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Review

A right hemisphere role in cognitive reserve

Ian H. Robertson*

Institute of Neuroscience and School of Psychology, Trinity College Dublin, Dublin, Ireland

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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 the evidence that the neurotransmitter, noradrenaline mediates cognitive reserve's protective effects (Robertson, 2013) this review identifies the neurocognitive 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 gray matter) and functional integrity and connectivity, cognitive reserve should benefit and behavioral expression of pathologic damage should thus be mitigated.

1. 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 2 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 et al. (2012). Older adults vary in the degree of age-related cellular damage to basic brain structures, according to this theory 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 article, 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 noradrenergic activity (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 6 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. Although this does not rule out the role of other neurotransmitter systems in mediating cognitive reserve, it does provide strong support for highlighting a particular —though

* Corresponding author at: Trinity College Dublin, Institute of Neuroscience and School of Psychology, Dublin, Ireland. Tel.: +353 18962684; fax: +353 8963183.
E-mail address: iroberts@tcd.ie.

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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 (Troadec 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 the 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 article is the identification of one set of candidate cognitive processes, which may facilitate the impaired brain's maintenance of cognitive function.

The present article addresses 4 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?

Each of the questions is discussed below.

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

Stern et al. propose 3 possible types of cognitive processes underlying reserve (Stern, 2009, 2012). The first, "neural reserve", is an augmented efficiency and capacity of well-practiced 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 because of 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 present article, 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 (e.g., language based) linked to other neurotransmitter systems having a separate role in mediating cognitive reserve.

The aim of this review, therefore, 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 et al.'s evidence in favor 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 7- 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.

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

There are 4 main interlinked types of cognitive process, which the following studies show, have a particularly strong linkage to the NA system. These are arousal or alertness, response to novelty, sustained attention, and self-monitoring or error awareness. In addition, a fifth system—working memory—is strongly modulated by the NA system.

3.1. Arousal or 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 and/or LC activity precede variations in arousal or 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 1 Hz, but in the presence of an arousing stimulus they show "phasic bursts" of firing. With drowsiness the firing declines below 1 Hz 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 or 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 electroencephalography (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).

3.2. Response to novelty

Novelty provides a key trigger for arousal and it is therefore not surprising to find that LC and/or NA activity occurs strongly in response to novel stimuli (Kitchigina, 1997; McQuade et al., 1999;