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Introduction

Variability in post-stroke aphasia has been attributed to several established factors, like age, lesion size, and time post-stroke (Plowman et al., 2012). However, predicting language recovery remains imprecise. We examine whether genetic biomarkers and electrophysiological indicators of neuroplasticity improve abilities to predict language recovery, measured by aphasia severity (Western Aphasia Battery-Aphasia Quotient [WAB-AQ]; Kertesz, 2007). We specifically investigate whether language recovery predictions are improved by examining interactions between 1) a common genetic polymorphism, the brain-derived neurotropic factor gene (BDNF) and 2) neurophysiological indicators of plasticity – cortical excitability measured through motor-evoked potentials (MEPs) before and after continuous theta burst stimulation (cTBS).

Methods

Participants were 19 adults with chronic aphasia subsequent to a left-hemisphere ischemic stroke. We collected MEPs pre- and post-cTBS to primary motor cortex and obtained saliva samples for genotyping. We evaluated the extent to which BDNF $Val^{66}Met$ polymorphism interacted with pre-cTBS cortical excitability (log-transformed MEPs [LnMEPs]), and cTBS-induced MEP-suppression (10 minutes post- minus pre-cTBS LnMEPs) to predict language recovery (WAB-AQ). These predictors were added to established predictors of age at stroke, lesion volume, and log-transformed time post-stroke. We fit a backward stepwise linear regression model with these factors.

Results

Table 1 reports results of the optimal model structure fit by the backward stepwise regression (adjusted $R^2 = 0.70$). While controlling for the effects of time post-stroke ($\beta = -0.63$, $p = 0.002$) and total lesion volume ($\beta = -0.10$, $p < 0.001$), BDNF genotype showed a main effect such that when all other factors are average, $Val^{66}Val$ carriers showed better language recovery than Met carriers ($\beta = 22.68$, $SE = 1.64$, $t = 13.86$, $p < 0.001$). Furthermore, BDNF genotype interacted with each predictor of interest: age at stroke, baseline MEP, and change in MEP.

First, increased age at stroke was associated with lower WAB-AQ for both groups, but had a stronger effect on language recovery for $Val^{66}Val$ carriers ($\beta = -1.17$, $p < 0.001$) than $Val^{66}Met$ carriers ($\beta = -0.81$, $p < 0.001$). This effect was driven by a significant difference for individuals who were younger ($\beta = -2.99$, $p < 0.001$) but not older at CVA

(β= -0.003, p = 1). Second, cortical excitability was positively associated with WAB-AQ for Val^{66}Val carriers (β = 6.48, p < 0.001), but negatively associated with WAB-AQ for Val^{66}Met carriers (β = -8.49, p < 0.001). Third, Val^{66}Met carriers whose language recovered less (i.e. lower WAB-AQ) showed increased paradoxical responses to cTBS (β = -8.29, p < 0.001), whereas cTBS-induced changes in MEP-suppression was not associated with variability in recovery/severity for Val^{66}Val carriers (β = 0.30, p = 0.59).

Conclusions

Neurophysiological indicators and genetic biomarkers of neuroplasticity improve ability to predict post-stroke language recovery. The Val^{66}Val genotype is associated with stronger neuroplasticity than Val^{66}Met, so factors like age at stroke had a stronger effect for Val^{66}Val carriers. Furthermore, BDNF genotype interacted with cortical excitability and stimulation-induced plasticity to predict aphasia recovery. These findings provide novel insights into mechanisms of variability in stroke recovery and may improve aphasia prognostics.

References

Kertesz, A. (2007). *Western aphasia battery – revised (WAB-R)*. Austin, TX: Pearson Assessment.

Plowman, E., Hentz, B., & Ellis, C. (2012). Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors. *Journal of evaluation in clinical practice*, 18(3), 689-694.

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Table 1. Linear Regression Results of Stepwise Backward-Fit Model.

	Estimate	SE	t value	Pr(>|t|)
(Intercept)	129.31	1.20	107.59	<0.001
LogMPO	-0.63	0.20	-3.11	0.002
LesVol	-0.10	0.004	-23.94	<0.001
BDNF	22.68	1.64	13.86	<0.001
BDNF_Val^{66}Met : AgeCVA	-0.81	0.02	-39.53	<0.001
BDNF_Val^{66}Val : AgeCVA	-1.17	0.02	-56.27	<0.001
BDNF_ Val^{66}Met : MEPbase	-8.49	0.44	-19.15	<0.001
BDNF_ Val^{66}Val : MEPbase	6.48	0.49	13.12	<0.001
BDNF_Val^{66}Met : MEPΔ	-8.29	0.20	-40.97	<0.001
BDNF_Val^{66}Val : MEPΔ	0.30	0.55	0.54	0.589

Notes: LogMPO = log-transformed months post-onset of stroke. LesVol = total lesion volume. BNDF = brain-derived neurotrophic factor, genotypes includeVal^{66}Met and Val^{66}Val (biomarker of propensity for neural repair and plasticity). AgeCVA = age at time of cerebrovascular accident. MEPbase = motor-evoked potential at baseline (measures cortical excitability). MEPΔ = motor-evoked potential change from baseline to post-stimulation (measures transient neuroplasticity).