Research Report

Cognitive reserve and regional brain volume in amyotrophic lateral sclerosis

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ABSTRACT

Objective: We investigated whether cognitive reserve measured by education and premorbid IQ allows amyotrophic lateral sclerosis patients to compensate for regional brain volume loss.

Methods: This was a cross-sectional study. We recruited sixty patients with amyotrophic lateral sclerosis from two specialist out-patient clinics. All participants underwent neuropsychological assessment; the outcomes were standardized z-scores reflecting verbal fluency, executive functions (shifting, planning, working memory), verbal memory and visuo-constructive ability. The predictor was regional brain volume. The moderating proxies of cognitive reserve were premorbid IQ (estimated by vocabulary) and educational years. We hypothesized that higher cognitive reserve would correlate with better performance on a cognitive test battery, and tested this hypothesis with Bayesian analysis of covariance.

Results: The analyses provided moderate to very strong evidence in favor of our hypothesis with regard to verbal fluency functions, working memory, verbal learning and recognition, and visuo-constructive ability (all BF01 > 3): higher cognitive reserve was associated with a mild increase in performance. For shifting and planning ability, the evidence was anecdotal.

Conclusions: These results indicate that cognitive reserve moderates the effect of brain morphology on cognition in ALS. Patients draw small but meaningful benefits from higher reserve, preserving fluency, memory and visuo-constructive functions. Executive functions presented a dissociation: verbally assessed functions benefitted from cognitive reserve,
1. Introduction

As a multi-systemic disorder, amyotrophic lateral sclerosis (ALS) features motor impairment and cognitive-behavioral impairment. The latter is present in approximately half of patients, ranging from mild to severe enough symptoms in up to 15% of all ALS patients to warrant a diagnosis of fronto-temporal dementia (FTD) (Montuschi et al., 2015; Ringholz et al., 2005). Characteristically, cognitive impairment in ALS entails verbal fluency deficits, language deficits, and executive dysfunction as well as behavioral changes such as apathy (Beeldman et al., 2016; Benbrika et al., 2019). On the pathological level, cognitive impairment is associated with transactive response DNA binding protein 43 (TDP-43) pathology in non-primary motor areas (Gregory et al., 2019; Prudlo et al., 2016). However, cognitively non-impaired ALS patients are also reported to have substantial extra-motor TDP-43 pathology (Gregory et al., 2019).

Similar to findings in Alzheimer’s disease (AD), proxies of cognitive reserve may moderate the association between such pathogenic factors and cognitive impairments, leading to better compensation with higher reserve. Cognitive reserve can be identified by detecting individual differences in functional task processing, which allows some individuals to compensate for increasing brain pathology, and in turn, perform to expected norms despite a high pathological burden (Stern, 2009). In contrast, brain reserve refers to the physical capacity for the brain to better cope with brain damage (Stern, 2009). Examples of proxies of cognitive reserve which improve compensatory ability include educational and occupational attainment, vocabulary size (Scarmeas et al., 2003; Stern, 2009; Stern et al., 2005), social connectivity and physical exercise (Xu et al., 2015). In a previous study, people with ALS-FTD had lower educational attainment compared with ALS patients without FTD, suggesting that cognitive reserve may enable compensation against cognitive impairment (Montuschi et al., 2015). While cognitive reserve is well-documented in AD (Stern, 2009; Xu et al., 2015) and has recently been explored in fronto-temporal lobar degeneration (FTLD) (Placek et al., 2016), reliable evidence is lacking in ALS. In FTLD, executive control and verbal fluency were partially mediated by markers consisting of educational years and occupational attainment.

Within ALS, higher levels of education have been suggested to result in a better ability to cope with impaired cerebral glucose metabolism (Canosa et al., 2020) while education and occupation are also associated with better cognitive performance (Montuschi et al., 2015; Canosa et al., 2014; Costello et al., 2019, 2021; Consonni et al., 2020). Consequently, further evidence to support reserve-based compensation in ALS is necessary. This has been considered a limitation within cognitive ALS research for some time now (Canosa et al., 2016; Matias-Guiu et al., 2016; Montuschi et al., 2015).

The present study aimed to address this gap by determining if vocabulary as well as educational attainment as cognitive reserve markers moderate the effect of pathology—measured by regional brain atrophy—on cognitive performance when controlling for brain size. We hypothesize that high cognitive reserve has a compensatory effect and is associated with better performance.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations and all measures in the study.

2.1. Design

This was a prospective, observational cross-sectional study. Our predictors were two cognitive reserve markers: educational attainment (years of education) and vocabulary (as a proxy of premorbid IQ), and regionally-relevant brain volume. Which regional volume was chosen as predictor depended on the outcome. The outcome variables included letter fluency and flexibility, category fluency and flexibility, working memory, planning ability, shifting, verbal learning, verbal recognition and visuospatial ability.

2.2. Ethical considerations

Data included in this analysis were from the ALS-FTD Intersite project of the German Centre for Neurodegenerative Diseases (DZNE), sites Rostock and Magdeburg. All patients gave written informed consent and study approval was obtained by the local ethics committees (reference numbers A2010–32 and A2011-56). Pseudonymized data (comma-separated values) and an HTML results file are available on the Open Science Framework: https://osf.io/jv4m7/.

2.3. Participants

We recruited 60 ALS patients. Persons with a history of brain injury, epilepsy, psychiatric illness or non-native command of the German language were excluded from the study (Table 1). These exclusion criteria were established prior to the research being conducted.

The patients had bulbar (n = 22), spinal (n = 29) or unknown (n = 9) disease onsets. Phenotypically, they presented with classical (n = 44), predominant upper motor neuron involvement (n = 7), flail arm (n = 4), flail leg (n = 3) or another (n = 2) ALS type. According to the El Escorial criteria, 20 patients had a possible ALS, 17 had a probable ALS, 13 had a definite ALS and the status of 10 patients was unknown. At examination, these 10 patients had pure upper or lower motor neuron syndromes.
and did not meet the revised El Escorial criteria by Brooks et al. (Brooks et al., 2000) However, these ten patients were diagnosed with restrictive phenotypes of ALS (Ludolph et al., 2015), see above. Of the 20 patients with possible ALS, two progressed to probable ALS and 9 progressed to definite ALS. Patient classification into ALS without cognitive-behavioral impairments (ALSci, n = 31, 52%), with cognitive impairments (ALSci, n = 15, 25%) and with FTD (ALS-FTD, n = 5, 8%) followed the Strong (Strong et al., 2017) and Rascovsky (Rascovsky et al., 2011) criteria using z-score cut offs of −2 to reflect impairment. Z-scores were based on an age-, gender- and education-matched sample of healthy controls (Kasper et al., 2015). Fifteen percent (n = 9) were unclassifiable because their neuropsychological testing was incomplete. Behavioral impairment was assessed for classification using the Frontal Systems Behavior Inventory but no participants were classified as ALS-C9orf72 but not the SOD1 mutations but not the FUS mutation. Three genetic mutations of ALS occurred in our sample: C9orf72 (n = 2), SOD1 (n = 2), and VAPB (n = 1).  

### 2.5. Procedure  
ALS patients were recruited from Magdeburg and Rostock university hospitals as part of a prospective, bi-centric study. Control participants were recruited through public advertisements. At each site, two neuropsychologists administered the neuropsychological test battery. Further procedural details can be found in our previous publications (Kasper et al., 2015, 2016; Machits et al., 2014). No part of the study procedures or analyses was pre-registered prior to the research being conducted.

### 2.6. MRI acquisition  
MRI scanning was performed with two with 3 T Siemens Magnetom VERIO scanners (Erlangen, Germany) using a 32-channel head coil; one single scanner at each site (Rostock and Magdeburg, Germany). High-resolution T1-weighted anatomical images were acquired using the magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: 256×256 image matrix with 192 sagittal slices, FOV 250 × 250 × 192 mm, voxel size 1 × 1 × 1 mm³, echo time 4.82 ms, repetition time 2500 ms, and flip angle 7°. The anatomical T1-weighted images were co-registered to each other, segmented into grey matter, white matter and cerebrospinal fluid partitions using the CAT12 toolbox longitudinal pipeline in MATLAB 2019a. Then, the Diffomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) algebra algorithm (Ashburner, 2007) was used in combination with the default CAT12 brain template to normalize the mean T1-weighted image to the Montreal Neurological Institute (MNI) reference coordinate system. The estimated deformation field was subsequently applied to the grey matter segments of all time points to bring them in MNI space as well, followed by modulation to preserve the total amount of grey matter and smoothing with an 8 mm Gaussian kernel. In phantom tests according to the American College of Radiology guidelines (American College of Radiology, 2018), both sites’ scanners met the criteria for geometric accuracy, high contrast spatial resolution, slice thickness accuracy, slice position accuracy, image intensity uniformity, percent signal ghosting and low contrast object detectability. The conditions of our ethics approval do not permit sharing of any raw imaging data supporting this study with any individual outside the author team under any circumstances.

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**Table 1 – The participants’ demographic background (n = 60).**

| Variable                  | Mean (SD)  |
|---------------------------|------------|
| Women (n)                 | 25         |
| Age                       | 59.93 (11.14) |
| Educational attainment (years) | 12.68 (2.51) |
| Premorbid IQ              | 98.62 (11.53) |
| Disease Duration (months) | 22.55 (5.37) |
| ALS-FRS-R                 | 38.58 (5.37) |
| Progression Speed (ALSFRS-R 8) | .71 (.69)  |

We applied these predictors separately—rather than as a composite measure—to investigate their individual influences. Our outcomes were z-scores of ALS-specific cognitive functions: letter fluency, letter flexibility, category fluency, category flexibility (all indices corrected for speech motor impairment (Abrahams et al., 2000; Aschenbrenner and Tucha, 2001)), working memory (digit span backward (The Psychological Corporation, 1987)), shifting (Trail Making Test (TMT), corrected for motor impairment as ratio B/A (Reitan, 1958)), planning ability (“Tower of London” task), verbal learning and recognition as well as visuospatial ability (Rey Complex Figure Test, copy).
2.7. Statistical analysis

As classical null hypothesis significance testing (NHST) only permits the rejection of the null hypothesis but not the acceptance of an alternative hypothesis, we applied a Bayesian modeling approach to allow us to quantify support in favor of the cognitive reserve hypothesis. *Bayes factor (BF)* hypothesis testing (BFHT) facilitates the comparison of one or more alternative hypotheses against the null hypothesis (i.e., the assumption that there is no effect of cognitive reserve markers on disease markers and cognitive performance, H₀). This encompasses the possibility to quantify evidence in favor of any hypothesis, including the hypothesis that cognitive reserve exists in ALS (Goodman, 2008; Wagenmakers, 2007; Wagenmakers, Marsman et al., 2018). Modelling took place in *Jeffreys’ Amazing Statistics Program* *(The JASP Team, 2020).*

We conducted ANCOVA to investigate the interaction effects between regional volume and reserve markers on performance. Known risk factors of cognitive impairment (ALS onset type (Portet et al., 2001), sex, age, progression speed) as well as recruitment location (Magdeburg vs Rostock) and total intracranial volume (TIV) were corrected for by including them into the null model. Recruitment location was incorporated into the analyses to account for the potentially confounding effects of two MRI scanners. As the C9orf72 repeat expansion is associated with cognitive impairment (Irwin et al., 2013), we report the full results including both C9orf72-positive participants. A summary of the results excluding the C9orf72 patients can be found in Table 3; details can be found in the corresponding HTML file on the Open Science Framework.

To address potential issues with non-normally distributed residuals in the ANCOVA we applied Markov-Monte Carlo chain sampling to each analysis 1,000 times. JASP was set to report the best model first, and then compare all other models against this best model. We report the Bayes Factor (BF₀¹) quantifying evidence in favor of the best model against the lower-ranked models, the BFₐₐ indicating the informativeness of our data given the prior (P(M)) and posterior distributions (P(M|data)) and the BFₚₚ in comparison to the null model (Van Doorn et al., 2019; Wagenmakers, 2007, 2017; Wagenmakers, Love, et al., 2018; Wagenmakers, Marsman et al., 2018). We further report the effect size $R^2$ and beta coefficients of the predictors, along with their 95% credible intervals.

We applied the following evidence categories: a BF₀¹ above 3 provides “moderate evidence”, a BF₀¹ above 10 provides “strong evidence”, a BF₀¹ above 30 provides “very strong evidence” and a BF₀¹ above 100 provides “extreme evidence” in favor of the best model (Wagenmakers, Love, et al., 2018). We will consider the cognitive reserve hypothesis supported, if an interaction between reserve and volume is the best model, or if the reserve marker(s) alone provide the best model, and if the evidence favouring this best model is at least moderate.

3. Results

Based on previous literature, we expected verbal fluency functions to be associated with volume of the middle frontal gyrus, executive functions with the superior frontal gyrus and verbal memory as well as visuospatial functions to be associated with volume of the hippocampus (Benbrika et al., 2019; Carlin et al., 2000; Yochim et al., 2007). Cognitive test results within each domain, and the number of contributing participants can be found in Table 2.

There was moderate evidence supporting the absence of a correlation between premorbid IQ and ALSFRS-R score (non-parametric Kendall’s $\tau = .02$, BF₀¹ = 5.67).

3.1. ALS-specific functions

**Letter fluency.** The best model was Premorbid IQ*Middle Frontal Gyrus (P(M) = .07, P(M|data) = .43, BFₐₐ = 8.99): the best hypothesis for our data is that higher premorbid IQ (β = .06, 95%CI [−.06, .02], BF₀¹ = 5.12) and larger volume (β = 3.438e-4, 95%CI [-2.246e-4,9.512e-4]) are associated with an increased letter fluency performance. This model accounted for 33% ($R^2 = .33$, 95%CI [16.48%]) of the variance and explained our data 76 times better than the null hypothesis model (BF₀¹ = 75.82, error % = 2.67). Consequently, letter fluency strongly supports the cognitive reserve hypothesis in ALS.

**Letter flexibility.** The best model explaining fluctuations in letter flexibility performance contained the main effects of education, premorbid IQ, middle frontal gyrus volume and the interaction between premorbid IQ and middle frontal gyrus (P(M) = .07, P(M|data) = .29, BFₐₐ = 4.84, $R^2 = .27$, 95%CI [11.42]). Higher education (β = .34, 95%CI [-19, 92]), premorbid IQ (β = .06, 95%CI [-.05,18]) and middle frontal gyrus volume (β = 3.50e-4, 95%CI [-7.296e-4,0.002]) were associated with better performance. This model was 29 times better than the null hypothesis model (BF₀¹ = 29.31, error% 3.77). Thus, letter flexibility provides strong evidence in favor of the cognitive reserve hypothesis.

**Category Fluency.** The best model for fluctuations in category fluency consisted of the main effects of premorbid IQ and middle frontal gyrus (P(M) = .08, P(M|data) = .20, BFₐₐ = 2.95, $R^2 = .25$, 95%CI [11.41]). The effects of premorbid IQ (β = .04, 95%CI [-4.696e-4,0.08]) and middle frontal gyrus volume

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### Table 2 - Measures of dispersion and number of participants in each domain.

| Variable                     | N  | Mean (SD)          |
|------------------------------|----|-------------------|
| Regional Volume (mm³)        | 60 | 8900.04 (1309.23) |
| Middle Frontal Gyrus         | 60 | 10073.65 (1373.83) |
| Superior Frontal Gyrus       | 60 | 3622.76 (513.95)  |
| Left Hippocampus             | 60 | 3369.38 (516.36)  |
| Fluency Functions            |    |                   |
| Letter Fluency               | 50 | -1.14 (2.48)      |
| Letter Flexibility           | 50 | -2.67 (4.65)      |
| Category Fluency             | 50 | -0.71 (1.93)      |
| Category Flexibility         | 49 | -1.16 (2.20)      |
| Executive Functions          |    |                   |
| Shifting                     | 53 | -61 (1.25)        |
| Planning Ability             | 34 | -29 (1.29)        |
| Working Memory               | 59 | -86 (1.66)        |
| Verbal Memory                |    |                   |
| Verbal Learning              | 51 | -46 (1.60)        |
| Correct Recognition          | 51 | -35 (1.55)        |
| Visuospatial Functions       |    |                   |
| Rey Figure Copy              | 42 | -1.31 (2.15)      |
was not better or worse than the null hypothesis (BF$_{01}$ = 4.38, error% = 3.66), providing moderate support for the cognitive reserve hypothesis.

Category Flexibility. Here, the best model consisted of the main effects of education, premorbid IQ, middle frontal gyrus volume and the interaction between education and middle frontal gyrus volume ($P(M) = .08$, $P(\text{M data}) = .35$, BF$_M = 6.42$, $R^2 = .27$, 95%CI [-.11; .44]). Education ($b = .05$, 95%CI [-.19; .31]), premorbid IQ ($b = .05$, 95%CI [-.02; .11]) and middle frontal gyrus volume ($b = 1.267e-4$, 95%CI [-.4.217e-6; .504e-4]) were all positively associated with category flexibility performance. This model performed 39 times better than the null hypothesis model (BF$_{01}$ = 38.99, error% = 3.01), providing very strong evidence in favor of cognitive reserve.

Planning ability. Premorbid IQ alone provided the best explanation for fluctuations in planning ability ($P(M) = .08$, $P(\text{M data}) = .16$, BF$_M = 2.26$, $R^2 = .27$, 95%CI [.09; .46]). Its effect was protective but weak ($b = .03$, 95%CI [-.01; .05]). This model was not better or worse than the null model (BF$_{01}$ = 1.19, error% = 5.11).

Shifting. Performance fluctuation in shifting was best explained by premorbid IQ alone ($P(M) = .08$, $P(\text{M data}) = .17$, BF$_M = 2.47$, $R^2 = .18$, 95%CI [.06; .32]). Its effect was positive but weak ($b = .02$, 95%CI [-.01; .05]). This model was not better than the null model (BF$_{01}$ = 1.88, error% = 2.20).

Working memory. The best model for working memory performance showed that longer education ($b = .05$, 95%CI [-.12; .24]), higher premorbid IQ ($b = .04$, 95%CI [.002; .08]) and larger superior frontal gyrus volume ($b = 2.993e-4$, 95%CI [-.6.993e-5; .6.922e-4]) were associated with better performance ($P(M) = .08$, $P(\text{M data}) = .32$, BF$_M = 5.68$). This model explained 32.5% of the variance in working memory performance ($R^2 = .32$, 95%CI [.17; .47]) and was 70 times better than the null hypothesis model (BF$_{01}$ = 70.02, error% = 3.74). Consequently, there is very strong evidence favoring the cognitive reserve hypothesis in ALS patients’ working memory performance.

3.2. ALS-non-specific functions

Verbal learning. The best model for our data yielded that longer education ($b = .17$, 95%CI [.03; .30]) and larger hippocampal volume on the left side ($b = 0.01$, 95%CI [2.784e-4; .002]) were associated with better verbal learning performance ($P(M) = .08$, $P(\text{M data}) = .26$, BF$_M = 4.17$). This model accounted for 43% of the variance ($R^2 = .43$, 95%CI [.26; .52]); it was 131 times better than the null hypothesis model (BF$_{01}$ = 131.19, error% = 5.62).

Verbal recognition. Here, the best model for our data showed that longer education ($b = .20$, 95%CI [.06; .34]) and larger hippocampal volume on the left side ($b = 8.405e-4$, 95%CI [1.280e-6; .002]) were associated with better verbal recognition performance ($P(M) = .08$, $P(\text{M data}) = .33$, BF$_M = 5.95$). This model explained 31% of the variance ($R^2 = .31$, 95%CI [.15; .46]) and was 50 times better than the null hypothesis (BF$_{01}$ = 49.89, error% = 2.75), providing very strong evidence in favor of the cognitive reserve hypothesis.

Visuo-constructive ability. The best model was that a higher premorbid IQ ($b = .06$, 95%CI [.01; .12]) was associated with better visuospatial performance ($P(M) = .08$, $P(\text{M data}) = .17$, BF$_M = 2.43$). This hypothesis explained 31.8% of the variance ($R^2 = .31$, 95%CI [.14; .48]) and was 11 times better than the null hypothesis (BF$_{01}$ = 11.43, error% = 2.06).

Table 3 summarises the evidence in favor of cognitive reserve in ALS, highlighting that the evidence prevailed when both C9orf72-positive participants were excluded from analysis.

4. Discussion

We aimed to establish support for the cognitive reserve hypothesis in ALS, using vocabulary and education in addition to regional volume. Verbal fluency functions provided very strong evidence in favor of the cognitive reserve hypothesis, which explained a moderate amount of variance in each function even though there was a weak correlation between individual predictors and outcomes: a higher IQ moderated the influence of cortical atrophy, leading to better performance. Within the executive domain, results were inconclusive: there were weak associations between planning ability and shifting with reserve factors and volume, which did not support the cognitive reserve hypothesis. Working memory, however, provided strong evidence in its favor. Within the typically-preserved memory and visuospatial functions, our data provided strong to extremely strong support for the cognitive reserve hypothesis. In summary, our study shows that longer education and higher premorbid IQ were associated with higher cognitive performance. While this association provided a better explanation of cognitive performance than other currently known risk factors for cognitive impairment in ALS, the advantages derived from a larger reserve were small.

It has previously been documented that ALS-FTD patients have a typically lower educational attainment than those without FTD (Montuschi et al., 2015; Ringholz et al., 2005; Beeldman et al., 2016; Benbrika et al., 2019; Prudlo et al., 2016; Gregory et al., 2019; Stern, 2009; Scarmeas et al., 2003; Stern et al., 2005; Xu et al., 2015; Placek et al., 2016; Canosa et al., .
that occupation and education are associated with verbal fluency, executive and memory functions (Canosa et al., 2014), and that ALS patients classified as having a “high reserve” perform better on cognitive tasks (Costello et al., 2019). Such findings support the notion that people with a higher reserve tend to perform better on cognitive tasks in general (Wilson et al., 2013). Recently, two studies have proposed that premorbid lifestyle factors may influence ALS patients’ cognitive performance longitudinally, and clinical expression cross-sectionally (Costello et al., 2021; Consonni et al., 2020). A third study showed that higher education is associated with an increased pathological burden in medial frontal regions independently of the level of cognitive impairment in ALS patients, supporting the notion that the level of education results in a larger cognitive reserve and thus provides a coping mechanism against brain pathology (Canosa et al., 2020). We extend these previous findings by describing the strength and nature of these previously proposed associations, and by adding estimates of pathology in the form of regional volume while correcting for overall intercranial volume. The advantage of larger regional volume documented in our present study also lends support for the hypothesis that physical brain reserve (Stern, 2009) may facilitate better coping with neuronal damage in ALS. This hypothesis and our present findings are consistent with our previous work showing that ALSni and ALS-FTD patients exhibit cortical thinning in comparison to ALSni patients (Schuster et al., 2014), and with recent work documenting higher longitudinally increasing atrophy rates with cognitive impairment (van der Burgh et al., 2020). Specifically, language deficits may be associated with left-hemispheric fronto-temporal atrophy (Ash et al., 2015). However, the effect sizes of our cognitive reserve proxies consistently exceeded those of regional volume, suggesting that cognitive lifestyle factors are more influential than regional volume when it comes to cognitive functioning in ALS. Our support for the cognitive reserve hypothesis is congruent with the above literature and our separate reserve markers of pathology, or direct assessment of TDP-43 pathology in clinico-pathological studies is promising: a high cognitive reserve was associated with fewer senile plaques in AD (Bennett et al., 2003), a similar effect is conceivable in ALS with regard to TDP-43 pathology.

In conclusion, our findings reveal that ALS patients’ verbal fluency functions, working memory, verbal memory and visuospatial abilities are protected by their cognitive reserve: a higher reserve was associated with better performance despite volume loss. This protective effect was small, but it still explained a moderate amount of variance in performance. Within the executive domain, shifting and planning ability performances were not associated with cognitive reserve markers. This study provides an additional compo-
nent with which to predict cognitive impairment in ALS; however, further investigation into wider risk factors is required to improve our understanding of cognitive and behavioral dysfunction in ALS.

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**Credit author statement**

Dr Anna G. M. Temp; Conceptualization, application of statistical analysis, Writing – original draft writing. Johannes Prudlo; Supervision, Conceptualization, Funding acquisition, neurological data collection, manuscript review & editing. Stefan Vielhaber; Conceptualization, neurological data collection, manuscript review. Dr Judith Machts; Conceptualization, manuscript review & editing. Andras Hermann; Conceptualization, manuscript review & editing. Stefan Teipel; Conceptualization, manuscript review & editing. Dr Elisabeth Kasper: Conceptualization, neuropsychological test battery design, neuropsychological data collection, manuscript review & editing. Dr Anna G. M. Temp; Conceptualization, application of statistical analysis, Writing – original draft writing. Johannes Prudlo; Supervision, Conceptualization, Funding acquisition, neurological data collection, manuscript review & editing. Stefan Vielhaber; Conceptualization, neurological data collection, manuscript review. Dr Judith Machts; Conceptualization, manuscript review & editing. Andras Hermann; Conceptualization, manuscript review & editing. Stefan Teipel; Conceptualization, manuscript review & editing. Dr Elisabeth Kasper: Conceptualization, neuropsychological test battery design, neuropsychological data collection, Data curation, manuscript review & editing.

**Declaration of competing interest**

AGMT reports no disclosures. JM reports no disclosures. AH reports no disclosures. ST reports no disclosures. JP reports no disclosures. SV reports no disclosures. JM reports no disclosures. AH reports no disclosures. ST reports no disclosures. SV reports no disclosures. JM reports no disclosures.

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**REFERENCES**

Abrahams, S. (2011). Social cognition in amyotrophic lateral sclerosis. Neurodegenerative Disease Management 1(5), 397–405. https://doi.org/10.2217/ndm.11.54

Abrahams, S., Leigh, P. N., Harvey, A., Vythelingum, G. N., Grisé, D., & Goldstein, L. H. (2000). Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia 38(6), 739–747. https://doi.org/10.1016/s0028-3932(99)00146-3

American College of Radiology (2018). Phantom Test Guidance for Use of the Large MRI Phantom for the ACR MRI Accreditation Program.

Aschenbrenner, S., & Tucha, O. (2001). Regensburg Wortflüssigkeitstest. Göttingen Germany: Hogrefe testzentrale.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113.

Ash, S., Olm, C., McMillan, C. T., Boiler, A., Irwin, D. J., McCluskey, L., Elman, L., & Grossman, M. (2015). Deficits in sentence expression in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 16(1-2), 31–39. https://doi.org/10.3109/21678421.2014.974617

Beeldman, E., Raaphorst, J., Klein Twennaar, M., de Visser, M., Schmand, B. A., & de Haan, R. J. (2016). The cognitive profile of ALS: A systematic review and meta-analysis update. Journal of Neurology Neurosurgery and Psychiatry 87(6), 611–619. https://doi.org/10.1136/jnnp-2015-310734

Benbrika, S., Desgranges, B., Eustache, F., & Viader, F. (2019). Cognitive, emotional and psychological manifestations in amyotrophic lateral sclerosis at baseline and overtime: A review. Frontiers in Neuroscience 13, 951. https://doi.org/10.3389/fnins.2019.00951

Benedict, R. H., Morrow, S. A., Weinstock-Guttman, B., Cookfair, D., & Schretlen, D. J. (2010). Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients. Journal of the International Neuropsychological Society 16(5), 829–835. https://doi.org/10.1017/S1355617710000688

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Mendes de Leon, C. F., Arnold, S. E., Barnes, L. L., & Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 60(12), 1909–1915. https://doi.org/10.1212/01.wnl.0000069923.64550.9f

Brooks, B. R., Miller, R. G., Swash, M., Munsat, T. L., & World Federation of Neurology Research Group on Motor Neuro-Disorders. (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 1(5), 293–299. https://doi.org/10.1080/146608200300079536

Canosa, A., Montuschi, A., Iazzolino, B., Calvo, A., Moglia, C., Bertuzzo, D., Lopiano, L., Restagno, G., Brunetti, M., Ossola, I., Lo Presti, A., Cammarosano, S., & Chio, A. (2014). Cognitive reserve in ALS with comorbid frontotemporal dementia (FTD): A Population-Based Study (P5.081). Neurology 82.

Canosa, A., Pagani, M., Cistaro, A., Montuschi, A., Iazzolino, B., Fania, P., Cammarosano, S., Ilardi, A., Moglia, C., Calvo, A., & Chio, A. (2016). 18F-FDG-PET correlates of cognitive impairment in ALS. Neurology 86(1), 44–49. https://doi.org/10.1212/WNL.0000000000002424

Carlin, D., Bonerba, J., Phipps, M., Alexander, G., Shapiro, M., & Graffman, J. (2000). Planning impairments in frontal lobe dementia and frontal lobe lesion patients. Neuropsychology 38, 655–665.

Consolani, M., Dalla Bella, E., Bersano, E., Teleca, A., & Lauria, G. (2020). Cognitive reserve is associated with altered clinical expression in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 1–11. https://doi.org/10.1080/21678421.2020.1849306

Costello, E., Rooney, J., Pinto-Grau, M., Burke, T., Elamin, M., Bede, P., McMackin, R., Dukic, S., Vajda, A., Heverin, M., Hardiman, O., & Pender, N. (2021). Cognitive reserve in amyotrophic lateral sclerosis (ALS): a population-based analysis.
longitudinal study. Journal of Neurology Neurosurgery and Psychiatry 1–6. https://doi.org/10.1136/jnnp-2020-324992
Costello, E., Ryan, M., Pender, N., & Hardiman, O. (2019). COG-03
Cognitive reserve as a mediator of cognitive decline in Amyotrophic Lateral Sclerosis. International Symposium for ALS-FTD. Perth Australia.

Goodman, S. (2008). A dirty dozen: twelve p-value misconceptions. Seminars in Hematology 45(3), 135–140. https://doi.org/10.1053/j.seminhematol.2008.04.003
Gordon, P. H., Delgadillo, D., Pradat, P. F., Prudlo, J., Abdulla, S., Kellawe, K., Petri, S., Dengler, R., Heinze, H. J., Vielhaber, S., Schoenfeld, M. A., & Bittner, D. M. (2014). Memory deficits in amyotrophic lateral sclerosis are not exclusively caused by executive dysfunction: A comparative neuropsychological study of amnestic mild cognitive impairment. BMC Neuroscience 15(83). https://doi.org/10.1186/1471-2202-15-83
Matias-Guiu, J. A., Pytel, V., Cabrera-Martin, M. N., Galan, L., Valles-Salgado, M., Guerrero, A., Moreno-Ramos, T., Matias-Guiu, J., & Carreras, J. L. (2016). Amyloid- and FDG-PET imaging in amyotrophic lateral sclerosis. European Journal of Nuclear Medicine and Molecular Imaging 43(11), 2050–2060. https://doi.org/10.1007/s00259-016-3434-1
Montuschi, A., Iazzolino, B., Calvo, A., Moglia, C., Lopiano, L., Restagno, G., Brunetti, M., Ossola, I., Lo Presti, A., Cammarosano, S., Canosa, A., & Chio, A. (2015). Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. Journal of Neurology Neurosurgery and Psychiatry 86(2), 168–173. https://doi.org/10.1136/jnnp-2013-307223
Neudeck, C., Wasner, M., & Borsato, G. D. (2001). Patients’ assessment of quality of life instruments: a randomised study of SIP, SF-36 and SEIQoL-DW in patients with amyotrophic lateral sclerosis. Journal of the Neurological Sciences 191(1–2), 103–109. https://doi.org/10.1007/s00222-510x(01)00612-8
Osmanovic, A., Wieselmann, G., Mix, L., Siegler, H. A., Kumpje, M., Ranxha, G., Wurster, C. D., Steinke, A., Ludolph, A. C., Kopp, B., Lule, D., Petri, S., & Schreiber-Katz, O. (2020). Cognitive performance of patients with adult 5q-spinal muscular atrophy and with amyotrophic lateral sclerosis. Brain Sciences 11(1). https://doi.org/10.3390/brainsci11010008
Pinto-Grau, M., Hardiman, O., & Pender, N. (2018). The study of language in the amyotrophic lateral sclerosis: frontotemporal spectrum disorder: a systematic review of findings and new perspectives. Neuropsychology Review 28(2), 251–268. https://doi.org/10.1007/s11065-018-9375-7
Placek, K., Massimo, L., Olm, C., Ternes, K., Firn, K., Van Deerinck, V., Lee, E. B., Trojanowski, J. Q., Lee, V. M., Irwin, D., Grossman, M., & McMillan, C. T. (2016). Cognitive reserve in frontotemporal degeneration: Neuoroatomic and neuropsychological evidence. Neurology 87(17), 1813–1819. https://doi.org/10.1212/WNL.000000000003250
Portet, F., Cadilhac, C., Touchon, J., & Camu, W. (2001). Cognitive impairment in motor neuron disease with bulbar onset. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 2(1), 23–29. https://doi.org/10.1086/426680201300079382
Prudlo, J., Konig, J., Schuster, C., Kasper, E., Buttner, A., Teipel, S., & Neumann, M. (2016). TDP-43 pathology and cognition in ALS: A prospective clinicopathologic correlation study. Neurology 87(10), 1019–1023. https://doi.org/10.1212/WNL.000000000003062
Raschovskiy, J., van der Vlis, M., Linsen, W. H. de Haan, R. J., & Schmand, B. (2010). The cognitive profile of amyotrophic lateral sclerosis: A meta-analysis. Amyotrophic Lateral Sclerosis 11(1-2), 27–37. https://doi.org/10.3109/17482968026845008
Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., van Swieten, J. C., Seelaar, H., Dopper, E. G., Onyike, C. U., Rankin, K. P., Josephs, K. A., Johnson, J. K., Gorno-Tempini, M. L., Rosen, H., ... Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 314(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179
Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills 8, 271–276. https://doi.org/10.2466/pms.1958.8.3.271
Ringholz, G. M., Appel, S. H., Bradshaw, M., Cooke, N. A., Mosnik, D. M., & Schulz, P. E. (2005). Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 65(4), 586–590. https://doi.org/10.1212/01.wnl.0000172911.39167.b6

Scarmeas, N., Zarahn, E., Anderson, K. E., Habeck, C. G., Hilton, J., Flynn, J., Marder, K. S., Bell, K. L., Sackeim, H. A., Van Heertum, R. L., Moeller, J. R., & Stern, Y. (2003). Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. *Archives of Neurology* 60(3), 359–365. https://doi.org/10.1001/archneur.60.3.359

Schipolowski, S., Wilhelm, O., & Schroeders, U. (2014). On the nature of crystallized intelligence: the relationship between verbal ability and factual knowledge. *Intelligence* 46, 156–168. https://doi.org/10.1016/j.intell.2014.05.014

Schuster, C., Kasper, E., Dyrba, M., Machts, J., Bittner, D., Kaufmann, J., Mitchell, A. J., Benecke, R., Teipel, S., Vielhaber, S., & Prudlo, J. (2014). Cortical thinning and its relation to cognition in amyotrophic lateral sclerosis. *Neurobiology of Aging* 35(1), 240–246. https://doi.org/10.1016/j.neurobiolaging.2013.07.020

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia* 47(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, J. F., Flynn, J., Sackeim, H., & van Heertum, R. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex* 15(4), 394–402. https://doi.org/10.1093/cercor/bhh142

Strong, M. J., Abrahams, S., Goldstein, L. H., Woolley, S., McLaughlin, P., Snowden, J., Mioshi, E., Roberts-South, A., Benatar, M., HortobaGyi, T., Rosenfeld, J., Silani, V., Ince, P. G., & Turner, M. R. (2017). Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotroph Lateral Scler Frontotemporal Degener* 18(3–4), 153–174. https://doi.org/10.1080/21678421.2016.1267768

The JASP Team. (2020). JASP (Version 0.14.1).

The Psychological Corporation. (1987) *Wechsler memory scale - revised*. San Antonio.

van der Burgh, H. K., Westeneng, H. J., Walhout, R., van Veenhuijzen, K., Tan, H. H. G., Meier, J. M., Bakker, L. A., Hendrikse, J., van Es, M. A., Veldink, J. H., van den Heuvel, M. P., & van den Berg, L. H. (2020). Multimodal longitudinal study of structural brain involvement in amyotrophic lateral sclerosis. *Neurology* 94(24), e2592–e2604. https://doi.org/10.1212/01.wnl.0000000000009499

Van Doorn, J., Van den Bergh, D., Böhm, U., Dablander, F., Derks, K., Draws, T., Evans, N. J., Gronau, Q. F., Hinne, M., Kucharsky, S., Ly, A., Marsman, M., Matzke, D., Komarliu, A., Gupta, N., Sarafoglou, A., Stefan, A., Voelkel, J. G., & Wagenmakers, E.-J. (2019). The JASP Guidelines for Conducting and Reporting a Bayesian Analysis.

Wagenmakers, E.-J. (2007). A practical solution to the pervasive problems of p values. *Psychonomic Bulletin & Review* 14(5), 779–804. https://doi.org/10.3758/bf03194105

Wagenmakers, E.-J. (2017). *Proof-reading or Feedback on JASP-Based Bayes in Thesis?*

Wagenmakers, E.-J., Love, J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Selker, R., Gronau, Q. F., Dropmann, D., Boutin, B., Meier, J. M., Toonk, A., van kesteren, E.-J., van Doorn, J., Smirnoff, M., Epskamp, S., Etz, A., Matzke, D., Morey, R. D. (2018). Bayesian inference for psychology. Part II: Example applications with JASP. *Psychonomic Bulletin & Review* 25(1), 58–76. https://doi.org/10.3758/s13423-017-1323-7

Wagenmakers, E.-J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Love, J., Selker, R., Gronau, Q. F., Smirnoff, M., Epskamp, S., Matzke, D., Rouder, J. N., & Morey, R. D. (2018). Bayesian inference for psychology. Part I: Theoretical advantages and practical ramifications. *Psychonomic Bulletin & Review* 25(1), 35–57. https://doi.org/10.3758/s13423-017-1343-3

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., & Bennett, D. A. (2013). Life-span cognitive activity, neuropathologic burden, and cognitive aging. *Neurology* 81(4), 314–321. https://doi.org/10.1212/WNL.0b013e31829c5e8a

Xu, W., Yu, J. T., Tan, M. S., & Tan, L. (2015). Cognitive reserve and Alzheimer’s disease. *Molecular Neurobiology* 51(1), 187–208. https://doi.org/10.1007/s12035-014-8720-y