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FACTS, OPINIONS & IDEAS

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The Changing Brain

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There is a saying that you can never dip your toe into the same river twice. The same applies to the brain because at a quite fundamental level it is continuously changing. Indeed, it is somewhat incredible that throughout our lives we are able to maintain a more-or-less unified concept of who we are given there is little constancy of substance to anchor this most basic of notions. Beyond this philosophical curiosity, there has accumulated a formidable body of science specifically focused on how experience can affect the brain. Neuroplasticity in particular refers to a range of biological changes which occur in the brain in response to experience or environmental stimuli. These changes vary vastly in terms of scale and timecourse — from molecular cascades that can be triggered in a matter of hours, to whole-brain cortical network reorganisation which can evolve over months if not years. Neuroplasticity is therefore more akin to a federation of complex biological phenomena, rather than any single process. Here, some of these are introduced with the aim of sketching out the potential of the human brain to continue to adapt, grow and develop throughout the lifespan.

Use it or lose it

Most of what we know about the changing brain is due to a remarkably simple experiment called, 'environmental enrichment'. In this, animals are moved from their normal 'boring' cages to one in which there is more space, more toys, more

littermates and the addition of running wheels. It goes without saying that rodents vastly prefer to spend their time in an enrichment environment. For more that 50 years now, scientists have been studying the impact of enrichment on these animal's mental abilities (cognition), as well as their brain's structure and function.

In terms of cognition, enrichment produces a number of mental benefits. This type of stimulation improves reaction time, increases memory ability and makes animals more resistant to the effects of ageing and degenerative brain changes. Remarkably, similar effects also seem to apply to humans. Our research has shown that those individuals who stay more mentally active throughout their lifespan are about 50% less likely to develop dementia in later life compared to those that do not use their brains as much (Valenzuela & Sachdev, 2006). How this happens is still not clear, but our research and that of many others suggests that different mechanisms may be at work, all of which come together to protect more mentally active individuals from cognitive dysfunction. So the maxim of 'use it or lose it' seems to apply equally to the brain as to the rest of the body. Some the different biological processes which may be activated are considered below.

The fast track

A basic unit of biology these days are so-called molecular changes, referring to cascades of large molecules which govern the regulation of important physiological processes. Molecular biology being highly reductionistic discipline, these processes generally end up with a genetic explanation for things. In simplistic terms, our inherited genetics (DNA) dictates what proteins and macromolecules possibly can be produced (or through some genetic fault what cannot be produced); our environment (in this special case everything outside of the DNA) reveals what is produced. Let's consider two examples to help distinguish between genes, genetic translation and gene expression.

At one extreme are inherited disorders whereby an affected individual is born with a genetic abnormality in their DNA. If we were to unravel the DNA of someone with inherited early-onset Alzheimer's disease (AD), and compare it side-by-side with an unaffected individual, we would see one or more discrepancies. On chromosome 21, for example, the gene that codes for a membrane protein called amyloid precursor would have an error on it, the kind of error that means too much of the amyloid precursor message is communicated out of the cell nucleus, leading to the production of too much actual amyloid protein. Eventually, in one's 30s, 40s or 50s, the affected individual's brain cells would be swamped with amyloid plaques, and sadly, a form of dementia ensue. While some environmental factors may possibly be able to modify this course of events, clearly the fault here lies at the start of the chain, the scrambled genetic code in each and every cell.

Consider now the case of someone with non-familial AD who may develop the sticky plaques later in their 70s. In this person there is no primary fault in the inherited DNA, but rather too many amyloid messages coming out of the cell nucleus, and again too much amyloid protein invading the brain cells. How can this be? We do not completely know, but clearly the inherited code is only part of the story. Other non-amyloid genes may be interacting to alter the amount of amyloid messages being produced, or some environmental events (such as a fatty diet leading to high blood pressure) signaling that the normal amyloid gene becomes 'switched on'.

So here is where the complexity of human biology becomes apparent. Our genetic code is only a rudimentary alphabet of sorts; what genes are turned 'on' or 'off', 'high' or 'low', 'hyperactive' or 'hypoactive', ends up in most cases to be a mind-boggling interaction of gene-on-genes, messengers-on-genes, genes-on-messengers, environment-on-genes, and so on. Most of medicine's more insidious and intractable problems, including dementia, heart disease, diabetes, arthritis and so forth are in this category.

We have hopefully clarified an important distinction between genes that code for a particular protein or large molecule (product), and the messengers (mRNA) that deliver the message to produce that product in the rest of the cell. In the end, it is the difference in mRNAs running around a cell which means an eye cell produces 'eye stuff', while a skin cell produces 'skin stuff', recalling that all cells are reading off the same DNA blueprint. Equally, it should also be apparent that there is a close link between the mRNA message for a product and the end product itself — lots of amyloid precursor mRNA correlates with lots of actual sticky amyloid protein.

With this in mind, the development of a very powerful technology called 'microarray' now means that we can probe the activation status (known as gene expression) of >30,000 mRNAs in a sample of tissue in a matter of hours. What's more (and coming back to the point), investigators have used this technology to see what changes in a rodent's brain after being exposed to the enrichment environment compared to those rats that have been maintained in standard housing. Two fascinating lessons have emerged. First, 60 different gene pathways changed. That is, the brain's gene expression status is altered by the simple act of increasing an animal's level of stimulation. Some of these gene expression pathways are very interesting. For example, some relate to the ability of our brain cells to be resistant to stress, others to synaptic plasticity (more about that latter), and remarkably, some relate to the breakdown process of amyloid plaques. So if environmental enrichment increases mRNA for proteins involved in breaking down plaques, what happens to the plaque itself? Equally amazingly, studies of rodents engineered to resemble some aspects of early onset (inherited) AD show vast reduction in brain plaques (and improvements in memory) after being moved to an enriched environment for a few months. Whether similar processes can happen in humans in completely unknown, but these studies do show that mental activity is a vital regulator of quite fundamental molecular processes implicated in brain ageing and brain health.

The second stunning result from microarray studies of enrichment has to do with the timecourse they suggest. One study found dozen of gene expression changes in rodents that had spent only three hours in an enriched environment! So to extrapolate to the human condition, each time we spend a focused period of time learning something new or challenging our minds, we induce the expression of several gene expression pathways in our brain; conversely long period of mental inactivity could have the opposite effect. Through our lifestyle choices we are, therefore, continuously shaping the molecular conditions of our own minds. I believe this to be one of the most empowering concepts in modern neuroscience, and it is up to each person to take the fullest advantage of it.

Cells, cells, cells

No brain cell like no man is an island. Brains cells acquire informational and representational capacity through the intricate and transitory connections they form. These connections are called synapses, and as mentioned above, one of the fast-paced molecular changes that occur in response to enrichment is an increase in synaptic plasticity. What this means at a physical level is revealed if we continue to expose an animal to this enriched environment for a number of weeks. This time is necessary for the change in mRNA to become translated to actual changes in synaptic proteins. In fact, a whole range of protein changes occur so that a massive increase in the number of synapses between brain cells can now be seen under the microscope. The changes are truly striking. In some studies, increases in synapses of between 200–250% have been observed after a couple of months of enrichment.

These changes appear to be very important to cognition. In animals, the number of synapses between brain cells correlates to how well they do on memory tests, especially in a part of the brain called the hippocampus. The hippocampus is the memory centre of the brain, and connections between cells in this area are essential to good memory function. In humans also, the severe memory deficits seen in AD is associated with a

drastic decrease in synapses in several brain regions. So it would appear that regular mental activity over several weeks can help build up our store of synapses. More synapses means better cognition and, hopefully, less chance of developing cognitive dysfunction or dementia.

Another fascinating cellular change that takes some weeks to develop is neurogenesis. In a complete reversal to scientific orthodoxy of only 10 years ago, we now know that the adult brain is capable of producing new neurons (brain cells) through the process of neurogenesis. Neurogenesis, however, does not occur everywhere, but in two special regions. One is the hippocampus again, which is perhaps the most neuroplastic organ of the brain. The other is the lining of our ventricles, which are fluid sacs deep at the heart of our brain filled with cerebrospinal fluid. Neurogenesis in the ventricular areas seems to be quite important to our ability to smell, since the baby neurons produced here travel half the length of the brain to end up in our olfactory lobe. The function of neurogenesis in the hippocampus is highly controversial, with some scientists arguing it is vital to everything from memory, depression and anti-depressant medication effects (Kempermann, 2006), to others who suggest it is an interesting but trivial remnant from our days on four legs. In any case, environmental enrichment is a strong positive stimulant of neurogenesis. Adult animals, as well as older animals, produce many more new neurons when placed in an interesting (and fun) environment than otherwise. So consistent mental activity may not only increase the number of vital connections between brain cells, but also increase the number of brain cells in specific parts of the brain, including the hippocampus. There is perhaps no better example of a brain that can change itself (Doidge, 2007).

Malleable minds

A game I like to play with molecular and cellular biologists (perhaps I need to get out a bit), is after an eloquent presentation of how important a particular molecule, cell or group of cells may be to this, that or the other, to ask (politely) how the

hell does this end up affecting a person's ability to remember something, feel normal, do day-to-day activities, laugh, learn or speak? It's plain mischief of course, because a mechanistic or reductionist account of these 'higher-order' mental abilities lies well, well beyond our grasp.

What we do understand is that these complex abilities are the result of distributed neural networks across the brain, rather than the product of a specific brain centre. Neuroscience has, thankfully, moved from a region-obsessed way of thinking about thinking (taken to the extreme by the phrenologists), to a connectionist or neural network paradigm (Knight, 2007). Take, for example, the 'famous' Broca's area, a part of the brain implicated in speech production and problems since the early 1860s. In the first instance, everyone's Broca's area is in a slightly different place, and is hardly the only brain region that if affected would result in speech problems. In fact, if you were to line up 10 people and ask them to read words out loud while undergoing a functional MRI scan for detecting brain activity, each would exhibit a distinct network pattern. Brain regions (like neurons) only function in a neural context, which encompass all the regions they directly connect to, including close neighbours and distant zones, as well as those they indirectly connect to. At each level one wishes to consider the brain, there is complexity and inter-connectivity, specialization as well as integration.

Let's take another famous and emphatic example of cortical plasticity. The most posterior part of the brain is called the occipital lobe, mostly occupied by visual cortex. Given its name, it is no surprise that it is the primary centre for processing of basic visual stimuli. Entire libraries could be dedicated to the amount of neuroscience experiments showing the subtle and remarkable way that visual information is processed in the visual cortex. Hubel & Wiesel, for example, won a Nobel prize for their discovery of very specific cells in the visual cortex, which start firing when a line is orientated in one direction, but not in another. For many cognitive neuro-

scientists, it goes without saying that the occipital lobe, and visual cortex in particular, simply does vision. It is therefore somewhat incredible that a very simple intervention can transform this part of the brain from an area specialized for visual processing to one for tactile processing. Researchers blindfolded volunteer subjects and in as little as a few days without visual input their occipital lobes began to respond to tactile stimulus (Merabet et al., 2008). Within hours of removing the blindfolds, the visual cortex stopped responding to texture and touch and reverted to its 'normal' role of visual processing. Very clearly, the way the brain handles information on a grand scale — across and between whole cortical regions — is malleable. Brain networks, like the molecules, synapses and neurons they subordinate, can also change with time in response to experience.

A unified theory of neuroplasticity

Neuroplasticity cannot and should not be thought of as only something that happens inside our heads. On the contrary, the intensity and duration of the enriched environments we encounter will to a large degree determine the nature and durability of the neuroplastic changes which follow. A brief period of stimulation may trigger off dozens of molecular cascades which prime our cells for growth and connectivity should this stimulation continue. Even longer term stimulation may consolidate and refine the connectivity of these new brain cells, and so facilitate dynamic changes in the way our brain handles information. At a functional level we may eventually become faster at handling problems which previously we found difficult, or more capable of doing two things at once. These changes will in turn enable us to participate in more complex mental challenges and diverse cognitive activities, and so a virtuous cycle can begin. The opposite is also possible. At one extreme, zero environmental stimulation is incompatible with life for the developing brain. Even an impoverished environment — as is the case for rodents which spend their entire life in an unchanging box or those millions of children who never

will finish even primary school — has a range of negative implications for brain growth, brain development and most importantly, for brain potential. Neuroplasticity therefore occurs at multiple spatial scales and across multiple temporal epochs (Valenzuela et al., 2007). Neuroplasticity and the environment we mentally inhabit are inherently co-dependent.

Of mice and men — translating basic science to public health policy

So how can we best convert this wealth of scientific knowledge about neuroplasticity into practical steps to increase our brain health and help avoid dementia? This has been a continuing interest of mine, and fortunately there are many things we can all do to increase brain fitness at whatever phase of life. Let's consider three examples.

An eminent group in the United States led by Professor Joe Verghese some years ago reported on the results of a study that had tracked several hundred older people for a number of years to try to determine what attributes predicted who would develop dementia, and who wouldn't. One of the main findings was that overall cognitive activity level was an important protective factor — more cognitive activity in one's life was associate with less dementia risk. Moreover, not all activities appeared to be equal. When cognitive and physical activities were compared, only one type of physical exercise appeared to be effective: dancing. Frequent dancers (very loosely defined) had about 70% less risk of developing dementia than non-dancers. Being a long-time fan of dancing myself it's not hard to understand why; dancing is not only incredibly good physical exercise, but is also mentally quite challenging and great social stimulation.

Another US-based study has also recently illustrated the power of social and community engagement. In this case older African Americans who were at high risk of developing dementia because of cardiovascular risk factors (like hypertension, diabetes, and so on), were by the toss of coin assigned to either an intervention or a wait-and-see condition. The inter-

vention involved going to a local primary school and helping teach the kids to read. This beautifully simple intervention (called 'Experience Corps') had a powerful effect on the brain, leading to increased blood flow to important areas generally most affected by ageing and disease. It goes without saying that these individuals also felt better about themselves having the opportunity to get out of the house, engage with young kids and contribute to their community. Most definitely a win-win situation.

The final example is what could be termed the 'pointy end' of the neuroplasticity stick. Cognitive brain training considers the brain like a muscle that needs to get a good workout, and like going to the gym, the best type of brain training involves diverse exercises which stimulate and challenge our memory, problem solving, attention-span, reaction time and general mental faculties. Many products are now on the market, based on either computer, internet or handheld devices. Research is starting to show that these may be effective for keeping our cognitive abilities in top form for as long as possible, but much further research is required. It is also worth pointing out that some of the companies behind these products take this endeavour seriously and actively support research, whilst for others it is simply a commercial enterprise. At our institute we have developed a consumer information summary for those interested in more information available at www.brainage.med.unsw.edu.au.

The Three Keys

Perceptive readers would have noted that the main research tool that scientists have used to uncover some of the mysteries of neuroplasticity, environmental enrichment, is actually made up of multiple components. Animals under these conditions enjoy more exercise through the introduction of running wheels, more social company through a bigger cage with more littermates, and more mental stimulation through games, toys, mazes and so forth. Furthermore, research has shown that the beneficial effects of enrichment seem to be more than the sum

of its parts; there appears to be a degree of synergy from combining physical, mental and social stimulation. Similarly, in the examples cited above, activities with a different mix of physical, social and cognitive stimulation appear to be effective at maximizing our brain health and minimising dementia risk. For these reasons, in my recent book I consider in some detail both the art and science of the Three Keys principle for promoting and cultivating brain health — Cognitive, Social and Physical activity (Valenzuela, 2009). For optimal brain fitness, we need to incorporate new activities which satisfy the Three Keys principles into our lifestyles, particularly after retirement. While there is of course no guarantee that we can avoid dementia, by taking on new fun and challenging activities with a cognitive, physical and social component we will be doing a lot to mitigate and minimise this risk.

Given these considerations, and the approaching tidal wave of baby-boomers moving into the 'at-risk' age-range for dementia, a new approach is required. A cost-benefit analysis is needed to calculate the future cost of 'business as usual', versus a whole of government and community focus on preventative mental health, one in which retired Australians can access community-based wellness centres, with facilities for learning, community action and physical activity. Many such groups and organisations of course already exist, but often exist on goodwill alone and may not fully appreciate their own value. I believe that in order to avoid harsh decisions in the future about whether or not we can continue to afford the excellent health system we currently enjoy, initiative such as these — based on the science of neuroplasticity — will become increasingly important.

Summary

Neuroplasticity has revolutionised the science of the brain in the last decade, and will soon begin to revolutionise the way we think about preventative mental health, especially in relation to prevention of dementia. We already understand a great deal about how experience and the world around us can

affect the brain. A range of dynamic and important biological processes are stimulated, starting at the level of molecules and cells, and aggregating to influence cortical brain networks and cognitive and mental function. This exciting scientific journey is sure to continue, with a great challenge understanding how the effects at one level of biological inquiry affects processes at other levels. But an even greater challenge is a socio-political one, about whether we invest now in translating these hard-won scientific gains into preventative mental health policy which in the end will benefit all Australians.

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