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The brain: body and mind

The issue of relationship between the body and what can best be called the mind–for lack of a concept better understood by science–is certainly not a new one. Even today, and for good reason, many mental health professionals have difficulty associating and integrating the two, often resulting in a dichotomy, albeit simplistic, where psychotherapy is considered appropriate for "psychologically based" disorders and psychopharmacology, for "biologically based" disorders. On the front side of that dichotomy, two conceptualizations of mental disorders oppose each other: one where existential or emotional distress is key, and another where a disorder or affliction of the brain is considered to be at issue. And yet, an individual's psychology, including what is most subjective about it, exists and is expressed through processes within the brain (e.g., Gabbard, 2000; see Cromby, Newton & Williams, 2011). Thus, it should come as no surprise that psychotherapy, like any significant event in our lives, changes the brain. Indeed, nearly 20 studies on the matter arrive at that same conclusion (see Karlsson, 2011, for a summary).

A different approach is needed to the issue of psychology, neurology and neuropsychology, or more simply that of the body and mind, beyond philosophical considerations and individual beliefs. The Decade of the Brain resulted in significant progress, which is continuing today at a frenetic pace. Simply think of the breakthroughs that have been achieved with the development and use of new imaging and analysis techniques and technologies in neuroscience, but also in biology and genetics. They have helped forge the way for new treatments such as transcranial stimulation, used initially to treat Parkinson's disease but now used as well in the treatment of depression and certain anxiety disorders (Holtzheimer & Mayberg, 2011), or the use of video games or other exercises to develop or restore cognitive functions and now being considered to treat mood or anxiety disorders (Etkin, 2012; Rabinovitz, 2012), or even optogenetics (Deisseroth, 2010), the use of which is mostly at the experimental stage at the moment but seems promising for the treatment of certain neurological disorders. These technological innovations have also helped develop new theories about mental disorders, by defining, for example, mental disorders as a disruption in neural circuits, and neurological disorders as being related to brain tissue damage or cell loss. More recently, some authors have even proposed defining mental disorders as developmental brain disorders caused by impaired development of neural circuits (e.g., Insel, 2011).

The neurosciences–and science in general–will continue to advance our knowledge, often through trial and error. We need to welcome scientific progress enthusiastically, confident that we will be able to find ways to better help the people we serve. But we also need to remain humble and critical because, regardless what some may say and despite the progress that has been made, we still know very little about the functioning of the brain. Our most recent techniques and theories will help us take the next step towards new techniques and theories; by then, the first ones may already seem outdated to us. We do not have to look far back to prove that point; think of the theory that depression is caused by a "serotonin imbalance," a theory broadly espoused and long held as valid, which some researchers today are beginning to question (Cai et al., 2013). That example, like many others, reminds us of how important it is to distinguish a process from a cause, a concept discussed in our very first statistics and research methodology courses on experimental and quasi-experimental models or more simply on regressions and correlations, but neglected all too often later on. Thus we

Our most recent techniques and theories will help us take the next step towards new techniques and theories; by then, the first ones may already seem outdated to us.

are quick to support that a mental disorder is caused by cognitive distortions or a chemical imbalance, to take those two examples only. Remission or recovery following a change in those distortions or the use of a medication that results in "increased" serotonin levels is then easily interpreted as proof positive that our theory was valid, as if the disappearance of a headache by taking aspirin demonstrated that the absence of aspirin was the cause of the headache.

Openness and rigour are therefore needed, especially since the evaluation and integration of learning lag considerably behind the publication of new knowledge. Thousands of studies are published each year; although a few institutions have begun summarizing the knowledge drawn from those studies for certain medical professions, much remains to be done in psychology. It is no longer enough to wait for organizations to decide to embrace that mission; it must be demanded, facilitated or perhaps even carried out, starting for example by fostering dialogue among research psychologists and clinical psychologists, but between psychologists and neuropsychologists as well.

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Neuroscience: implications for education and lifelong learning

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Research in neuroscience has produced new insights that have the potential to help clinicians and policy makers understand teaching and learning in new ways. In this paper, the authors review some key findings and conclusions drawn from the neurosciences, including findings on the interaction between genes and the environment, brain development and plasticity, cognitive enhancement, individual differences in learning ability, and adaptive learning technologies.

Keywords: neurosciences, learning, brain plasticity, learning technologies

The rapid progress in research in neuroscience is producing new insights that have the potential to help us understand teaching and learning in new ways. Education is far more than learning facts and skills such as reading. It is not confined to the school years, but plays an important role throughout the lifespan and helps individuals cope with adversity. Flexibility through learning enables people of any age to adapt to challenges of economic upheaval, ill health, and ageing.

Both nature and nurture affect the learning brain

Individuals differ greatly in their response to education, and both genes and the environment contribute to these differences. While it is widely agreed that individual differences can have a genetic basis, genetic influences on brain development and brain function are not yet well understood. For example, while genetic predispositions can partially explain differences in reading ability, there is no single gene that makes an individual a good or poor reader. Instead, there are multiple genes, the individual effects of which are small (Bishop, 2009). Furthermore genes can be turned on and off by environmental factors such as diet (e.g., Jaenisch & Bird, 2003), exposure to toxins (Dolinoy & Jirtle, 2008) and social interactions (e.g., Champagne & Curley, 2005). Genetic make-up alone does not shape a person's learning ability; genetic predisposition interacts with environmental influences at every level.

The brain is plastic

The brain is constantly changing and everything we do changes our brain. This is due to the process by which connections between neurons are strengthened when they are simultaneously activated. The effect is known as experience-dependent plasticity and is present throughout life (Lovden, Backman, Lindenberger, Schaefer, & Schmiedek, 2010). Neuroplasticity allows the brain to continuously take account of the environment. Key findings based on neuroplasticity include the following:

- Changes in the brain's structure and connectivity suggest there are sensitive periods in brain development extending beyond childhood into adolescence (e.g., Thomas & Knowland, 2009). Plasticity tends to decrease with age and this is particularly evident when we consider learning of a second2language: mastery of speech sounds and grammatical structure is generally better in those introduced to a second language before puberty compared with later in life (e.g., Hernandez & Li, 2007).

- The overall pattern of neural development appears to be very similar between genders, but the pace of brain maturation appears to differ, with boys on average reaching full maturation at a slightly later age than girls (Giedd & Rapoport, 2010).
- Dynamic changes to brain connectivity continue in later life. The wiring of the brain changes progressively during development for a surprisingly long time. Even after these developmental changes, activity dependent plasticity is evident throughout life. Just as athletes need to train their muscles, there are many skills where training needs to be continued to maintain brain changes (e.g., Draganski et al., 2004; Gaser & Schlaug, 2003; Hanggi et al., 2009).
- There are limits to neuroplasticity as well as individual differences. Not all learning appears to be subject to sensitive periods, and unlearning habits is remarkably hard. There appear to be limits on how internal predispositions and external stimulation can affect learning. We also know that after brain injury some functions seem to be more amenable to rehabilitation than others, and some cannot be relearned at all (Corrigan & Yudofsky, 1996). However many different factors play a role in recovery and compensation, and both pharmacological treatments and training regimes are being studied as potential means for extending plasticity into adulthood (Bavelier, Levi, Li, Dan, & Hensch, 2010).

The brain's response to reward is influenced by expectations and uncertainty

Neuroscience research has revealed that the brain's response to reward is influenced by many different factors including context (Nieuwenhaus et al., 2005) and individual differences (Krebs, Schott, & Duzel, 2009). Neuroscientists have studied the relationship between reward and learning in the context of reinforcement learning, in which we learn to attribute values to simple actions. In this type of learning, the individual's reward system responds to prediction error, which is the difference between the outcome we expect from an action and the outcome we actually get. It is this response of the reward system that allows us to learn which action has the most valuable outcome. Some neuroscientists think that just reducing prediction errors by making better predictions about outcomes can itself be rewarding. The brain's response to prediction error also supports other types of learning that are of great potential interest to educators, such as the ability to recall information (Howard-Jones, Bogacz, Demetriou, Leonards, & Yoo, 2009). Research also demonstrates that the degree of uncertainty about the reward one might receive is an important contributor to the magnitude of the neural response it generates (Fiorillo, Tobler, & Schultz, 2003). This challenges educational notions of a simple relationship between reward and motivation in school, and may suggest new ways to use reward more effectively in education to support learning (Howard-Jones & Demetriou, 2009)

Education is a powerful form of cognitive enhancement

Cognitive enhancement usually refers to increased mental prowess, for instance, increased problem-solving ability or memory. Such enhancement is usually linked with the use of drugs or sophisticated technology. However, when compared with these means, education seems the most broadly and consistently successful cognitive enhancer of all (Bostrom & Sandberg, 2009). The steady rise in IQ scores over the last decades is thought to be at least partially due to education (e.g., Flynn, 2007). Findings from neuroscience and cognitive enhancement also show that education can build up an individual's cognitive reserve and resilience, that is, their adaptive response to stressful and traumatic events and illness, including brain injury, mental disorder, and normal ageing. Cognitive reserve and resilience can be built up at any point during life. Research on cognitive reserve has found an inverse relationship between educational attainment and risk of dementia (e.g., Barnett & Sahakian, 2010).

There are individual differences in learning ability with a basis in the brain

There is wide variation in learning ability; some individuals struggle to learn in all domains, whereas others have specific difficulties. There is ample evidence that these individuals are at increased risk of poor social adaptation and unemployment (e.g., Beddington, et al., 2008). The costs to society are thus substantial and there is an urgent need to find educational approaches that will work.

Current work in neuroscience is directed toward identifying the brain basis of learning difficulties. As this research advances, prospects are raised for identification and diagnosis, and for designing interventions that are suitable for different ages and may overcome or circumvent the learning difficulties. Much neuroscientific research has focused on more specific learning difficulties, such as developmental dyslexia and developmental dyscalculia. Research has identified underlying cognitive deficits which can be assessed by experimental tests, and may explain other difficulties that are often associated with poor attainment. Although research has shown there are brain correlates, or markers, for learning difficulties, these markers are subtle and complex. As yet it is not possible to predict or assess an individual's specific learning disability from a brain scan (Giedd & Rapoport, 2010). In a similar vein, while there is strong evidence that genetic factors are implicated in specific learning disabilities (Willcutt et al., 2010), one can seldom identify a single gene as responsible. Furthermore, even when a genetic risk or neurological basis for a learning disability can be identified, this does not mean the individual is unteachable; rather, it means that it is necessary to identify the specific barriers to learning for that person, and find alternative ways. The study of dyslexia, using a combination of behavioural and neuroimaging methods, illustrates that it is possible to identify neurocognitive barriers to learning and to make suggestions for appropriate teaching methods. Results from functional neuroimaging studies show that dyslexic children and adults have abnormal patterns of activation in areas of the brain involved in language and reading (e.g., Maurer et al., 2007). The application of knowledge gained from these studies to improve intervention is still at an early stage, but educationally relevant randomised controlled trials of improving literacy are already available.

It is a mistake to regard biological predispositions as deterministic; their impact is probabilistic and context-dependent.

Neuroscience informs adaptive learning technology

Neuroscientific findings can often identify a specific locus for a particular kind of learning difficulty. They may not determine the exact form an intervention should take, but they may well suggest the nature of the concept or skill to be targeted, and the kind of cognitive activity that needs to be strengthened. However, even where successful teaching approaches have been developed for learners who cannot keep up with the mainstream classes, widespread implementation may fail because there are too few specially trained teachers, and the level of frequent and individual attention that many learners need is unaffordable.

Learning technologies have the potential to play a complementary role to that of the teacher in assisting the rehearsal of targeted learning activities. The experimental designs that give rise to neuroscientific insights can often be adapted to support remediation and transferred to technology-based platforms, such as laptops or mobile phones. Although we must treat claims about brain-training programs (e.g., Strong, Torgerson, Torgerson, & Hulme, 2010) and the use of neuroscience in diagnosis with the utmost caution, there is evidence to suggest that with practice, high quality targeted training can improve performance on specific tasks. A key question is whether training effects transfer to other tasks. In most studies, training effects seem highly task-specific (Owen et al., 2010).

Digital technologies can be developed to support individualized self-paced learning and highly specialized practice in a game-like way. Interactive games of this kind use a teacher-pupil model to adapt the task to the learner's needs, and a task model to provide meaningful feedback on their actions. This means interactive technologies can provide personalized help on a daily basis (e.g., Wilson et al., 2006) in a way that is difficult to achieve in a demanding classroom environment.

Conclusion

Neuroscience is often accused of 'medicalizing' the problems of people with educational difficulties. Critics of neuroscience fear that it represents: a reductionist view that overemphasizes the role of the brain at the expense of a holistic understanding of cultural life based on interpretation and empathy; and a determinist view that our neurological inheritance sets us on a path that is unchangeable. However, a neuroscience perspective recognizes that each person constitutes an intricate system operating at neural, cognitive, and social levels, with multiple interactions taking place between processes and levels. Furthermore, it is a mistake to regard biological predispositions as deterministic; their impact is probabilistic and context-dependent. The important point is that there are educational difficulties that have a biological basis, and cannot be attributed solely to parents', teachers' or society's expectations. If in these cases the biological risk factors are not taken into account, important opportunities to optimize learning will be missed.

'Knowledge needs to go in both directions' is a quote that typifies the sentiments expressed by neuroscience, policy and teaching communities. If educational neuroscience is to develop into an effective new discipline, and make a significant impact on the quality of learning for all learners, we need a long-term dialogue between neuroscientists and a wide range of other researchers and professionals from a variety of backgrounds.

This paper presents excerpts from *Brain Waves Module 2: Neuroscience: implications for education and lifelong learning*, The Royal Society Science Policy Centre, February 2011, report submitted by Professors: Uta Frith, Dorothy Bishop, Colin Blakemore, Sarah-Jayne Blakemore, Brian Butterworth, Usha Goswami, Diana Laurillard, Eleanor Maguire, Barbara J Sahakian, Dr. Paul Howard-Jones, Mss. Annette Smith, *et al*.
The complete report can be found at:
http://royalsociety.org/policy/projects/brain-waves/education-lifelong-learning/
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Genomics, epigenomics and mental health disorders

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The recent breakthroughs in neurosciences can change how mental health disorders are defined. The application of genomics and epigenomics can accelerate our understanding of how environmental and genetic factors interact and cause mental health disorders. Personalized clinical services for mental health problems is in its infancy but it may lead to major breakthroughs in diagnosis and treatments.

Keywords: neuroscience, epigenomics, genomics, mental health disorder

The blueprint of the thousands of synapses connecting the 100 billion nerve cells in our brain is not to be found in our DNA. However DNA provides nerve cells with tools so that the brain remains a life-long plastic and dynamic structure modeled not only by our genetic material but also by our interactions with the environment. No doubt, it is nature *and* nurture. But how does the environment interact with our genetic material and influence it? What happens when the interactions between genetic vulnerabilities and the environment go wrong?

Mental health problems are a major public health issue and present an immense burden with huge personal and societal costs. They usually appear during childhood and adolescence and affect the quality of life of patients and people around them, thus impacting on their productivity and social life. They can be treated but they cannot always be cured. According to the 2010 Global Burden of Disease Study (Murray et al. 2012), mental and behavioral disorders account for 7.4% of all disability-adjusted life years (DALYs), a proportion similar to the one attributed to all cancers together. Furthermore, individuals with mental health problems often experience long delays before receiving a diagnosis and an effective treatment. The stigma associated with mental health disorders and the limited access to mental health services prevent them from seeking help when they need it. However stigma and limited access to care are only partly responsible for the delays in diagnosing mental disorders and treating them.

The criteria defined in the DSM-5, to be published in May 2013, are still largely based on symptoms and their severity but many pathologies share symptoms and have blurred boundaries between them. The high prevalence of comorbidity also suggests a continuous spectrum of symptoms that crystallizes around classic diagnostic categories such as schizophrenia, bipolar disorder, major depressive disorder and autism spectrum disorder for example. No biomarkers that can be measured objectively are available to help the clinician with the diagnosis of mental health disorders.

The view of this paper is that mental health problems are brain disorders and that the environment interacts with genetic vulnerabilities inscribed in the genetic code to impact on how the brain functions in health and disease. Mental health care providers would benefit from integrating the recent advances made by genomics and epigenomics to basic neuroscience. These advances could lead to diagnoses based on measurable markers instead of behavioral symptoms which often overlap between disorders.

This is the infancy of a personalized care approach to diagnosis and treatment of mental health problems.

Genomics

The etiology of most mental health disorders is incomplete but many have a strong familial and genetic component. The heritability of schizophrenia, autism spectrum disorder, bipolar disorder or major depressive disorder implies a genetic etiology which, for a long time, could only be studied in identical twins or affected family members raised in different environments. The mapping of the human genome ten years ago was a major advance and prompted studies to identify genetic variants associated with various mental health problems. However, the identification of these genetic variants proved to be difficult. Like hypertension and diabetes, mental disorders are complex genetic disorders where many variants showing only small size effects are involved in the etiology.

Genome-wide association studies scan the entire genome for single-nucleotide polymorphisms (SNP) that may be associated with certain behaviors or clinical phenotype. It has the advantage to highlight genes than would not be considered as candidate genes based on our knowledge of the pathophysiology of a disorder. Linkages are easier to reveal for low prevalence and high heritability disorders, such as schizophrenia, bipolar disorder and autism association. On the other hand, disorders with high prevalence and lower heritability, such as major depressive disorder, prove to be more challenging. Clinical studies for complex disorders with high prevalence but low heritability require larger sample sizes to identify genome-wide significant regions. The difficulty is probably due to a smaller number of risk alleles, lower risk allele frequencies and/or smaller effect sizes. The effects of single gene polymorphism are more subtle than expected and their impact on the clinical phenotype complex.

Sets of genetic variants may use different pathophysiological pathways to produce similar symptoms; this phenomenon can contribute to blurred clinical categories and comorbidity. People with major depressive disorder often suffer concomitantly of anxiety disorders; schizophrenia and bipolar disorders share symptoms. If we could define clusters of variants resulting in similar clinical phenotypes although using different pathophysiological mechanisms, we may establish disorder subtypes leading to more precise diagnostics and targeted effective pharmacological treatments or behavioral interventions.

Identical genetic risk factors may be shared by different disorders. In fact, a study published by the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) showed that a specific single nucleotide polymorphism (SNP) associated to a single pathway, the voltage-gated calcium channel signaling, is involved in the pathogenesis of five major disorders: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder and schizophrenia. However, although calcium channel signaling genes have a role in all five disorders, they explain only a small portion of the clinical phenotype of each disorder individually. These results support the idea that the classification of disorders would be more accurate if biological etiology was used rather than behavioral manifestations. We can expect that other studies will discover genes having overlapping effects in different mental health disorders.

Epigenomics

Epigenetics refers to genetic variations that are not due to changes in DNA sequence. Basically, epigenetic mechanisms involve DNA methylation or acetylation of histones, the proteins around which DNA molecules wind. During DNA methylation, a methyl group is added to cytosine nucleotides in the DNA sequence resulting in a stable modification of its transcriptional state which in turn results in silencing gene expression. DNA methylation can also recruit enzymes that alter the chromatin protecting the DNA molecule and also silencing the gene. DNA methylation

Mental health problems are brain disorders and the environment interacts with genetic vulnerabilities inscribed in the genetic code to impact on how the brain functions in health and disease.

and histone acetylation modify the expression of the genes thus providing a mechanism for the interaction of the environment (psychosocial relations, diet, etc.) with the genetic material. Through epigenetic changes the same DNA sequence can give rise to different phenotypes. When these changes happen during the development of the brain, before and after birth, they can have lasting effects in the adult (Szyf and Bick, 2013).

One of the first examples of early life events translated in long lasting effects in the adult by epigenetics mechanisms comes from studies conducted by the team of Michael Meaney at McGill University (Meaney, 2010). In rodents, adult offsprings of mothers exhibiting high levels of maternal care (licking and grooming of pups) showed lower behavioral and endocrine response to stress compared to animals raised by mothers exhibiting lower levels of maternal care. On the other hand, pups born to mothers with high levels of maternal care but fostered at birth by mothers with low levels of maternal care (and vice versa) showed that the rearing mother determines the phenotype of the offspring. Further studies of adult offspring of mothers exhibiting high levels of maternal care showed a higher expression of the glucocorticoid receptor in the hippocampus and moderate behavioral and endocrine response to stress compared to adults offspring of mothers exhibiting lower level of maternal care. The differences in glucocorticoid receptor expression were due to differences in DNA methylation of the glucocorticoid receptor gene in the hippocampus.

Similar results were observed in humans when suicide victims having experienced neglect and abuse during childhood were compared to others with a similar history but who had not committed suicide and to controls. Suicide victims with childhood abuse exhibited a pattern of DNA methylation and glucocorticoid receptor expression similar to the one observed in adult rodents who experienced lower maternal care as pups (McGowan et al., 2008, 2009). The control group and the suicide victims who had not experienced abuse during childhood had a pattern similar to the adult rodents who had mothers providing high maternal care. These results are consistent with the rodent studies that have examined the effect of maternal care on glucocorticoid receptors in the hippocampus. In both cases, adverse early life events affect, through epigenetic mechanisms, the expression of relevant genes in a specific brain area. The adaptive value of such epigenetic regulation of genome expression is probably that it allows for a better adaptation to the environment given a determined genetic background. For the offspring of mothers exhibiting low maternal care, exhibiting higher stress responses is an advantage in a difficult environment; one needs to be more alert to avoid threats and adverse events (McEwen & Getz, 2013; Meaney 2010).

A better understanding of the factors leading to epigenetic modifications in the brain could lead to ways to reverse them either with pharmacological treatments. In fact, the effect of low maternal care on hippocampal glucocorticoid receptor expression can be reversed through a cascade initiated by trichostatin A (TSA), a histone deacetylase inhibitor, and leading to the demethylation of DNA and an increase in receptor expression (Weaver et al., 2004). But if social interactions early in life can shape our reaction to stress, the question remains if and how social interactions in adulthood reverse the epigenetics markers. We still need to understand how environmental factors such as maternal care are translated into epigenetic regulation of DNA expression in the brain and other tissues, how DNA methylation is maintained during the life and how it can be reversed by targeted pharmacological treatments or possibly behavioral interventions.

Conclusion

In this article, we have mainly discussed the deleterious effects of genetic vulnerability and the environment. A supporting environment would help overcome the vulnerability inscribed in the genetic code. There is a constant dynamic interaction between the genome and the environment that shapes our brain and behavioral response.

Genomics and epigenomics can change the way mental health problems are categorized. Instead of clinical phenotypes difficult to assess, clinicians will be able to rely on sound biological etiology to prevent and treat mental health problems based on the unique profile of each individual. This personalized care approach will still have to take into account the particular socio-economic environment of the person.

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PRACTICE GUIDELINES FOR THE EVALUATION AND TREATMENT OF NEUROPSYCHOLOGICAL/NEUROLOGICAL CONDITIONS

Attention Deficit Disorder and Hyperactivity

Le trouble déficit de l'attention avec ou sans hyperactivité : traitement pharmacologique (2006), by the Collège des médecins du Québec and the Ordre des psychologues du Québec: http://www.ordrepsy.qc.ca/sn_uploads/02006_06_Lignes_directrices_TDAH_MAJ.pdf.

Diagnosis and management of ADHD in children, young people and adults (2008), by the National Institute of Clinical Excellence: www.nice.org.uk/CG072.

Evidence-based guidelines for management of ADHD in adolescents in transition to adult services and in adults (2007), by the British Association for Psychopharmacology. These guidelines also cover different aspects of neuropsychological assessments and intervention : *Journal of Psychopharmacology, 21*(1), 10-41.

Alzheimer's disease

Practice guideline for the treatment of patients with Alzheimer's disease and other dementias (2007), by the American Psychiatric Association: http://www.guidelines.gov/content.aspx?id=11533.

Autism

Screening, Assessment and Diagnosis of Autism Spectrum Disorders in Young Children - Canadian Best Practice Guidelines (2008), by the Fondation Miriam: http://www.autismsocietycanada.ca/DocsAndMedia/KeyReports/Miriam_Best_Practices_guidebook_english.pdf.

Les troubles du spectre de l'autisme : l'évaluation clinique (2012), by the Collège des médecins du Québec and the Ordre des psychologues du Québec: http://www.ordrepsy.qc.ca/sn_uploads/2012_02_Lignes_directrice_Troubles_du_spectre_de_lautisme.pdf.

Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders (2007), by the Scottish Intercollegiate Guidelines Network: http://www.sign.ac.uk/guidelines/fulltext/98/index.html.

Recognition, referral and diagnosis of children and young people on the autism spectrum (2011), by the National Institute of Clinical Excellence: www.nice.org.uk/CG128.

Recognition, referral, diagnosis and management of adults on the autism spectrum (2012), by the National Institute of Clinical Excellence: www.nice.org.uk/CG142.

Delirium and Dementia

Delirium: Diagnosis, prevention and Management (2010), by the National Institute of Clinical Excellence: http://www.nice.org.uk/nicemedia/live/13060/49909/49909.pdf.

Dementia and Age-Related Cognitive Change - Guidelines (2012), by the American Psychological Association: http://www.apa.org/pi/aging/resources/dementia-guidelines.pdf.

Guideline on supporting people with dementia and their carers (2007), by the National Institute of Clinical Excellence-Social Care Institute for Excellence http://guidance.nice.org.uk/cg42.

Management of patients with dementia: A national clinical guideline (2006), by the Scottish Intercollegiate Guidelines Network: http://guideline.gov/content.aspx?id=8809.

Parkinson's disease

Parkinson's disease – diagnosis and management in primary and secondary (2006), by the National Institute of Clinical Excellence: www.nice.org.uk/CG035.

Diagnosis and pharmacological management of Parkinson's disease: A national clinical guideline (2010), by the Scottish Intercollegiate Guidelines Network: http://guideline.gov/content.aspx?id=15595.

New realities about aging: what clinicians should know

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Canadian society is facing a growing number of diseases related to aging. In 2011, the number of new cases of dementia has surpassed the 111,000 per year. By 2030, it is estimated that the number of Canadians with Alzheimer's disease or related dementia will reach 750,000. However, a growing number of studies on the prevention of neurodegeneration have identified important factors in the prevention of cognitive decline associated with aging. In this article, the author focuses on a set of risk factors known as metabolic syndrome.

Keywords: aging, neurosciences, neurodegeneration, cognitive disorders

The elderly are the fastest growing segment of the population in Canada. Never before in our history did so many people grow so old. Concurrent with this, Canadian society faces an increasing number of age-related diseases in the elderly population. While one in 13 Canadians between the ages of 65 and 74 years is affected by Alzheimer Disease (AD) and related dementias, this number changes to one in nine between ages 75 to 84, and one in four over the age of 85. In 2011, new cases of dementia reached over 111,000 per year. By 2030, the total number of Canadians suffering from AD or related dementia will have reached 750,000. This dramatic increase of new cases of dementia does not reflect a change in incidence of dementia; it is simply a consequence of the aging population.

However, research into primary prevention of dementia has demonstrated that there is no inevitable decline in cognitive functioning with age; not all older people will show continuous reduction of intellectual abilities and become dependent. An increasing number of prevention studies have indeed identified important factors in the prevention of cognitive decline with aging. For example, the Alzheimer Disease Cooperative Study (Sano et al., 2006) has shown that memory training is efficacious when trying to slow down the progression, or delay the onset of dementia. Likewise, the multicenter 'ACTIVE' study has shown that memory training improves self-esteem and self-report of cognitive problems (Willis et al., 2006). Unfortunately, it is at this point unclear whether this, or other types of interventions (e.g., Schneider & Sano, 2009) can serve as a substitute for cholinergic stimulation, and whether these effects are long-lasting (Bentley et al., 2008). Ultimately, because dementia is likely to have a multifactorial origin (Coley et al., 2008), prevention programs will need to rely on a multidomain approach to prevention (exercise, nutrition, cognitive stimulation). These are challenges that all prevention programs will have to deal with.

Realities of aging: known risk factors for neurodegeneration

There are a number of known risk factors for aggravated cognitive decline with aging: family history, genetics (APOE4), gender, cardiovascular disease, obesity, insulin resistance, and known brain abnormalities (e.g. reduced hippocampal volume). Recent studies have identified that a cluster of these factors commonly occur together, perhaps as a consequence of specific life events and trajectories. One such cluster that has received considerable attention in recent years is referred to as the metabolic syndrome.

The metabolic syndrome involves a combination of an increased body mass index, an increased waist-to-hip ratio, a reduced insulin sensitivity combined with hyperglycemia, hypertension, and increased levels of LDL-cholesterol and other lipids in the blood stream (dyslipidemia). The exact threshold and combination of these factors constituting the metabolic syndrome varies among different researchers, and health agencies. In September 2011, a study reported that the prevalence of the metabolic syndrome is now roughly one in five (19.1%) of adult Canadians (18-79 years). Age was found to be the strongest predictor, as the prevalence increased from 17% in the youngest age bracket (18-39 years) to 39% in the oldest (70 to 79 years). The study used a representative sample of roughly 1,800 subjects from the Canadian Health Measures Survey, which originally covered over 96% of the Canadian population in the age range of 6-79 years (Riediger & Clara, 2011). An assessment of a representative sample of the Canadian population in the context of the Canadian Heart Health Survey in the years 1986 to 1992 reported a prevalence of the metabolic syndrome of 8.6% in women and 4.6% in men in the age range of 18 to 39 years, suggesting that the prevalence is increasing (Brien and Katzmarzyk, 2006).

The adverse health consequences of the metabolic syndrome are enormous – it contributes substantially to chronic disease, and thus indirectly to morbidity and mortality of the Canadian population. Thus, the economic costs of this syndrome are also substantial. Available studies suggest that having metabolic syndrome doubles a person's risk to develop cardiovascular disease and type II diabetes, independently of other risk factors (e.g., Khang et al., 2010; Padwal & Sharma, 2010). Studies have reported associations between the metabolic syndrome and increased risk for neurodegeneration and dementia, likely mediated through the adverse effects of the metabolic syndrome on the vasculature in the brain (e.g., Abraham et al., 2007).

Early life adversity and the metabolic syndrome

Causes of the metabolic syndrome are likely multifactorial and complex, with various epidemiological studies reporting factors like socioeconomic status, years of education, cultural background, dietary habits, chronic stress, among others, to play a significant role (Alberti et al., 2006). One interesting line of research investigates the effects of early life adversity on metabolic consequences in adulthood, including obesity and diabetes. Here, epidemiological studies have shown how stressful events in early life, both *pre-* and *postnatal*, are linked to a number of adverse developmental outcomes across the life of the individual. There are numerous studies, both from animal and human studies, documenting how adverse factors during early development can have permanent effects on metabolism in adulthood, with long-term consequences on the health of the individual.

Research into *prenatal adversity* has shown that two of the most common consequences of adverse events during the development of the fetus (e.g. hypoxia, ischemic insults or trauma) are reduced size and weight at birth. Low birth weight, in particular, shows a strong association with subsequent occurrence of the metabolic syndrome in adulthood including lowered insulin sensitivity, increased prevalence of type-2 diabetes and obesity, as well as hypertension (Reynolds, 2010). Downstream, the metabolic syndrome is associated with increased risk for cardiovascular disease (Barker, 1997). Another study has demonstrated an association between low birth weight and glucose intolerance in later life (Hales et al., 1991). Those with the lowest birth weight showed a six-fold increased risk of type-2 diabetes (compared to the heaviest at birth) and an 18-fold increase for the occurrence of metabolic syndrome. Importantly, this study controlled for other lifestyle factors like smoking, current stressors, and dietary patterns and found them to be independent, although obesity was associated with worse glucose tolerance. Another conclusion from this study was that the association between birth weight and adult disease is continuous, hinting at a linear relationship. In addition, numerous studies have reported on the relationship between low birth weight and glucose intolerance, combining various cohorts and populations, making this a commonly accepted finding (Drake and Walker, 2004). Complementing these other effects, several epidemiological studies have linked low birth weight with central adiposity in

adulthood. The initial report of such an effect stems from a study of 300,000 men exposed in utero to a severe famine occurring in the Netherlands towards the end of the Second World War. As a consequence of this special form of early life adversity, these men had a significantly lower birth weight and developed significantly higher obesity rates at the age of 19 years (Simmons, 2008). Perhaps most interestingly, new findings suggest that these effects were not limited to the generation exposed in utero, but were further transmitted to the offspring of those men who were initially exposed to the famine as well, who are now also reported to be at increased risk of obesity. This likely points to epigenetic effects, influencing gene expression that lasts over several generations, with the exact mechanisms still under investigation (Painter et al., 2008).

Postnatal adversity also seems to contribute significantly to the risk for cognitive and health decline with aging. In a 35-year follow-up study to the 'Harvard Mastery of Stress Study', which retrospectively investigated the effects of low parental care and overprotection on health parameters in humans (Russek & Schwartz, 1997a,b), 95% of the participants who as students reported an initial cold and distant relationship with their parents now complained of health problems including cardiovascular disease, hypertension, and ulcers. Subjects that had been suffering from (self-reported) cold and distant parenting also showed more signs of addictive behaviors (alcohol and drug abuse) when compared to participants who reported close and warm relations to their parents. The authors concluded that the perception of high parental caring while in college is predictive of better health behaviors and health, and of less disease late in adulthood. Further studies supporting a link between childhood conditions and metabolic health problems have associated childhood poverty with long-term illness (Bartley and Plewis, 2002), poor childhood housing and elevated blood pressure (Mitchell et al., 2002, 2005), and childhood poverty and cardiovascular disease (Morris et al., 2000). In a previous study from our group, we investigated the risk for coronary heart disease in relationship to early life adversity and found that among women, a one unit increase in the parental emotional care resulted in a 4.6% decrease in the 10-year risk for coronary heart disease (Almeida et al., 2010).

Taken together, these studies suggest a strong effect of various forms of early life adversity – ranging from stress in utero by ischemic insults or malnutrition to various forms of postnatal stressors (like physical or sexual abuse, or poor parenting), on the occurrence of the metabolic syndrome in adulthood. While the mechanisms by which early life adversity leads to the occurrence of metabolic syndrome later in life are likely complex and multifactorial, recent findings suggest a strong role for the systems regulating the organism's stress response in mediating the association between early-life adversity and the metabolic syndrome.

Conclusion

With the aging of the Canadian population, it is critical to identify factors that contribute to health and cognitive well-being in old age. If the theory of life trajectories is valid, then clinicians should be able to identify subjects at risk of neurodegeneration in old age by looking at signs for a developing metabolic syndrome, and its psychological and sociodemographic risk factors. Recent research seems to suggest that early life adversity is such a risk factor, with pre- and postnatal adversity having cumulative effects. Interventions for the population at risk then need to include a longitudinal database of adult subjects with cognitive assessment, but also physiological and hormonal assessments, to be sensitive to early changes. One problem related to these cognitive assessments is that, to date, almost all of them are based on cross-sectional assessments, which fails to take into account individual differences in cognitive abilities. As a result, an individual test score needs to drop by 20% to be picked up by cross-sectional norm data while a longitudinal, intra-individual comparison could raise suspicions after a change of 5% (e.g., Clark, 1992). This is why a strong case can be made for a clinician following patients over long periods of time, to engage in proper database setup and management, in order to allow longitudinal comparisons of test scores. In addition, known prevention activities (physical exercise programs, nutrition workshops, stress reduction programs) with proven efficiency need to be promoted by means of psychological education.

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USEFUL WEBSITES/RESOURCES FOR PATIENTS

Baycrest
Provides information about the types of memory, normal aging, risk factors for memory impairment, types of cognitive disorders, dementia, and memory loss, and coping with memory loss and dementia. Other resources include video clips explaining the different disorders.
http://www.baycrest.org/memoryandaging

Canadian Psychological Association (CPA)
Provides a fact sheet for cognitive disorders and dementia. In particular, information about cognition, dementia, Alzheimer's disease, cognitive disorders, prevalence rates, related conditions, signs and symptoms, psychological treatment and care, and further resources for seeking help.
http://www.cpa.ca/psychologyfactsheets/cognitivedisordersanddementia

McGill University: The Brain from Top to Bottom
Includes information for beginners, intermediate, and advanced levels of knowledge in the area of the brain, related functions, and cognitive disorders.
http://thebrain.mcgill.ca/index.php

Montreal Neurological Institute: Neuro-Patient Resource Centre
Provides information on several neurological and neuropsychological disorders and conditions for children, adolescents, and adults. The resources include fact sheets, websites for further information, and resources for treatment centres.
http://infoneuro.mcgill.ca

Neurological Health Charities Canada
Provides information on various neuropsychological and neurological conditions, and provides specific organizations that focus on each respective disorder.
http://www.mybrainmatters.ca/en/brain-conditions

On Memory
Information is provided about what dementia and Alzheimer's disease is, the related symptoms and signs, the normal versus abnormal process of aging, treatment options, guidance for seeking health care, information for caregivers, informative videos, as well as resources for testing memory and a symptoms diary for monitoring signs and symptoms.
https://www.onmemory.ca

World Health Organization
Provides several fact sheets for mental health problems, including neuropsychological disorders. The fact sheets provide information about key facts about the disorders, defining the disorders such as signs and symptoms, forms of the disorder, prevalence rates, treatment and care, risk factors, and the impact on society, affected individuals, and caregivers.
http://www.who.int/mediacentre/factsheets/en
http://www.who.int/mental_health/neurology/neurodiso/en
http://www.who.int/mental_health/neurology/neurological_disorders_report_web.pdf

Other resources
Amyotrophic Lateral Sclerosis (ALS)
http://www.als.ca/en/living-als/education

Muscular Dystrophy Canada
http://www.muscle.ca

The Alzheimer's Society of Canada
www.alzheimer.ca

Tourette Syndrome Foundation of Canada
www.tourette.ca

Ontario Federation for Cerebral Palsy
www.ofcp.ca

Dystonia Medical Research Foundation Canada
www.dystoniacanada.org

Canadian Epilepsy Alliance
www.epilepsymatters.com

Huntington Society of Canada
www.huntingtonsociety.ca

Multiple Sclerosis Society of Canada
www.mssociety.ca

Parkinson Society Canada
www.parkinson.ca

Ontario Rett Syndrome Association
www.rett.ca

National Institute of Neurological Disorders and Stroke (USA)
www.ninds.nih.gov/index.htm

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The next issue of the journal, scheduled to appear in November 2013, will be devoted
TO RESEARCH ON COUPLES