Parkinsonism and Related Disorders xxx (2013) 1–7

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review

# Cognitive reserve in Parkinson's disease: A systematic review and meta-analysis

John V. Hindle [a,b,*], Anthony Martyr [c], Linda Clare [c]

[a] School of Medical Sciences, Bangor University, Bangor, United Kingdom
[b] Department of Care of the Elderly, Betsi Cadwaladr University Health Board, Llandudno Hospital, Conwy, United Kingdom
[c] School of Psychology, Bangor University, Bangor, United Kingdom

ARTICLE INFO

*Article history:*
Received 5 April 2013
Received in revised form
19 August 2013
Accepted 20 August 2013

*Keywords:*
Parkinson's disease
Cognition
Dementia
Cognitive reserve
Education

ABSTRACT

*Background:* The concept of cognitive reserve is proposed to explain the mismatch between the degree of pathological changes and their clinical manifestations and has been used to help understand the variation in the rate of cognitive decline and the development of dementias. It is not clear whether this concept applies to cognitive performance, cognitive decline and dementia in Parkinson's disease (PD).
*Methods:* A systematic review was conducted using the most commonly described proxies for cognitive reserve of education, occupation and leisure activities. Thirty four papers were found on education and cognition in PD but there were no studies of the other proxies of reserve. A random effects meta-analysis was used to assess the associations between education and cross-sectional cognitive assessments, longitudinal global cognitive decline and a long term dementia diagnosis.
*Results:* There was a significant association between higher education and cross-sectional performance of MMSE, global cognition, mild cognitive impairment, attention, executive function, visuospatial function and memory. There was a small but significant association between higher education and a reduced rate of cognitive decline. There was no association with a final dementia diagnosis. There was not enough information to perform an analysis on the rate and timing of transition to dementia.
*Conclusions:* Higher levels of education are associated with significantly better cognitive performance and a small but significant slowing in cognitive decline but are not associated with a reduction in long-term dementia in PD. More detailed, standardized, longitudinal studies are required to study conclusively the effects cognitive reserve in PD.



## 1. Introduction

Cognitive reserve has been proposed to explain the mismatch between the degree of brain damage or pathological changes and clinical manifestations [1] including the variation in the rate of cognitive decline and the development of dementias such as Alzheimer's disease (AD) [2]. It is not clear whether cognitive reserve affects the development of cognitive impairment and dementia in Parkinson's disease (PD).

### 1.1. Cognitive reserve

Cognitive reserve postulates that individual differences in cognitive processes or neural networks underlying task performance allow some people to cope better with brain damage than others [1]. The cognitive reserve hypothesis states that these individual differences in the processing of tasks provide reserve against brain pathology [2]. Cognitive reserve has been divided into passive and active forms [1]. Passive reserve, sometimes called brain reserve, comprises long standing inter-individual variations in the brain which allow some people to cope better. Life experiences can influence brain reserve through processes that include neurogenesis. In active reserve, also sometimes called cognitive reserve, the brain actively enlists pre-existing cognitive programmes and compensatory strategies. The demarcation between active and passive models is equivocal and the concepts are now subsumed under the single heading of cognitive reserve [2]. Childhood intelligence, higher education and level of occupation contribute to cognitive reserve which may influence cognitive aging and decline [2,3] although not all studies confirm this [4,5]. Although the theory of cognitive reserve suggests that performance in high reserve is maintained despite the severity of pathology, one study has shown that factors promoting cognitive reserve may themselves also be protective against amyloid related cognitive impairment [6] resulting in a lower risk of AD.

* Corresponding author. Llandudno Hospital, Llandudno, Conwy LL30 1LB, United Kingdom. Tel.: +44 1492 862366.
*E-mail address:* j.v.hindle@bangor.ac.uk (J.V. Hindle).

1353-8020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.parkreldis.2013.08.010

Cognitive reserve has been associated with a reduced rate of conversion from mild cognitive impairment (MCI) to dementia, and decline in executive function, attenuating the effects of brain atrophy [7]. A systematic review has confirmed that higher reserve is associated with less cognitive decline with time [8]. Cognitive reserve has been proposed to be associated with protective effects in other disorders including delirium [9], schizophrenia, bipolar disorder and depression [10].

All studies use proxies for cognitive reserve with education, occupation, leisure activities and cognitive activities having the most supportive evidence [1,2,10] and have been used in a previous systematic review of cognitive reserve and cognitive decline [8]. Less common proxies include height, head and brain size [11] and some such as bilingualism are controversial with both positive [12] and negative results [13,14]. Structural and functional imaging has been used to explore the relationship between cognitive reserve, brain structure and function, and cognitive decline [11]. Animal studies have shown that early cognitive and behavioral enrichment, which may enhance cognitive reserve, can help protect against age related cognitive decline possibly through promotion of neurogenesis later in life [15]. Late life cognitive activities may continue to influence cognitive reserve [16] which may provide the substrate for cognitive training and rehabilitation [1,2].

### 1.2. Cognition in PD

Up to 25% of non-demented PD patients will have MCI and are at increased risk of developing PD dementia (PDD) [17]. Frontostriatal executive deficits in PD [18] progress as a function of disease duration [19] whereas dementia in PD is predicted more by posterior cortical deficits of visuospatial function, memory and language [19–21]. The Sydney Study has shown that after 20 years dementia affects at least 80% of people with PD, most commonly after the age of 70 years although the long term numbers in the study were relatively small [22]. The main risk factor for PDD is current age, but more severe motor symptoms and postural instability with gait disorder, MCI, a family history of dementia, and depression are also important [20,23,24]. One early study suggested that a low level of education may be a risk factor [25].

Previous reviews have promoted a role for cognitive reserve in PD [26,27]. A recent paper on the effects of education and premorbid intelligence on cognition in PD suggested that cognitive reserve needs to be taken into account when monitoring the evolution of cognition in PD but that verification of results on a larger patient sample would be desirable [28]. This systematic review and meta-analysis aims to look at the evidence for the effects of cognitive reserve in PD in detail by examining standard proxies for cognitive reserve described in the literature. The hypotheses are that (1) proxies of reserve should be associated with a beneficial effect on cross sectional performance of cognitive tests, (2) produce a slower rate of decline in cognition, and (3) delay the onset but not prevent dementia in PD.

## 2. Method

### 2.1. Search method

A systematic review of the literature was conducted using the databases Psycinfo, Pubmed, CINAHL and Cochrane supplemented by a manual search of the references from included papers. The search was based on the most commonly used proxies for cognitive reserve, namely education, occupation and leisure activities.

The search terms used were “Parkinson’s disease” AND “cognitive reserve”, “Parkinson’s disease” AND “dementia” OR “cognition” AND “education”, “Parkinson’s disease” AND “dementia” OR “cognition” AND “occupation”, “Parkinson’s disease” AND “dementia” OR “cognition” AND “leisure”, “Parkinson’s disease” AND “cognition” AND “longitudinal”, “Parkinson’s disease” AND “cognition” AND “progression”, “Parkinson’s disease” AND “cognition” AND “prognosis”.

### 2.2. Inclusion and exclusion criteria

Research articles were included which had been published over 20 years (January 1993–January 2013). Studies had to utilize at least one standard neuropsychological test or diagnostic tool for dementia or cognitive impairment. Cross-sectional and longitudinal studies were included. In order to be representative of PD as a whole, studies were included that used unselected outpatients, community samples and incident cases. Studies which only utilized highly selected patients such as those undergoing deep brain stimulation or scanning were excluded. Reports published only in abstract form were excluded. The abstracts were screened for suitability and potentially relevant papers reviewed in full, references screened, (JVH) and then papers selected for inclusion through structured discussion based on a checklist of the inclusion criteria (JVH, LC). The included papers were independently reviewed (JVH and LC), data extracted using a standard datasheet which included study type, demographics, PD diagnosis and severity measures, the proxies of cognitive reserve, neuropsychological tests, statistical methods, results, conclusions, interpretation, limitations and missing data (JVH) and prepared for analysis (JVH, AM). Where data from included papers were incomplete and missing data could potentially add to the meta-analysis authors were contacted and a second contact made two months later to the corresponding author and senior author if there was no response.

### 2.3. Statistical analysis

An analysis was undertaken for the effects of education on cognition in PD since this was the only proxy of cognitive reserve with sufficient available data. Studies used various measures of education including mean values for years, actual years and definitions of low and high education based on differing cut-offs depending upon local definitions with the latter taking into account local norms. For simplicity in the analysis we used any available result and effect size of education from each paper independent of the definition of education. Neuropsychological tests from domains which were used in more than one cross-sectional study and more than one longitudinal study were selected for the analysis (Table 1); an additional analysis was conducted for education and a long-term DSM diagnosis of dementia (either DSM-III-R or DSM-IV). For the analysis, neuropsychological tests measuring a number of aspects of cognition were grouped based on definitions in two standard psychology textbooks [29,30], into screening tests of global cognition, frontal function (the Frontal Assessment Battery FAB), memory, attention, executive and visuo-spatial functions. The results for studies using diagnostic categories based on all different definitions of MCI were analysed together as were results of studies based on all different definitions of dementia (Table 1).

Effect sizes were calculated using the procedure outlined by Borenstein et al. (2009) [31]. If a study reported correlations these were entered directly, if a study reported $p$ values or included regression analyses, odds ratios, $t$ or $F$ statistics these were converted to correlations. A standardized correlation direction was used, and

**Table 1**
Neuropsychological tests included in domains for meta-analysis.

| Cognitive domain | Tests |
|---|---|
| Dementia | DSM-III-R, DSM IV |
| Mild cognitive impairment | MCI—Various definitions used—see Table 2 in Supplementary Material |
| Global cognition | Folstein Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), modified Mini Mental State (mMMS), (Dementia Rating Scale (DRS), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score. |
| Clinical assessment of frontal function | Frontal Assessment Battery (FAB) |
| Memory | Rey Osterrieth Complex Figure (ROCF) delayed recall, Rey Auditory Verbal Learning Test (RAVLT) 1, 2 and 3, California Verbal Learning Test (CVLT), Wechsler memory scale (WMS). |
| Attention and processing speed | Number cancellation 1 and 2, Digit span forwards, Trail making test (TMT) A, Stroop A, Wechsler Adult Intelligence Scale letter number sequence (WAIS-III-R). |
| Executive | Semantic fluency, phonemic fluency, Digit span backwards, Tower of Hanoi time and moves, Wisconsin Card Sorting Test (WCST), Trail making test (TMT) B, Stroop B. |
| Visuo-spatial | Benton Judgement of Line Orientation (JLO), Judgement of line orientation (JOLO), Mental rotation test (MRT), Rey Osterrieth Complex Figure (ROCF) copy |

Please cite this article in press as: Hindle JV, et al., Cognitive reserve in Parkinson’s disease: A systematic review and meta-analysis, Parkinsonism and Related Disorders (2013), http://dx.doi.org/10.1016/j.parkreldis.2013.08.010