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Unraveling the mystery of cognitive reserve

In 1913, no less than Santiago Ramon y Cajal, pioneer of the neuron doctrine, wrote, 'In the adult brain, nervous pathways are fixed and immutable; everything may die, nothing may be regenerated' (Cajal 1913/1959, p 750). This stagnant view of the brain lingered in neurology for several decades, and was regularly provided as an explanation when a patient's recovery from a stroke or brain injury was minimal or elusive. Our current understanding, however, is radically and very importantly different. The human brain – even the adult human brain – is, in fact, remarkably plastic. This enduring neuroplasticity is fundamental to the brain's mechanisms for coping with disease and injury. As the world's population ages, this is becoming increasingly evident. The question now emerging in the field, however, lies not in the ubiquity of age-related disorders such as Alzheimer's disease (AD), but in the individual variability of their onset.

Alzheimer's can now be diagnosed with reasonable consistency: several academic centres report up to 90% correlation between clinical diagnoses and autopsy diagnoses of AD (Cummings *et al.* 1998). However, the relationship between the severity of clinical symptoms and observable neuropathology is far from direct. This was particularly brought to light in 1989, when Katzman *et al.* performed postmortem analyses of the brains of 137 nursing home patients. The patients' cognitive abilities had been monitored at the nursing home, and these records were compared with the neuropathology observed during dissection. They unexpectedly found that the brains of 10 of the subjects, who had been assessed as having unimpaired cognitive function throughout their lives, in fact displayed neuropathology that surpassed the criteria for diagnosis of AD. These individuals also happened to have heavier and more neuron-dense brains than controls, which they concluded must have afforded some 'reserve' that prevented the symptoms of the disease from manifesting.

There are two primary theories that attempt to explain such a discrepancy. Brain reserve (BR) refers to tangible individual differences such as brain size and dendritic density, as was noticed by Katzman *et al.* (1989), BR is considered a passive 'threshold' model of reserve: once a certain threshold for brain damage is exceeded, symptoms of cognitive decline begin to manifest. Cognitive reserve (CR), on the other hand, is considered an active model: the brain attempts to compensate for cognitive damage by implementing alternate mechanisms in place of the damaged networks. A brain that has engaged in activities that enhance this cognitive flexibility is therefore better equipped to cope with damage than one that has not (Stern, 2002). Barulli and Stern (2013) argue that these theories are complementary rather than competing. Like any complex human trait, resilience against brain damage appears to be constructed of a cocktail of genetics, environment and experience. The greater the resolution with which brain structures can be visualized and molecular pathways leading to plasticity are understood, the more the two theories are liable to overlap. Nevertheless, it remains that the environmental component can be manipulated to favour reserve.

As a result, much of the current literature concerning reserve focuses on identifying lifestyle factors that may improve CR. Higher level of education, occupational complexity and physical and intellectual leisure activities have all been found to consistently correlate with increased CR (Verghese *et al.* 2003; Potter *et al.* 2008; Valenzuela and Sachdev 2009). Recently, bilingualism as a CR-improving factor has received much attention. The original studies in this area found a highly significant effect of lifelong bilingualism on the onset of AD, and are textbook examples of CR in effect. The first, by Craik, Bialystok and Freedman (2010), retrospectively analysed the medical records of 211 elderly Canadians diagnosed with AD. The records contained detailed language histories, based on which 102 were classified as bilingual and 109 as monolingual. On comparison, the bilingual group showed an onset of AD symptoms on average 5.1 years

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later than the monolingual group. The findings were supported by a subsequent neuroimaging study by Schweizer *et al.* (2012) on a group of 10 monolinguals and 10 bilinguals (matched for age and education) with AD. Computed tomography (CT) scans showed that the 10 bilinguals were exhibiting significantly more AD neuropathology than the 10 monolinguals. Despite this, the bilingual group was functioning at an equivalent cognitive level to the monolingual group.

The attention that has recently turned to factors that may improve CR, both in scientific literature and popular discourse, is to be expected. In the search for viable treatment for AD, surgical and pharmaceutical approaches have not yielded extensive results. The emergence of a new variable that influences cognitive function offers, in the meantime, alternate ways to approach such disorders. Indeed, the public health impact of delaying the onset of dementia is great. According to Brookmeyer *et al.* (2007), delaying the onset of AD by just one year is enough to reduce its global incidence by 9.2 million in the year 2050. Even beyond dementia, the clinical implications are far-reaching. CR has already been seen to aid recovery or delay clinical onset in traumatic brain injury, Parkinson's disease, HIV and multiple sclerosis (Glatt *et al.* 1996; Farinpour *et al*. 2003; Kesler *et al.* 2003; Sumowski *et al.* 2009). But could CR be more than just a crutch in lieu of a definitive cure? It is possible that understanding the neural mechanisms underlying reserve may identify new molecular targets for pharmaceutical treatment of AD and other neurological disorders. Furthermore, factors that promote CR, such as musical education, have also been seen to reduce cognitive decline in healthy aging (Hanna-Pladdy and Gajewski 2012). Human life expectancy has increased dramatically in the last two centuries, and constructing a 'recipe' for a healthy and enriched lifestyle structured around the concept of CR could well be the key to extending it further. From a theoretical perspective, there is also much insight to be gained in studying how the brain encodes environmental input to generate reserve.

Environmental enrichment (EE) was first endorsed as a scientifically quantifiable entity by Donald Hebb in the 1940s, and is measured by the quantity, complexity and novelty of stimuli in an organism's environment. The factors that have been seen to contribute to CR are strongly resonant with the concept of EE. Nithianantharajah and Hannan (2009) posit that these two concepts are closely interrelated, and the findings from animal models of EE will elucidate existing theories of the neural correlates of reserve. The two most prominent of these theories, 'neural reserve' and 'neural compensation', were proposed by Yaakov Stern (2009/2013). These suggest respectively that cognitive networks that have frequently been exposed to stimulating activity over an individual's life develop in density or in efficiency and flexibility. This is reminiscent of Hebb's famous remark that laid the groundwork for a theory of synaptic plasticity: 'When an axon of cell A is near enough to excite cell B, and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased' (Hebb 1949). These 'growth processes' and 'metabolic changes' have been studied in great depth, particularly in the CA3-CA1 synapse of the hippocampus, which is primarily attributed to learning and memory. This theory is now better known as long-term potentiation (LTP).[1] Learning and other forms of EE have been shown to increase LTP both in the hippocampus and the anterior cingulate cortex, anda higher level of cognitive and physical activity across the lifespan is correlated with a reduced rate of hippocampal atrophy with age (van Praag *et al*. 1999; Valenzuela *et al*. 2008). LTP and EE therefore seem logical starting points for further understanding the molecular mechanisms contributing to reserve.

There are certain areas in the field, however, that require more attention. Studies of EE have largely only been conducted in animal models. Developing practical and ethical methods to study the same concepts in humans is essential to ensure any translational outcomes. The effects of EE in later life have also received little attention, despite much debate over the theory of 'critical periods' for acquisition of certain skills such as language. An evolutionary perspective is likely to shed light on healthy aging, the cognitive contribution to the 'grandmother effect' (the uniquely high post-menopausal life-expectancy of human females) and

[1] LTP, in short, relies on the successful activation of a 'cell B' in a network, either by a high-intensity stimulus or a summation of lower-intensity stimuli in rapid succession. In the synapse between A and B, this leads to an efflux of glutamate from the presynaptic cell, which bind to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors on the postsynaptic membrane, causing an influx of sodium ions into cell B. The consequent change in potential in cell B, along with the presence of glutamate in the synapse, shifts a magnesium blockage in a second type of postsynaptic receptor, NMDA-R (*N*-methyl-D-aspartate receptor). NMDA-R subsequently becomes permeable to calcium ions, which crucially promote the activity of transcription factors, leading to the expression of more AMPA receptors (leading to increased synaptic efficiency) and nerve growth factors (leading to neurogenesis and increased dendritic density) (Bliss and Lomo 1970).

selection for traits that motivate novelty-seeking behaviour (Herndon 2010). Neuroepigenetics will clearly have much to offer, but the field itself is a fledgling and studies in the area are as yet in early stages. Perhaps the most interesting of relevant theories is that plasticity, memory consolidation and susceptibility to disease in adults may be reliant on post-transcriptional RNA editing in individual cells, suggesting that individual neurons may have minute differences in genome sequences defined by their spatiotemporal histories (Mehler and Mattick 2007). Such changes may therefore be transmitted transgenerationally. This is quite a claim, but at least one study has shown that enhancement of LTP in mothers due to EE can be observed in their offspring, even when the offspring themselves are not exposed to EE (Arai *et al*. 2009).

There may be an opportunity for more detailed study in this area presented by a relatively untapped population: older adults with Down's syndrome (DS). People with DS have an extra 21st chromosome, which encodes the gene for beta-amyloid precursor protein (β-APP). β-APP is cleaved by a membrane protein called gamma-secretase into beta-amyloid, which accumulates to form the oligomers and plaques characteristic of AD (Glenner and Wong 1984). In a recent series of very elegant experiments, Wang *et al.* (2013) found that people and mice with DS have low levels of SNX27, a sorting nexin responsible for the regulation of membrane proteins, including gamma-secretase. Unregulated active gamma-secretase results in increased levels of neurotoxic beta-amyloid. They found that miRNA-155, which restricts the production of SNX27, is also encoded on chromosome 21. As a consequence, people with DS have a significantly increased risk of developing AD: it is almost certain that a person with DS will exhibit some AD neuropathology by the age of 60. However, only 50–70% of people with DS will actually show symptoms of AD (Janicki and Dalton 2000). Despite this, few studies have investigated the effects of EE on the onset of AD in this population, particularly in people with DS who are asymptomatic of AD. A cavalcade of questions may be raised. How might physical and cognitive activity influence epigenetic changes to cells in the brains of people with DS? Is miRNA-155 implicated in post-transcriptional editing and consolidation of memory? Will neuroimaging reveal characteristic patterns of compensation during cognitive tasks in asymptomatic elderly individuals with DS? Do lifestyle factors that delay the onset of AD in a general population also do so in people with DS? If not, why? This last question in particular may be an instance of the rare scientific double-sided coin: significant results may lead us to consider new possibilities for the education of children with DS and prevention of AD in this group; non-significant results will give us new questions to ask in the pursuit of understanding CR, and perhaps new ways in which to answer them.

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