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BRAIN RESEARCH REVIEWS

Review

Complex mental activity and the aging brain: Molecular, cellular and cortical network mechanisms

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ABSTRACT

There is strong evidence to suggest that high levels of complex mental activity can improve clinical outcome from brain injury. What are the neurobiological mechanisms underlying this observation? This paper proposes that complex mental activity induces a spectrum of biological changes on brain structure and function which can be best understood in a multiscalar spatiotemporal framework. Short-term molecular changes may include induction of BDNF, NGF and endopeptidase genes and elevation of the high-energy phosphocreatine–creatine resting state equilibrium. Animal models have implicated these processes in the reduction and even reversal of neurodegenerative changes secondary to mental work. These mechanisms can therefore be described as neuroprotective. Medium-term cellular changes are diverse and include neurogenesis, synaptogenesis, angiogenesis and formation of more complex dendritic branching patterns. Importantly, these effects parallel behavioral improvement, and thus a neurogenerative class of mechanisms is implicated. Finally, in the post-lesion context, computation principles such as efficiency, small world connectivity and functional adaptation are identified as important, with supportive clinical evidence from neuroimaging studies. Thus, dynamic compensatory cortical network mechanisms may also be relevant, yet take some time to evolve. This paper will explore the neurobiological and clinical implications of this framework, in particular in the context of age-related brain disease.

Contents

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1. Introduction

> "It is the enormous disparities in degree of mental decline observed among those in late and middle life that constitute the most powerful challenge. On the one hand, there are those exemplified by Casals, Picasso, Bertrand Russell, Verdi and Michaelangelo: creative, intellectually rigorous, active and committed with the fire and intensity of youth to the values and causes that had inspired them through their lives. At the other extreme is the substantial proportion of those already in an advanced state of dementia at 70 and some even in their 40s or 50s.
>
> It is the conviction that there must be causes definable by science underlying such disparities that inspires and sustains the efforts of those engaged in research in this field. Any success they achieve will contribute to freeing old age from the spectre of dying in a state of mental oblivion and so eliminate the worst scourge of our age…"
>
> Sir Martin Roth. *British Medical Bulletin* 1986 (42): p50.

Theorists have long been fascinated by how our environment and past experience can change the brain. The impact of complex mental activity and complex environments has gained increasing interest, particularly in the field of aging and neurodegeneration because of the suggestion that staying mentally active may help in the prevention of cognitive impairment.

From a social science perspective, complex environments have been noted to aid the development and maintenance of higher cognitive abilities by virtue of inherent demand characteristics (for a review of this area, see Schooler et al., 1987). Individuals who excel in the ability to switch between cognitive tasks, who can develop successful task strategies 'on the fly', or make decisions under ambiguous conditions will generally tend to be preferentially rewarded and also challenged with even more complex scenarios. Complex mental activity and complex environments are therefore intimately and reciprocally related. One of the earliest practical illustrations of this was a study in which university students were tested on a standard battery in 1919, 1950 and then in 1961 (Owens et al., 1966). Further education, college specialization, rural to urban migration, and number of hobbies and recreational activities were all found to predict more positive changes in cognitive abilities in subsequent epochs. Autobiographical variables such as years of education, occupational complexity and frequency of cognitive lifestyle activities are hence often used to estimate an individual's level of complex mental activity (Valenzuela and Sachdev, 2006b).

Perhaps the richest data have come from studies of complex mental activity on dementia risk. This phenomenon is commonly referred to as 'brain reserve' or 'cognitive reserve', yet these terms have acquired competing meanings (for contrasting views on these concepts, see Satz et al., 1993, and Stern et al., 2002). A straightforward account suggests that brain or cognitive reserve refers to the epidemiological observation that greater complex mental activity appears to be functionally protective in the context of a brain insult. The mechanisms which may underlie such a brain reserve effect, particularly with reference to brain aging and dementia, will form the focus of this paper.

2. Complex mental activity and dementia risk

If conventional wisdom suggests that the brain, like one's muscles, suffers from disuse, what is the strength of the relationship between mental activity and dementia? A recent meta-analysis of cohort studies which examined the impact of educational level, occupational complexity or cognitive lifestyle activities on incident dementia identified twenty-two studies, including data from over 29,000 individuals (Valenzuela and Sachdev, 2006b). The results were highly consistent: there was an overall relative risk reduction of 46% for high mental activity levels (OR 0.54, CI: 0.49–0.59). Furthermore, the effects of education years (OR 0.53), occupational complexity (OR 0.56) and cognitive lifestyle (OR 0.50) were all in close agreement.

An important conceptual question has been whether cognitive lifestyle is a prospective predictor of dementia, or that drop-off of activities is in fact an early sign of preclinical disease (Gallacher et al., 2005). This question was partially addressed by a second meta-analysis that brought together studies focused on cognitive decline rather than dementia incidence (Valenzuela and Sachdev, 2006a). Importantly, this meta-analysis looked at decline after adjusting for covariates. Individuals with high levels of mental activities were found to have significantly less risk for prospective cognitive decline than those with lower activity levels, complementing the results from the first meta-analysis.

More recent studies have focused on cognitive activity in later life, and suggest that activity at this stage of life may have a beneficial effect independent of earlier experiences. Table 1 summarizes the six cohort studies that have so far replicated a protective effect of approximately 40–50% after simultaneous control for other risk factors, including education level. Moreover, a number of these studies point to a dose-dependent relationship between complex mental activity and dementia risk (see Table 1) (Valenzuela et al., 2006). One study, for example, found that the risk for dementia in a group with a moderate level of leisure activities was 50% compared to the low activity group, while those with the highest activity levels had their risk reduced to 33% (Verghese et al., 2003).

Epidemiological evidence for a clinically meaningful effect for complex mental activity in the area of aging and dementia is persuasive and mounting. This evidence meets many of the risk factor tests proposed by Hall in 1936: association, dose dependency and consistency (Valenzuela and Sachdev, 2006b). The questions of direction and mechanism of causality, however, remain unresolved. In particular, a coherent framework which covers the spectrum of biological changes related to complex mental activity and how this may modulate the development of dementia has been proven elusive.

An important distinction in this regard is level of analysis. At one extreme, complex mental activity may result in the purposive construction of more effective coping strategies, allowing for proficiency in certain tasks to be maintained for a longer period. The opposing extreme may involve epigenetic effects, allowing for higher fidelity protein transcription. Clear cut distinctions between intermediate levels are not straightforward. For the purpose of this review, evidence at the approximate scales of molecule, cell and cortical network will be assessed, with the focus on studies relevant to aging and age-related degenerative brain disease.

3. Rapid-cycle molecular scale mechanisms

In order to better understand molecular changes linked to complex mental activity researchers have over almost four decades investigated the effects of the 'environmental enrichment' paradigm. Enrichment comprises of augmented living conditions, including more space, increased social contact, increased cognitive stimulation through toys, wheels, mazes and so forth, and generally more opportunities for physical activity (Nithianantharajah and Hannan, 2006). As yet there is no 'standard' enrichment paradigm and so close attention to experimental details is required when comparing results. Despite such variability, enrichment appears to produce consistent benefits on measures of cognition, arousal and affect (Nithianantharajah and Hannan, 2006; Rosenzweig and Bennett, 1996; van Praag et al., 1999). Learning and memory

Table 1 – Recent cohort studies of incident dementia as predicted by cognitive lifestyle activities

Author	Predictor	N	Follow-up (years)	Covariates	Adjusted risk	CI
(Wang et al., 2002)	Frequency and type of activities in mental, physical, social, productive and recreational domains	776	6	Age, gender, **education**, **baseline cognition**, co-morbidity, physical functioning, depressive symptoms	0.54	0.34–0.87
(Fratiglioni et al.*, 2000)	Social network summary scale	1203	3	Age, gender, **baseline cognition**, physical function, vascular disease, depression	0.63	0.48–0.83
(Scarmeas et al., 2001)	Participation in past month in a list of 13 intellectual and social activities	1772	2.9	Age, ethnicity, **education**, **occupation**, health limitations, depression, cardiac disease, HT, DM, stroke	0.62	0.46–0.83
(Wilson et al., 2002)	Cognitive activities frequency–time spent in 7 common activities	801	4.5	Age, gender, **education**, **baseline cognition**, depression, comorbidity, APOE	0.67	0.49–0.92
(Fabrigoule et al.*, 1995)	Social and leisure activities — participation and difficulty experienced in 10 common activities	2040	2	Age, cognitive performance, physical activity, **occupation**	0.41	0.18–0.90
(Verghese* et al., 2003, 2003)	Activity days in cognitive tasks (reading, writing, crosswords, playing cards, group discussions, music)	469	5.1	Age, gender, **education**, chronic medical disease, **baseline cognition**	0.48	0.29–0.74

Adjusted risk refers to odds ratio or relative risk after control for covariates. Studies marked with (*) demonstrated dose-dependent effects. Covariate control for pre-retirement or premorbid mental activity levels is shown in bold.

have been of particular interest, with data pointing to between 20 and 40% superior performance when learning spatial information (Kempermann et al., 2002, 2006). Molecular mechanisms which may underpin these higher order benefits are reviewed below.

3.1. *Synaptic plasticity*

Long-term potentiation (LTP) and depression (LTD) play an important role in hippocampus-dependent cognition (Malenka and Bear, 2004). Postmortem hippocampal electrophysiological studies reveal that following 5 weeks of enrichment, significant increases in measures of LTP and LTD are observed (Artola et al., 2006). The molecular machinery of LTP is partly based on post synaptic AMPA receptor change (Malenka and Bear, 2004), and strikingly, upregulation of AMPA receptor proteins is seen following only 5 days of enrichment (Naka et al., 2005). NMDA receptor changes are also implicated, since naive NR2B mice which exhibit enhanced NMDA receptor function, and already perform as well as wild-type enriched mice on a range of cognitive tests, fail to show any further benefit from enrichment themselves (Tang et al., 2001). On the other hand, mice with strategic defects in NMDA receptor function in the hippocampus, which partially abolishes LTP and leads to severe memory deficits in untrained animals, perform as well as control animals after 180 h of enrichment (Rampon et al., 2000b). LTP-related processes in the hippocampus are therefore not likely the full story.

What could be the minimum timescale for enrichment to effect a detectable biological change? Remarkably, one group has found using microarray analysis that as little as 1 h of enrichment induced a range of expression changes, involving genes related to synaptic plasticity as well as neuronal structure, transmission and cell survival (Rampon et al., 2000a).

3.2. *Neurotrophic factors*

Brain-derived neurotrophic factor (BDNF) is a critical hormone in the regulation of neural proliferation and growth during development and for continued cell survival in adulthood (Mohammed et al., 2002). Studies consistently find large increases in BDNF levels after enrichment, particularly in the hippocampus (Mohammed et al., 2002) and after voluntary exercise (Adlard et al., 2004). One year of enrichment, for example, induced a fivefold increase in BDNF levels from 5 ng to 25 ng/g wet tissue (Ickes et al., 2000). More recently, BDNF has been implicated in promotion of *in vivo* neurogenesis (Lee et al., 2002). Knockout out of one BDNF allele also leads to severe deficits in both LTP (Patterson et al., 1996) and experience-dependent synaptogenesis (Genoud et al., 2004). BDNF may therefore have a key role in bridging the effects of complex environments from the molecular scale to the level of synaptic and cellular plasticity.

The closely related nerve growth factor (NGF) is also increased after behavioral stimulation (Pham et al., 1999). NGF has an important function in regulation of cell body size and dendritic arborization and spine density (Sofroniew et al., 2001). The role of NGF in the pathogenesis of Alzheimer's disease (AD) has also been suggested by a series of studies showing the development of AD pathology, neurotoxicity and behavioral changes in NGF transgenic mice (De Rosa et al., 2005). Whether enrichment can reverse AD-like changes in these animals is as yet unknown.

3.3. *Disease modification*

The R6 rodent model of Huntington's disease (HD) contains abnormal amino acid sequences in the *huntington* gene and faithfully replicates many of the features of the human disease (Spires et al., 2004). These mice show neurodegeneration of striatal neuronal populations with associated motor deficits. R6 mice also exhibit profound reductions in BDNF in the basal ganglia, a finding reported in humans with HD (Ferrer et al., 2000). Remarkably, R6 mice exposed to 5 months of environmental enrichment had improved survival, diminished peristriatal atrophy and less motor deficits (Spires et al., 2004). Moreover, these effects were associated with regionally specific rescue of BDNF levels in the striatum, with levels increasing from 60% to 140% of normal levels. Motor performance similarly improved from 60% to 120% of normal.

A number of enrichment studies have now been completed using transgenic "AD" mice with altered amyloid- or tau-protein processing. One study showed a more than 50% reduction in amyloid burden in immature animals exposed to 5 months of enrichment sessions (Lazarov et al., 2005), while another showed an improved behavioral outcome, but increased amyloid burden, resulting from continuous enrichment housing (Janowsky et al., 2005). A third group has found that the cognitive benefit from continuous enrichment in transgenic AD animals may proceed via both amyloid-dependent and independent mechanisms, with the intensity of behavioral testing a potential key factor (Arendash et al., 2004; Costa et al., 2006). Yet another study has found a 38% reduction in amyloid burden secondary to 5-month voluntary wheel running (Adlard et al., 2005). Such widely diverging results may be influenced by the genetic background and age of the animals in these studies, specific transgenic modifications or differences in the particular enrichment protocols. Apolipoprotein (APOE) status may also be relevant given that behavioral and synaptic effects in the hippocampus were limited to APOE4 negative animals in one report (Levi et al., 2003).

A recent finding has been particularly informative because by using a stepwise layering of impoverished, social, physical and enhanced cognitive activity housing, the enrichment effect was broken down into its social, physical, and cognitive subcomponents (Cracchiolo et al., in press). The main result was that only AD mice raised in complete enrichment (i.e., with enhanced cognitive activities) exhibited a trifecta of (i) protection against cognitive impairment, (ii) decreased brain amyloid burden, and (iii) increased hippocampal synaptic immunoreactivity. Intervention with only social or physical activity subcomponents, either alone or in combination, did not lead to any cognitive or neurohistologic benefits. The authors concluded that enhanced cognitive activity is required for these benefits and suggested that humans who emphasize a high lifelong level of cognitive activity should attain the maximal environmental protection against AD.

Interestingly, there is some evidence for disease modification in humans as well. The well-known Nun study showed that the mean number of medial temporal lobe neurofibrillary tangles in those sisters with high levels of complex ideas in

written works from their early 20s was 6.5 per mm^2, compared to 38.7 per mm^2 in sisters with low early life written complexity — a highly significant difference despite similar rates of exposure to other lifestyle and health risks (Snowdon et al., 1996). Some have preferred to argue that this points to a subtle disease process in those with lower grammatical complexity, a process begun more than 50 years before typical symptom onset (Coyle et al., 2003). There is as yet no further human data to arbitrate between these interpretations.

How could mental activity possibly affect the course of AD? Transgenic animal studies focusing on the amyloid pathway suggest that increased amyloid breakdown may be one potential mechanism. A myriad of enrichment-dependent gene expression changes were found using microarray analysis, including augmented expression of neprilysin, a major amyloid breakdown enzyme (Lazarov et al., 2005). Similarly, another group has found a 3-fold increase in the expression of transthyretin, which sequesters amyloid in the kidney and liver, and may do so in the brain as well (Costa et al., 2006). The signal linking increased physiological neural activity to increased amyloid breakdown has yet to be established. BDNF or NGF would be strategically placed to play such a role given their upregulation in response to mental activity (see Fig. 1).

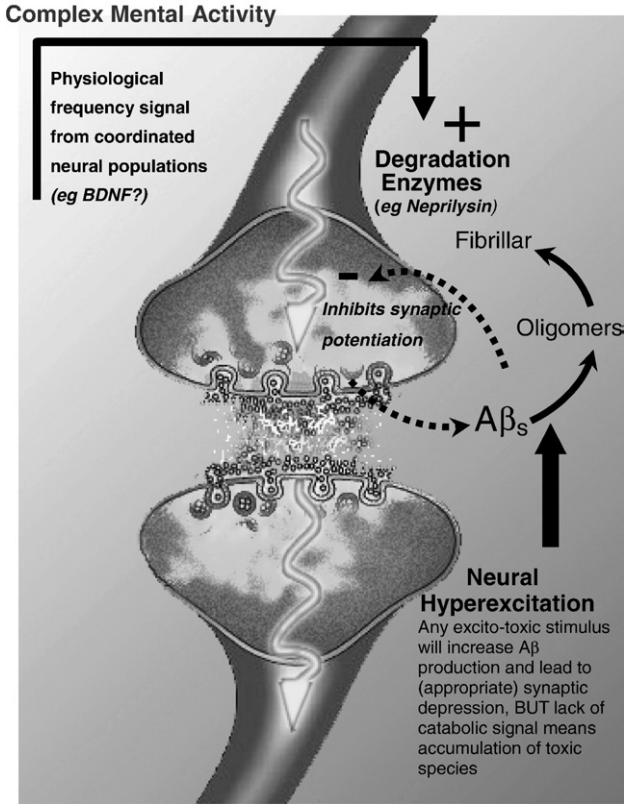

Fig. 1 – Amyloid (Aβs) is produced in response to high-frequency presynaptic stimulation and participates in a physiological negative feedback loop on synaptic potentiation. Excess excitatory stimuli from whatever source may, however, drive this adaptive cycle towards over-production of amyloid species. Cognitive neural activity may be particularly beneficial given evidence for the induction of enzymes related to amyloid plaque breakdown, including neprilysin. The signal linking physiological neural activity and amyloid catabolism is unknown, with the suggestion that BDNF is well placed to mediate such a function.

On the other hand, under certain conditions neural activity appears to also augment the production of beta-amyloid and its parent molecule, amyloid precursor protein (APP). There is for example a close relationship between hyperpolarization of afferent neurons and extracellular APP production in hippocampal circuits when high-frequency stimulation is applied (>30 Hz) (Nitsch et al., 1993). This has recently been demonstrated in an *in vivo* model as well, with increased extracellular beta-amyloid observed within hours of induction of seizure activity (Cirrito et al., 2005). This probably occurs near the synapse, because presynaptic hyperpolarization induces production of beta-amyloid through the beta-secretase pathway and this subsequently inhibits synaptic plasticity (Kamenetz et al., 2003). Participation of beta-amyloid in a physiological 'synaptic dampening' negative feedback loop is therefore plausible (Pearson and Peers, 2006). The role of such an inhibitory loop is not known, but could be protection of the post synaptic neuron from noxious hyperexcitation.

Importantly, studies linking APP production with neural activity have all investigated the impact of epileptiform high-frequency neural activity as opposed to cognitive neural activity, which involves both high and low frequencies (Axmacher et al., 2006). The distinction between experience-dependent versus reactive neural plasticity is potentially quite profound. Increased secretion of APP and beta-amyloid is, for example, a common end point to a variety of noxious stimuli: ischemia (Wakita et al., 1992), brain injury (Emmerling et al., 2000) and seizures (Sheng et al., 1872) increase production of APP and beta-amyloid.

A frequency-specific effect may therefore underlie the apparent paradox. Firstly, complex mental activity may predispose neural firing rates towards the lower end of the frequency spectrum when 'offline', such as during rest or sleep (Peigneux et al., 2004). Secondly, APP and amyloid production could be counteracted by a concomitant increase in amyloid breakdown during normal mentation, however, at persistently higher frequencies this signal may become inactive or ineffective, allowing amyloidogenic build up.

An altogether different molecular mechanism was suggested in a preliminary randomized control trial (RCT) looking at the effect of 5 weeks of systematic memory exercises on the brain biochemistry of older individuals (Valenzuela et al., 2003). Using pre- and post-multi-voxel magnetic resonance spectroscopy, localized increases in phosphocreatine–creatine (PCr) in the medial temporal lobe were found in the training group. PCr works to buffer inorganic phosphorous levels at the subcellular level, particularly crucial for the synthesis of ATP. PCr has been found depleted in the early stages of AD (Valenzuela and Sachdev, 2001) and is neuroprotective in *in vitro* models of neurotoxicity (Brustovetsky et al., 2001). PCr supplementation has been used for years in the sports industry for increased athletic performance — similar increases in cognitive performance also occur, particularly in timed neuropsychological tests (Rae et al., 2003). Beneficial short-term cognitive effect may therefore be related to enhanced supply of high-energy ATP for critical subcellular processes; whether long-

term neuroprotective benefits may also occur due to endogenous upregulation of PCr through complex mental activity is unknown.

3.4. *Summary*

The timescale for molecular change related to enrichment is not fully established, with some evidence for induction of very rapid effects. Although a range of mechanisms are relevant, neuroprotective processes are prominent. Mental activity may also interact with AD-related pathogenesis, perhaps through increased amyloid breakdown or the provision of high-energy molecules. Such a disease-modifying role for complex mental activity remains controversial and will certainly provide much fascinating data.

4. Medium-term cellular scale mechanisms

4.1. *Neurogenesis*

Despite decades of orthodoxy to the contrary, it is now widely appreciated that neurogenesis occurs in mature mammals, including humans. Enrichment specifically increases neurogenesis in the hippocampus (Kempermann et al., 2006; van Praag et al., 2000). Furthermore, it has been shown that induction of neurogenesis in this manner is conserved well into the 'old age' of mice (Kempermann et al., 2002): basal rates of neurogenesis increased by more than 5 times following 10 months of enrichment in 10-month-old rats compared to controls. Nevertheless, there is an overall attrition of neurogenesis with age (Kempermann et al., 2006).

Neurogenesis occurs in the subgranular layer of the dentate gyrus, with newly divided neurons eventually migrating to the granular layer and forming axonal connections to CA3 neurons. Whether neurogenesis is actually more responsive to the physical activity inherent in the enrichment paradigm rather than the cognitive or social activity remains unresolved (van Praag et al., 2000) (Olson et al., 2006). Similarly, there is conflicting data on whether raised neural numbers seen postmortem actually reflect increased neural proliferation or increased cell survival (Kempermann et al., 2006). A recent study, in which radiotherapeutic abolishment of neurogenesis in mice did not cancel the behavioral benefits of enrichment, has questioned whether neurogenesis is actually necessary for such behavioral effects (Meshi et al., 2006). The functional significance of neurogenesis in this context therefore continues to be debated.

At a quantitative level, the rate of production has been estimated at about 9000 neurons per day (Taupin et al., 2007). Hippocampal neurons, in particular in CA3, are however exquisitely sensitive to neurotoxins such as high cortisol level (Gould et al., 1997; Sapolsky et al., 1992). The combined deleterious effects of age, stress and pathology probably far outstrip the regenerative potential of endogenous neurogenesis.

Despite this, some studies implicate neurogenesis with certain types of memory processes (Shors et al., 2001; van Praag et al., 2002) and mood regulation (Jacobs et al., 2000; Malberg et al., 2000). How could a modest number of new neurons contribute to the function of the distributed networks theorized to underpin memory and emotion? Non-linear effects of this type are not uncommon in nature (May et al., 2007), with mathematical theories for so-called 'butterfly effects' based on dynamical systems (Hilborn et al., 2004) and complexity theory (Casti et al., 1994).

A computational example of how a minute alteration to a complex network can change the functional dynamics of the system as a whole is shown in Fig. 2. This simulation illustrates the transmission of information throughout an interconnected system – in this case based on the anatomical connectivity of the medial temporal lobe – via physiologically derived mathematical evolution equations. A rise in neurogenesis was modeled by increasing coupling strength between the dentate gyrus and CA3 by a modest 10%, yet resulted in widespread effects on functional correlations throughout the network. Whether new neurons in the hippocampus actually contribute to *in vivo* computational dynamics in this dramatic way is yet to be established.

4.2. *Synaptogenesis*

Environmental stimulation appears to also induce a prodigious rate of new synapse formation. Quantitative studies have found basal rates increased by 150–200% following 17 weeks of stimulation (Levi et al., 2003). As little as 36 h of enrichment is enough to increase synaptophysin levels by more than 30% in the hippocampus (Frick and Fernandez, 2003).

Generative effects such as these are not without clinical parallels. Using highly labor-intensive Golgi staining methods, Jacobs et al. (1993) and Scheibel et al. (1990) observed that individuals with either more advanced education levels or more sophisticated occupations had more complex dendritic branching patterns in postmortem analysis of the lateral temporal lobe. Microstructural changes of this type have been observed in animal enrichment studies as well throughout the lifespan (Diamond et al., 1988; Ivanco and Greenough, 2000; Kramer et al., 2004).

More fundamentally for AD, loss of synaptic density in the frontal lobe is perhaps the most robust biophysical predictor of premorbid cognitive state. Two independent laboratories have found correlations between these measures and clinical scores in the 0.7–0.8 range (Scheff and Price, 2003; Terry et al., 1991). If complex mental activity over a lifetime can increase the density of synapses in the frontal lobe and other brain areas, then it can be speculated that a greater disease burden will be required before clinical symptoms begin. Such a 'buffer' or linear threshold mechanism has been influential in the development of both brain (Satz et al., 1993; Schofield et al., 2002) and cognitive reserve (Stern et al., 2002) ideas.

4.3. *Angiogenesis*

At rest the brain is the body's most metabolically active organ, with a close relationship between neural activity and vascular supply of metabolic substrates (Magistretti and Pellerin, 1999). It is therefore interesting that production of new blood vessels seems to accompany the trophic effects

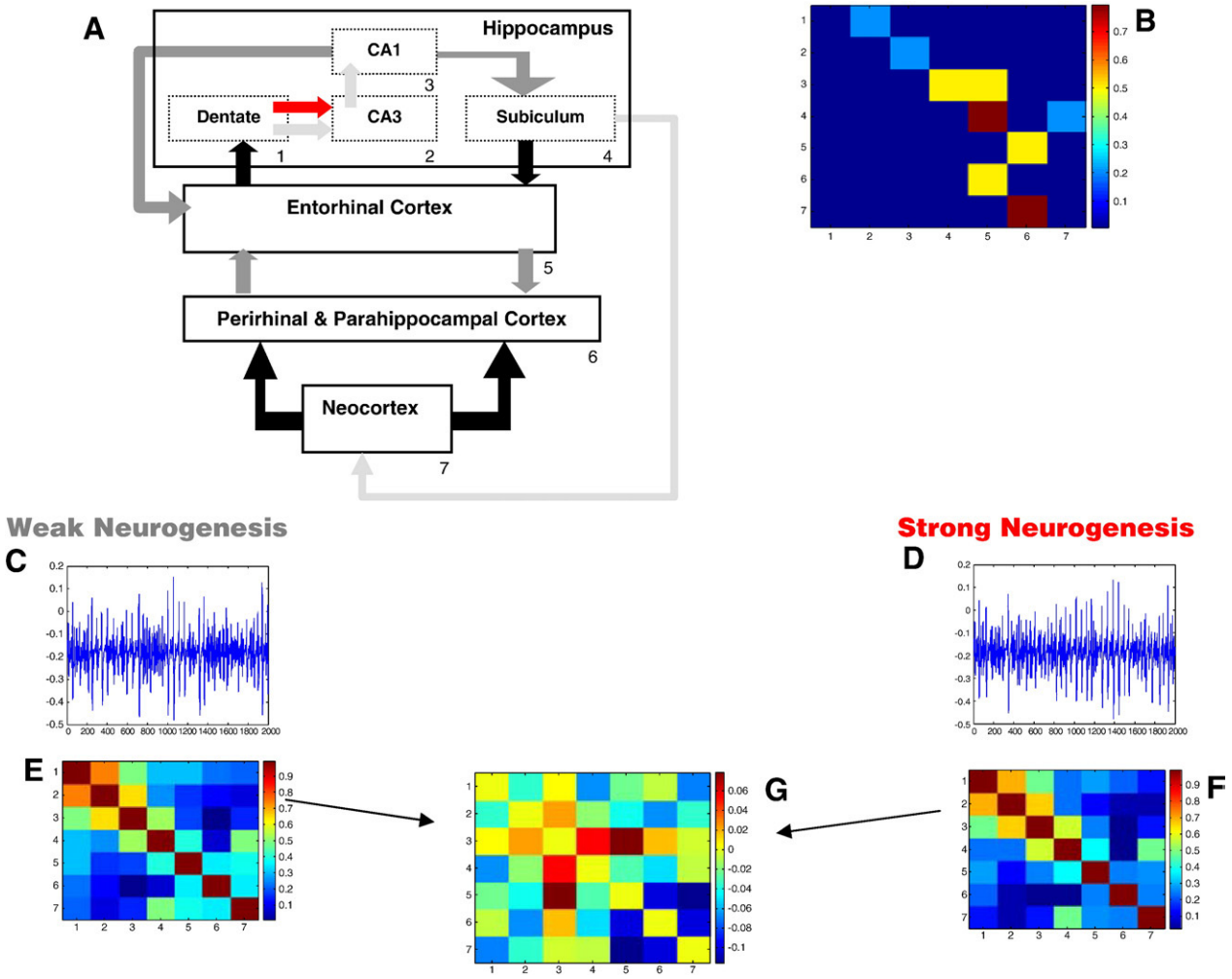

Fig. 2 – Neurogenesis and the Connectivity of Medial Temporal Lobe. A dynamic mathematical simulation was run based on a basic model of medial temporal lobe connectivity (A). Presence and direction of connections were based on neuroanatomical reviews (Rolls, 2000; Lavenex and Amaral, 2000). Strength of inter-regional connections were graded as nil (0), low (0.2), moderate (0.5) or strong (0.8), and were estimated from cell counts within the communicating brain regions (Treves and Rolls, 1994; Patton and McNaughton, 1995). Anatomical connectivity is represented in the model below by the heaviness of the arrow (A) and by the hue brightness in the correlation matrix (B). This correlation matrix represents all possible connections between the 7 brain regions (labelled in A and B). The dynamical equations used here have been described in detail elsewhere (Breakspear et al., 2003). Briefly: (i) Each anatomical region is modelled by a 'node' of densely interconnected local neural units with excitatory and inhibitory elements, which behave and interact under the influence of physiologically derived equations, (ii) Membrane potentials from a node sum to produce a simulated 'local field potential'; (iii) Interactions between local field potentials evolve dynamically over time based on the connectivity pattern between brain regions, allowing a general field potential across the entire system to be calculated as a function of time. This approach has been used recently to explore how the anatomical connectivity of the monkey cortex influences the expression of different functional modes (Honey et al., in press). The overall signal in the case of 'strong' and 'weak' neurogenesis is shown below. This was simulated by altering coupling strength between the dentate→CA3 connection. Weak neurogenesis (C) was modelled by a coupling strength of 0.2; strong neurogenesis used a modest increase in strength to 0.22 (D). The functional connectivity of the dynamical model is also represented in correlation matrix form. Colours of increasing intensity indicate a stronger correlation between the average time-series across the 7 x 7 possible model connections. Panel E shows the matrix under 'weak' neurogenesis conditions and F under 'strong' neurogenesis conditions. Panel G shows the subtraction between these functional connectivity matrixes. This figure illustrates that whilst initial conditions were otherwise conserved, an increase in neurogenesis modelled by a modest increase in anatomical connectivity between two brain regions can have widespread effects on system-wide interdependencies.

on neuron. Angiogenesis in the cerebellum, for example, was found to increase by approximately 30% in a study of 4 weeks of enriched activity, although physical exercise seemed to be more specifically pro-angiogenesis (Black et al., 1990). This may have specific relevance not only to the development of vascular dementia, where ischemic lesions

are believed to disrupt fronto-subcortical neural networks (Obrien et al., 2003), but also AD, given the burgeoning evidence base for a linkage with vascular risk factors (Burke et al., 2007; Kalaria and Ince, 2000). Keeping mentally active may therefore not only increase neural parameters, but also augment vasculature density in metabolically active brain areas.

4.4. *Bulk effect*

The combined trophic consequences of complex mental activity would seem to favor a 'bulk effect'. Indeed, early studies reported that enrichment increased the overall mass of the rodent brain (Altman et al., 1968; Rosenzweig and Bennett, 1969). An influential human study also showed that individuals with high AD disease burden at autopsy, but who were not demented in life, had larger than average cortical neurons (Katzman et al., 1988). Findings such as these led investigators to study whether maximal brain size was associated with a better outcome from brain injury. A number of studies have found, for example, a link between greater head circumference (Borenstein et al., 2001) or intracranial volume (ICV) (Schofield et al., 1995) and reduced risk for dementia. Not all results, however, have been affirmative (Edland et al., 2002; Jenkins et al., 2000). One study found increased risk only for those in the lowest head circumference quintile (Schofield et al., 1997). In the largest cohort study to examine the issue (Borenstein et al., 2001), the association was evident in only those with APOE4 alleles. It may be preferable to consider ICV as a risk factor for dementia only when in the low to very low range, and is perhaps more relevant when in combination with other risk factors.

A criticism on the use of measures such as ICV and head circumference is that they rely on effects limited solely to early life experiences, and so neglect structural plasticity that may remain active across the lifespan. A 3-year longitudinal study has, for example, shown that lifespan mental activity is significantly associated with the rate of hippocampal atrophy (Valenzuela and Sachdev, 2006c). After accounting for a range of possible confounds, including ICV, those with a background of higher mental activity experienced less than half the amount of hippocampal shrinkage over the follow-up period than those with lower activity. Studies showing volumetric brain increases following intensive behavioral training (Draganski et al., 2004), aerobic exercise (Colcombe et al., 2006) and transcranial magnetic stimulation (May et al., 2004) add further support to the notion of gross structural plasticity that is responsive to experience.

4.5. *Summary*

Complex mental activity appears to lead to an increase in neural numbers, as well as their connections and vascular supply. In some case, these effects may together contribute to macroscopic change in regional brain volumes and consequently altered rates of brain atrophy. In general, the temporal scale for these generative mechanisms appears to be slower than that for molecular changes, perhaps in the order of weeks to months.

5. Long-term cortical scale mechanisms

The brain is not a static organ and so it is important in the context of neurodegeneration to understand how cortical activity responds to the disruption of specialized processing areas. Closely related to this is what factors may allow prediction of a better whole-brain response? Recent insights from computational network theory will be introduced to further explore these issues.

5.1. *Small worlds in the brain*

As a form of biological network, the organization of the human brain must address the competing demands of local specialization versus global integration (Tononi et al., 1998). Using graph theory for the analysis of complex networks, a particular type of network was found to exhibit an optimal level of local clustering while conserving long-range interconnectedness (Watts and Stogratz, 1998), collectively termed small world networks. Small world networks are efficient and adaptive solutions to their particular task requirements, and there is now ample evidence for their existence in nature, including the pattern of connectivity in the brain at the neuroanatomical (Sporns and Zwi, 2004) and cortical scales (Salvador et al., 2005; Stam et al., 2004). Interestingly, loss of the optimized characteristics of small world networks has been found in individuals with AD using EEG data (Stam et al., 2007). While the impact of complex mental activity on the brain's small world structure is yet to be established, there is emerging evidence to suggest an effect on the related principles of efficiency and adaptation, as will be reviewed below.

5.2. *Efficiency*

Glucose-labeled PET has been used to show that repeated practice of a complex task – essentially a type of cognitive training – produces a profound change in metabolic efficiency (Haier et al., 1988). Five weeks training on the 'tetris' task not only increased behavioral performance, but also produced a 25–30% reduction in the absolute level of global and regional glucose usage. Similarly, when naive subjects were tested on a complex speeded task, a highly significant inverse correlation was evident between proficiency and brain metabolism ($r = -0.75$) (Haier et al., 1992). Similar inverse associations have also been found between general intelligence and basal rates of glucose metabolism (Alexander et al., 1997). Thus, for a given fixed task, individuals may differ not only on their level of task effectiveness, but also the level of metabolic efficiency by which they realize such effectiveness. Furthermore, these factors are plastic, and can change significantly with practice and experience.

5.3. *Functional adaptation*

In computational neuroscience degeneracy refers to a network's ability to functionally reorganize so as to solve a variety of different problems (Tononi et al., 1999). In order to avoid confusion, this will be referred to as adaptation. Adaptive systems arise in order to balance the competing constraints of maximizing efficiency while maintaining a level of resilience to

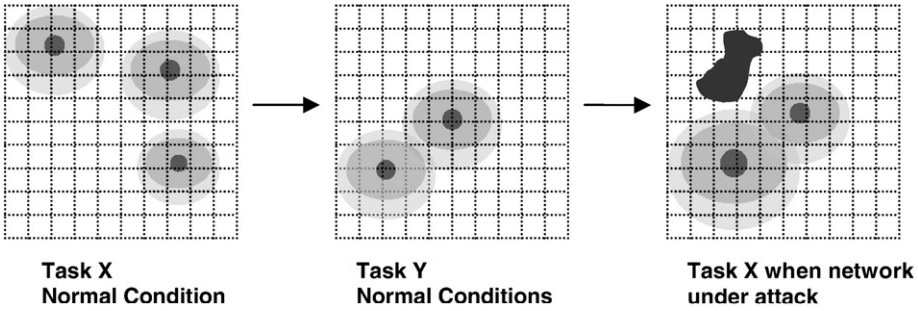

Fig. 3 – Illustration of network adaptation. The background grid refers to the potential crossmatrix between connected neurons, and the colored 'blobs' to focal neural activity in this hypothetical 'brain space'.

'network attack'. This is conceptually depicted in Fig. 3. Before considering this more closely, we first need to understand how complex mental activity may impact on brain network dynamics in the absence of any lesion.

Gradual adaptive changes over a 14-week season of pistol shooting practice by initial novices have, for example, been noted in the form of a higher rate of change in temporal lobe alpha-wave power in the moments prior to the trigger pull (Kerick et al., 2004). Moreover, such cortical adaptations were directly related to increases in shooting accuracy over the season. Using fMRI, Olesen et al. (2004) have shown that 5 weeks of working memory training leads to a selective increase in activity in working-memory-dependent areas, including the mid-frontal gyrus and parietal regions. Similar brain network changes have also been implicated over shorter training time frames (Moore et al., 2006).

Interestingly, while the behavioral advantage afforded by such practice appears to continue for some weeks after the cessation of training, at this timescale no differences in cortical activity between trained and untrained individuals are detectable (Hempel et al., 2004). How such long-term functional benefits are mediated at the cortical level therefore remains a central question for the area. For example, it has been shown that practice on an initial set of cognitive tasks modulates cerebral processing of unrelated tasks in the hour following training, and that furthermore these changes are directly correlated to improvements in subsequent performance of the initial task (Peigneux et al., 2006). At longer timescales post training, there is increasing interest in complex, non-linear 'offline' processing effects, with speculation that consolidation of trained information may involve low-frequency changes at rest (Achard et al., 2006) and during sleep (Peigneux et al., 2004). The full range, timescale and nature of cortical network adaptation in the healthy individual is thus only beginning to be understood.

5.4. *Network responses to lesions*

We will now consider more theoretically two types of possible lesions on task effectiveness and associated network response. The first is the occurrence of a sudden brain insult such as a stroke or closed head injury, occurring in a brain region 'normally' used for solution of Task X. The dimension of task effectiveness, assessed with neuropsychological tests or a clinical scale, will be represented by the line graph.

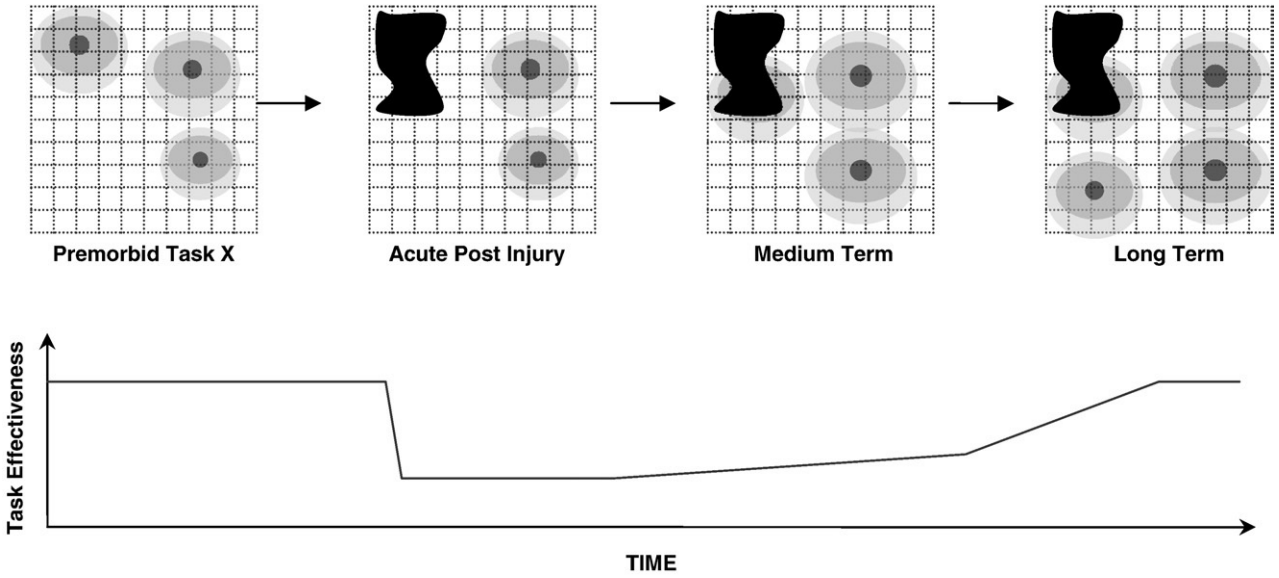

Fig. 4 – Successful network recovery from an acute injury.

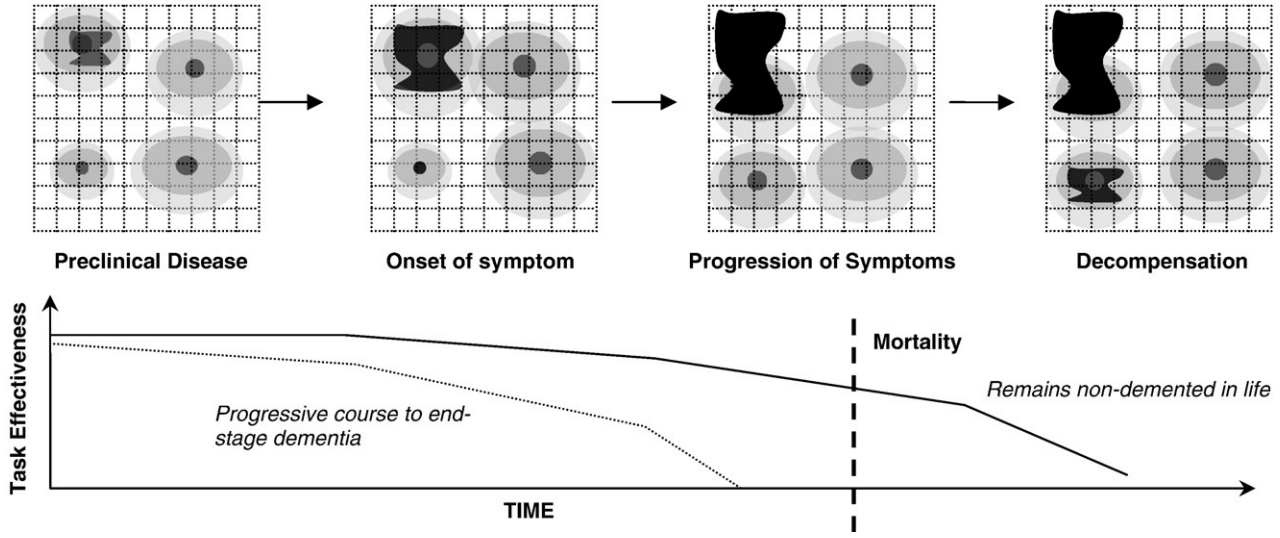

Fig. 5 – Network compensation against a chronic and progressive brain disease. A successful response is shown in the upper series and the darker trace in the line graph below. A hypothetical mortality point shows that successful network compensation could mean that underlying degenerative pathology does not become clinically expressed in life. Contrastingly, a progressive decline to complete dysfunction may occur in the absence of compensation as depicted in the lighter trace in the line graph.

In this example (Fig. 4), an acute injury severely impairs function of a task-related network. Over time, however, ecological demands for task effectiveness drive the system to undergo network adaptation. Network adaptation signifies that zones not originally involved in Task X become recruited for solution of the task. Almost complete functional recovery may therefore be observed in the long term. The converse is also equally plausible: a poor level of adaptation may signify that there is little the system can do to recover lost function and so overall effectiveness remains low.

A very different course is possible in the event of a slowly evolving brain lesion, as occurs in the neurodegenerative diseases. At the preclinical stage, the individual has already instantiated a range of compensatory network changes in order to allow for conservation of task effectiveness (Fig. 5). Increased metabolic work and network adaptation are used in order to counteract the effects of incipient disease. Thus, outwardly no problem may be suspected. At some point, however, compensatory strategies can no longer completely counteract the effects of an evolving lesion, and so the first symptoms may arise. Finally, the natural history of the disease may start to affect those brain areas most directly involved in the compensatory host response, and an acute decompensation may occur. In AD, it is often around this stage that a clinical diagnosis is made. A highly inferior response could lead to little or no compensatory changes, and so onset of symptoms many years earlier. Alternatively, some individuals may possess such robust compensatory resources that they may die from an unrelated somatic cause, never exhibiting the brain disease which had been progressing inexorably, yet silently, below the surface.

5.5. *Clinical applications of network theory*

In the highly publicized case of Dr. Richard Wetherill, this retired university lecturer and chess aficionado became worried about dementia when his usual forward planning of 8 moves in advance was reduced to less than five (Melton, 2005). These concerns prompted neuropsychological tests and structural imaging which eventually ruled out dementia. Remarkably, after a sudden death from unrelated causes, an autopsy revealed a brain riddled with overwhelming levels of plaques and tangles.

Older individuals such as Dr. Wetherill who conserve effective memory performance may be unique for exhibiting bilateral prefrontal activation, as opposed to unilateral activation seen in less competent peers and in younger individuals (Cabeza et al., 1997). Other studies have similarly found that effective memory in early AD is mediated by a prefrontal network that is different from the pattern in healthy individuals (Grady et al., 2003; Rosen et al., 2002). Rypma and colleagues specifically implicate the mid-frontal lobe in effective performance in those older individuals that need more time for task completion (Rypma et al., 2006). These studies suggest that the prefrontal lobe function may be critical for the compensation response, and agree with histological and ultrastructural reports linking cognitive dysfunction in AD with loss of frontal lobe synaptic density (Scheff and Price, 2003; Terry et al., 1991). Not all imaging studies, however, concur on the prefrontal region in the compensation response, with parieto-occipital region also implicated (Stern et al., 2000).

What about brain activity in the medial temporal lobe, the likely site of greatest pathology in early AD? Results have been highly varied, with reports of both decreased and increased activity in the prodromal syndrome of mild cognitive impairment (Dickerson et al., 2005; Machulda et al., 2003). Variation in the BOLD hemodynamic response with age-related disease needs to be carefully considered (D'Esposito et al., 2003). Beyond this, it can be speculated whether increased hippocampal fMRI activity in MCI may represent compensatory neural activity in the affected tissue.

If network response is important to long-term functional outcome, what is the relationship with complex mental activity?

A series of studies from the one group seem to confirm the prediction that individuals with a background complex mental activity require greater disease in order to manifest a given clinical severity. More profound metabolic decrements in the temporo-parietal lobe were seen in those individuals with either greater education, occupational complexity or range of cognitive lifestyle activities for the same level of clinical impairment (Scarmeas et al., 2003; Stern et al., 1992, 1995). Close examination of these studies, however, also reveals systematic increases in brain activity in some brain areas as well. Functional changes in these individuals may therefore represent complex compensatory network alterations rather than the one dimension of disease burden.

5.6. *Are network responses behind a clinicopathological disconnect?*

It is tempting to hypothesize that compensatory network changes may explain the startling disconnect between AD pathology and clinical status. In the most comprehensive community-based postmortem study of its kind, the MRC CFAS group found that over 30% of individuals with moderate to high AD at death were not demented in life (Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study (CFAS), 2001). While compensatory network change could potentially underlie these phenomena, neurogenerative changes could be equally implicated. Distinguishing between these mechanisms will be challenging.

5.7. *Summary*

There exist a number of dynamic compensatory network mechanisms that could potentially counteract the effects of brain injury and disease. The general computational principles of network efficiency, effectiveness, and adaptation are suggested for better understanding these complex processes. The time course for these mechanisms is likely to be in the order of months, as the brain needs time to test and refine new processing networks. Prefrontal brain areas may be vital to successful implementation of such changes and there is emerging evidence that complex mental activity is associated with this adaptive function.

6. Conclusions

6.1. *Theoretical implications*

The terms brain or cognitive reserve are misleading if they suggest a single underlying process, resource or entity. How mental activity affects cognitive function over time seems to involve several processes at different temporal and spatial scales. The multiscalar framework that we propose is presented in Fig. 6. Molecular mechanisms related to neuroprotection, and possibly disease modification, seem to occur at the most rapid timescale. Cellular generative mechanisms may take weeks to manifest. Both classes of mechanisms would appear to conform to a linear threshold principle, in which either more disease or the extended progression of a lesion is required before the onset of clinical symptoms. Compensatory network changes are likely to interact with disease in a non-linear fashion and are best conceived as multi-dimensional. Adaptive network changes take time to occur and, in the context of brain injury, are responsive to a lesion first disrupting normal processing pathways.

The heuristic presented here could be applied to understanding long-term functional outcomes due to any progressive or static brain lesion. In the context of aging which we

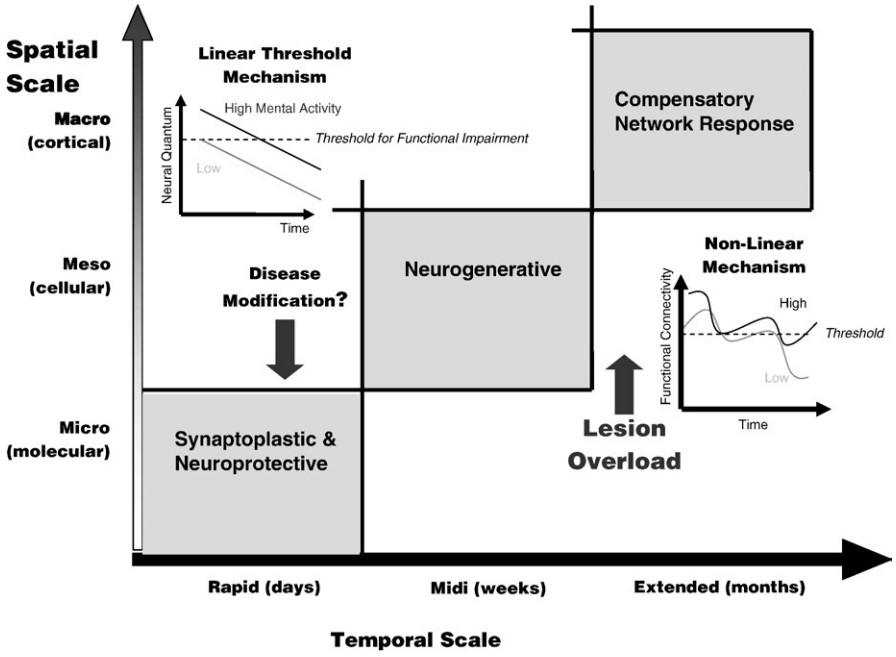

Fig. 6 – A multiscalar spatiotemporal framework for potential mechanisms underlying complex mental activity. Different mechanisms are suggested to be relevant at different time and spatial scales. See text for further explanation.

have focused on, clinical dementia may be better conceptualized as a balance of network compensation versus disease load, rather than simply a build up of the latter.

A significant theoretical challenge for the future will be to more precisely describe how the effects of stimulation at one biophysical level influences and determines effects on higher levels (Breakspear and Stam, 2005). Links between molecular changes and trophic cellular changes are beginning to be clarified, with BDNF a potential critical intermediary (Mohammed et al., 2002). How changes at the more basic levels constrain or direct compensatory network changes is on the other hand almost completely unknown.

6.2. *Clinical implications*

An important practical issue is how to best estimate an individual's level of complex mental activity? In the past, investigators have relied on basic autobiographical data such as highest education level or most complex occupation. More recently, it has been based on how active an older person is at the time, usually in the post-retirement context (see Table 1). These measures emphasize the variety of leisure activities, the frequency of participation, or the inherent level of cognitive challenge in the past-time. We have combined these approaches in the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela and Sachdev, 2007). Overall LEQ score significantly predicted change in general cognition over 18 months ($r=0.37$) as well as over 3 years ($r=0.36$), and is inversely related to the rate of hippocampal atrophy (Valenzuela and Sachdev, 2006c).

Patients and interested individuals often ask 'what activity should I be doing?' This is a challenging question given the general pattern of results from epidemiological studies which do not favor one activity over another. Animal work may be instructive, which has found that for an optimal outcome, animals needed opportunity for cognitive, social and physical activity (Cracchiolo et al., in press). A similar imperative for older adults, particularly post-retirement, seems sensible. The activity also needs to be fun and enjoyable for the individual, because long-term participation is anticipated to be required for the most benefit. Possible examples include learning tai-chi, taking up sailing or learning to dance. Interestingly, of all the physical activities surveyed by Verghese and colleagues for a possible association with reduced risk for incident dementia, only dancing was significant (Verghese et al., 2003).

The strength of the epidemiological, clinical, basic science and neuroimaging evidence seems to strongly support testing whether an intervention of 'complex mental activity' is preventative against development of dementia (Valenzuela et al., 2006). Recent major clinical trials have been promising, finding that a prescribed period of cognitive training can lead to lasting benefits in the specific trained domain (Ball et al., 2002), which may furthermore translate into enduring functional advantages (Willis et al., 2006). Given the precipitous demographic predictions for dementia in modern societies, further trials of this nature should become an urgent priority.

Finally, translation of naturalistic experience-dependent molecular changes into pharmacological cognitomimetics is a potentially promising extension for this area. The finding that enrichment can reverse some of the adverse effects in animal neurodegenerative models, presumably through increased expression of BDNF, has focused research interest on this molecule (Fumagalli et al., 2006). In AD, there are also suggestions that increased amyloid breakdown via induction of neprisylin may be a natural consequence of complex mental activity, and so increasing interest in the therapeutic potential of this pathway is to be expected.

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