A noradrenergic theory of cognitive reserve: implications for Alzheimer’s disease

Ian H. Robertson*

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

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Abstract

The gap between symptoms and pathology in Alzheimer’s disease has been explained by the hypothetical construct of “cognitive reserve”—a set of variables including education, intelligence, and mental stimulation which putatively allow the brain to adapt to—and hence mask—underlying pathologies by maintaining cognitive function despite underlying neural changes. This review proposes a hypothesis that a biological mechanism may mediate between these social/psychological processes on the one hand, and apparently reduced risk of Alzheimer’s disease on the other, namely repeated activation of the noradrenergic system over a lifetime by the processes implicated in cognitive reserve. Noradrenaline’s neuroprotective effects both in vivo and in vitro, and its key role in mediating the neuroprotective effects of environmental enrichment on the brain, make noradrenaline’s key role in mediating cognitive reserve—by disease compensation, disease modification, or a combination of both—a viable hypothesis.

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1. The cognition-pathology gap in Alzheimer’s disease

One of the major obstacles to developing effective treatments or preventions for Alzheimer’s disease (AD) is the imperfect correlation between biological measures of pathology in the brain on the 1 hand—amyloid plaques, neurofibrillary tangles, positron-emission tomography (PET)-measured cerebral perfusion or volumetric magnetic resonance imaging for instance—and measured cognitive function and real life performance on the other (McKhann et al., 2011). In the famous “nun study” for instance (Riley et al., 2002), no less than 32% of elderly participants with Braak Stage III and IV pathology (out of a maximum of 6 stages determined postmortem) had normal memory function before death. Furthermore, while there was a modest but significant correlation of 0.57 between autopsy-determined pathology and general cognition among individuals who had some memory impairment, there was no significant relationship between pathology and global cognition in those with intact memory function, despite the existence of other types of other cognitive impairment in many of this latter group.

A common explanation for this cognition-pathology discrepancy is that cognition and memory function are maintained at relatively high levels despite the developing underlying pathology, of which the presence of amyloid plaques may be 1 important disease-specific marker; this might happen because of compensatory adjustments made by the brain which help it reorganize to maintain function despite the developing pathology (Dubois et al., 2010; McKhann et al., 2011). The development of a human amyloid marker in the form of amyloid PET scanning with Pittsburgh Compound B (PiB) (Klunk et al., 2004) appears to offer a promising advance toward better characterization of, and treatment for, such underlying amyloid pathology. Such a development was hoped to help close the cognition-pathology gap. Unfortunately this gap remains very large despite this important development.
Roe et al. (2008) examined PiB amyloid load in relation to measures of cognitive deterioration in a sample of elderly individuals with and without diagnosed AD and did indeed find that those who were PiB positive showed very significantly lower cognitive function and significantly higher clinical dementia ratings than those who were PiB negative. There was one important caveat to this finding, however—this reassuring relationship between pathology and cognition disappeared in the group with the highest levels (postcollege) of education and was significantly attenuated on most measures for those with intermediate education (some college or graduate college education). The cognition-pathology gap among the best educated in other words, widened to the extent that no correlation remained between these 2 sets of variables.

Such findings do not just apply to education as a variable, however. In a study of social networks (Bennett et al., 2006), the researchers found that while postmortem pathology and predeath cognition showed a reasonable correlation among individuals with relatively sparse social networks, the cognition-pathology correlation again disappeared—as in the case for education and cognition in Roe’s PiB study—among groups with a high level of social contact and strong social networks.

Discrepancies between cognition and pathology such as these have been explained by the concept of “cognitive reserve,” a concept first developed by Yaakov Stern (Stern et al., 1999). Individual differences in the efficiency, capacity, or flexibility of brain networks (“neural reserve” in Stern’s terminology) or individual differences in the ability to compensate for brain pathology (Stern’s “neural compensation”), may allow brains affected by Alzheimer’s pathology to maintain adequate cognitive functioning (Stern, 2009).

The aim of this report is not to review comprehensively the variables and processes linked to cognitive reserve, as this has been well done elsewhere (Stern et al., 1992, 1994, 1999; Tucker and Stern, 2011; Valenzuela and Sachdev, 2006), nor does the paper attempt to elucidate the distinction between cognitive reserve and the concept of “brain reserve,” which Stern and colleagues propose refers to intra-individual differences in biological substrates of the brain leading to different degrees of resilience to the effects of disease or injury. Cognitive reserve and brain reserve have been used interchangeably by other authors such as Valenzuela and Sachdev (2006), but the question posed in this report pertains to a hypothetical biological mediating mechanism by which either cognitive or brain reserve may shape the considerable pathology-cognition discrepancy commonly observed in Alzheimer’s disease and other brain disorders.

The magnitude of this cognition-pathology discrepancy is considerable, estimated by Valenzuela and Sachdev in their meta-analysis of education, occupation, IQ, and mental activities components of brain reserve as a mean odds ratio of 0.54 for lowered risk of incident dementia over a median 7.1-year period (Valenzuela and Sachdev, 2006). There are 3 main theoretical interpretations of this finding.

The first is that the reserve variables and the reduced risk of AD diagnosis are correlated not due to any direct causal link, but rather because each is associated with a third common, possibly genetic, factor that causes both the high brain/cognitive reserve factor (educational and occupational attainment and IQ) and the increased resilience to the disease process. This view would hold that the observed correlation between, say, education and lowered risk of AD, is therefore more reflective of the pre-existing resilience than a direct effect of, say, education per se (Whalley et al., 2004). A Swedish study of identical twins, however, showed that those who had the minimal legal level of education for their age cohort had significantly higher levels of dementia than their identical twins who had higher levels of education, confirming that pre-existing genetic variables could not account for the cognitive reserve-symptom relationship (Gatz et al., 2007).

The second theoretical explanation for this relationship is that the apparently protective variables such as education build the brain’s capacity to compensate for a disease process which in itself is unaffected by education, mental stimulation, or social interaction. Such compensatory variables could range from the increased cortical volume that has been shown to arise from intensive new learning during examination preparation in students (Draganski et al., 2006) or by learning a new skill such as juggling (Draganski et al., 2004); it could also arise from cognitive-training-related increases in white matter volume (Takeuchi et al., 2010) or from changes to critical neurotransmitter receptor densities (McNab et al., 2009). Changes to brain regions crucial for compensatory adjustments such as the prefrontal cortex may play a particular role (Erickson et al., 2007).

The third theoretical explanation is that education, mental stimulation, and social interaction directly impact the Alzheimer’s disease process itself, and not only the brain’s capacity to compensate for the disease (Landau et al., 2012).

Only the second and third of these theoretical positions propose a causal role for the protective effects of these cognitive reserve variables and the aim of this report is to advance a hypothesis about a possible biological route (enhanced noradrenergic signaling) which might mediate between cognitive reserve and reduced AD vulnerability in both of these theoretical cases 2 and 3 above, which I will term “compensatory” and “disease modifying” respectively. I ask in other words whether variables such as education/IQ, mental stimulation, and social engagement reduce risk of AD by improving the brain’s ability to compensate for disease as outlined above and/or by directly influencing the AD disease process itself. Because it is currently not possible to measure directly brain noradrenergic function in
vivo in humans, however, it is first necessary to look to the animal literature on the cognition-pathology gap.

2. Environmental enrichment and neurodegeneration

Environmental enrichment improves cognitive function in a range of species. Dogs randomly allocated to enriched environments over a period of more than 2 years in one study showed lower amyloid plaque burden in their brains at postmortem than dogs kept in standard environments (Pop et al., 2010). Transgenic TgCRND8 amyloid-β (Aβ)-over-producing mice were randomly allocated to 60 days of enriched environment before Aβ plaques appeared or 60 days after they had begun to appear (Herring et al., 2011), thus allowing comparison of the “preventative” effects of enrichment and the “therapeutic, postdisease onset” effects. They found that the enriched environment before disease onset reduced the number and size of amyloid plaques, which the authors suggest may occur due to increased degradation and clearance of Aβ. “Therapy,” on the other hand, reduced the growth and fusion of plaque seeds, possibly by inhibiting Aβ aggregation, the authors suggested.

These and several other studies (Costa et al., 2007; Lazaro et al., 2005) suggests that one aspect of cognitive reserve—enrichment/mental stimulation—may at times directly influence various AD-linked pathologies, through for instance noradrenaline (NA) amelioration of amyloid cellular toxicity, and not only influence the brain’s capacity to adapt to existing pathology. This series of studies suggest that independently of any cognitive reserve-enhancing mechanisms that may be taking place, allowing better adaptation to pathology, there are also effects of enrichment on the pathologies themselves, thus perhaps increasing “neural reserve,” in Stern’s terms.

Recently, human evidence in favor of this hypothesis was obtained by Landau and colleagues (Landau et al., 2012) who found a significant correlation between estimated lifetime cognitive activity and amyloid burden the brain measured by PET [11C] PiB Aβ imaging in 65 people with a mean age of 76. Greater participation in cognitively stimulating activities such as reading books or newspapers, writing letters or e-mails, going to the library or playing games across the lifespan was associated with reduced [11C] PiB while controlling for age, sex, and years of education. Older participants in the highest cognitive activity group had [11C] PiB uptake comparable with young controls, whereas those with lowest levels had [11C] PiB uptake comparable with patients with AD. While greater cognitive activity was associated with greater physical exercise, exercise however was not associated with [11C] PiB uptake.

These 2 studies are in accord with the third theoretical position, namely that one aspect of cognitive reserve—stimulation/enrichment—may directly impact the disease process. Other studies, however, have found results more consistent with the second theory, namely that of compensatory capacity. For instance, 1 study with transgenic (APP) Aβ-overproducing mice, found that an enriched environment normalized memory performance in these mice despite increased neuritic plaque burden, a finding more consistent with the neural compensation hypothesis of heightened resilience to extant pathology (Jankowsky et al., 2005) and a similar finding was obtained with APPsw transgenic mice (Arendash et al., 2004) and with APP-23 mice (Wolf et al., 2006).

A similar conclusion has been reached in a longitudinal study of educational level in humans, with 872 brain donors, of whom 56% were demented at death: these authors found that while longer years in education were associated with decreased dementia risk, this association was found to be statistically independent from the effects of underlying pathology; this led them to conclude that the education mitigated the impact of pathology rather than directly influencing pathological processes (EClinPSE Collaborative Members et al., 2010). A similar conclusion was reached by another human study using estimated premorbid IQ (American National Adult Reading Test) as a proxy marker of lifetime environmental enrichment; the authors found that this measure of cognitive reserve predicted cognitive performance independently of, and additively to, the effects of amyloid and other measured pathologies (Vemuri et al., 2011).

While environmental enrichment may build reserve both altering key pathologies linked to Alzheimer’s disease, the human evidence for this is weaker than the animal data, and the strongest evidence is for such enrichment to help maintain improved cognition through other, possibly compensatory, mechanisms. So how does environmental enrichment produce its effects on cognition?

3. Mechanisms of action of environmental enrichment on cognitive function

Environmental enrichment across a range of species improves cognitive function and there is a range of mechanisms mediating these effects including neurogenesis, synaptogenesis, and increased levels of brain derived neurotrophic factor (BDNF) and related neurotrophins, among others (vanPraag et al., 2000). Reduced intracerebral inhibition and epigenetic changes at the level of chromatin structure have also been implicated (Baroncelli et al., 2010). In addition, environmental enrichment has significant effects on neurotransmitter function, and in particular on noradrenergic tone.

Noradrenaline concentrations in brains of mice spending 40 days in enriched versus standard environments increased significantly in parieto-temporo-occipital cortex, the cerebellum and the pons/medulla oblongata (Naka et al., 2002) with no corresponding changes observed in serotonin or dopamine (DA) levels in these brain regions. Selective enrichment-induced modulation of noradrenaline release in
mouse hippocampus via presynaptic NMDA receptors has also been observed (Grilli et al., 2009). The specific aspects of environmental enrichment that improved a key cognitive function—memory—in mice, was investigated in another study (Veyrac et al., 2009). These researchers compared enrichment via novelty versus enrichment via complexity, in the context of odor enrichment and its effects on odor memory. Daily exposure to single novel odorants improved memory while daily exposure to a complex bouquet of odors which remained stable over the enrichment period, did not. Furthermore, the daily changing single odor novelty condition produced increased neurogenesis in the olfactory bulb, while the stable complex odor environment did not.

This study showed novelty as a key feature of the cognitively enriching and neuropsychologically-enhancing aspects of the enriched environment. These positive effects of enrichment were however mediated by noradrenaline, the authors showed, because they were blocked under labetalol, a mixed b with A1-adrenoceptor antagonist. The short-term enhancing effects of novelty on hippocampal-dependent memory had already been demonstrated, as had the mediating role of noradrenaline (Kitchigina et al., 1997). Furthermore, age-related long-term potentiation deficits in rats have been shown to be significantly reduced by novelty, and these effects may be mediated noradrenergically (Sierra-Mercado et al., 2008). In humans, Tulving and colleagues found that the probability of long-term storage of information varies directly with the novelty of the information (Tulving et al., 1996).

Noradrenaline activation then, may be 1 important mechanism by which environmental enrichment improves cognitive function, and novelty may be a key feature of environmental enrichment’s beneficial effects. These effects would affect the brain’s ability to compensate for disease—for instance by neurogenesis-induced raised cortical volume, increased connectivity or other effects on brain structure and function that would allow better compensation for the AD disease process. They would not, however speak to the possibility of a direct effect on the disease process itself. Is there then any evidence of a more specific relationship of NA function to Alzheimer’s disease?

4. Noradrenaline and Alzheimer’s pathology

The locus coeruleus (LC) is the major source of NA in the brain and projects synaptically and extrasynaptically to the entire cerebral cortex, as well as thalamic nuclei, limbic structures and the hippocampus; the basal ganglia regions is the only major structure that does not receive input from the LC (Sara, 2009). While AD research has strongly focused on deficits in the cholinergic system (Babic, 1999; Ikonomovic et al., 2011; Terry and Buccafusco, 2003), a number of studies have shown significant cell loss in the LC in Alzheimer’s disease (Dringenberg, 2000; Insua et al., 2010; Matthews et al., 2002; Szot et al., 2006; Tomlinson et al., 1981). In addition, LC degeneration is seen in very early, pre-AD disorders such as mild cognitive impairment and the drop in NA levels in such patients is tightly linked to the progression and extent of memory dysfunction and cognitive impairment (Grudzien et al., 2007). Furthermore epidemiological research shows that the DA β-hydroxylase-1021C/T polymorphism, which influences NA availability in the brain, is a significant risk factor for AD, with genotypes indicating low NA availability having as much as a doubled risk of AD (Combarros et al., 2010).

The LC therefore may suffer early degeneration in the AD disease process. Because NA plays a role as an anti-inflammatory molecule, 1 impact of the resulting decrease in NA-ergic neurons is likely to be on inflammatory processes. NA, for instance, downregulates transcription of inflammatory genes in astrocytes and microglia (Feinstein et al., 2002), and reduces amyloid neutral toxicity via anti-inflammatory mechanisms, both in vitro and in vivo in APP mouse models (Heneka et al., 2010). NA also stimulates BDNF production (Mannari et al., 2008) which in turn reduces amyloid toxicity on hippocampal neurons (Counts and Mufson, 2010) and also promotes neurogenesis (Masuda et al., 2012). Furthermore, NA in vitro has been shown to rescue cholinergic (Traver et al., 2005) and dopaminergic neurons (Traudec et al., 2001) by reducing oxidative stress; more generally, NA also stimulates both DA and glutamate release in the brain (Grinberg et al., 2011). This combination of mechanisms—anti-inflammatory, BDNF-increasing, neurogenesis-inducing, amloid toxicity-reducing, amloid-depleting, DA and cholinergic cell-rescuing, DA and glutamate-stimulating, constitutes a set of NA-induced neuroprotective mechanisms which may offer a possible biological basis for the phenomenon of cognitive or brain reserve. Such mechanisms offer the theoretical possibility of a direct noradrenergically-mediated effect on the disease process and not just on the compensatory process.

5. Noradrenaline’s role in cognitive function

There is a critical missing link in the hypothesis outlined above. While noradrenaline may have a number of neuroprotective and compensation-enhancing effects on the brain, and cognitive reserve variables such as mental activity and education may be associated with lower levels of AD pathology, is there any evidence that these cognitive reserve variables have any effects on NA function? To address this question, a brief review of the role of NA in cognitive processes is required.

The brain’s LC-noradrenaline system is crucially involved in task engagement and optimizing performance according to environmental contingencies (Aston-Jones and Cohen, 2005). High-frequency phasic LC activity is elicited by salient or task-relevant stimuli, and the resultant release of NA to the cerebral cortex enhances stimulus processing by selectively increasing neuronal gain within task-relevant
regions—in short, it increases signal-to-noise ratio for important signals (Aston-Jones et al., 1991, 1994; Sara, 2009). The role of phasic LC activity in facilitating stimulus processing is supported by animal studies that highlight the phasic LC response as an important antecedent to appropriate behavioral responding in stimulus detection paradigms (Aston-Jones et al., 1994; Usher et al., 1999).

Based primarily on such intracranial recordings from animals, the adaptive-gain theory of LC-NE function (Aston-Jones and Cohen, 2005) states that relative levels of tonic and phasic LC activity relate to task performance in a manner that reflects the classic Yerkes–Dodson arousal curve (Yerkes and Dodson, 1908): performance and phasic LC responding are optimal at an intermediate level of tonic LC activity, but shifts toward either end of the tonic activity continuum are associated with declining performance and nonspecific or attenuated phasic responses. The importance of this LC arousal function in humans has been highlighted by pharmacological and genetic studies that corroborate the role of NA as a critical determinant of engagement and task performance on tests of attention (Coull et al., 2001; Greene et al., 2009; Minzenberg et al., 2008; Murphy et al., 2011; Smith and Nutt, 1996).

Assessing NA levels directly in the living human brain is not currently possible, but recent research suggests that LC/NA activity may be indexed by the pupillary response to motivationally salient or novel stimuli (Aston-Jones and Cohen, 2005; Einhäuser et al., 2008; Gabay et al., 2011; Gilzenrat et al., 2010; Jepma and Nieuwenhuis, 2011), including in primates (Bouret and Richmond, 2009). For many decades, pupil dilation has been shown to covary with ongoing cognitive processes in the human brain (Beatty, 1982; Loewenfeld, 1993). This is quite distinct from the cholinergically-mediated hypersensitivity in pupil dilation response to a cholinergic antagonist, tropicamide, that has been demonstrated in people suffering from Alzheimer’s disease (Scinto et al., 1994), and also in a reduced dilation response to light (Fotiou et al., 2000). In contrast to this, the NA-based pupil dilation is a response to a number of different cognitive challenges which shows considerable variation within and between healthy individuals of all ages.

Cognitive or mental effort increases pupil size, in proportion to the difficulty or challenge, across the domains of memory (Kahneman and Beatty, 1966; Peavler, 1974), problem-solving (Bornemann et al., 2010; Hess and Polt, 1964), auditory perceptual processing (Kahneman and Beatty, 1967), attention (Laeng et al., 2011; Murphy et al., 2011) and mathematical cognition (Kahneman, 1973), among others. Furthermore, stimulation of the LC with consequent upregulation of NA activity has been shown to improve cognitive, perceptual, and memory performance in monkeys and rodents (Berridge and Waterhouse, 2003; Bornemann et al., 2010; Sara, 2009).

Bearing in mind the evidence that human NA activity may be indexed by pupillary responses to cognitive challenge, let us now consider the evidence for pupillary dilation responses—our proxy marker for NA activity—in relation to the 4 cognitive reserve variables.

6. Cognitive reserve and noradrenergic function

Is there any evidence that 4 of the most common elements of “cognitive reserve”—education/IQ, mental activity, social interaction and enriched/novel environments— influence noradrenergic activity as indexed by pupillary measures? Let us consider each in turn.

6.1. Education/IQ

Education levels are very strong predictors of reduced risk of diagnosis with Alzheimer’s disease (Dumurgier et al., 2010; EClipSE Collaborative Members et al., 2010; Gatz et al., 2007; Kidron et al., 1997; Roe et al., 2010; Stern, 2009; Stern et al., 1994) as are premorbid IQ levels (Tucker and Stern, 2011; Vemuri et al., 2011), with education levels and the IQ being highly correlated (Ceci and Williams, 1997).

Van Der Meer and colleagues (Van Der Meer et al., 2010) showed that adults with higher than average IQ (fluid intelligence) showed similar pupil dilation to moderately challenging problems to those shown to moderately challenging problems by people of average IQ. When the analogies were made more difficult, however, the higher IQ participants showed much bigger pupil dilation to these problems, which the authors interpret as the deployment of greater cognitive resources in those of higher intelligence; this finding was replicated by Bornemann et al. (2010). Given the evidence that pupil dilation indexes noradrenergic activity (Gilzenrat et al., 2010; Laeng et al., 2011; Murphy et al., 2011), 1 element of the putative “resource” in question is likely to be increased noradrenaline levels. Increased NA levels improve and “clean” neural signals in the brain (Sara, 2009) and contribute to the increased level of optimal arousal which more challenging tasks demand, in line with the original observation by Yerkes and Dodson (1908) and in line with what is known about the inverted-U function of neurotransmitters such as NA (Arnsten et al., 1996).

These limited data offer some support to the hypothesis that Education/IQ may influence cognitive reserve in part via the enhanced noradrenergic activity in the brain, with possible resulting consequent neuroprotective or compensation-enhancing downstream effects as outlined earlier in this article.

6.2. Mental activity

Mental activity is correlated with reduced risk of Alzheimer’s disease (Landau et al., 2012; Valenzuela and Sachdev, 2006, 2009; Valenzuela et al., 2012; Verghese et al., 2003; Wang et al., 2002; Wolf et al., 2006), though there is no consensus as to whether this is purely due to mental activity’s effects in improving brain robustness (e.g., neuron
density), as Valenzuela and colleagues have argued (Valenzuela et al., 2012), or whether in addition actual AD pathology (e.g., amyloid load) may also be affected (Landau et al., 2012).

Mental activity and engagement, however, robustly and reliably increases pupil dilation, with the size of the dilation proportional to the level of the mental challenge (Kahneman, 1973). This has been shown across a range of cognitive challenges, ranging from auditory pitch discrimination (Kahneman and Beatty, 1967) to the Stroop effect, where the difficult incongruent words elicit a much greater pupillary response than the congruent or control words (Laeng et al., 2011) and to perception of ambiguous figures, where pupil dilation occurs immediately before the alternative percept comes into awareness (Einhäuser et al., 2008). Similar findings apply in the memory domain, where pupils have been shown to dilate to a greater extent when participants correctly remember previously learned items, even when the words were presented acoustically. The pupil dilation was also greater when items when memory encoding was deep compared with shallow (Otero et al., 2011).

Undoubtedly mental activity, in particular challenging and engaging mental activity, stimulates pupil dilation and therefore may be triggering NA release in the brain. To the extent that over a lifetime a person is—maybe many hundreds of times per day—repeatedly stimulating the LC to secrete noradrenaline, this could offer a possible mechanism by which such activity could both build a brain better able to resist the disease process through mechanisms such as NA- and BDNF-enhanced neurogenesis or synaptogenesis, for instance, and/or actually offer neuroprotection to neurons through its anti-inflammatory and other related mechanisms as outlined earlier.

6.3. Novelty

While novelty and change have not been regarded as contributing to cognitive reserve in the human literature, the evidence cited earlier in this article on the role of environmental enrichment on protecting against AD-type symptoms in rodents suggested that novelty may be the crucial element mediating between effects of enrichment and its beneficial neural and cognitive effects (Veyrac et al., 2009). Given that factors such as rich leisure and occupational activities throughout life have been linked to cognitive reserve, the possibility arises in the light of Veyrac’s study, that novelty may be a potentially potent component of these effects. Is there any evidence that in humans, novelty has any specific effects on the noradrenergic system? It seems that there is; Steiner and colleagues examined electroencephalographic, skin conductance, and pupil dilation responses to auditory stimuli. While all 3 types of response were apparent in response to target tones, the researchers found that “the pupillary dilation response, however, demonstrated an unexpected sensitivity to stimulus novelty only” (Steiner and Barry, 2011; pp. 1648). Other studies have shown a specific pupillary sensitivity to surprise, which is closely linked to novelty (Reisenzein et al., 2006). To the extent that the pupillary response is a marker of NA activity, there is therefore evidence that novelty—a possible key factor in mediating rodent environmental enrichment effects—does indeed selectively upregulate NA activity in humans also.

6.4. Social interaction

Social interaction may be a special case of mental activity, but given that human beings are a fundamentally social species, evolved to live in groups, it warrants separate attention, particularly in the light of evidence that social networks can, like education/IQ, and mental activity, strongly moderate the relationship between AD pathology and cognitive function, to the extent that no correlation between postmortem pathology and cognitive function while alive was found in individuals with strong social networks (Bennett et al., 2006). This finding has been replicated (Crooks et al., 2008), though a further study, that suggested that it may be the quality more than the quantity of social networks that protects against AD (Amieva et al., 2010).

There is relatively little direct evidence about the effects of social stimuli on pupil dilation/NA response, though Kuchinke and colleagues showed that the pupil response to words spoken with either positive or negative prosody was much larger than to words spoken in a neutral voice (Kuchinke et al., 2011).

7. Working memory and cognitive reserve

IQ is one of the key elements of cognitive reserve (Stern, 2009; Vemuri et al., 2011), and a considerable amount of research has shown that the central cognitive component of fluid intelligence is working memory capacity—the ability to hold and manipulate a constantly changing stream of information (Engle et al., 1999). In that context, it is very interesting to note the results of a follow-up of 801 elderly individuals over a period of 4.5 years (Wilson et al., 2002). In line with previous studies on mental activity, the authors found that baseline participation in cognitively stimulating activities was protective against subsequent cognitive decline, with those at the highest—90th percentile—of baseline cognitive activity being 47% less likely to develop AD than were those at the lowest—10th percentile—of baseline mental activity: there was no such link with level of physical activity. Furthermore, high baseline cognitive activity predicted a lower rate of cognitive decline, but level of mental activity was specifically predictive of rate of change in only 2 categories of cognitive function—working memory capacity and perceptual speed. Level of baseline mental activity did not significantly predict rate of change of other types of memory or of visuospatial ability, for instance.

Working memory capacity, therefore, may be a possible
mediator between 2 aspects of cognitive reserve—IQ and mental activity—on the 1 hand, and reduced risk of cognitive decline on the other. This finding is particularly interesting given the evidence that working memory capacity has been shown to be improvable with training (Jaeggi et al., 2008; Klingberg, 2010), and indeed to result in alterations that the cognition-pathology gap is explained by a bigger non-specific changes to the brain—cortical volume, white matter density, synaptic density, neurotransmitter receptor densities among others—and that the cognition-pathology gap is explained by a bigger and better connected brain being able to reorganize around the pathology caused by the AD disease process. Noradrenaline plays a key role in the learning and stimulation that underpins these cognitive reserve variables because of its unique neuromodulation and long-term potentiation-enhancing (Harley, 1987) characteristics and central role in mediating the effects of environmental enrichment on neurogenesis, synaptogenesis, the stimulation of BDNF and many other mechanisms.

An early review made this observation about the LC/NA system: “(it) affects synapses throughout the CNS, suppressing most, but permitting or even accentuating activity in those that are transmitting novel or significant stimuli ... this favours the development of persistent facilitatory changes in all synapses that are currently in a state of excitation” (Kety, 1972). Kety also predicted that NA would have a crucial role in the cornerstone of learning and neural plasticity, a prediction subsequently confirmed after the discovery of long-term potentiation (Harley, 1987). This included evidence that NA increases caused by stimulation of the LC improved memory retrieval in rats (Devauges and Sara, 1991).

Sara’s review of the LC/NA system (Sara, 2009) concluded that its intra- and extracellular dispersion throughout the brain exceeded that of most other neurotransmitters, with the only major region not receiving input from the LC being the basal ganglia. Noradrenaline is centrally and specifically involved in mediating environmental stimulation, attention, and learning, and therefore is a strong candidate for mediating the compensatory aspect of cognitive reserve. The resulting synaptogenesis and neurogenesis, among other mechanisms, leads to a brain structure better able to resist pathological processes; the human research (EClipSE Collaborative Members et al., 2010; Valenzuela et al., 2012) tends to support this compensatory model of mediation, whereby the cognitive reserve acts brain’s ability to withstand the pathology.

What about the pathology; does NA have a role, as the disease-modifying model proposes, in reducing the AD pathology itself? The evidence from human research is scant, and where it does exist, does not tend to support this hypothesis. The animal research, on the other hand, offers the possibility that in addition to the compensatory mechanism, NA optimization may also reduce pathology, or at least diminish the neural toxicity-inducing effects of pathology (Heneka et al., 2010), and there is some limited human evidence in support of this also (Landau et al., 2012).

Fig. 1 schematically outlines the hypothesized role of NA in cognitive reserve, outlining the 2 possible modes of action that NA may have in facilitating both compensation to the disease processes, and also to modifying the disease processes themselves.

While accepting that the balance of the human evidence is for an indirectly protective effect of cognitive reserve on resistance to pathology rather than on the pathology itself—the compensatory theory—a hypothetical role for noradrenaline in mediating between cognitive reserve and reduced risk of AD offers a number of potentially useful lines of research to test this hypothesis. Mental stimulation or cognitive enrichment effects may for instance be potentiated by noradrenergic agonists, with the sorts of enhanced rehabilitation effects that have been found, for instance, in stroke rehabilitation (Crisostomo et al., 1988; Walker-Batson et al., 2001). Use of possible NA markers such as pupil dilation may further offer a method for more precisely measuring how cognitive reserve variables affect the ability to compensate for neurodegenerative pathologies. If this is successful, then it may be possible to quantify and hence control for these variables which otherwise complicate the evaluation of novel pharmaceutical agents whose symptomatic effects may be otherwise masked in patients with high
cognitive reserve. Furthermore, by identifying such a possible biological correlate of cognitive reserve, it may be possible to more easily identify people in the very early stages of Alzheimer’s disease, with a view to offering pharmacological treatment before too much neuronal death has occurred because of amyloid toxicity or other mechanisms. Finally, the intriguing possibility—supported largely by animal research—that NA may directly affect the AD disease process, is 1 which demands further testing and exploration.

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