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# Critical Issues to be Addressed in Undertaking Brain-Science Based Cohort Studies

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## I. Introduction

A biological perspective makes new definitions of learning and education possible. Here, learning is the process of making neuronal connections in response to external environmental stimuli, whereas education is the process of controlling or adding stimuli, and of inspiring the will to learn (Koizumi 2000, 2004). These neurological concepts of learning and education are comprehensive, covering the whole human life span. In these definitions of learning and education, the meaning of environment is everything except self. The cases of self-learning or self-education should also be considered, which is learning or education by self-preparation of environmental stimuli. Therefore, there are two kinds of learning: passive and active. During infancy, passive learning from the natural environment is important because newly formed neuronal connections occur only when the neurons acquire signals caused by environmental stimuli during a critical period (Koizumi 1996, 1998). The formation of the visual cortices is a typical example of a critical period. Active learning is initiated by primitive reflexes. The reaching that appears at around three months old is a typical example of active learning as is the beginning of locomotion-like crawling. Babies have a strong will to reach their objectives, so the reaching and locomotion help the integration of brain functions. Active learning might be an auto-poetic process throughout human life.

Because development is a dynamic process with age, we must observe the developmental processes over time. Furthermore, individual diversity has to be taken into account even within the case of typical development. Therefore, a cross-sectional study at one time point is insufficient. A longitudinal study over time is necessary to elucidate the mechanisms of human development by learning and education. Also, aging

is a time-dependent process. Both development and aging require cohort studies (Koizumi 2006).

**II. Why are cohort studies important?**

Human cohort studies based on the concept of "brain-science & education" will likely have three major sets of implications.

1. Human cohort studies based on brain science are expected to produce scientific evidence that will contribute to policy-making, especially on education and related issues that pose serious problems for modern human society. For example, we might uncover implications for policy on childcare, school education or aging.

2. We will be able to assess the potential effects of new technologies on babies, children and adolescents. For example, because humans have only recently had experience with electronic information technology, we have little information on whether such technology affects the human brain and mind. If it does have effects, we need to find out what they are.

3. Human cohort studies will allow us to test hypotheses drawn from animal and genetic case studies to see if they actually apply to people. The results of animal studies can neither conclusively prove nor disprove the validity of the hypothesis. Although a number of recent animal studies have indicated links between the behavior and expression of particular genes, we do not know whether these findings have implications for human development.

**III. Examples of cohort studies based on brain science**

1. A longitudinal study of twins in infancy and childhood ("Tokyo Twin Cohort Project: ToTCoP") directed by Prof. Juko Ando, Faculty of Letters, Keio University

Human behavioral and psychological development is affected by environmental and genetic factors. The "twin method" can reveal the relative contribution and interaction of each factor. This study constructs a population-based twin registry in the Tokyo metropolitan area. About 1,000 pairs of newborn twins were recruited, and longitudinal studies were conducted for five years by mailed questionnaires, individual interviews, near-infrared spectroscopic (NIRS) imaging and other methodologies.

The purpose of this study is to clarify the developmental effects of genetic and shared/non-shared environmental factors on temperament, motor skills, cognitive-linguistic abilities and other behavioral traits at an early stage of human development. These results are expected to provide basic information useful for the education of children.

2. "A cohort study of autism spectrum disorders: A multidisciplinary approach to the exploration of social origin in atypical and typical development" directed by Dr. Yuko Kamio, Division Head of the National Institute of Mental Health, National Center of

Neurology and Psychiatry

Autism spectrum disorders (ASDs) are developmental disorders characterized by social deficits with varying manifestations based on gene-brain-behavior relations, although the causal factors have not yet been identified. This cohort study aims to elucidate the developmental trajectory in ASDs and in typical development, and to identify the earliest signs of ASDs and their social origin in typical development. Our final goal is to establish a prospective database of behavioral development and the corresponding neural networks to understand the pathogenesis and variability in manifestations. The outcomes of this project could contribute to early detection and intervention for children with ASDs. Also, understanding the variations of social development could provide us with solutions for the current problems in school settings in Japan.

3. "Cohort studies of higher brain function of normal elders and children with learning disabilities" directed by Prof. Ryuta Kawashima, New Industry Hatchery Center, Tohoku University

A major goal of this study is to create a hopeful future by overcoming the difficulties observed in a society with fewer children and an increasing number of elderly persons from the viewpoint of brain science. The specific research topics include R&D for anti-aging methods to maintain and improve brain functions in elderly persons, and R&D for intervention methods to develop healthy brain functions in children with learning disabilities.

Two cohort studies for each group of subjects are being performed. One is a comprehensive assessment of brain function for each group from the viewpoints of psychology and neuroscience. In this study, special attention will be paid to analyzing relationships between the subject's daily life activities and the higher order cognitive functions of the brain. Another is active cohort studies with intervention for those people by randomized controlled trials. The intervention programs to be used in the active cohort studies will be provided from the results of the preceding cohort studies.

4. "Cohort studies on language acquisition, brain development and language education" directed by Prof. Hiroko Hagiwara, Tokyo Metropolitan University

In modern human society, in which the daily exchange of information is accelerated on a worldwide scale, it is a commonly shared view that improving communication skills is a key to success in life. This has led to a growing social interest in early education especially for foreign languages. The introduction of English as a compulsory course at the elementary school is, in fact, under consideration by the Japanese Ministry of Education, Sports, Culture, Science and Technology (MEXT). Although acquisition of a second language from early childhood is not undesirable, our main concern is whether it has negative effects on the normal course of language development in one's native tongue. At present, there is no scientific data available on the relationship between language acquisition (both the first and second) and brain maturation. Neither longitudinal investigations nor cross-linguistic studies exist that take into consideration

how language functions are acquired as the brain develops.

The objectives of this study are to 1) investigate the mechanisms of first (L1) and second language (L2) acquisition in relation to cerebral specialization and functional plasticity in the brain, 2) identify "sensitive period(s)" for second language learning and 3) propose a cognitive neuroscience-based guideline for second language learning and education, especially for English, including the optimal ages and conditions surrounding it. The cohort studies are conducted on three types of populations: 1) English learners of Japanese, 2) Japanese learners of foreign languages in Japan and 3) native speakers of Japanese ages 2 to 5. Each study will last about four years.

5. "Development of novel biomedical tools for student mental health" project directed by Prof. Kazuhito Rokutan, Institute of Health Biosciences, The University of Tokushima Graduate School

Social and environmental stressors profoundly affect the normal development of children's minds and, as a consequence, mental disorders are one of the most serious problems addressed in universities worldwide. An urgent need for society is the establishment of a simple new biomental tool to objectively assess stress response and improve the quality of life of students and younger children. High throughput analysis of gene expression via microarray has a potential advantage in studying complex stress response.

An original DNA array specifically designed to measure the mRNA levels for stress-related genes in peripheral blood leukocytes proved successful in detecting abnormal gene expression profiles that are closely related to mental disorders. In this study, after the collection of questionnaires from freshmen, the mental state of volunteers at our university (more than 200 students) is being studied. To detect biological risk factors for mental disorders, high-throughput analyses, measurement of stress-related molecules in saliva and evaluation of brain function by optical topography are systematically performed.

Using these biological approaches combined with commonly used questionnaires, both environmental and biological risk factors for mental disorders in students will be identified. A new microarray-based biomedical tool will be established for student mental health.

6. "Cohort study with functional neuroimaging on motivation of learning and learning efficiency" directed by Prof. Yasuyoshi Watanabe, Osaka City University School of Medicine

This study explores the brain mechanisms of the motivation for learning, leading to proposals for or the development of high-efficiency learning by maintaining high motivation and lowering fatigue during the learning process. Motivation of learning or the will to learn is related to interest, creativity and reward, but is also influenced by the extent of fatigue. Because the molecular and neural mechanisms of fatigue, especially the quantification of fatigue, have been investigated at this laboratory, it is a logical extension to proceed to a study of the motivation of children with newly developed

tasks, which might be in inverse proportion to the extent of fatigue, and to follow up with them as a cohort study to correlate the extent of learning motivation with that of fatigue in the learning situation. Mainly, it was planned to perform functional MRI studies to reveal the neural basis of motivation, which has not yet been well studied, while simultaneously measuring the extent of fatigue of the volunteers (adults and children during the tasks of motivational learning). This study also includes children with learning disturbances or difficulties, in which their genetic and environmental factors will be analyzed to evaluate whether their problem is in the mechanisms of motivation or something else.

In our program of "Brain-Science & Society," a preparation project for future large-scale developmental cohort studies is ongoing. This project, the "Japan Children's Study (JCS)," is directed by Prof. Zentaro Yamagata, Graduate School of Medicine and Engineering, University of Yamanashi, and the following description of this study was slightly modified from that prepared by Prof. Norihiro Sadato of the National Institute for Physiological Sciences.

The objectives of the JCS are to elucidate the developmental mechanisms behind "Sociability" or "Social abilities," and to identify the factors that make a nurturing environment suitable or unsuitable for babies and children. The mechanisms of social development, particularly the biological aspects, are still largely unknown. Hence, the JCS will be led by a well-equipped laboratory with behavioral observation, neuron-imaging techniques and statistical analysis. The following cohort studies will test the findings/hypothesis regarding the social development from the preceding laboratory studies at the population level. All components of the JCS are systematically controlled by the center in the R&D Area, "Brain-Science & Society," within RISTEX. There are two major organizations in the JCS, one is the laboratory and the other is the three regional groups that prepare the cohort studies.

The purpose of the laboratory is to elucidate the developmental mechanisms of sociability and its neural representation using experimental settings. Some of the laboratories are at Kyoto University (infant laboratory for behavioral experiments), the National Institute for Physiological Sciences (for neuron-imaging studies for sociability) and Tottori University (for evaluation of peer relationships). In the infant laboratory, the mental processes of sociability, from the precursors of the more complicated functions such as morals and empathy, will be systematically analyzed and quantified using rigid experimental control. The neural substrates of these processes are being depicted and analyzed using functional MRI. The results will be extended to the application of near infrared spectroscopic (NIRS) imaging for infants. Regarding peer relationships, a novel method of sociometry based on the observation of the interaction among peers in an experimental setup will be developed.

The purpose of the regional infant cohort studies is to evaluate the progress of sociability with the chronological interaction of other factors. The factors are categorized as individual and environmental. Individual contains 1) temperament, 2) mental function other than sociability and 3) medical problems (perinatal or later).

Environmental includes 1) family, 2) peers and 3) social environment. These factors and sociability will be quantified using direct observation, psychological measurement and a structured questionnaire. Also, a neurologist's observation with diagnostic techniques should contribute to the clarification of neurological development.

Several types of preliminary cohorts will be launched at the same time: an infant cohort starting with a 4-month old baby, a preschool cohort starting with 5-year-old children and so on. The results obtained from these preliminary cohort studies with around 500 children over several years will provide invaluable information for further large-scale cohort studies.

## IV. Conclusion

We have to recollect the emergence of the concept of environmental assessment in the 1980s. People became aware of the necessity of science and technology assessment. The natural environment might be affected by human artifacts produced by civilization. The ozone hole and global warming are typical examples. People are aware of environmental issues, however, only from a physical viewpoint. Drastic environmental changes in our civilized society could be from the result of metaphysical problems. A flood of information, virtual media, individualism and the pursuit of efficiency might be transforming our brain and its functions. An environmental assessment from the metaphysical aspect could be essential to providing an appropriate environment for future generations (Koizumi 1996, 2000b, 2006). The author would like to discuss the critical issues to be addressed in undertaking brain-science based cohort studies.

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