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Cognitive reserve in amyotrophic lateral sclerosis (ALS): a population-based longitudinal study

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ABSTRACT

Background Amyotrophic lateral sclerosis (ALS) is often associated with cognitive and/or behavioural impairment. Cognitive reserve (CR) may play a protective role in offsetting cognitive impairment. This study examined the relationship between CR and longitudinal change in cognition in an Irish ALS cohort.

Methods Longitudinal neuropsychological assessment was carried out on 189 patients over 16 months using the Edinburgh cognitive and behavioural ALS screen (ECAS) and an additional battery of neuropsychological tests. CR was measured by combining education, occupation and physical activity data. Joint longitudinal and time-to-event models were fitted to investigate the associations between CR, performance at baseline and decline over time while controlling for non-random drop-out.

Results CR was a significant predictor of baseline neuropsychological performance, with high CR patients performing better than those with medium or low CR. Better cognitive performance in high CR individuals was maintained longitudinally for ECAS, social cognition, executive functioning and confrontational naming. Patients displayed little cognitive decline over the course of the study, despite controlling for non-random drop-out.

Conclusions These findings suggest that CR plays a role in the presentation of cognitive impairment at diagnosis but is not protective against cognitive decline. However, further research is needed to examine the interaction between CR and other objective correlates of cognitive impairment in ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of the upper and lower motor neurons that results in a relentless paralysis and death.¹ Fifteen percent of patients with ALS meet criteria for frontotemporal dementia (FTD), while 30% of non-demented patients will have cognitive impairment.² These changes have a detrimental effect on patient adherence to treatment, their survival and are associated with greater caregiver burden.^{3–5}

It remains unclear as to the point at which cognitive impairment emerges and the extent to which cognition declines in ALS. Recent studies suggest that cognitive decline coincides with disease stage (using both Kings and MiTos staging

systems),^{6,7} although these data are based on cross-sectional design. Longitudinal studies have largely found that cognitive impairment emerges early in the disease. Those who are impaired at diagnosis subsequently decline over time while those who are unimpaired at diagnosis appear to remain cognitively intact throughout their illness.^{8–11} These studies are often limited by their high attrition rates, biasing estimates of true decline due to drop-out of those with faster disease progression. Joint longitudinal and time to event models (joint models) have gained popularity for their utility in handling data missing-not-at-random and improving statistical power.¹² By applying joint modelling to longitudinal neuropsychological data in ALS, we can get a better estimate of the true rate of cognitive decline.

A potential mediator of cognitive change, which may account for some of the varied presentations in ALS, is cognitive reserve (CR). Theories of CR stipulate that neural enrichment, through education, occupation and physical activity increases an individuals' neural resources (eg, greater grey matter volume or white matter tract integrity).¹³ As the disease spreads across networks, individuals recruit reserve neural resources to deal with cognitive demands, a process known as compensation. Educational attainment, occupational complexity and leisure activity are often used as proxy measures of CR, either in isolation or combined to form a latent construct.

There is indirect evidence that CR plays a protective role in ALS. ALS patients with comorbid FTD are older, have lower educational attainment and poorer survival.¹⁴ Executive functioning and verbal memory are protected by CR in a range of other neurodegenerative conditions.^{14–18}

Here, we have examined the relationship between CR and longitudinal neuropsychological performance in ALS. We hypothesise that higher CR is associated with improved cognitive performance at baseline and with a reduced slope of decline over time. We have applied a multiple variable model, using the shared variance of several variables, to create a 'latent' measure of CR which can offer a less biased measure than using an individual proxy in isolation.¹⁹

METHODS

Participants

One hundred and eighty-nine patients with ALS were recruited for this longitudinal,

population-based research study. Participants were recruited as part of ongoing longitudinal studies of neuropsychological deficits in an Irish ALS cohort from 2012–2019.⁸ Participants were assessed within the first year of their diagnosis and reassessed three further times, 4 months apart. Assessments took place in a quiet room in Beaumont Hospital, Dublin, Ireland or in the participants home. Exclusion criteria included: (1) history of an intellectual or learning disability, (2) history of a comorbid neurological, psychiatric or medical condition affecting cognition, (3) alcohol dependence syndrome, (4) if the person was a non-native English speaker or (5) a comorbid diagnosis of FTD. Occupational history, education and physical activity data were derived from Irish EuroMOTOR project data, a study of environmental risk factors of ALS.²⁰ Clinical data were accessed through the Irish ALS register.

Materials

CR score was calculated by combining traditional proxies of CR, namely: education, occupation and physical activity. Education score was the total years an individual spent in full time education. Occupation was coded according to complexity using the International Standard Classification of Occupations-88, inverted so that jobs with increasing complexity had higher scores, and then categorised into nine categories ranging from 1 (elementary occupations) to 9 (legislators, senior officials and managers). Occupation score was the sum of years a person spent in each occupation multiplied by its category. This approach matches how the CR index questionnaire was developed,²¹ capturing the time an individual spent in a job as well as the cognitive complexity of that job. Physical activity score was the total number of years a person reported as engaging in each sport/exercise. Each CR subdomain was converted to a z-score using the sample mean and SD and then averaged to give a CR total score.

In the absence of direct biomarkers of the underlying spread of pathological changes, disease progression was approximated using time from disease onset to neuropsychological assessment,¹⁹ as described in previous studies.^{15 22 23}

The Edinburgh cognitive and behavioural ALS screen (ECAS) is a sensitive screening tool of cognition in ALS.²⁴ It measures three ALS-specific functions, language, verbal fluency and executive functioning, and 2 ALS non-specific functions, memory and visuospatial functioning. To examine cognition over time, while limiting the influence of practice effects, alternative ECAS versions were used, that is, ECAS A-B-C.²⁵

Participants were also administered the FAS verbal fluency test, the Boston Naming Test (BNT), the Reading the Mind in the Eyes Test (RMET), the Colour-Word Interference Test (CWIT), the Logical Memory test from the Wechsler Memory Scale-III and the Rey Auditory Verbal Learning Test (RAVLT). These provided accurate measurements of executive functioning,²⁶ verbal fluency,²⁷ language,²⁸ memory^{29 30} and social cognition.³¹ To limit the influence of motor disability, Verbal Fluency Index was calculated on verbal fluency tasks and total errors was used instead of completion time on the CWIT, as described in previous studies.³² Cognitive performance raw scores were converted to z-scores using test manuals and published age, IQ and gender matched healthy control normative data.^{26–31} A summary of each neuropsychological test, the cognitive domain it measures, and a brief description of the task can be found in [table 1](#).

Statistical analysis

Linear mixed effects models were used to examine the association between CR and neuropsychological performance over the course of 16 months. Linear mixed effects models are a robust means of dealing with missing data, a particularly relevant issue with such a rapidly progressing population with high attrition. We applied additional methods to cater for non-linear data (see online supplemental material). In these models the intercept and slope were fitted as random effects, allowing them to vary for each individual. Each mixed model included fixed effect terms for time, age, CR score and an interaction between CR and time. The fixed effect term for CR represents the association between baseline neuropsychological performance and CR. The time by CR interaction term represents

Table 1 Neuropsychological battery

Cognitive domain	Test name	Description
Cognitive screening	ECAS total	Composite score of ALS specific and ALS non-specific scores.
	ECAS ALS specific	Includes short tests of language, verbal fluency and executive functioning.
	ECAS ALS non-specific	Includes short tests of visuospatial functioning and memory.
Verbal fluency	FAS (unrestricted) fluency*	Generate as many words as possible beginning with F, A and S, 1 min for each letter.
	Restricted fluency*	Generate as many words as possible beginning with C, with only four letters. Given 1 min.
Language	Boston naming test	Name 30 items.
Social cognition	Reading the mind in the eyes test	Infer the emotional state from 30 faces, given four options on each item.
Memory	Logical memory (LM) WMS-III+—immediate recall	Recall two short stories, immediate recall and delayed recall after 20 min
	LM WMS-III—delayed recall	
	List recall RAVLT‡ immediate recall	Recall a list of 15 words five times, delayed recall after 20 min
	List recall RAVLT delayed recall	
Executive functioning	Colour-Word Interference Test (CWIT) inhibition§	Must identify the ink colour of incongruent word-colour pairs.
	CWIT switching/Inhibition§	Must switch between two rules; identify the ink colour or name the word of incongruent word-colour pairs

*Verbal fluency index was calculated to account for motor impairment.

+Wechsler Memory Scale, Third version.

‡Rey Auditory Verbal Learning Task.

§Total errors used instead of completion time to control for bulbar impairment.

ALS, amyotrophic lateral sclerosis; ECAS, Edinburgh cognitive and behavioural ALS screen; RAVLT, ‡Rey Auditory Verbal Learning Test; WMS, Wechsler Memory Scale.

Cognition

Table 2 Demographic characteristics, including age, education, sex, site of onset, time from onset to baseline, familial/sporadic family history and C9orf72 status at each time point

Participant characteristics	Time 1 (n=189)	Time 2 (n=117)	Time 3 (n=80)	Time 4 (n=49)
Age, mean years (SD)	63.59 (11.42)	61.64 (12.09)	60.52 (12.64)	58.94 (12.57)
Education, mean years (SD)	13.8 (3.82)	13.97 (3.41)	14.28 (3.36)	13.94 (2.93)
Sex, n				
Male	119	77	54	34
Female	70	40	27	15
Site of onset, n				
Bulbar	44	24	12	4
Spinal	145	93	69	45
Time from onset to assessment, mean months (SD)	19.48 (13.29)	25.4 (15.1)	30.11 (14.74)	34.53 (15.52)
ALSFRS-R, mean (SD)	36.5 (7.6)	33.43 (7.84)	32.34 (8.29)	31.4 (8.63)
Delta ALSFRS-R, change in ALSFRS-R per month	–	0.52	0.23	0.21
Familial/sporadic, n				
Familial	31	23	17	13
Sporadic	158	94	63	36
C9orf72 status, n				
Positive	15	11	6	4
Negative	174	106	75	45
El escorial diagnostic status, n				
Definite	92	50	33	23
Probable	59	44	29	14
Possible	38	23	18	12
Strong criteria status, n				
ALSn	140	89	67	43
ALSci	33	19	9	5
ALSbi	6	2	1	0
ALScbi	10	7	3	1

ALS, amyotrophic lateral sclerosis; ALSbi, ALS with behavioural impairment; ALScbi, ALS with cognitive and behavioural impairment; ALSci, ALS with cognitive impairment; ALSFRS-R, ALS Functional Rating Scale -Revised; ALSn, ALS with normal cognition and behaviour.

the association between the slope of change over time and CR. A Cox survival model was constructed with survival as the outcome variable, and known risk factors for shorter survival as predictors, namely age,³³ diagnostic delay,³⁴ site of onset³⁵ and C9orf72 repeat expansion status (see [table 2](#)).³⁶

The longitudinal mixed model and Cox survival models were then used to create joint longitudinal and time-to-event models (joint models), using the R package JMBayes.³⁷ This analysis enabled the model to control for non-random drop-out in our longitudinal data, resulting in less biased effect estimates. Joint models also provide a measurement of the association between each cognitive measure and death.³⁸ Analyses were carried out using R statistical software V.3.6.3.³⁹

Informed written consent was given by all participants.

RESULTS

Demographic information

Participant demographic information at each time point is provided in [table 2](#). Participants first assessment occurred on average 19 months after their first symptoms. Attrition rate was 79% over the course of the study, representative of the rapidly progressive nature of the disease.

CR as a predictor of cognition at baseline

CR score was a significant predictor of baseline performance on the ECAS (including ALS-specific and non-specific subscores), RMET, CWIT (inhibition and switching scores), BNT and logical memory (immediate and delayed recall). Higher CR was positively associated with higher test performance. However, CR was not a significant predictor of baseline verbal fluency or RAVLT (total or delayed) score (see [table 3](#)). Full model summaries are provided in online supplemental table 1.

CR as a predictor of longitudinal cognition

Longitudinal neuropsychological scores, adjusted for age, site of onset, diagnostic delay and C9orf72 status through joint modelling, are displayed in [figure 1](#).

Individuals were divided into high (CR z-score greater than 1), medium (CR z-score between –1 and 1) and low (CR z-score <–1) CR groups to illustrate the effect of CR over time. For ECAS, RMET, CWIT and BNT, high CR individuals displayed greater performance than medium and low CR groups over time. For logical memory, high medium and low CR regressed towards the mean over time, with high CR groups declining and low CR groups improving.

Table 3 Cognitive reserve fixed effect for each neuropsychological test from joint model summary

Outcome	β (SE)	95% CI	P value
ECAS total	0.37 (0.003)	0.11 to 0.64	0.003
ECAS ALS specific	0.40 (0.002)	0.21 to 0.59	<0.001
ECAS ALS non-specific	0.26 (0.003)	0.06 to 0.44	0.01
Reading the mind in the eyes	0.66 (0.005)	0.26 to 1.04	0.002
Verbal fluency (unrestricted)	0.49 (0.007)	-0.15 to 1.16	0.13
Verbal fluency (restricted)	0.61 (0.02)	-0.73 to 1.99	0.39
CWIT inhibition	0.87 (0.008)	0.27 to 1.49	0.009
CWIT switching	0.63 (0.09)	0.17 to 1.07	0.008
Boston naming task	0.55 (0.005)	0.13 to 0.98	0.01
RAVLT total	0.29 (0.004)	-0.02 to 0.59	0.07
RAVLT delayed	0.27 (0.004)	-0.15 to 0.58	0.25
Logical memory immediate	0.38 (0.004)	0.02 to 0.72	0.04
Logical memory delayed	0.56 (0.005)	0.11 to 0.99	0.03

ALS, amyotrophic lateral sclerosis; CWIT, Colour-Word Interference Test; ECAS, Edinburgh cognitive and behavioural ALS screen; RAVLT, Rey Auditory Verbal Learning Test.

Survival risk factors

Joint models rely on the construction of Cox survival models to control for non-random drop-out. Controlling for the effects of age, diagnostic delay, site of onset and C9orf72 repeat expansion status, lower ECAS ALS-specific and RAVLT total score were associated with shorter survival. Conversely, higher logical memory immediate score was associated with shorter survival. Table 4 displays the association between each longitudinal outcome and survival after joint modelling using JMBayes, specified with the current value association structure.

DISCUSSION

This study found that CR is associated with baseline differences in neuropsychological performance in a population-based cohort. These differences were most notable for ECAS, social cognition, executive functioning and confrontational naming, where higher performance in high CR individuals was maintained 16 months from baseline. Verbal fluency was not associated with higher CR despite the fact that fluency is often the most sensitive test for cognitive impairment in ALS. These findings may suggest that CR does not protect against fluency deficits, or that the disease has progressed to the stage where it has overcome any protective effect for this function.

For episodic memory (ie, logical memory tasks), high CR individuals performed better at baseline but then declined to a greater extent than low CR groups over time. This may suggest that CR plays a differential role in protecting functions commonly affected by ALS, namely executive functioning, language and social cognition, but is less influential on less implicated functions, such as memory.

ECAS ALS-specific deficits were associated with shorter survival, which is consistent with previous studies,³ as was RAVLT total score. Higher logical memory immediate score was associated with shorter survival. While executive impairment is a known risk factor for shorter survival in ALS, the role of memory is less established. Similar findings have been observed in Alzheimer's research, where individuals with higher CR perform better on memory tasks in the early disease stage, but then suffer from a more rapid disease decline.⁴⁰

These findings in an ALS cohort are similar to those of other neurodegenerative diseases. In Parkinson's disease high CR patients perform better on attention, executive functioning and

visuospatial tasks, and show a slightly reduced rate of decline.¹⁵ In Huntington's disease, higher CR is associated with better cognition in patients and in prodromal gene carriers over time.¹⁶ In Alzheimer's disease, there is evidence of a different pattern. Higher CR is associated with better performance at baseline, but this is followed by a sharper rate of decline once symptoms emerge.⁴⁰ This suggests that CR may operate by delaying the onset of clinical symptoms rather than reducing the overall rate of decline.

The factors that contribute to preserved cognition in high CR individuals remain unclear, but could relate to overall network integrity, mediated by in part by preserved grey matter volume.¹³ In this case, the high CR individual may be better able to compensate for disease mediated neuronal injury and network disruption.

The results of this study support previous longitudinal studies in ALS that those with normal cognition remain relatively stable over time, at least following diagnosis.⁸⁻¹⁰ The utilisation of joint models to control for non-random drop-out, suggests that the lack of decline is not solely attributable to the drop-out of highly impaired patients.

Limitations

Our analysis of cognition was limited to 16 months follow-up; therefore, we have not characterised the rate of decline over the longer-term disease course. This study is also limited by the lack of a control group which would have given an indication of practice effects and the extent to which scores regress towards the mean. Future studies should compare the role of CR over a longer period, and relative to healthy controls and similar patient groups.

Disease progression was approximated using time since symptom onset to the point of neuropsychological assessment. This assumes a linear relationship between time and disease progression, which is not often the case. Furthermore, this study is limited by the lack of neuropathological and neuroimaging data. Further work will be required to characterise the relationship between CR and the underlying neuropathological, neuroimaging and neuroelectric changes associated with cognitive impairment in ALS. Specifically, studies may consider examining if CR moderates the relationship between DT-MRI (Diffusion Tensor Magnetic Resonance Imaging) abnormalities in the corpus callosum and frontotemporal tracts and neuropsychological outcomes.⁴¹ Similarly, studies could explore if CR mediates the association between ¹⁸F-FDG-PET (Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography) measured hypometabolism in the frontal cortex and cognitive impairment.⁴²⁻⁴⁴

Conclusion

Our findings show that higher CR is associated with better neuropsychological performance, particularly in domains associated with ALS, where the differential between high and low CR was maintained over time. However, given the limitations of the study, future research is required to explore the relationship between CR and the underlying neuroimaging, neuroelectric and neuropathological signatures of impairment in ALS.

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Contributors EC, OH and NP designed and conceptualised the study. EC, JR, MP-G, TB, ME, PB, MH and AV played a major role in the acquisition of data. EC and JR analysed and interpreted the data. EC drafted the manuscript for intellectual

Figure 1 High CR defined as having a CR Z score >1 ; medium CR defined as having a CR Z score between $+1$ and -1 ; low CR defined as having a CR Z score <-1 . ALS, amyotrophic lateral sclerosis; CR, cognitive reserve; CWIT, Colour-Word Interference Test; ECAS, Edinburgh cognitive and behavioural ALS screen; LM, logical memory; RAVLT, Rey Auditory Verbal Learning Test.

content. EC, JR, MP-G, TB, ME, RM, SD, PB, MH, OH and NP revised the manuscript for intellectual content.

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Competing interests NP serves as Associate Editor of the International Journal of Neuroscience and has received speaker honoraria from Novartis. OH has received speaking honoraria from Janssen Cilag, Biogen Idec, Sanofi Aventis, Novartis and

MerckSerono. She has been a member of advisory panels for Biogen Idec, Allergan, Ono Pharmaceuticals, Novartis, Cytokinetics and Sanofi Aventis. She serves as editor-in-chief of the journal Amyotrophic Lateral Sclerosis and Frontotemporal Dementia.

Patient consent for publication Not required.

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Table 4 Estimate of HR for neuropsychological scores after joint longitudinal and time to event modelling

Variable	HR (95% CI)
ECAS total	0.88 (0.73 to 1.06)
ECAS ALS Specific	0.65 (0.55 to 0.77)*
ECAS ALS-non-specific	0.99 (0.84 to 1.16)
Reading the mind in the eyes	1.17 (0.89 to 1.64)
Verbal fluency (unrestricted)	0.93 (0.85 to 1.02)
Verbal fluency (restricted)	1.04 (0.99 to 1.25)
CWIT inhibition	1.09 (0.89 to 1.32)
CWIT switching	0.99 (0.97 to 1.01)
Boston naming test	0.99 (0.86 to 1.17)
RAVLT total	0.99 (0.92 to 0.99)*
RAVLT delayed	0.81 (0.55 to 1.02)
Logical Memory immediate	1.80 (1.17 to 3.07)*
Logical memory delayed	1.39 (0.57 to 2.68)

*P<0.001.

ALS, amyotrophic lateral sclerosis; CWIT, Colour-Word Interference Test; ECAS, Edinburgh cognitive and behavioural ALS screen; RAVLT, Rey Auditory Verbal Learning Test.

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REFERENCES

- Hardiman O, Al-Chalabi A, Chio A, et al. Amyotrophic lateral sclerosis. *Nat Rev Dis Primers* 2017;3:1–19.
- Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry* 2012;83:102–8.
- Elamin M, Phukan J, Bede P, et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. *Neurology* 2011;76:1263–9.
- Martin NH, Landau S, Janssen A, et al. Psychological as well as illness factors influence acceptance of non-invasive ventilation (NIV) and gastrostomy in amyotrophic lateral sclerosis (ALS): a prospective population study. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:376–87.
- Chiò A, Vignola A, Mastro E, et al. Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. *Eur J Neurol* 2010;17:1298–303.
- Crockford C, Newton J, Loneragan K, et al. ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS. *Neurology* 2018;91:e1370–80.
- Chiò A, Moglia C, Canosa A, et al. Cognitive impairment across ALS clinical stages in a population-based cohort. *Neurology* 2019;93:e984–94.
- Elamin M, Bede P, Byrne S, et al. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. *Neurology* 2013;80:1590–7.
- Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS: a prospective study. *Neurology* 2005;64:1222–6.
- Kilani M, Micallef J, Soubrouillard C, et al. A longitudinal study of the evolution of cognitive function and affective state in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004;5:46–54.
- Bersano E, Sarnelli MF, Solara V, et al. Decline of cognitive and behavioral functions in amyotrophic lateral sclerosis: a longitudinal study. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21:373–9.
- van Eijk RPA, Rooney J, Hardiman O, et al. Two heads are better than one: benefits of joint models for ALS trials. *J Neurol Neurosurg Psychiatry* 2019;90:1071–2.
- Cabeza R, Albert M, Belleville S, et al. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci* 2018;19:701–10.
- Montuschi A, Iazzolino B, Calvo A, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. *J Neurol Neurosurg Psychiatry* 2015;86:168–73.
- Hindle JV, Hurt CS, Burn DJ, et al. The effects of cognitive reserve and lifestyle on cognition and dementia in Parkinson's disease—a longitudinal cohort study. *Int J Geriatr Psychiatry* 2016;31:13–23.
- Bonner-Jackson A, Long JD, Westervelt H, et al. Cognitive reserve and brain reserve in prodromal Huntington's disease. *J Int Neuropsychol Soc* 2013;19:739–50.
- Placek K, Massimo L, Olm C, et al. Cognitive reserve in frontotemporal degeneration. *Neurology* 2016;87:1813–9.
- Borroni B, Premi E, Agosti C, et al. Revisiting brain reserve hypothesis in frontotemporal dementia: evidence from a brain perfusion study. *Dement Geriatr Cogn Disord* 2009;28:130–5.
- Jones RN, Manly J, Glymour MM, et al. Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc* 2011;17:593–601.
- D'Ovidio F, Rooney JPK, Visser AE, et al. Critical issues in ALS case-control studies: the case of the Euro-MOTOR study. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18:411–8.
- Nucci M, Mapelli D, Mondini S. Cognitive reserve index questionnaire (CRIQ): a new instrument for measuring cognitive reserve. *Aging Clin Exp Res* 2012;24:218–26.
- Singh-Manoux A, Marmot MG, Glymour M, et al. Does cognitive reserve shape cognitive decline? *Ann Neurol* 2011;70:296–304.
- Steward KA, Kennedy R, Novack TA, et al. The role of cognitive reserve in recovery from traumatic brain injury. *J Head Trauma Rehabil* 2018;33:E18–27.
- Abrahams S, Newton J, Niven E, et al. Screening for cognition and behaviour changes in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:9–14.
- Crockford CJ, Kleynhans M, Wilton E, et al. ECAS A-B-C: alternate forms of the Edinburgh cognitive and behavioural ALS screen. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19:57–64.
- Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan executive function system*. Psychological Corporation, 2001.
- Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: Fas and animal naming. *Arch Clin Neuropsychol* 1999;14:167–77.
- Kaplan EF, Goodglass H, Weintraub S. *The Boston naming test*. 2nd ed. Philadelphia, PA: Lea & Febiger, 1983.
- Wechsler D. *Wechsler memory scale*. 3rd ed. Psychological Corporation, 1997.
- Rey A. *L'examen clinique en psychologie*. Oxford, England: Presses Universitaires de France, 1964.
- Baron-Cohen S, Wheelwright S, Hill J, et al. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry* 2001;42:241–51.
- Pinto-Grau M, Burke T, Loneragan K, et al. Screening for cognitive dysfunction in ALS: validation of the Edinburgh cognitive and behavioural ALS screen (ECAS) using age and education adjusted normative data. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18:99–106.
- Marin B, Fontana A, Arcuti S, et al. Age-Specific ALS incidence: a dose-response meta-analysis. *Eur J Epidemiol* 2018;33:621–34.
- Calvo A, Moglia C, Lunetta C, et al. Factors predicting survival in ALS: a multicenter Italian study. *J Neurol* 2017;264:54–63.
- Knibb JA, Keren N, Kulka A, et al. A clinical tool for predicting survival in ALS. *J Neurol Neurosurg Psychiatry* 2016;87:1361–7.
- Rooney J, Murray D, Campion A, et al. The C9orf72 expansion is associated with accelerated respiratory function decline in a large amyotrophic lateral sclerosis cohort. *HRB Open Res* 2019;2:23.
- Rizopoulos D. The R package JMBayes for fitting joint models for longitudinal and Time-to-Event data using MCMC, 2014. Available: <http://arxiv.org/abs/1404.7625> [Accessed 12 May 2020].
- Sudell M, Kolamunnage-Dona R, Tudur-Smith C. Joint models for longitudinal and time-to-event data: a review of reporting quality with a view to meta-analysis. *BMC Med Res Methodol* 2016;16:168.
- Team RC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2020.
- Stern Y, Albert S, Tang MX, et al. Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology* 1999;53:1942–7.
- Agosta F, Ferraro PM, Riva N, et al. Structural brain correlates of cognitive and behavioral impairment in MND. *Hum Brain Mapp* 2016;37:1614–26.
- Canosa A, Pagani M, Cistaro A, et al. 18F-Fdg-Pet correlates of cognitive impairment in ALS. *Neurology* 2016;86:44–9.
- Pagani M, Chiò A, Valentini MC, et al. Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis. *Neurology* 2014;83:1067–74.
- Canosa A, Palumbo F, Iazzolino B, et al. The interplay among education, brain metabolism, and cognitive impairment suggests a role of cognitive reserve in amyotrophic lateral sclerosis. *Neurobiol Aging* 2021;98:205–13.