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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 $BF_{01} > 3$): 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,

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non-verbally assessed functions did not. This motivates future research into cognitive reserve in ALS and practical implications, such as strengthening reserve to delay decline.

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/jv4mt/.

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

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 δ)	.71 (.69)

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 (ALSni, $n = 31$, 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-bi or -cbi (Grace and Malloy, 2001). See Table 1 for the participants' background. All patients underwent genetic testing for the *C9orf72* repeat expansion (for details, please see Krüger et al., 2016). Where a familial history, young onset or a juvenile variant of ALS indicated additional genetic testing, we tested for *SOD1*, *VAPB* and *TARDBP* mutations but not the *FUS* mutation. Three genetic mutations of ALS occurred in our sample: *C9orf72* ($n = 2$), *SOD1* ($n = 2$), and *VAPB* ($n = 1$).

2.4. Measurements

Our predictors were the cognitive reserve markers of educational attainment (years spent in school and at university or in vocational training) and premorbid IQ, measured by passive vocabulary (Schmidt and Metzler, 1992). Estimates of premorbid verbal IQ were obtained after disease onset by asking the participants to identify correct target words among distractor pseudo-words. The number of correctly identified target words was converted to an IQ estimate based on published norms (Schmidt and Metzler, 1992). We chose passive vocabulary as a proxy for three reasons: firstly, it relies less on the patients' frequently impaired ability to access their mental lexicon actively (Pinto-Grau et al., 2018); secondly, ALS patients' performance on this specific test has previously been shown to remain intact (Neudert et al., 2001), indistinguishable from healthy controls (Lange et al., 2016), and independent from physical disability (Osmanovic et al., 2020); thirdly, this particular test has been shown to measure verbal-crystallised intelligence reliably (Schipolowski et al., 2014). Executive impairment is common and would diminish performance on classical IQ estimation tests such as the Raven matrices, performance on the passive vocabulary test fell within the normal range (Table 1). 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).

Legal copyright restrictions prevent public archiving of the various clinical assessments and tests used in this study, which can be obtained from the copyright holders in the cited references.

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; Machts 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 T_1-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 mm^3, echo time 4.82 ms, repetition time 2500 ms, and flip angle 7°. The anatomical T_1-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 *Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL)* algebra algorithm (Ashburner, 2007) was used in combination with the default CAT12 brain template to normalize the mean T_1-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.

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, H_0). 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 (BF_{01}) quantifying evidence in favor of the best model against the lower-ranked models, the BF_M indicating the informativeness of our data given the prior (P(M)) and posterior distributions (P(M|data) and the BF_{01} 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 BF_{01} above 3 provides "moderate evidence", a BF_{01} above 10 provides "strong evidence", a BF_{01} above 30 provides "very strong evidence" and a BF_{01} above 100 provides "extreme evidence" in favor of the best hypothesis (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.

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

Variable	N	Mean (SD)
Regional Volume (mm^3)		
Middle Frontal Gyrus	60	8900.04 (1309.23)
Superior Frontal Gyrus	60	10073.65 (1373.83)
Left Hippocampus	60	3622.76 (513.95)
Right 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	−.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)

There was moderate evidence supporting the absence of a correlation between premorbid IQ and ALSFRS-R score (non-parametric Kendall's $\tau = .02$, $BF_{01} = 5.67$).

3.1. ALS-specific functions

Letter fluency. The best model was Premorbid IQ*Middle Frontal Gyrus (P(M) = .07, P (M|data) = .43, $BF_M = 8.99$): the best hypothesis for our data is that higher premorbid IQ ($b = .06$, 95%CI [.02|.12]) and larger volume ($b = 3.438e\text{-}4$, 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 ($BF_{01} = 75.82$, 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, BFM = 4.84, $R^2 = .27$, 95%CI [.11|.42]). Higher education ($b = .34$, 95%CI[-.19|.92]), premorbid IQ ($b = .06$, 95%CI [-.05|.18]) and middle frontal gyrus volume ($b = 3.50e\text{-}4$, 95%CI [-7.296e-4|.002]) were associated with better performance. This model was 29 times better than the null hypothesis model ($BF_{01} = 29.31$, 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, BFM = 2.95, $R^2 = .25$, 95%CI [.11|.41]). The effects of premorbid IQ ($b = .04$, 95%CI [-4.696e-4|.08]) and middle frontal gyrus volume

(b = 3.870e-4, 95%CI [-7.98e-5|8.891e-4]) improved performance. This model was four times better than the null hypothesis model (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 (M|data) = .35, BF_M = 6.42, R^2 = .27, 95%CI [.11|.44]). Education (b = .05, 95%CI [-.19|0–31]), premorbid IQ (b = .05, 95%CI [-.002|.11]) and middle frontal gyrus volume (b = 1.267e-4, 95%CI [-4.217e-4|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 (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 (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 [-6.693e-5|6.922e-4]) were associated with better performance (P(M) = .08, P (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 = .001, 95%CI [2.784e-4|.002] were associated with better verbal learning performance (P(M) = .08, P (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 (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 (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 – A summary of the evidence for cognitive reserve in ALS.

Cognitive Function	Evidence Category	BF_{01} (incl. *C9orf72*)	BF_{01} (excl. *C9orf72*)
ALS-typically impaired functions			
Letter Fluency	Very strong	75.82	77.43
Letter Flexibility	Strong	29.31	33.41
Category Fluency	Moderate	4.38	3.78
Category Flexibility	Very strong	38.99	26.70
Planning Ability	Inconclusive	1.18	1.29
Working Memory	Very strong	70.02	20.57
Shifting	Inconclusive	1.88	2.94
ALS-atypically impaired functions			
Verbal Learning	Extremely strong	131.19	134.26
Verbal Recognition	Very strong	49.89	60.87
Visuo-constructive Ability	Strong	11.43	9.24

Note: This table contains the BF_{01} comparing the cognitive reserve hypothesis to the null hypothesis model. No ANCOVA supported the null hypothesis over the cognitive reserve hypothesis.

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.,

2014, 2020), 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 ALSci 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 expands it by showing that ALS patients derive only small benefits from cognitive reserve. We further expand previous findings by distinguishing between functions: while verbal fluency, memory, visuospatial functions and working memory benefit from a reserve, shifting and planning ability do not. This corresponds with Raaphorst et al. (Raaphorst et al., 2010) who found no association between education and executive functioning.

Our findings are also congruent with AD research, suggesting that a higher cognitive reserve is associated with better cognitive functioning (Stern, 2009; Xu et al., 2015). Similarly, Placek et al. showed that executive control and verbal fluency were mediated by educational and occupational attainment in FTLD (Placek et al., 2016). Our results partially replicate their findings: higher education predicted better verbal memory, working memory and category flexibility. The small but beneficial coefficient size has been shown previously in AD when using hippocampal volume as a pathology marker (Lo et al., 2013), in addition to in multiple sclerosis (Benedict et al., 2010). Both these studies showed weak relationships between cognitive reserve and performance and failed to reject the null hypothesis, whereas our study provided evidence against the null hypothesis and in favor of the cognitive reserve hypothesis.

Our results further suggest a dissociation between educational attainment and premorbid IQ (measured by passive vocabulary): premorbid IQ was included in the best models more frequently than education, but when education was included, its effect was stronger than that of premorbid IQ. Furthermore, there may be a dissociation as to which functions benefit from cognitive reserve: functions related to verbal and semantic ability were associated with vocabulary and education. Non-verbal, non-semantic executive functions did not benefit from higher attainment in either reserve marker. It is conceivable that vocabulary is less-related to these functions, explaining why no associations were observed. Contradictions in results related to education and executive functioning highlight the necessity for further research (Canosa et al., 2014; Costello et al., 2019; Raaphorst et al., 2010). This information may be vital as cognitive impairment is associated with shorter survival (Gordon et al., 2010, 2011).

A key strength of this work is that we tested the cognitive reserve hypothesis directly and quantified support in its favor with BFHT, an approach more informative than NHST (Goodman, 2008; Wagenmakers, 2007; Wagenmakers, Love, et al., 2018; Wagenmakers, Marsman et al., 2018). In combination with the separated reserve markers—in contrast to a composite measure—this reveals that passive vocabulary as an indicator of premorbid IQ should be considered in future cognitive ALS research. Demographically, our participants' age in combination with their location means that they received their education in the German Democratic Republic (GDR), free of charge, reducing potential confounds from socio-economic influences.

Limitations include the absence of a non-verbal measure of premorbid IQ. A non-verbal, non-executive measure of IQ would have been preferable. Similarly, genetic influences on IQ and cognitive reserve should be considered in future work. Moreover, additional reserve markers, such as occupational attainment or social and physical life—time activities, would have expanded our understanding of cognitive reserve in ALS further. Social cognition may also be impaired in ALS (Abrahams, 2011) but was not included in our battery. Further research is required to address these limitations and replicate our findings.

In addition, investigating the relationship between cognitive reserve, cognitive impairment and other surrogate markers of pathology, or direct assessment or 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, neuropsychological test battery design, neuropsychological data collection, manuscript review & editing. Andreas 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. JP reports no disclosures. SV reports no disclosures. JM reports no disclosures. AH reports no disclosures. ST reports no disclosures. EK reports no disclosures.

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