REVIEW ARTICLE

Assessment of cognitive reserve

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Abstract
Cognitive reserve (CR) is a construct that can be used to describe individual differences in the relationship between brain state and cognitive status. It refers to an individual's potential to limit cognitive decline despite the effects of brain pathology and ageing. Multiple longitudinal population-based studies have shown that factors that increase CR contribute to dementia risk, and this has been confirmed by pathological and clinical data. CR cannot be directly measured because it is the cumulative effect of several protective and risk factors. However, the use of surrogate measures of CR remains controversial. Proxy-based measurements are quantitative methods of assessing CR. Commonly-used proxies for CR include years of education, occupational attainment and participation in leisure activities. In this review, we identify and summarize published methodologies for quantitative assessment of CR from overseas, and outline the small number of CR proxy-focused studies from Japan. CR can be used to infer prognostic predictors of cognitive function due to lesion or injury, as well as the extent of cognitive decline. Better assessment scales for CR could lead to more effective cognitive rehabilitation.

INTRODUCTION

Cognitive reserve (CR) describes a discrepancy between brain pathology and actual levels of cognitive function (Stern, 2009; Stern, 2012; Stern, 2020). Even if extensive neuropathological findings suggest there should be some cognitive impairment, some individuals may surprisingly retain good cognitive function. CR refers to an individual's potential to limit cognitive decline despite the effects of brain pathology and ageing. Individuals with high CR are theoretically less likely to have functional impairment following brain injury than those with low CR. Further, there will likely be variation in the degree of cognitive decline between individuals, even those with healthy ageing (Stern, 2002).

CR is, however, a hypothetical/theoretical concept and it cannot be directly measured. Quantitative methods of assessing CR currently include proxy-based measurement methods using years of education, and/or in relation to occupational and leisure activities. Positive associations between CR proxies and cognitive abilities or status have been consistently observed (Staekenborg, 2020; Yang, 2020), while results from longitudinal tests are mixed (Jin, 2023; Lane, 2017; Wilson, 2019; Zahodne, 2015). Many studies have focused on the role of just one CR proxy, such as educational background or occupational complexity (Staekenborg, 2020; Lane, 2017; Wilson, 2019; Zahodne, 2015).

Many questionnaires for CR assessment have been published overseas, but there are likely to be a number of cultural differences and differences in the use of established assessment methods. Interestingly, in a study based in the USA, the impact of years of education on cognitive functioning has been reported to vary by race (Avila, 2020). We therefore think it is necessary to establish assessment methods unique to Japan. In this review, we outline proxy-based measurement, which is frequently used overseas, and then introduce the questionnaires that have been used to assess CR in Japan.

The contribution of factors that increase CR in relation to dementia has been made evident in several studies (Fratiglioni, 2004; Stern, 2009) and has been confirmed by pathological and clinical data (Bennett, 2003). According to one classification, educational history is an early life factor (Fratiglioni, 2020), and the longer the period of formal education, the higher the reserve capacity will be (Seblova, 2020). Into mid-life, occupation is a factor; the higher the complexity of the decisions required at work, the higher the reserve capacity will be (Then, 2014). Psychologically stressful or less stimulating or passive jobs may impede the development of CR (Andel, 2012; Wang, 2017). In later life, social relationships and leisure activities are thought to contribute to reserve capacity (Andel, 2012; Wang, 2017). Social isolation, for example, has been reported to contribute to cognitive decline and the development of dementia (Evans, 2019). Leisure activities in old age have also been widely studied as a factor that increases CR (Hertzog, 2008; Yates 2016). One study synthesized an original proxy index for each of the three periods of life: early, middle and late life (Wang, 2017). Using multiple models, they showed that exposure to factors that increase CR during all three periods of life was associated with lowering the risk of developing dementia, and this supports the possibility of an accumulation of reserve capacity.

As mentioned above, CR is predicted to be related to and to accumulate via previous education, occupation and leisure activities, which further influence functioning from the onset of certain neuropsychiatric disorders. This concept of CR should therefore be considered in various psychiatric and neurological disorders. For example, a relationship between brain function and CR has been reported in disease recovery and after surgery (Ebina, 2023). Healthcare professionals may consider the degree of CR, including consideration of an individual's background and qualities, as a reference when considering their diagnosis and treatment, their prognosis, and the potential for their social reintegration. This review also introduces Japan-based studies on CR and prognosis.

CR EVALUATION SHEETS FROM OUTSIDE OF JAPAN

Widely-reported studies from outside of Japan include the Cognitive Reserve Index Questionnaire (CRIq) (Nucci, 2012), the Cognitive Reserve Scale (CRS) (Leon, 2011), the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela, 2007), and the Cognitive Reserve Questionnaire (CRQ) (Rami, 2011). The characteristics of these assessment tables and some of the measurement properties (Kartschmit, 2019) are summarized in Table 1.

CRIq has the advantage of having been adapted into many languages. CRS and LEQ, meanwhile, features three life stages, allowing it to specifically address earlier stages of life. CRQ has the key advantage of a shorter application time for the clinical population compared with CRIq, LEQ and CRS. CRQ has only eight questions and only approximately 2 min is required to complete it. CRIq uses dichotomous responses, which allows questions to be considered and measured in terms of frequency or proficiency. CRS uses a five-point Likert-type scale. LEQ requires a combination of a six-point Likert scale and free responses on the frequency and degree of participation in specific activities, while CRQ uses a three to six-point Likert-type scale (Nogueira, 2022).

The measurement characteristics of each of these questionnaires were determined based on the COnsensus based Standards for the selection of health Measurement INstruments (COSMIN). Each questionnaire was first examined for validities (cross-cultural validity, content validity, construct validity, convergent validity, structural validity, internal consistency, reliability, measurement error, and responsiveness). The measurement properties of each questionnaire and the consistency of above assessments given the number of studies are summarized in Table 1.

'Content validity' is the extent to which the content of the CR questionnaire adequately reflects the CR construct (Stern, 2009), while 'structural validity' is the extent to which the questionnaire scores adequately reflect the dimensions of the CR construct. 'Internal consistency' is the degree of interrelationship between the items, while 'reliability' is the proportion of total variance due to 'real' differences between participants. 'Construct validity' is the extent to which the questionnaire scores are consistent with the CR hypothesis (Pettigrew, 2019), while 'convergent validity' is the extent to which the total questionnaire scores are related to common CR proxies (e.g., education, pre-sickness intelligence). Finally, 'responsiveness' is the ability of the CR questionnaire to measure changes in cognitive function over time (Kartschmit, 2019). Kartschmit states that among these questionnaires, questionnaires CRS and LEQ are relatively advantageous (Kartschmit, 2019).

Table 1. General characteristics of the studied CR questionnaires for general adult population in foreign countries

Questionnaire	Applicable age	Number of items, response options	Dimensions/ subscales	time	Available in	Content validity	Structural validity	Internal- consistency	Reliability	Construct validity	Convergent validity	Responsiveness
CRIq	Unrestricted	20 items, numerical scale (number of years) and dichotomous answers	Education, working activity, leisure time	15 min.	Italian, Greek, English, French, German, Spanish, Portuguese, Catalan, Czech, Dutch, Latvian	+	NA	?	NA	+	+	?
CRS	3 stages (18-35 years, 36-64 years, over the age of 65)	24 items, 5-point Likert scale	Daily activities, training information, hobbies, and social life	15 min.	Spanish, Italian, English	+	+	-	+	+/-	+/- (3 studies)	NA
LEQ	3 stages (between 13-30 years, 30-65 years, over the age of 65)	42 items, 6-point Likert scale and open questions	Specific (education, occupation) and non-specific mental activity (leisure time) for each life-span	30 min.	English	+	?	-	+	+/-	+	+
CRQ	Unrestricted	8 items, 3 to 6-point Likert scale	Education, parent's education, leisure time, bilingualism	2 min.	Spanish, Portuguese	?	+	+	NA	+	+	-

CRIq, Cognitive Reserve Index Questionnaire; CRS, Cognitive Reserve Scale; LEQ, Lifetime of Experience Questionnaire; CRQ, Cognitive Reserve Questionnaire. Content validity, The degree to which the content of the CR questionnaires adequately reflects the CR construct as defined by Stern et al. (Stern, 2009); Structural validity, The degree to which the scores of the questionnaire adequately reflect the dimensionality of the CR construct, which can be ascertained with item response theory test, exploratory or confirmatory factor analysis.; Internal- consistency, the degree of interrelationships among items, which is calculated with the Cronbach's alpha; Reliability, The proportion of total variance due to 'real' differences between participants; Construct validity, the degree to which the scores of the questionnaire are in line with the CR hypothesis; Convergent validity, The degree to which the total score of the questionnaire is related to a common CR proxy (e.g. education, premorbid intelligence); Responsiveness, The capacity of a CR questionnaire to measure cognitive changes over time. + or -, moderate evidence positive or negative results; +/-, conflicting evidence; ?, only methodological studies or not all information for proper assessment reported; NA, not applicable. Modified from the report by Kartschmit et al. (Kartschmit, 2019).

In clinical studies, CRIq has been conducted in patients with hepatitis (Amodio, 2017), multiple sclerosis (Fenu, 2016) and dementia (Puccioni, 2012). CRQ has been conducted in patients with mild Alzheimer disease (AD) (Rami, 2011) and mild cognitive impairment (MCI) (Harris, 2015). CRS and LEQ mostly targeted people without neurological or psychiatric disorders who were recruited in the community. This suggests that CRIq and CRQ will be effective in sick populations, while CRS and LEQ will be effective in healthy populations. Another consideration is that LEQ is a long questionnaire that contains many different important CR proxies, whereas the CRS is a measure of CR across educational and occupational status and it is a relatively short questionnaire that can be introduced into large epidemiological studies.

RESEARCH USING CR PROXIES IN JAPAN

In this section, we summarize the CR proxies in studies conducted in Japan (Table 2). Education, work complexity and leisure activities are also commonly used components of CR assessments in Japan.

Two reported studies used education and pre-morbid intelligence quotient (IQ) as proxies, and the pre-morbid IQ has also been used in some cases. It is important to obtain information on previous cognitive status, mainly in clinical populations, which is often inaccessible. In many cases, premorbid intelligence is an indirect means of addressing this and it plays an important role in the diagnosis of cognitive decline. Moreover, it is also considered to be a proxy for CR (Starr, 2008). A 2015 report cross-sectionally investigated whether education, pre-morbid IQ and brain imaging morphology were associated with the risk of progression from MCI to AD (Osone, 2015). The results showed a significant difference between these two groups in pre-morbid IQ measured by the Japanese version of the National Adult Reading Test (JART); the AD group had significantly lower JART scores. No statistical differences were found between the two groups in years of education or in the loss of grey matter in the intra-olfactory and hippocampal regions. Pre-morbid intellectual functioning may therefore explain the discrepancy in clinical status between patients with MCI and patients with AD with similar levels of brain pathology and comorbid medical impairments. A later report investigated whether CR captured as educational history and pre-morbid IQ (assessed with JART), or brain reserve (BR; i.e., brain volume), was associated with conversion and reversion in MCI patients at 12-month follow-up (Osone, 2016). There were no statistically significant differences between the two groups, reversion and conversion in MCI patients after 12 months of follow-up with regard to years of education. Voxel-based morphometric MRI showed no significant differences in intra-olfactory and hippocampal grey matter loss between the reversion and conversion groups; the patients in the reversion group who returned to normal from MCI had higher pre-illness IQ scores at baseline than patients in the conversion group. Higher CR thus contributed to protection against cognitive decline during the 12-month follow-up period, whereas higher BR at baseline was the strongest predictor of return and conversion. In both papers, education was represented by years of formal education. From these two papers, it appears that the contribution of educational history is low in the pathogenesis of MCI and AD, and its indication as a CR proxy in these conditions is low.

One report investigated the interaction effects of amyloid beta/tau load and educational/occupational/socioeconomic status as proxies for CR on cognitive performance (Yasuno, 2020). Predictors of ADAS-cog were determined based on the interaction between tau protein accumulation and CR proxies (education, occupation and socio-economic status) in clinically cognitively normal individuals, patients with MCI, and patients with AD. All assessments were based on the Hollingshead Index of Social Status (HI). Education was classified into HI scores 1-7, occupation into HI scores 1-9 and socio-economic status into four levels based on education level × 3 + occupation × 5 (Hollingshead, 1957). A significant positive partial correlation was shown between education level and tau pathology in the Braak stage 1/2 area, with significantly higher tau accumulation in the more educated participants when ADAS-cog scores were used as covariates. The interaction between tau and education was a good predictor of cognitive function, with a stronger association between higher tau accumulation and higher ADAS-cog scores in participants with lower levels of education. The interaction between tau and education was a good predictor of cognitive function, with higher tau accumulation being more strongly associated with higher ADAS-cog scores in less educated participants than in more highly educated participants. The results indicate a protective effect of education on cognitive impairment in the early stages of AD and that education may have a beneficial effect by reducing the negative cognitive effects of tau aggregation.

A study aimed to determine whether discrepancies between cognitive and imaging findings are associated with CR (Sato, 2021). It analyzed factors associated with the degree of cognitive impairment and discrepancies between MRI (medial temporal lobe atrophy) and SPECT (posterior cerebral hypoperfusion) findings in patients with suspected AD. The discrepancy index was calculated as the difference between the degree of imaging abnormality and the degree of cognitive impairment. Proxies for CR in this study were education, occupation, comorbidities, disability and frailty, and leisure activities over a 12-month period. Education was classified into three groups (years of education < 9 years, 9-12 years and >12 years) and occupation was classified into three levels according to job complexity (Anderson, 2007). Comorbidities were determined by the Valenzuela comorbidity index (CCI) (Charlson, 1987) for the incidence of the major chronic diseases. Disability and frailty were assessed by the Kihon Checklist (KCL) (Satake, 2016; Sewo, 2016). The lifestyle behavior assessment was modified and classified into three levels. Leisure activity and education were significantly associated with discrepancies between cognitive and imaging findings. The three groups of levels of CR based on leisure time activity and education showed that the high CR group had significantly greater discrepancy index than the moderate and low CR groups. Discrepancies between cognitive and imaging findings in patients with AD were suggested by the report to be associated with CR and can be measured by a combination of two indicators: leisure time activity and education.

Another study sought to determine the effect of CR on the rate of cognitive decline and cerebral blood glucose metabolism in patients with amnestic MCI (Kato, 2022). CR proxies were based on educational level only, and subjects were divided into two groups: the highly educated group (≥13 years of schooling) and the less educated group (≤12 years of schooling). The higher education group revealed more severe hypometabolism than the lower education group. Glucose metabolism in the hippocampus and temporoparietal regions was inversely related to years of schooling in the high- and low-education groups. The higher-educated group also showed a more rapid decline in cognitive function during the three-year follow-up period. Patients with higher CR of amnestic MCI are suggested to have lower brain glucose metabolism and faster cognitive decline.

Another group studied the relationship between AD-related neuroimaging biomarkers such as educational history, depression, amyloid-β deposition, glucose metabolism and brain volume and ApoE genotype in three groups of normal cognitive, MCI, and AD, and their relationship with ApoE genotype (Wada, 2018). In the normal cognitive group, a relationship was found between total brain volume and age and sex, while in the MCI group, educational history, age and sex were related to total brain volume. In the AD group, ApoE genotype, MMSE, total brain volume and hippocampal volume were related. In summary, educational duration was positively associated with total brain volume only in participants with MCI. However, duration of education did not correlate with amyloid-β deposition or brain metabolism in any of the groups. Education may exert a protective effect on total brain volume during MCI, but not during normal cognitive or AD.

The relationship between factors constituting reserve capacity among older people living in the community has recently been studied (Ishioka, 2023). Education in youth, work complexity in middle age and leisure activities in later life were used as CR proxies. Education was categorized into three groups: non-graduation from high school, high school graduation and further/higher education. Job complexity in middle age was retrospectively assessed in three dimensions: data, people and goods. Questions were asked about the specific occupation in which they had worked the longest, including age of entry, age at end of employment, job title, industry, size of employment in the company/office and whether they were involved in management tasks. The work complexity score for each dimension consisted of three indicators: (a) position-based score, (b) content-based score and (c) effort-based score (Ishioka, 2015). Leisure activities in later life were classified into 12 leisure categories according to type. These categories were further used to extract a latent factor model consisting of eight leisure categories: physical activity, games, personal social activity, public social activity, developmental activity, hobbies, technology use and travel. Age, gender and childhood ability were also included as control variables. Primary school language and arithmetic abilities were rated on a scale of below average, average and above average, respectively. Educational history was shown to be indirectly related to cognitive ability through the mediation of work complexity and leisure activities in old age. These results indicate that factors in close temporal proximity are directly related to cognitive ability, suggesting that reserve capacity may be enhanced in adulthood and old age.

Table 2. General characteristics of proxy for CR for Japanese

Study	Target population (years)	Assessed CR proxy	Cognitive scale	Results
Osone, 2015	Patients with MCI (mean age; 77.7 y: n=51) or AD (mean age; 79.3 y: n=59)	Education, premorbid IQ (JART)	CDR, MMSE, ADAS-J	Comparison of preoperative IQ, educational history and brain imaging morphology in the MCI and AD groups showed that only pre-onset IQ differed between the MCI and AD groups. No statistical differences were found between the two groups in years of education or in the loss of grey matter in the intra-olfactory and hippocampal regions.
Osone, 2016	Patients with MCI (mean age; 77.5y: n=123)	Education, premorbid IQ (JART)	ADAS-cog, MMSE	Patients in the reversion group who returned to normal from MCI after 12 months of follow-up had higher baseline IQ scores and higher brain reserve compared with patients in the conversion group. Years of education were not associated with MCI reversion and conversion.
Wada, 2018	Normal cognitive people, Patients with MCI or AD (55-90 y: n=1304)	Education	CDR, MMSE	Years of education was positively associated with brain capacity in the MCI group, but not in the normal cognitive or AD groups.
Yasuno, 2020	Clinically normal subjects and Patients with MCI and AD (mean age; 72.4y, 61-80 y: n=127)	Education (HI), occupation (HI), socioeconomic status (HI)	ADAS-cog	There was a significant positive partial correlation between education level and Braak stage 1/2 area tau pathology, with significantly higher tau accumulation in participants with higher education when ADAS-cog scores were used as a covariate. The interaction between tau and education was a good predictor of cognitive function, with a stronger association between higher tau accumulation and higher ADAS-cog scores in participants with lower levels of education.
Sato, 2021	Patients with probable AD (58-92 y: n=135)	Education, leisure activity during the previous 12 months, comorbidities (CCI), occupation, disability/ frailty (KCL)	MoCA-J	Leisure activity and education were significantly related to the discrepancy between cognitive function and brain imaging results (discrepancy index). The results showed that leisure activity and education were significantly related to the discrepancy index between cognitive function and brain imaging results. When CR levels were classified into three groups based on these two items, the discrepancy was more pronounced in the group with higher CR levels.
Kato, 2022	Patients with amnestic MCI (mean age; 71.9 y: n=57)	Education	ADASJ-cog, CDR, EMCL, WMS-RLM	More severe hypometabolism was evident in the high-education group than in the low-education group. Glucose metabolism in the hippocampus and temporoparietal regions was inversely correlated with years of schooling in the high- and low-education groups. The higher-educated group also showed a more rapid decline in cognitive function during the three-year follow-up period.
Ishioka, 2023	Community-dwelling elders of two cohorts (69-71 y, 79-81 y: n=1721)	Early-life education, three domains of work complexity (data, people, and things) based on the longest-held occupation, leisure activities in late-life	MoCA-J	Educational history was indirectly related to cognitive ability through the mediation of work complexity and leisure activities in old age.

AD, Alzheimer's disease; MCI, mild cognitive impairment; IQ, Intelligence Quotient; JART, Japanese version of the National Adult Reading Test ; HI, Hollingshead Index of Social Status; CCI, Charlson comorbidity index; KCL, Kihon Checklist; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; ADAS-J, Japanese version of the cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale, MoCA-J, Montreal Cognitive Assessment; EMCL, Everyday Memory Check List; WMS-R LM, Logical Memory Subset of the Wechsler Memory Scale Revised

We have outlined Japanese research on CR evaluation. Education as a CR proxy has a weak relationship with normal cognitive function and AD, and no consistent results have been obtained for MCI. In the future, it will be important to consider questionnaires that are used overseas in line with life stages. The term 'cognitive resilience' as has been endorsed as a combination of BR, CR, compensatory and brain maintenance (Stern, 2019). In clinical cases, this cognitive resilience helps to address ageing and to reduce the impact of symptoms due to neurodegeneration. As part of cognitive resilience, the use of a CR assessment for clinical populations is important to detect both those with low CR (and thus fewer neural resources to cope with the disease), and those with high CR levels and who benefit from the palliative effects of behavioral symptoms. CR can be used to infer prognostic predictors of cognitive function due to lesion or injury, as well as the extent of cognitive decline. Better assessment scales for CR could lead to more effective cognitive rehabilitation.

CONCLUSION

We reviewed the CR questionnaires that are widely used outside of Japan and summarized the knowledge about CR used in domestic CR studies. Questionnaires must be carefully selected based on the location, background of subjects, and the purpose of use. There are few CR studies based in Japan, so consideration of the use of questionnaires that are used overseas in line with life stages is required.

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