Accepted Manuscript

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PII: S0197-4580(13)00612-X

DOI: [10.1016/j.neurobiolaging.2013.11.028](https://doi.org/10.1016/j.neurobiolaging.2013.11.028)

Reference: NBA 8688

To appear in: *Neurobiology of Aging*

Received Date: 29 May 2013

Revised Date: 10 November 2013

Accepted Date: 27 November 2013

Please cite this article as: Robertson, I.H, A Right Hemisphere Role in Cognitive Reserve, *Neurobiology of Aging* (2013), doi: [10.1016/j.neurobiolaging.2013.11.028](https://doi.org/10.1016/j.neurobiolaging.2013.11.028).

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A Right Hemisphere Role in Cognitive Reserve

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Abstract

High levels of education, occupational complexity and/or premorbid intelligence are associated with lower levels of cognitive impairment than would be expected from a given brain pathology. This has been observed across a range of conditions including Alzheimer's Disease (Roe, et al., 2010), stroke (Ojala-Oksala, et al., 2012), traumatic brain injury (Kesler, et al., 2003), and penetrating brain injury (Grafman, 1986). This cluster of factors, which seemingly protect the brain from expressing symptoms of damage, has been termed 'cognitive reserve' (Stern, 2012). The current review considers one possible neural network which may contribute to cognitive reserve. Based on evidence that the neurotransmitter noradrenaline mediates cognitive reserve's protective effects (Robertson, 2013) this review identifies the neuro-cognitive correlates of noradrenergic (NA) activity. These involve a set of inter-related cognitive processes (arousal, sustained attention, response to novelty and awareness) with a strongly right hemisphere, fronto-parietal localization, along with working memory which is also strongly modulated by NA. It is proposed that this set of processes is one plausible candidate for partially mediating the protective effects of cognitive reserve. In addition to its biological effects on brain structure and function, NA function may also facilitate networks for arousal, novelty, attention, awareness and working memory which collectively provide for a set of additional, cognitive, mechanisms that help the brain adapt to age-related changes and disease. It is hypothesized that to the extent that the lateral surface of the right prefrontal lobe and/or the right inferior parietal lobe maintain structural (white and grey matter) and functional integrity and connectivity, cognitive reserve should benefit and behavioral expression of pathological damage should thus be mitigated.

Key Words: Cognitive reserve, Brain Reserve, Alzheimer's Disease, Brain Damage, Brain Disorder, Noradrenaline, Sustained Attention, Novelty, Arousal, Awareness, Aging.

Introduction

High levels of education, occupational complexity and/or premorbid intelligence are associated with lower levels of cognitive impairment than would be expected from a given brain pathology. This has been observed across a range of conditions including Alzheimer's Disease (Roe, et al., 2010), stroke (Ojala-Oksala, et al., 2012), traumatic brain injury (Kesler, et al., 2003), and penetrating brain injury (Grafman, 1986).

This cluster of seemingly protective factors has been termed 'cognitive reserve' (Stern, 2012) and Stern distinguishes between two types of 'reserve'. The first is brain reserve, which refers to differences in brain structure, such as neuronal density (Valenzuela, et al., 2011) which may increase the brain's tolerance of disease. The second is cognitive reserve, which refers to performance differences in cognitive processing which may make the person more likely to maintain cognitive functioning in spite of disease or damage.

A closely related and complementary concept is that of 'brain maintenance', proposed by Nyberg and Colleagues (Nyberg, et al., 2012). Older adults vary in the degree of age-related cellular damage to basic brain structures, according to this theory and these differences are reflected in an age-related increase in variability in cognitive function. Cognitive and brain reserve may mitigate these variations in brain maintenance and are so the concepts of reserve and maintenance are complementary ones.

In a previous paper, the author (Robertson, 2013) proposed the hypothesis that the neurotransmitter noradrenaline offered a candidate mechanism mediating between reserve and reduced risk of diagnosis of AD. Strong support for such a protective role of NA emerged in a recently published study from the Rush Memory and Aging Project, of 165 older adults who

had had brain autopsy following approximately six years of annual cognitive assessments (Wilson, et al., 2013). These researchers found that when modeled together with other brainstem nuclei, only the neural density of the NA-secreting locus coeruleus predicted cognitive decline. While of course this does not rule out the role of other neurotransmitter systems in mediating cognitive reserve, it does provide strong support for highlighting a particular – thought not unique – role of the NA system in cognitive reserve as hypothesized in Robertson (2013).

Noradrenaline mediates the effects of environmental enrichment on neurogenesis and enhanced memory in mice (Veyrac, et al., 2008) and is a neuromodulator which increases synaptic plasticity (Ahissar, et al., 1996). It is also neuroprotective of cholinergic (Traver, et al., 2005) and dopaminergic (Troade, et al., 2001) cells, in part by reducing oxidative stress. Repeated noradrenergic activation over a lifetime may therefore enhance brain reserve both by synaptogenesis and neurogenesis effects, as well as by protecting other crucial neurotransmitter systems such as dopamine and noradrenaline. Cognitive reserve variables such as education, occupational complexity and premorbid intelligence, activate the brain's noradrenaline system and are likely to contribute to increased brain reserve through a well-connected set of networks better able to function under the stress of disease and damage, (Robertson, 2013).

Research on animals suggests furthermore that NA may actually suppress the accumulation of amyloid plaques in the brain, reduce their aggregation, or diminish the inflammatory toxicity of amyloid to surrounding cells (Heneka, et al., 2010). These possible disease-modifying effects of NA will not, however, be discussed further here as the focus of this paper is the identification of one set of candidate cognitive processes which may facilitate the impaired brain's maintenance of cognitive function.

The current paper addresses four main questions:

1. What are the candidate cognitive processes which might contribute to cognitive reserve?
2. Which cognitive processes are most closely linked to noradrenergic function, given NA's proposed role in reserve?
3. What are the neural correlates of these processes?
4. How and why might these particular cognitive processes play a particular role in cognitive reserve?

I will address each of these questions in turn.

1. What are the candidate cognitive processes which might contribute to cognitive reserve?

Stern and colleagues propose three possible types of cognitive processes underlying reserve (Stern, 2009, Stern, 2012). The first, 'neural reserve', is an augmented efficiency and capacity of well-practised skill-specific circuits, which, through the enhanced connectivity from many years of practice, helps maintain a relative invulnerability to neuronal damage. The second, termed 'neural compensation', refers to a set of compensatory processes where different brain areas become engaged in the performance of a particular task due to degradation of the original circuits. The third is one or more hypothetical sets of cognitive processes and associated neural circuits which serve a non-task-specific function which allows the individual to maintain performance across a range of tasks.

Education is a key element of cognitive reserve and education in particular develops the brain's language systems; furthermore language-based semantic memory (Nyberg, et al., 2003) functions are among the few which are preserved or even improved with age. Language functions are also likely to be important in self-regulation (Vygotsky, 1986) and have indeed been a key part of successful cognitive training for brain impairment (Robertson, et al., 1995).

Furthermore, memory encoding has been shown to be strongly associated with left dorsolateral prefrontal cortex function (Grady, et al., 1995).

In this light, it is entirely possible that there may be more than one ‘cognitive reserve network’ of the type proposed by Stern and a language-based self-regulatory system would be a plausible candidate. In the current paper, however, the aim is to identify the network which would arise from a noradrenergically-mediated cognitive reserve system, without ruling out the possibility of other networks (eg language based) linked to other neurotransmitter systems having a separate role in mediating cognitive reserve.

The aim of this review is to identify the candidate mechanisms and neural circuits which underlie one potential network within the third category proposed by Stern – one which can plausibly be linked to the noradrenergic system because of the latter’s hypothesized distinct, though not necessarily unique, role in mediating cognitive reserve (Robertson, 2013).

The justification for focusing on this neurotransmitter over others comes in part from Wilson and colleagues’ evidence in favour of the NA hypothesis (Wilson, et al., 2013). They showed that when modeled together with other brainstem nuclei, only the neural density of the NA-secreting locus coeruleus predicted cognitive decline over a seven year period in a group of older adults. The next question follows directly from this argument: to identify which cognitive processes are most closely linked to NA function.

2. Which cognitive processes are most closely linked to noradrenergic function?

There are four main interlinked types of cognitive process which, the following studies show, have a particularly strong linkage to the NA system. These are arousal/alertness, response to novelty, sustained attention and self-monitoring/error awareness. In addition, a fifth system – working memory – is strongly modulated by the NA system.

Arousal/Alertness

The NA system is part of the brain's arousal system, originating from the locus coeruleus (LC) in the brain stem pons. It is part of what used to be known as "the reticular activating system (Moruzzi and Magoun, 1949) and changes in NA/LC activity precede variations in arousal/alertness such as in sleep-wake cycles (Aston-Jones and Bloom, 1981). In a state of quiet wakefulness, neurons in the LC fire at around 1Hz, but in the presence of an arousing stimuli they show 'phasic bursts' of firing. With drowsiness the firing declines below 1Hz and decline even further during slow wave sleep. The evidence for NA's role in arousal is abundant, consistent and strong and does not have to be reviewed here as it is well reviewed elsewhere (Aston-Jones and Cohen, 2005, Samuels and Szabadi, 2008, Sara, 2009).

Human studies where NA activity is pharmacologically manipulated confirm that reducing NA levels reduces arousal/alertness in humans (Coull, et al., 2004). They also show that raising NA activity, with agents such as atomoxetine, increase arousal (Barry, et al., 2009, Graf, et al., 2011, Ripley, 2006). Finally, pupil dilation may index NA activity in humans and, to the extent that it does, it shows the classic decrement in alertness that occurs over the course of a monotonous task (Gabay, et al., 2011, Murphy, et al., 2011). Spectral power measures in the EEG (Dockree, et al., 2005, Makeig and Inlow, 1993) also can be used to assess arousal and these are also noradrenergically sensitive (Sebban, et al., 1999).

Response to Novelty

Novelty provides a key trigger for arousal and it is therefore not surprising to find that LC/NA activity occurs strongly in response to novel stimuli (Kitchigina, 1997, McQuade, et al., 1999, Pudovkina, et al., 2001, Vankov, et al., 1995). Human genetic studies have shown that processing novel stimuli, as measured by EEG ERP P300 responses, is associated with genes influencing noradrenergic availability (Liu, et al., 2009). This accords with strong evidence that

the P3A novelty response is strongly linked to noradrenergic activity (Nieuwenhuis, et al., 2005, Polich, 2007). Novelty response, in summary, has strong linkage to the NA system.

Sustained Attention

Just as novelty triggers arousal, so both novelty and arousal activate attention. Although the NA system has widespread projections throughout the brain, they are particularly dense in areas involved in attention, notably the parietal cortices, the superior colliculus and the pulvinar nucleus, among others (Morrison and Foote, 1986). The leading theorists of NA function are unanimous in linking NA function specifically to attentional salience.

Attention is not, however, unitary, and there are three proposed separate supramodal attentional systems in the brain, for selective attention, attentional control/switching and alertness or vigilant/sustained attention respectively (Posner and Petersen, 1990). It is this third type of attention which has been linked most closely to NA function with the control/switching and selective systems being hypothetically linked to the dopamine and cholinergic systems respectively (Posner and Rothbart, 2007).

LC neurons fire as soon as attentionally-relevant targets appear (Aston-Jones, et al., 1994) and in humans, pharmacological down-regulation of the NA system results in decreases in sustained attention (Coull, et al., 2004). Pharmacological up-regulation of the NA system, on the other hand, results in improvements in sustained attention, including its closely-associated function, inhibitory control (Chamberlain, et al., 2007, Grefkes, et al., 2010).

Sustained attention's link to the NA system has also been confirmed by cognitive genomic research. The Sustained Attention to Response Test (SART) has been shown, to be associated with a DBH C-1021T marker in both children with attention deficit hyperactivity disorder (ADHD) (Bellgrove, et al., 2006) and in healthy adults (Greene, et al., 2009). The balance of

dopamine and noradrenaline in the cortex is influenced by the DBH gene and thus the T allele at this locus is hypothesized to result in a slower rate of dopamine to noradrenaline conversion than the C allele. Both ADHD children, and health adults who had one or two copies of the T allele made more errors of commission on the SART which is indicative of lapses in sustained attention. Another well-established measure of sustained attention is the Continuous Performance Test (CPT) (Cornblatt, et al., 1988) which is also sensitive to NA levels in the brain (Kollins, et al., 2008).

It is thus plausible to suggest that the third cognitive process strongly associated with NA activity is sustained attention.

Error awareness/self-monitoring.

Self-monitoring refers to the accurate, conscious representation of one's own behavior, when validated against either objectively measured performance, or the assessments of people who know you well. Error awareness is a specific aspect of self-monitoring pertaining to the ability to detect mistakes.

A number of studies have confirmed highly specific linkages between error awareness and the NA system. One recent study, for example, showed that atomoxetine, a selective noradrenaline reuptake inhibitor, specifically increased the error signal in inferior frontal and supplementary motor areas in an fMRI study in healthy volunteers (Graf, et al., 2011). Another study confirmed this finding using EEG ERP methodology, finding that yohimbine, which increases LC/NA activity, specifically increased the ERP error-related negativity without having any effect on the other major ERP components. (Riba, et al., 2005)

A third study showed that reboxetine-triggered NA activation increases pupil dilation (Phillips, et al., 2000) which is in line with the hypothesis outlined above that attentionally-triggered

pupil dilation may index NA activity in the human brain. A further study (Wessel, et al., 2011) also showed a very specific linkage between aware (but not unaware) errors and pupil dilation in healthy adults. It is thus proposed that the fourth cognitive process linked to NA, is self-monitoring/error awareness.

Working Memory

Working memory has a privileged role in many higher level cognitive processes, including reasoning, problem-solving, distractibility, executive functions and fluid intelligence among many others (Carpenter, et al., 1990, Unsworth and Engle, 2005); it is particularly sensitive the effects of aging (Grady, et al., 1998, Nyberg, et al., 2010).

Working memory involves the temporary storage and manipulation of changing information and depends on intact prefrontal cortex and striatal functioning (Dahlin, et al., 2008). Prefrontal cortex cells in aging monkeys decline in their ability to maintain the firing of neurons which temporarily store information and this has widespread consequences for a range of tasks. The mechanism for this, according to Wang and colleagues, is age-related increases in cyclic-AMP signaling, which reduces the persistent neural firing via the opening of certain cellular potassium channels. Noradrenaline is known to inhibit cyclic-AMP signalling, and Wang and colleagues demonstrated that giving the selective α_{2A} receptor agonist guanfacine to the aged monkeys improved the neural delay firing and increased their working memory capacity the level of young monkeys.

Increased NA activity in the brain, then, has additional effects to those associated with novelty, attention, arousal and self-monitoring, effects likely to have consequences on the majority of higher cognitive functions.

3. What are the neural correlates of these processes?

These processes – arousal, novelty, sustained attention, self-monitoring and working memory – are all quite specifically affected by changes in noradrenergic activity, and vice versa. There is however a further linkage between them through a common neuroanatomical circuitry. Three of these variables (sustained attention, novelty and alertness/arousal) were subjected to a thorough meta-analysis (Singh-Curry and Husain, 2009) which showed convincingly that each were underpinned by a very similar network in the brain, namely the right dorsolateral prefrontal cortex and the right inferior parietal lobule.

The fourth process – self-monitoring – has been linked strongly to one part of the same network, the right dorsolateral prefrontal cortex (Stuss, 2011). In change blindness studies, where healthy participants were at times aware of a change to a masked stimulus and sometimes not, activation of the right fronto-parietal network distinguished consciously detected changes from those not detected (Beck, et al., 2001) and it is also a key part of a network that distinguishes errors which are consciously recognized versus those that are not in error detection studies (Hester, et al., 2005).

In clinical studies with a range of different types of abnormal brain processes, a common method for assessing awareness is by comparing self-report of deficits with those of close relatives. A remarkable consistency exists across diverse conditions suggesting a privileged role of the right dorsolateral prefrontal cortex in mediating accurate self-monitoring of deficits in conditions as Alzheimer's Disease (Harwood, et al., 2005), post-stroke hemiplegia (Pia, et al., 2004), traumatic brain injury (Schmitz et al, 2006) schizophrenia (Shad, Muddasani, & Keshavan, 2006) and focal lesions (Hoerold, et al., 2013, Stuss, 2011).

A comparable analysis of a common underlying neural network underpinning four different, but related cognitive functions has been carried out (Naghavi and Nyberg, 2005). In a

review of a large number of imaging studies, they showed that episodic memory, working memory, attention and conscious visual perception all showed a strong overlapping network of activation involving bilateral fronto-parietal cortices. Interestingly, for each of these functions, only the right sided activations of the more anterior aspects (BA 9) of the prefrontal cortex were associated with each of the four processes, with the left prefrontal activations being confined to more posterior regions (BA 6). Furthermore, noradrenaline plays a significant, but not exclusive role in episodic memory formation (McIntyre, et al., 2012) and the evidence reviewed above shows that it plays a major role in attention and working memory. The phenomenon of conscious visual perception clearly maps onto that of awareness which, as reviewed above, also has a privileged linkage to the NA system.

There is therefore a strong overlap between the processes outlined above and those proposed by Naghaz and Nyberg to have a common fronto-parietal underpinning. Their concept of ‘attention’ however, is more general and less specific than that of ‘sustained attention’ which has been shown to be strongly lateralised in the right hemisphere (Singh-Curry and Husain, 2009) which explains the less lateralized (with the exception of the anterior prefrontal cortex) activations of these more general attention functions.

The networks activated by ‘conscious visual perception’ in the Naghaz and Nyberg review show a bilateral activation as well, but again with the exception of the more anterior right dorsolateral prefrontal cortex which appears to play a specialised role in this type of awareness, in accord with the conclusions relating to awareness. The same is true for working memory.

Only one of Naghaz and Nyberg’s processes – episodic memory – does not map onto the networks outlined in the current paper. But again, the particular role of the more anterior right dorsolateral prefrontal cortex emerges from their review, which may be explained by

the requirement for sustaining a ‘retrieval mode’ in many memory tasks (Henson, et al., 1999) and which draws on a sustained attention system which has been shown (see above) to be strongly right lateralised.

In summary, the three sets of cognitive processes – arousal/alertness, novelty, and attention all share a common right hemisphere fronto-parietal network, while the fourth and fifth, awareness and working memory respectively, share at least the more anterior, frontal part of that network. Furthermore, the NA-sensitive SART test, sensitive to variations in NA availability (Bellgrove, et al., 2006, Greene, et al., 2009) and associated with right dFPLC-parietal activation (Manly, et al., 2003, O'Connor, et al., 2011) has also been shown to be selectively impaired by lesions to the right inferior frontal gyrus (Molenberghs, et al., 2009), which further cements the associations observed. Finally when NA is pharmacologically up-regulated, the dominant alterations in neural activation include the right dorsolateral prefrontal cortex (Chamberlain, et al., 2007, Grefkes, et al., 2010).

These NA-linked cognitive processes thus provide a strong basis on which to address the question as to a possible role for this network in mediating some of the protective effects of cognitive reserve in Alzheimer’s Disease and other conditions. Given the strongly right hemisphere-biased nature of these candidate processes, is there any evidence that the right hemisphere of the brain is particularly susceptible to aging?

The right hemisphere aging hypothesis (Brown and Jaffe, 1975) was based on a number of observations that right-hemisphere-based cognitive and perceptual tasks appeared to decline more readily with age than did left-hemisphere based language and perceptual tasks. This account was questioned by a swathe of imaging studies and a number of influential reviews (Cabeza, 2002, Dolcos, et al., 2002) which suggested a bilateralization of function in the older brain, rather than any more pronounced unilateral decline in right hemisphere function.

Meanwhile the HAROLD model proposed by Cabeza and colleagues (Cabeza, 2002) suggested that those functions which were lateralized in either hemisphere in young people tended to be bilaterally represented in older people. Dolcos, Rice and Cabeza did however propose that the HAROLD model was not incompatible with the right brain aging model and that both might apply (Dolcos, et al., 2002). Nevertheless, the right brain aging theory has become largely ignored, being replaced by the HAROLD model.

There is, however, a number of studies suggest that hemispheric changes with age involve the right hemisphere more than the left. One early study (Clark and Knowles, 1973) examined memory for dichotically presented stimuli and found an age-related decline which was significantly greater for left- than for right- ear presented stimuli, suggesting an age-related impairment not attributable to peripheral hearing loss and which affected the right hemisphere in older people. In another study (Cherry and Hellige, 1999), involving letter matching tasks which could be carried out within and/or between hemispheres, it was found that while the young showed a clear right hemifield/left hemisphere advantage, the older adults showed no such advantage, leading the authors to conclude that there had been greater age-related declines in right over left hemisphere function.

A number of imaging studies have also provided results suggesting that the right hemisphere theory of aging should not be rejected. the Dallas Lifespan Brain Study found that, when young and old participants were compared , the old had significantly lower cerebral blood flow, particularly in the right prefrontal region, compared to younger participants (Lu, et al., 2011). Another study (Small, et al., 2000) discovered that healthy 50-84 year older adults who were APOE-4 positive showed a PET-measured cerebral metabolic decline over a 2 year period while APOE-4 negative participants did not. This decline was particularly marked in the right hemisphere of the brain, and there was an associated drop in episodic memory performance. Notably, the size of the drop in performance over two years was significantly correlated with

metabolic rates in the right inferior parietal lobule only in the APOE-4 positive group, but not in the APOE-4 negative group.

A further study (Brickman, et al., 2006) examined white matter volumes in a large group of old and young participants and found that age was associated with particularly large reductions in prefrontal white matter volume in older participants. Strikingly, they found that it was the volume of white matter in the right prefrontal cortex which predicted neuropsychological test performance, including verbal memory, verbal fluency and attentional tests.

A six year follow up of a cohort of healthy older adults (Nyberg, et al., 2010) unusually studied longitudinal patterns in fMRI performance on incidental episodic encoding task. In contrast to common cross-sectional findings whereby older adults show increased - putatively compensatory - recruitment in frontal regions as would be in line with the HAROLD model, Nyberg et al., showed that the opposite was the case when the same participants were followed up over a 6 year period. Participants showed consistently *lower* recruitment on second testing on this memory paradigm, and the drop in recruitment was particularly prominent in the right dorsolateral prefrontal cortex. This finding leads to some doubt in the validity of cross-sectional studies of aging, as these researchers showed comparable effects for structural imaging, and indeed for behavioral memory performance measures themselves (Rönnlund et al 2005).

There are, however, many studies which fail to show a clear right hemisphere lateralization for aging rendering the account still very much hypothetical (Cabeza, 2002, Dolcos, et al., 2002). Apart from the possible problems of the cross-sectional studies which Nyberg identified, one other possible factor could be gender, albeit that this is suggested in only a single study by Chen et al (Chen, et al., 2011). This showed that spatial bias, which in younger people is left biased because of the right hemisphere dominance for spatial processing, changes to a right bias in older men but not older women, who remain left biased.

The evidence is thus mixed regarding a right hemisphere theory of aging but the existence of a hypothetical right hemisphere network which contributes (albeit not necessarily uniquely) to cognitive reserve does not depend on the validity of the notion of a specific vulnerability to the right hemisphere to the aging process: cognitive aging could still be rather general but still be mitigated by a more specialized and lateralized network.

A related question concerns whether there is a lateralization of noradrenaline in the brain. While a primate study found strong evidence of greater NA levels in the right thalamus than the left (Oke, et al., 1978), there are not enough studies to justify the claim that NA is right-lateralised. An incomplete review of the evidence (Fitzgerald, 2012) purporting to show a right hemisphere dominance for serotonin and a left hemisphere dominance for NA in fact only shows evidence for serotonin and not for noradrenaline. What there *is* evidence of – contrary to the conclusion of the paper – is that up-regulating the NA system in humans results in a strong and clear right hemisphere effect (Grefkes, et al., 2010) consistent with another study reviewed above in the present paper but not cited in the Fitzgerald paper (Chamberlain, et al., 2009). This may be because noradrenaline has particular effects on cognitive functions such as novelty processing and sustained attention which happen to be based in right hemisphere networks. Up-regulating these networks through pharmacologically-induced increased NA activity increases processing which is reflected in increased right hemisphere activity, it is proposed.

In summary, noradrenaline has been implicated as playing a role in cognitive reserve. The neural circuits closely associated with noradrenaline have a strongly right hemisphere base, and in particular right fronto-parietal, lateralization.

4. How and why might these particular cognitive processes play a particular role in cognitive reserve?

Having established the case for a right fronto-parietal lateralization for the cognitive processes in question, it is now possible to consider whether, in addition to its biological effects on brain structure and function (Robertson, 2013), optimal NA function provides a set of additional, cognitive, mechanisms that help the brain adapt to age-related changes and disease. The working hypothesis is that the extent of structural (white and grey matter) and functional integrity (connectivity,) of the lateral surface of the right prefrontal lobe and/or the right inferior parietal lobe, should partially predict cognitive reserve, perhaps together with other possible candidate language-based, networks, and to the ability to mitigate the psychological consequence of pathological changes in patients with the same condition.

To test this hypothesis requires demonstrating that the four NA-linked processes are empirically linked to the known cognitive reserve-related variables such as education and environmental complexity. The following section considers each of these in turn.

Arousal/alertness

In 1908, Yerkes and Dodson studied the effects of different degrees of arousal (by varying the degree of shock) on the ability of mice to discriminate between the luminance of two compartments (Yerkes and Dodson, 1908). They found that where lightness levels were easily discriminated, the mice performed better at high levels of arousal, whereas difficult light discriminations were best learned at low levels of arousal. On the basis of these experiments, they formulated the Yerkes-Dodson law. This law proposed that any task will have an optimal level of arousal below and beyond which performance will decline; they hypothesised this optimal level is lower in challenging tasks than in routine tasks. Similarly, Broadbent (1971) showed that while stress can improve performance on routine, non-demanding tasks, the same levels of stress can impair performance on more complex and demanding tasks.

While acknowledging that there are many different neurotransmitters associated with arousal, locus coeruleus-mediated noradrenergic activation is a key element, whose action firstly, enhances signal to noise ratio of the neural signals underpinning perceptual and cognitive representations, and secondly, increases error rate, particularly at high levels of NA activation (Aston-Jones and Cohen, 2005, Sara, 2009). Arousal varies with circadian rhythms and shows an inverted U function such that performance is impaired when NA levels are both below and above optimal levels (Aston-Jones and Cohen, 2005), exactly as the Yerkes-Dodson function would predict. The term '*alerting*', used by Posner and Petersen in their seminal article on the attention systems of the brain (Posner and Petersen, 1990a), is approximately co-terminous with the above working definition of arousal, albeit that '*alerting*' has connotations of the behavioural (e.g. reaction time shortening contingent on phasic '*alerting*' stimuli), as well as on the phenomenological ('feeling alert') aspects of the more biologically defined concept of 'arousal'.

In a comprehensive review of catecholamine modulation of prefrontal cognitive function, Arnsten (1998) showed that many studies confirmed a Yerkes-Dodson type inverted-U relationship between levels of noradrenaline release on the one hand and behavioural performance on the other.

When older adults successfully maintain near-optimal levels of arousal/alertness, then cognitive performance should also be maintained at higher levels compared to a situation in which arousal levels are too low or too high. This is true across many types of cognitive function including sustained attention (Manly, et al., 2002b), memory (Cahill, et al., 2003, Finn and Roediger, 2012), reasoning (Folkard, 1975), executive function (Manly, et al., 2002a) and spatial attention (Robertson, et al., 1998).

Arousal/alertness therefore can plausibly be linked to cognitive reserve, insofar as optimal level of arousal has far-reaching effects on a wide range of cognitive functions. It could therefore reasonably be expected to contribute to a reserve-linked neural network which mitigates the effects of disease on those cognitive symptoms on which the diagnosis of Alzheimer's Disease depends.

Novelty

As illustrated above, novel stimuli or situations trigger NA activity and activate predominantly right fronto-parietal regions of the brain. They are thus closely linked to the arousal/alertness network just described. However novelty requires distinct consideration since arousal/alertness can be produced by stimuli which are not necessarily novel but which are nevertheless arousing, such as emotional or challenging stimuli. Furthermore, novelty is not completely determined by the stimulus or situation itself, but perhaps equally by the individual's perception of that stimulus: for instance, a curious person can find novelty in a situation or stimulus which an incurious individual may not, and their NA-linked networks will respond accordingly differently. For this reason curiosity and responses to the same 'novel' stimuli will be considered different in different people. Nevertheless, repeated experiences of novel stimuli and situations will increase arousal and alertness, as documented above, and novelty as such may contribute to a cognitive reserve network via the arousal/alertness mechanisms already outlined.

But what about individual differences in response to novelty? Self-reported curiosity independently predicts academic performance over and above measured intelligence and assessed effort (von Stumm, et al., 2011). Older adults' measured curiosity levels predict their mortality over and above other measured cognitive, demographic and medical variables (Swan and Carmelli, 1996). Response to novelty also distinguishes high-cognitively-performing older

people from their less-well performing peers: they both look significantly longer at novel stimuli which are presented in the course of an attentional task, and they show significantly elevated P300 ERP responses to these novel stimuli (Daffner, et al., 2006). These authors previously showed that these same measures – length of time viewing novel stimuli and P300 response to them, were characteristic of the responses of patients with frontal lobe lesions. They further showed that these measures correlated significantly with the degree of apathy shown by the patients. There is also strong evidence that curiosity is lower among older adults people when compared with younger ones, and one study found that that over a six year period curiosity declined significantly in the older participants (Giambra, et al., 1992).

Exposure to novel stimuli and situations throughout life could plausibly enhance arousal/alertness directly and hence increase cognitive reserve by boosting cognitive function more generally. But individual differences in curiosity may enhance these novelty effects, thus offering an additional augmentation of the NA-linked novelty network response in the right hemisphere and thus further enhancing reserve.

Sustained Attention

Attention is defined as the capacity to selectively allocate processing resources to particular stimuli or classes of stimuli. There are many different ways in which the brain does this, and these can be broadly arranged into a continuum according to which the allocation is driven by bottom-up, externally driven factors, at one end versus top-down, internally driven factors, at the other. If a truck horn blares as I am about to step off the road, all my processing resources will be allocated to the relevant stimuli in an almost entirely bottom-up way. If I am proof-reading this article for minor typographical errors, on the other hand, the attention required for this tedious task is almost entirely dependent on top-down.

As described above, there are at least three different supramodal attentional systems for selection, control and vigilance respectively, but it is only the latter which has a strong linkage to NA activity and a clear right hemisphere fronto-parietal neural basis as shown in many studies (Manly, et al., 2003, Paus, et al., 1997, Sturm, et al., 1999). This network monitors and modulates activity in subcortical regions governing arousal to match current task demands (Critchley, et al., 2002, Foucher, et al., 2004). The appearance of a low-probability target stimulus among foils leads to increased LC activity and widespread noradrenergic release (Berridge, 2008). The influence of the LC system in humans was demonstrated in a study showing that suppressing the release of noradrenaline through clonidine administration resulted in the sorts of attentional lapses that are characteristic of diminished vigilant attention (Smith and Nutt, 1996).

Experience-dependent cortical-plasticity is ‘gated’ by attention. Experience-dependent cortical-plasticity is ‘gated’ by attention. Recanzone and colleagues showed that experience-dependent changes in sensory-maps did not re-map if the animal was rewarded to attend to a second, auditory task (Recanzone, Schreiner et al. 1992). In line with such findings, a number of human studies suggest that the ability to sustain attention is an important factor in determining recovery of motor and other functions following stroke (Ben-Yishay, et al., 1968, Blanc-Garin, 1994).

Furthermore motor recovery following stroke over a 2-year period was significantly predicted by measures of sustained attention taken 2 months after right hemisphere stroke. Specifically, the ability to sustain attention to a tone counting task (a validated measure of sustained attention which is related to right frontal function) at two months post-stroke predicted not only everyday life function 2 years later, but also the functional dexterity of the left hand in a pegboard task (Robertson, et al., 1997).

It is for similar reasons that sustained attention is a good candidate for mediating some of the effects of cognitive reserve. To the extent that this capacity is preserved in older people, and given the ‘gating’ function of attention on experience-dependent plasticity, then social, educational and environmental challenge will have a stronger plasticity-affording effect on the brains of individuals whose capacity for sustained attention to these factors is high.

Attention increases neural firing in primary and secondary sensory cortices, thus augmenting the degree of cortical excitation produced by a given stimulus (Luck, et al., 1997, Mishra, et al., 2011, Woldorff, et al., 1993). Attentive older people, therefore, will by necessity experience greater ‘enrichment’ from a given set of environmental contingencies because their enhanced attention will gate the neural responses to these and enhance the overall effects on their brains.

Sustained attention, along with arousal and novelty, therefore, is empirically an excellent candidate for mediating at least some of cognitive reserve’s protective effects.

Self-monitoring/error awareness

It is very difficult to compensate for underperformance of which one is not consciously aware. If I am unaware that I am prone to absent-minded errors for instance, then I will be much less likely to take remedial action to try to compensate for the problem. Accurate monitoring of one’s abilities – and of the associated errors and underperformance – are crucial for taking compensatory action such as taking extra care, using reminder strategies or putting in extra effort to be less absent-minded. It is likely that successful aging requires compensatory adjustments to mitigate even small declines in neural integrity (see ‘brain maintenance’ above) which are likely to be present even in successful, high performing older adults.

The extent of recovery from brain damage is strongly predicted by the degree of deficit awareness across a range of conditions (Robertson and Murre, 1999) and it is therefore highly

likely that this principle will apply to age-related cognitive decline. A number of studies have, for instance, shown strong evidence of reduced electrophysiological responses to errors in old versus young adults (Mathalon, et al., 2003, Nieuwenhuis, et al., 2002, Schreiber, et al., 2012). We (Harty, et al., in press) found that, even with performance equated between young and old, older people were extremely less likely to be aware of the errors they made in a Stroop-like task than young people. Furthermore, the degree of objectively measured laboratory error unawareness correlated significantly with discrepancy scores between self- and other-reports of attention and memory failures.

Furthermore, some studies have shown that awareness and cognitive reserve are significantly associated. One such study for instance (Suchy, et al., 2011) found that high cognitive reserve was associated with lower discrepancy scores in self- and other- ratings of everyday life performance among healthy adults. A further study in individuals with questionable or mild dementia also showed a strong association between high cognitive reserve and high awareness of deficits (Spitznagel, 2005). Finally, low awareness of deficits in individuals with Alzheimer's Disease is associated with low rated ability to make decisions about their medication (Cosentino, et al., 2011).

Awareness – and particularly awareness of errors and performance – then, is the fourth cognitive process which can be associated with a putative cognitive reserve network. Furthermore, it has been shown to be empirically associated with cognitive reserve. Given the central importance of error-feedback in learning (Rumelhart, et al., 1986), there are strong grounds to predict that low error awareness will result in low levels of compensatory adjustment to age- or disease-related decline across cognitive domains. Awareness, in short, associated with a right hemisphere network, albeit generally within the prefrontal elements of the network, remains a strong candidate for a cognitive-reserve linked cognitive process.

Working memory capacity affect a wide range of functions: The higher the WM capacity, for instance, the greater the resistance to distraction (Edin, et al., 2007) and enhanced WM allows greater scope for simultaneous self-monitoring of performance during attention-demanding tasks (Dunning, et al., 2004). Furthermore increased arousal may in turn increase WM capacity (Chamberlain, et al., 2006). Hence working memory is likely to have widespread effects on awareness and attention, among other functions, which is likely to increase cognitive reserve.

Conclusions

Arousal, novelty, attention and awareness share similar neural circuitry, are strongly linked to noradrenaline function and constitute, along with working memory capacity, a plausible cluster of mechanisms by which cognitive reserve variables such as education could allow the aging brain better to adapt to disease and degradation.

Each of these processes can also have reciprocal effects on NA levels. A person who is alerted and aroused by a stimulating environment or social network will secrete higher levels of NA as a result of the increased arousal. Novelty in a person's life will also increase NA secretion, as will focusing attention on the environment and detecting events, objects and people of interest. Self- and error-monitoring – as opposed to habit-driven behavior high in automaticity - will also likely increase NA levels.

Given NA's widespread distribution in the brain (both intra- and extra-cellularly), to every region save the basal ganglia (Sara, 2009), it is to be expected that repeated activation of the these processes should have widespread consequences on most cognitive, motor and perceptual functions in the aging brain, because of its neuromodulatory, synaptogenesis and even neurogenesis effects (Robertson, 2013). This helps explain why Brickman and colleagues (Brickman, et al., 2006) found that right frontal white matter volume in older people predicted

neuropsychological performance across many different functions, including verbal functions, not normally associated specifically with the right prefrontal cortex. Arousal, novelty, attention and awareness increases may therefore, via their direct effects on compensatory processes, but also indirectly via their facilitation of NA secretion, have widespread effects across cognitive functions.

It should be emphasized however that the hypothesis does not invoke an exclusive role for this NA system in mediating cognitive reserve and that one or more other dispersed networks, for instance language-based ones, may have an additional role and predictive value in cognitive reserve. Nevertheless, the extraordinarily widespread dispersion of NA throughout the brain, much wider than other neurotransmitters such as dopamine, acetylcholine and serotonin, justifies the special focus on the network linked to NA which is the focus of this paper.

Figure about here.

In the figure, the relationship between the proposed elements of this cognitive reserve system and their hypothesized interactions are outlined, and relatively protected cognitive function in later life on the other.

The top right quadrant of the figure shows the CR-NA relationship based on previously reviewed evidence that cognitive reserve variables increase NA activity (Robertson, 2013). Increased NA activity, on the other hand, should also potentiate the effects of environmental enrichment aspects of CR, including mental stimulation and social engagement, given NA's properties as a neuromodulator fostering synaptic plasticity (Ahissar, et al., 1996, Grefkes, et al., 2010).

The top left quadrant of the figure illustrates the hypothetical relationship between CR and the hypothetical CR network. Different elements of CR may activate other elements of the

CR network to varying degrees. Education for instance should increase curiosity and hence exposure to novelty. Mental stimulation and social engagement will increase arousal, and with it, attention and awareness.

The bottom right quadrant shows the enhancement of working memory by NA inhibition of cAMP signaling. Working memory enhancement may increase NA activity, but there is no direct evidence for this, hence this is the only unidirectional relationship.

Finally, the bottom left quadrant illustrates the influence of enhanced WM on elements of the CR network, particularly attention and awareness.

Implications for Research in Aging and Neurodegeneration

If it is the case that the proposed cognitive reserve network mediates some of the effects of cognitive reserve, then it is crucial that the processes implicated in it are adequately assessed in research studies and controlled for in intervention studies. Unfortunately however, few of these functions are routinely measured, in spite of standard assessment methods being available.

Arousal is not routinely measured in spite of it being a correlate of impaired functioning with age (Hartikainen, et al., 1992), but, as mentioned earlier in this review, methods such as EEG spectral power analysis (Dockree, et al., 2005, Makeig and Inlow, 1993), and pupillometry (Gilzenrat, et al., 2010, Murphy, et al., 2011) make routine assessment of this variable possible. Response to *novelty* can also be assessed routinely with ERP responses to ‘oddball’ stimuli and purely behavioral measures using length of time viewing novel stimuli are also available (Daffner, et al., 2006). Standardized measures of sustained attention also exist such as the the Continuous Performance Test (CPT) (Cornblatt, et al., 1988) and subtests of the Test of Everyday Attention (Robertson, et al., 1994). *Sustained attention* is not captured by routinely used attention tasks such as the Trails tests (D’Elia, et al., 1994). Rather, sustained attention tests

assess the maintenance of attention during routine, non-demanding activities and most aging studies do not assess this particular type of attention. *Awareness* problems are also not routinely measured in spite of even healthy older adults showing very significant reductions in everyday error awareness but they can be measured routinely, for instance by discrepancy between self- and informant- reports on standard everyday performance self-report measures (Harty, et al., 2012).

If future research supports the hypothesis that these five sets of cognitive processes – arousal, novelty, sustained attention, awareness and working memory - do indeed constitute a CR network capable of mitigating the effects of age- or disease-related damage on expressed cognitive function and everyday performance, then a number of practical implications follow .

From a clinical rehabilitation, public health and educational perspective, attempts to delay or prevent unnecessary cognitive decline could include practical, and specific, advice encouraging cognitive activities and mental stimulation. While mental stimulation would indeed increase arousal, repetitive mental stimulation would not activate novelty processing in the brain. A focus on variety of experiences and of cultivating curiosity, however, could be prioritized.

Furthermore, the nature of sustained attention is such that experiences fostering this capacity could be actively encouraged. Perhaps the most well-developed and validated is mindfulness meditation training, which is also known as ‘attentional control training’ (Kabat-Zinn, et al., 1992) and which has been shown to have very significant effects on brain structure and function (Lou, et al., 1999, Pagnoni and Cekic, 2007).

Other methods of improving sustained attention have also been developed for conditions such as spatial neglect following stroke and Attention Deficit Hyperactivity Disorder in Adults

(O'Connell, et al., 2008, Salomone, et al., 2012). Self-administered versions of these for older adults have been successfully piloted and are currently being evaluated in our laboratory.

Self-awareness of performance could be of paramount importance in helping older people adapt so as to maintain, or indeed extend, their functional independence in spite of changes to brain structure. Regular engagement in meaningful activities with other people may be one of the most potent ways of revealing cognitive errors to a person, and because social engagement has so many other positive effects on cognition, emotions and motivation (Saczynski, et al., 2006, Seeman, et al., 2001), a public health focus on social engagement would be implicated.

The role of physical exercise, in particular aerobic exercise in modifying cognitive function in older people (Anderson-Hanley, et al., 2012, Colcombe, et al., 2006) may also play a part in the strengthening of cognitive and/or brain reserve, as well as 'brain maintenance' (Nyberg, et al., 2012). It is worth noting that such exercise significantly upregulates not only brain derived neurotrophic and other factors, but also noradrenaline (Segal, et al., 2012).

The hypothetical cognitive reserve network proposed clearly requires further experimental and clinical research but, if confirmed, would have considerable implications for future measures of aging, AD research and cost effective public health policies aimed at delaying cognitive aging and AD.

Acknowledgements

The question of what the nature of a cognitive reserve brain network might be, if it exists, and which prompted the present paper, was posed to me by Professor Yaakov Stern of Columbia University and I would like to thank him both for this and his generosity and intellectual stimulation during my sabbatical semester in his laboratory in the Sergievsky Center in Columbia Medical School, where I wrote this paper. I would also like to thank his colleagues for their generosity with their time and hospitality during this period.

Many thanks to Deirdre Robertson for her careful correction of this manuscript.

I would also like to thank my colleagues at Trinity College Institute of Neuroscience, in particular Sabina Brennan and Brian Lawlor, co-leaders of the NEIL (Neuroenhancement for Independent Lives) programme there, and my close collaborators Redmond O'Connell and Paul Dockree.

Finally, I would like to express my grateful thanks to Atlantic Philanthropies for funding the NEIL programme and for allowing me to do this research.

There are no actual or potential conflicts to declare.

Figure Legend

A hypothetical cognitive reserve network.

The figure outlines the role of a cluster of networks which hypothetically mediate between cognitive reserve variables such as education level on the one hand, and relatively protected cognitive function in later life on the other.

The top right quadrant of the figure shows the CR-NA relationship. The top left quadrant of the figure illustrates the hypothetical relationship between CR and the hypothetical CR network. Education for instance should increase curiosity and hence exposure to novelty. Mental stimulation and social engagement will increase arousal, and with it, attention and awareness.

The bottom right quadrant shows the enhancement of working memory by NA inhibition of cAMP signaling. Working memory enhancement may increase NA activity, but there is no direct evidence for this, hence this is the only unidirectional relationship.

Finally, the bottom left quadrant illustrates the influence of enhanced WM on elements of the CR network, particularly attention and awareness.

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