciplinary training activities are needed to stimulate and strengthen the interactions between basic and clinical science. Protecting the child's brain means, ultimately, protecting the dignity of human life.

UNIVERSITY OF HELSINKI

Professor Kai Kaila PhD

Department of Biosciences
University of Helsinki
PO Box 65 (Viikinkaari 1)
00014 Helsinki
Finland

Tel: +358 9 1911

kai.kaila@helsinki.fi
www.helsinki.fi/neurobiology
www.helsinki.fi/fgsn